

CONTINUING MEDICAL EDUCATION

Specific Immunotherapy—Indications and Mode of Action

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SUMMARY

Background: It is estimated that up to 24% of the population in Germany suffers from allergic rhinoconjunctivitis and 5% from allergic asthma. Allergic rhinoconjunctivitis is closely related to other atopic diseases.

Methods: This review is based on pertinent publications retrieved by a selective search of the Medline database, guidelines from Germany and abroad, and Cochrane meta-analyses.

Results: Specific immunotherapy (SIT) is the only disease-modifying treatment option for allergies. Meta-analysis reveals standardized mean differences in allergic rhinitis symptom scores of -0.73 for subcutaneous immunotherapy (SCIT) and -0.49 for sublingual immunotherapy (SLIT); the corresponding mean differences in medication scores are -0.57 and -0.32 , respectively. The treatment should be carried out for at least three years. It is indicated when the symptoms are severe and allergen avoidance is not a realistic option. The efficacy of treatment depends on the allergen dose; thus, every allergen preparation should be evaluated individually, independent of route of administration. SCIT can cause systemic adverse effects, including anaphylaxis. SLIT is safer but often causes allergic symptoms of the oral mucosa at the beginning of treatment.

Conclusion: Even though the efficacy of SIT is well documented, it is still underused. SIT should be offered as standard treatment to patients suffering from allergic rhinitis.

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An increase in allergies to ubiquitous aeroallergens over the last few decades has been well documented (1). Among 13- and 14-year olds around the world, the prevalence of self-reported rhinitis symptoms now ranges from 3.2% to 66% (2). It is estimated that up to 24% of the German population suffers from allergic rhinoconjunctivitis, and 5% from allergic asthma (3). The symptoms are classified as either intermittent (present for less than four weeks per year) or persistent (present for more than four weeks per year). They are called moderate to severe if rhinorrhea, nasal obstruction, and eye symptoms interfere with the untreated patient's daily activities and/or sleep. An inhalation allergy should always be considered as a diagnostic possibility when the symptoms tend to arise at certain times of year or in particular situations. The allergic march often starts in childhood with atopic dermatitis and food allergies, followed by allergic asthma and allergic rhinoconjunctivitis.

Allergies are often trivialized and held to be more of a nuisance than a disease (4). Allergy is often not even considered as a possible cause of the patient's symptoms. On the other hand, many people know they have allergies but still do not consult a doctor (3). In a recent Forsa survey (5), 58% of the persons with allergies who responded said that they treated their allergy themselves with non-prescription medications or allergen avoidance. 28% received specific immunotherapy (SIT), and 70% of those receiving SIT were satisfied with the outcome.

The purpose of treating allergies is to lessen the burden of symptoms and to prevent disease progression. SIT is currently the only disease-modifying treatment capable of inducing tolerance to individual allergens. When indicated, it can be performed successfully even in childhood (6, 7).

Prevalence

Among 13- and 14-year olds around the world, the prevalence of self-reported rhinitis symptoms now ranges from 3.2% to 66%.

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The socioeconomic cost of respiratory allergies in Europe has been estimated to lie between 36.7 and 385.1 billion euros per year, depending on the assumptions on which the calculation is based (8). The more severe the allergy, the more difficult and expensive the treatment. The overall cost per patient is about €1670/year for mild asthma and about €6000/year for severe asthma (9).

Learning objectives

This article is intended to inform readers of the current state of knowledge regarding specific immunotherapy:

- its indications, contraindications, and adverse effects,
- its efficacy and the principles of allergen extract selection,
- and the manner in which the treatment is administered.

Methods

This article is based on information from the following sources:

- recent analyses from the Cochrane Database (10–12),
- an S2 guideline on specific immunotherapy (SIT) (13),
- the position papers of
 - the European Academy of Allergy and Clinical Immunology (EAACI) (7, 14, 15),
 - the Global Allergy and Asthma European Network (GA2LEN) (16),
 - the World Health Organization (WHO) (17, 18),
- the recommendations of the British Society for Allergy and Clinical Immunology (19),
- the guidelines of the Committee for Medicinal Products for Human Use (CHMP) (20, 21), and
- pertinent publications retrieved by selective searches in the Medline database (main search term: “allergen-specific immunotherapy”), with special attention to recent large-scale, double-blind placebo-controlled (DBPC) clinical trials.

The treatment of allergic diseases of the respiratory tract

Allergen avoidance is the first recommendation for patients with inhalative allergies. It may be successful, for example, for patients with allergies to pets. For patients with mite allergies, however, adequate allergen avoidance is often impossible, while the attempt to avoid pollen would most probably interfere excessively with a “normal” lifestyle.

The cost of respiratory allergies

The socioeconomic cost of respiratory allergies in Europe has been estimated to lie between 37 and 385 billion euros per year, depending on the assumptions on which the calculation is based.

TABLE 1

Meta-analyses of SCIT and SLIT: Calculation of effect strengths

	SCIT (10) SMD (95% CI)	SLIT (11) SMD (95% CI)
Symptoms	-0.73 (-0.97 to -0.5)	-0.49 (-0.64 to -0.34)
Medications	-0.57 (-0.82 to -0.33)	-0.32 (-0.43 to -0.21)

SMD, standardized mean difference; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; CI, confidence interval

Antihistamines can be used for the symptomatic treatment of allergic rhinoconjunctivitis. Topical and systemic corticosteroids and leukotriene receptor antagonists can also be used to treat allergic asthma. These medications relieve symptoms, but they are not curative.

The efficacy of SIT has been documented in a large number of clinical trials. The results of many trials employing diverse allergen preparations in various dosages have been summarized in meta-analyses (10, 11) whose findings are presented in *Table 1*.

A meta-analysis of the efficacy of subcutaneous immunotherapy (SCIT) for allergic asthma yielded standardized mean differences (SMDs) of -0.59 (-0.83, -0.35) for the symptom score and -0.53 (-0.80, -0.27) for the medication score (12).

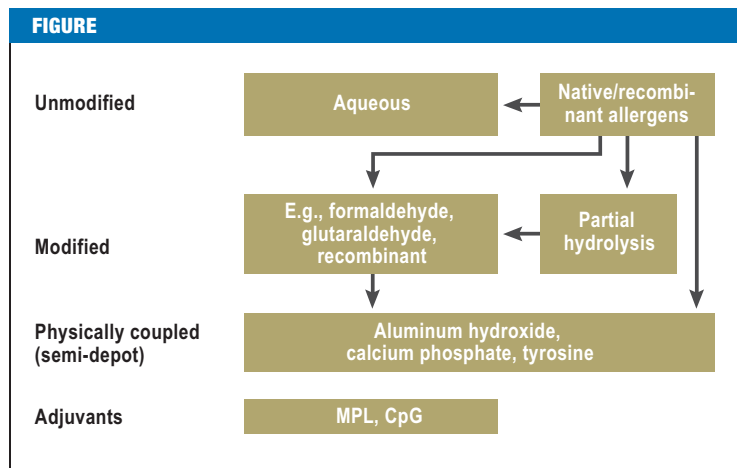
Despite differences in the study design of trials analyzing the efficacy of symptomatic treatments and of SIT there is evidence that the therapeutic effect of SCIT is superior to that of symptomatic medication even during the first year of treatment (*Table 2*) (22).

The mechanism of action of specific immunotherapy

Until a few years ago, specific immunotherapy was thought to exert its beneficial effect mainly by inducing “blocking” IgG antibodies. This concept, with its functional implications for antigen presentation and effector cell function, has now been supplemented by that of regulation of the allergen-specific immune response. When the immune system is confronted with a high enough dose of allergen, tolerance is induced. The precise mechanism of action of specific immunotherapy has not yet been definitively characterized (23, 24).

Allergen avoidance

Allergen avoidance is the first treatment option that should be considered. It may be successful for patients with allergies to pets.



Allergen preparations for specific immunotherapy (SIT); modified from (21)
 MPL, monophosphoryl lipid A; CpG, cytosine phosphatidylguanine

Dose-dependence of the immunological effect—the definition of an optimal therapeutic dose

The dose-effect relationship of SIT has been shown in clinical trials (14). The clinical benefit of a mite extract containing 7 µg of Der p 1 per injection in the maintenance phase (Der p 1 is a major allergen of the house-dust mite *Dermatophagoides pteronyssinus*) cannot be significantly augmented by raising the dose to 21 µg of Der p 1, although this does lead to an increase in adverse effects. The efficacy of 0.7 µg of Der p 1 was in the range of placebo (25). Circa 8 µg of group 5 allergen in a grass-pollen tablet is about as effective as placebo, and three times this dose (25 µg per day) yields the maximum effect, without any further benefit from still higher doses (26). These findings imply that it is possible to determine optimal dosages for SCIT and SLIT.

Allergen quantification for immunotherapy

The standardization and characterization of allergen extracts was once left entirely up to the manufacturers. The characterization of extract strength is based on measurement of protein concentrations, electrochemical techniques such as immunoelectrophoresis, wheal diameter in prick tests, and *in vitro* inhibition tests (RAST inhibition). The development of obligatory, validated methods for allergen quantification has now become a matter of central importance.

Allergen extracts

Extract strength is determined by measurement of protein concentrations, biochemical methods, wheal diameter in prick tests, and *in vitro* inhibition tests.

Allergen extracts contain proteins, glycoproteins, lectins, DNA, pigments, and other substances. The immune system interacts with only a few allergens, which are called major allergens if more than 50% of patients sensitized against the allergen extract react to this particular protein. It should be a requirement that the concentration of a major allergen is declared. This is principally unproblematic when an allergen source contains only a single major allergen (e.g., Bet v 1 in birch-pollen extract), but extracts containing multiple major allergen proteins (e.g., grass-pollen extracts) are more difficult to characterize.

The quantification of individual proteins is further complicated by the fact that allergens are found in nature in different isoforms, with potentially varying biological activity. This may affect the results of protein quantification by immunological techniques.

A comparison of major allergen concentrations in different extracts can only be valid if obligatory and validated analytic methods have been used, with comparison to standardized reference allergens. In a continuation of the European CREATE project (27), a round-robin testing program (BSP90) is now being carried out with the support of the European Directorate for Quality Assurance in Medicine (EDQM) for the testing of biological reagents and standardized analytic methods for allergens in extracts. Once these reagents and methods have been published in the European Pharmacopoeia, they will become obligatory.

The allergen concentrations that are currently declared by manufacturers are an inadequate basis for the evaluation of allergen extracts. There is no substitute for clinical trials to demonstrate the efficacy of each and every allergen extract.

Requirements for allergen extracts that are to be used for SIT

A European technical guideline currently delineates the qualitative requirements for allergen extracts and their classification and composition. The most important new feature of this guideline is the definition of homologous groups of allergens, which is based on structural similarity, rather than on botanical relatedness (20). Another guideline of the European Medicines Agency (EMA) contains recommendations for the performance of clinical trials with allergen preparations; from now on, such preparations are to be developed in a standardized, stepwise algorithm with dose-finding studies and double-blind, placebo-controlled trials of efficacy (21). In Germany, more

Clinical trials to determine efficacy

Clinical trials are needed to determine the efficacy of allergen extracts. Efficacy can not be assessed on the basis of the allergen concentrations specified by manufacturers.

TABLE 2

The efficacy of SCIT compared to symptomatic medications*

	Total nasal symptom score, TNSS		Total symptom score, TSS	
	RCI	SMD	RCI	SMD
SCIT	-34.7% +/- 6.8%	-0.94; 95% CI, -1.45 to -0.43	-32.9% +/- 12.7%	-0.86; 95% CI, -1.17 to -0.55
Mometasone fuorate	-31.8% +/- 16.7%	-0.47; 95% CI, -0.63 to -0.32		
Montelukast	-6.3% +/- 3.0%	-0.24; 95% CI, -0.33 to -0.16		
Desloratadine			-12% +/- 5.1%	-1.0; 95% CI, -1.68 to -0.32

SCIT, subcutaneous immunotherapy; RCI, relative clinical improvement; SMD, standardized mean difference.
*Total nasal symptom score (TNSS) and total symptom score (TSS) according to (22); CI, confidence interval

than 6000 different allergen mixtures were commercially available until the Regulation on Therapeutic Allergens (*Therapie-Allergene-Verordnung*, TAV) went into effect in November 2008. Most of these mixtures were then withdrawn from the market (data from the Paul Ehrlich Institute).

At present, single-substance preparations are preferred, as defined according to the concept of homologous allergen groups. The major allergens of grass and grain pollens are so highly homologous that “mixtures” of pollens from these sources are considered to be monopreparations. The same holds for allergens from birch, hazel, and alder pollen.

The evaluation of clinical effects in SIT trials

The clinical effect of SIT is evaluated by a comparison of the symptom and medication scores (SMS) during the allergy season of patients receiving either the active substance or placebo. The results obtained in different trials cannot be directly compared for a number of reasons, but mainly because no standardized SMS has yet been defined.

A 30% difference in SMS between the active-substance group and the placebo group used to be required as the criterion for a clinically significant effect. This requirement was based on evaluation of the per-protocol (PP) population, measuring the real effect of SIT itself. At present, however, intention-to-treat (ITT) analysis is considered standard. In this method,

the data from all patients enrolled in the study, including those with low compliance, are included in the analysis so that the findings will more closely correspond to the effect that can be expected under real-life conditions. The two methods of analysis can yield very disparate results: In a trial of tree-pollen SIT, for example, the SMS improvement was found to be 38.9% by PP analysis, but only 11.5% by ITT analysis (28).

The selection of allergen products

One allergen preparation cannot be recommended over another, because the findings relating to products tested in different clinical trials cannot be compared. In general, the allergen to be used should be selected by a physician who has undergone further training in allergology within his or her specialty (e.g., internal medicine), or who has specialty certification in allergology itself. The recommendations of the current guideline (13) are as follows:

- The efficacy of allergen preparations should be evaluated individually and independently of route of administration (e.g., subcutaneous or sublingual).
- High-quality allergen extracts with demonstrated efficacy should be used.

Allergen extracts are categorized as either unmodified (native) or modified (allergoids). The latter are proteins that have been treated with formaldehyde or glutaraldehyde to lower their binding affinity for IgE.

Evaluating the clinical effect of SIT

The clinical effect of SIT is evaluated by a comparison of the symptom and medication scores (SMS) during the allergy season of patients receiving either the active substance or placebo.

The selection of an allergen product

The efficacy of allergen preparations should be evaluated individually and independently of route of administration, and high-quality allergen extracts of documented efficacy should be used.

BOX 1

Preconditions for SIT*

- Sensitization to an aeroallergen and demonstration of clinical relevance; for perennial allergens, specific provocation is generally necessary (nasal, conjunctival, sometimes bronchial [in adults]).
- SIT must have a documented effect against the disease to be treated; according to the current state of the evidence, this is now the case for allergic rhinoconjunctivitis and allergic asthma.
- A suitable allergen extract must be available. The extract's efficacy and adverse effects must be analyzed in clinical trials according to the specifications of the Paul Ehrlich Institute (double-blind, placebo-controlled trial of adequate size).
- The patient must be willing and able to keep up with treatment regularly for three years.

*modified from (13); SIT, specific immunotherapy

In the extracts that are commonly used today, aluminum hydroxide is the most common adsorbent for prolonging release of the allergen. Some preparations additionally contain adjuvants to enhance the immunological effect (*Figure*).

The best currently available evidence for the efficacy of SCIT and SLIT concerns the treatment of allergic rhinoconjunctivitis with grass-pollen extracts. Grass-pollen tablets (SLIT) have been officially approved for the treatment of adults and children on the basis of results from clinical trials. The German pediatric specialty society, however, currently hesitates to recommend SLIT because of concern about local adverse effects that are common at the start of treatment and that may interfere with long-term compliance. Long-term trials have been published that document the sustained effect of SLIT in adults after the end of treatment (29, 30). The efficacy of SLIT against allergic asthma, its potential preventive effect against asthma, and its potential preventive effect against new sensitization have not yet been adequately studied; large-scale prospective studies of these questions are currently in progress, and their

findings should be published in the next few years (31). The state of the evidence for SLIT with other antigens is held to be inadequate by most specialists in Germany (13), although individual extracts from other allergen sources have achieved the status of an approved product. Information about the approval status of allergen preparations in Germany is available on the Internet (32, in German).

It is currently up to the allergist to evaluate the efficacy of allergen preparations. In the future, however, all newly approved allergen extracts will be subject to the requirements of the TAV, and their efficacy will have to be demonstrated in clinical trials whose validity will be assessed by the Paul Ehrlich Institute. Some allergen extracts are still available today whose efficacy cannot be evaluated at all because they have not been clinically tested.

The available evidence for the efficacy of SCIT and SLIT against grass-pollen allergy currently supports a positive recommendation for the preparations that have been shown to be effective in clinical trials. Patients should be informed about both treatment options so that they can make an informed choice between them in collaboration with the treating physician. (Under the new Patients' Rights Law in Germany [*Patientenrechtegesetz*], patients have the right to participate in decision-making). For allergens of other sources, the evidence for SCIT is somewhat stronger and for this reason it is preferred by many allergists in Germany (*Table 2*). It bears pointing out once again that current evidence permits neither a comparison of SCIT against SLIT nor a comparison of different SCIT preparations with one another.

The indications for SIT

It is stated in the German guideline (13) that SIT is indicated when the causative allergen cannot be avoided, or when avoidance is not adequately effective; for further requirements, see *Box 1*.

As a rule of thumb, immunotherapy can be recommended if the symptoms have been present for more than two years, if allergen avoidance is impossible or insufficiently effective, and if the patient suffers from moderate or severe symptoms that would call for long-term symptomatic treatment. There is no longer any reason to set age limits (in the past, immunotherapy was said to be indicated only for patients between the ages of 5 and 50). The treatment of children requires special consideration of the individual compliance

Evidence

The best evidence for the efficacy of SCIT and SLIT is for the treatment of allergic rhinoconjunctivitis with grass-pollen extracts. Patients should be informed of both options and choose between them in collaboration with the physician.

Immunotherapy

Immunotherapy can be recommended if the symptoms are moderate or severe and have been present for more than two years, and if allergen avoidance is impossible or insufficiently effective.

factor; school-age children are generally capable of taking their medication as instructed. In elderly patients, the contraindications to SIT play an increasingly important role. These contraindications are derived from the potential dangers of treatment (*Box 2*).

The benefits and risks of the treatment should be weighed against each other for each patient. For medicolegal reasons, special attention should also be paid to all information contained in the package insert.

Predictors of the success of SIT

SIT is especially likely to succeed in patients who are sensitized against a single allergen and are in an early stage of disease. Thus, early treatment with SIT is recommended, particularly for children. The treatment is also effective, however, for patients sensitized against multiple allergens (33). For them, too, SIT is the only treatment that can have a lasting effect on the disease.

According to the guideline, patients may be treated with up to three allergen extracts at once (13). The selection is based on the severity and duration of symptoms, the degree to which they impair the patient's quality of life, and the avoidability of the individual allergens.

Individual prediction of the response to SIT is currently not possible. A potential approach that is currently under discussion is to analyze IgE antibodies against allergen components and then treat patients who are found to be sensitized to major allergens (34, 35).

The duration of the therapeutic benefit of SIT is also hard to predict in individual cases. The longest published follow-up to date is for SCIT with a grass-pollen allergoid: The effect was still demonstrable 12 years after the end of treatment (36).

The recommendation to repeat the treatment if allergic rhinoconjunctivitis recurs after initially successful SIT is based on clinical experience, rather than on data from clinical trials, as adequate evidence of this type is not yet available.

The performance of SIT

The recommendations contained in published guidelines from Germany and other countries are based on evidence from clinical trials and meta-analyses (10–19).

The treatment begins at a low dose, which is gradually increased until the maintenance dose is

BOX 2

Contraindications of SIT*

- Partly controlled or uncontrolled asthma with FEV1 less than 70% of normal despite adequate treatment
- Severe autoimmune diseases and immunodeficiency states
- Current cancer
- Beta-blockers (as eye drops as well) are, according to the guideline (13), a contraindication for SCIT, but not for SLIT. Nonetheless, the package inserts of certain high-dose preparations for SLIT name beta-blockers as a contraindication.
- Cardiovascular diseases that elevate the risk of complications after the administration of epinephrine.
- SIT should not be initiated during pregnancy, but an uncomplicated SIT may be continued if the patient becomes pregnant while SIT is ongoing.

*modified from (13); SIT, specific immunotherapy; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy

reached. This process may take up to 20 weeks with native allergens; with allergoids, a single day may suffice. Clinical trials have been conducted to test the efficacy of treatment with allergoid extracts of grass pollen (37–39), tree pollen (40), and mites (e1, e2).

Depending on the preparation, the treatment with with pollen extract can be given either before the allergy season or year-round; some allergoids have been approved for both treatment schedules. No adequate comparison of these two treatment schedules has yet been published.

The adverse effects of SCIT include allergic reactions that can range all the way to severe anaphylaxis. No official statistics on severe reactions have been published, but cases of fatal anaphylaxis are known to have occurred in recent years. The physician must inform the patient thoroughly of all possible adverse effects (including generalized skin reactions, systemic reactions, and anaphylaxis) and document in writing that this information has been provided. The injection must be performed by the

The success of SIT

SIT is likely to succeed in patients who are sensitized against a single antigen in an early stage of disease, but it is also effective in those sensitized against multiple allergens. SIT is the only treatment with a lasting effect on the disease.

SCIT

The adverse effects of SCIT include allergic reactions ranging all the way to severe anaphylaxis. The physician's office must be properly equipped for the treatment of anaphylaxis, and the injection must be carried out by the physician.

BOX 3

Obligatory questions before each injection

- Did you have any adverse effects from the last injection?
- Do you have any allergy symptoms now?
- Are you now suffering from any new medical condition?
- Are you now taking any other medication?

physician, who must have experience in the treatment of systemic allergic reactions. The physician's office should be properly equipped for the treatment of anaphylaxis, with the appropriate medications and equipment close at hand. As a minimum, the following must be available:

- a defibrillator
- an IV infusion set
- epinephrine
- an antihistamine
- an inhalable beta-2-sympathomimetic drug
- a corticosteroid for intravenous administration.

The patient should be asked about current contraindications before every injection (*Box 3*). 30 minutes of observation after each injection are obligatory. Intense physical activity shortly before or after the injection may induce an anaphylactic reaction and should therefore be strictly avoided.

SLIT is administered either year-round (pre-seasonal) or before and during the allergy season (pre/co-seasonal). In patients who are to receive high-dose preparations, the initial administration must be performed under medical supervision. The patient must have an intact oral mucosa, as mucosal injuries may promote adverse effects. After dental extractions or gingival treatments, SLIT should be temporarily interrupted. SLIT should not be administered immediately after tooth-brushing.

Pretreatment with an antihistamine is a useful means of diminishing the local reactions that often arise at the beginning of treatment. SLIT causes mild adverse effects more commonly, but severe ones less commonly, than SCIT. To our knowledge, fatal adverse reactions have never been reported for SLIT.

Whatever the mode of administration, SIT should be continued for at least three years. It has been shown for SCIT that longer treatment confers no statistically significant additional benefit (e3).

It is recommended that the treatment be continued until no further therapeutic benefit is observable, or for one further year after complete relief of symptoms has been achieved.

If allergic symptoms recur after initially successful SIT, repetition of the treatment is recommended.

The ideal time to start SIT

There was an earlier recommendation to start SIT before the allergy season. Updosing during the pollen season should be avoided, however, due to a potentially increased risk of adverse effects.

No studies have yet been published addressing the question of when the effect of SCIT sets in. For SLIT with a grass-pollen tablet, statistically significant efficacy has been documented 30 days after the start of treatment (e4).

The effect of concurrent medication on the efficacy of SIT

An effect of concurrent treatment on the efficacy of SIT has not been systematically studied in clinical trials. Immune suppressants would presumably diminish the treatment effect, and, as a rule, immune-suppressed or immunocompromised patients should not undergo SIT. In a small-scale trial in which children with asthma and house-dust mite allergy were treated with SIT with a house-dust mite extract, simultaneous treatment with montelukast apparently lowered the efficacy of SIT (e5).

There is insufficient evidence for further recommendations to avoid or specifically add any particular medication.

Adjuvants

The purpose of adding adjuvants is to enhance the immunological effect of SIT by modulating the allergen-specific T-cell response in the direction of tolerance. For this purpose an allergen extract containing monophosphoryl lipid A is available in Germany. The postulated enhancement of the immunological effect by the bacterial molecule contained in this preparation cannot be judged at present, as there has been no comparative clinical study of the efficacy of allergen treatment with and without added adjuvants.

Injuries of the oral mucosa and SLIT

Patients taking SLIT must have an intact oral mucosa, as mucosal injuries promote adverse effects.

Adverse effects of SLIT

SLIT causes mild adverse effects more commonly, but severe ones less commonly, than SCIT.

TABLE 3

SCIT versus SLIT: the available evidence

Studies on:	SCIT	SLIT
Dose-effect relationship	studied for various allergens (14)	studied for various allergens (14)
Definition of the optimal dose	documented in one DBPC trial of a mite allergen (23)	documented in one DBPC trial of a grass-pollen tablet (24)
Efficacy after 1 year of treatment	determined for multiple allergens in DBPC trials, some of which were on a large scale (10, 37, 39, 40, e1, e2)	determined in large-scale DBPC trials for grass-pollen extracts (11, 26, 30, e13–e19)
Efficacy after 2 and 3 years of treatment	shown in trials of various allergens (e3)	shown in large-scale DBPC trials of grass-pollen extracts (29, 30, e13)
Sustained therapeutic benefit	shown in multiple trials, most of which were controlled (6, 24, 36, e20)	shown in trials of adequate size for grass-pollen extracts for adults (27, 28)
Efficacy for allergic asthma	shown for various allergens (39)	small effect in meta-analysis (e21)
Asthma prevention	no DBPC trials; positive findings in controlled trials (e22)	no DBPC trials; positive findings (e23)
Prevention of new sensitization	shown in controlled trials of individual allergens (e22)	no DBPC trials; positive findings (e24)

SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; DBPC, double-blind, placebo-controlled

In animals, aluminum hydroxide has been found to have strong adjuvant effects (e6). No tests have yet been performed to determine whether it might act as one in man as well.

Other molecules that might be useful as adjuvants are now being clinically tested.

Recombinant allergens

The major allergens of the main inhaled allergen sources have been characterized and can be produced with recombinant techniques. The problem of standardization can thus be solved for SIT, as large amounts of these proteins can be produced with consistent quality. Clinical trials of the use of recombinant grass pollen, birch pollen, and cat allergens have been published.

In a proof-of-concept study, SCIT with a mixture of five recombinant grass-pollen proteins led to a 38.5% reduction in SMS compared to placebo (e7).

15 µg of natural or recombinant Bet v 1 were as effective as treatment with a native birch-pollen extract containing 15 µg of Bet v 1 (e8).

By analogy with the production of allergoids, the three-dimensional structure of recombinant proteins can be modified. Testing of a modified Bet v 1 mol-

ecule (folding variant) has shown it to be clinically effective and well tolerated at a high dose (80 µg) (e9).

Peptides containing the necessary T-cell epitopes are promising substances for treatment with relatively few adverse effects once the IgE-binding epitopes that cause adverse effects have been eliminated. This approach is used in the treatment of cat allergy (e10).

Modes of administration

Both the subcutaneous and the sublingual administration of allergen extracts are now well established. Recently, intralymphatic immunotherapy (ILIT) and epicutaneous allergen application have been described as potential alternatives. In a proof-of-concept study, three injections of very small allergen amounts in an inguinal lymph node sufficed for effective treatment (e11). Epicutaneous allergen application has also been found to have an effect (e12). It is not yet clear whether allergen preparations for intralymphatic or epicutaneous application will become commercially available.

Concluding remarks

SCIT and SLIT are now the only treatments for allergic diseases that induce long-lasting disease modification

Experimental alternatives

Recently, intralymphatic immunotherapy (ILIT) and epicutaneous allergen application have been described. In a proof-of-concept study, three applications of a very small amount of allergen in an inguinal lymph node sufficed for effective treatment.

SIT

If the patient's symptoms are clearly connected to allergen exposure, SIT should be offered as the standard treatment. To be successful, SIT must be given for at least three years.

with sustained improvement of symptoms. The therapeutic potential of SIT is not reflected by its current use in Germany. Patients with allergies are undertreated here. All allergic patients should undergo an appropriate diagnostic evaluation followed by appropriate allergy treatment, and SIT should be offered as the standard treatment for suitable patients.

Allergen preparations with documented safety and efficacy are to be preferred. The new German Regulation on Therapeutic Allergens (TAV) ought to simplify the choice of suitable preparations.

To be successful, SIT should be given for an adequate period of time (at least three years). Recent surveys indicate, however, that less than half of all patients who start SIT continue to receive it for the full three years (e25). The main reasons for premature termination of treatment are apparently adverse effects, insufficient efficacy, and the expenditure of time. Means of improving patient compliance need to be developed.

Conflict of interest statement

Prof. Brehler has received consultant's fees and reimbursement of participation fees for scientific meetings from Allergopharma, Novartis, and Stallergenes. He has received reimbursement of travel and accommodation expenses from Allergopharma, Novartis, Stallergenes, and ALK. He has also received honoraria for the preparation of continuing medical education presentations from Allergopharma, Novartis, Stallergenes, Bencard, and HAL. He has received payment for the performance of clinical trials on behalf of Allergopharma, Novartis, Leti, HAL, Stallergenes and ALK (funds deposited in an account of his hospital department for external research support).

Prof. Klimek has received consultant's fees from ALK, Allergopharma, Bencard, Boehringer, Lofarma, and Novartis. He has also received reimbursement of participation fees in scientific meetings and continuing medical education events, and of travel expenses, from ALK, Allergopharma, Bencard, HAL, Novartis, Lofarma, Roxall, and Stallergenes. He has received payment for the preparation of continuing medical education presentations from ALK, Allergopharma, Bencard, GSK, HAL, Lofarma, Novartis, Roxall, and Stallergenes. He has received honoraria for carrying out clinical trials on behalf of ALK, Allergopharma, ArtuBiologicals, Bencard, Biomay, Bionorica, BMBF, Cytos, EAACI, HAL, GSK, Leti, Lofarma, Novartis, PierreFabre, Roxall, Ursapharm, Teva, Stallergenes, and Zambon. He has received payment for a research project from Bencard, ALK, Allergopharma, and HAL.

Prof. Kopp has received consultant's fees from Bencard, ALK, Abelló, and Novartis. He has received honoraria for preparing continuing medical education events from Bencard and Novartis and for performing clinical trials on behalf of Novartis.

Prof. Virchow has received consultant's fees from Allergopharma, ALK, and Stallergenes.

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Solutions to the CME questions in Issue 1–2/2013:

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Solutions: 1c, 2a, 3c, 4c, 5e, 6c, 7e, 8c, 9b, 10d

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Which of these situations is the best indication for SIT?

- a) When symptomatic treatment is no longer adequate
- b) When symptoms of asthma are present
- c) When the patient is allergic to multiple allergens
- d) When marked symptoms are present in the early stage of the disease
- e) After the first season of symptoms

Question 2

Which of the following is a requirement for the approval of future drug products for use as treatment allergens?

- a) Their efficacy must be tested in large-scale clinical trials.
- b) They must consist of a mixture of multiple allergen extracts.
- c) There must be a standardized means of determining the quantity of major allergen.
- d) They must be characterized with electrochemical testing.
- e) The manufacturer must provide information about extract strength.

Question 3

How can the efficacy of allergen preparations be evaluated?

- a) By the allergen concentration declared by the manufacturer
- b) By the concentration of a major allergen
- c) By clinical trials
- d) By observations from clinical practice
- e) By *in vitro* testing

Question 4

Which of the following is a contraindication for SCIT with pollen extracts?

- a) The use of beta-blocker eye drops
- b) Sensitization to multiple allergens
- c) Longstanding allergy
- d) Mild allergic asthma
- e) A history of breast cancer, without recurrence

Question 5

For what type of extract is there the best evidence for efficacy against allergy, with either SCIT or SLIT?

- a) Birch
- b) Rye
- c) Wheat
- d) Grass pollen
- e) Hazelnut

Question 6

For what condition is SIT clearly indicated?

- a) Atopic dermatitis
- b) Mild, intermittent rhinoconjunctivitis
- c) Severe asthma
- d) Persistent allergic rhinoconjunctivitis
- e) Pollen-associated food allergy

Question 7

What is the main advantage of recombinant allergens?

- a) They can be precisely standardized.
- b) They are more effective.
- c) They are better tolerated.
- d) They are easier to produce.
- e) They have a longer shelf-life.

Question 8

For what condition(s) has sublingual immunotherapy been shown to be effective?

- a) Allergic asthma in children
- b) Mainly for rhinoconjunctivitis due to grass-pollen allergy
- c) For the prevention of new sensitization
- d) For allergic asthma in adults
- e) For all allergens

Question 9

Which of the following is particularly important for the evaluation of a potential causal link between a perennial allergen and rhinoconjunctivitis, as opposed to seasonal allergens?

- a) A nasal provocation test
- b) A prick test
- c) The demonstration of specific IgE antibodies
- d) An intracutaneous test
- e) An epicutaneous test

Question 10

After how many days of treatment has SLIT with a grass-pollen tablet been shown to have a statistically significant benefit?

- a) 25 days
- b) 30 days
- c) 35 days
- d) 40 days
- e) 45 days

CONTINUING MEDICAL EDUCATION

Specific Immunotherapy—Indications and Mode of Action

Randolf Brehler, Ludger Klimek, Matthias Volkmar Kopp, Johann Christian Virchow

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