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Review article

Allergen-specific immunotherapy in children

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HISTORICAL TIPS

The science of "*Immunology*" originated in the 19th century and grass pollens were identified for the first time as the likely trigger of seasonal hay fever in the 1870s. Skin allergy testing became an accepted assessment technique around 1910. Immunoglobulin E (IgE) was identified in the 1960s. The first scholarly report of immunotherapy for allergy appeared by Noon[1] and Freeman in 1911 in the medical journal, The Lancet. Clinical attempts to determine the best dose and route for allergy therapy increased dramatically in the 1920s and 1930s.[2] The oral route of immunotherapy was suggested earlier in 1900 by Curtis[3] but, the clinical use of sublingual immunotherapy (SLIT) for foods was described in 1969 by David Morris.[4] SLIT was reintroduced in 1970 for inhalant allergens.[5] Although some patients treated for food, pollen, pet dander and mold allergy by SLIT appeared to improve, the ideal dose, degree of expected improvement, and the mechanism of action were not established, and few studies were published in peer reviewed journals until the 1990s. Generally, sufficient research evidence on the effectiveness and mechanism of immunotherapy began to accumulate in the last 15 years of the 20th century.[6]

Background

The prevalence of allergic diseases has steadily increased in populations from western and some developing countries over the last three decades.[7] Allergic diseases result from an abnormal response of the specific immune system generating allergen-specific immunoglobulin-E (IgE) antibodies. These mediate the various symptoms of allergic diseases, such as asthma and allergic rhinitis (AR), upon re-exposure to this allergen.[8]

The late introduction of solid foods during the 1st year of life – that is generally recommended by many physicians – is associated with increased risk of allergic sensitization to food and inhalant allergens at the age of 5 years.[9]

Allergic patients who are challenged with an allergen to which they are sensitive often display a biphasic inflammatory response. This occurs after both nasal and bronchial challenges, and a similar phenomenon can be seen in the skin after allergen testing. An early phase of symptoms develops within minutes of challenge and, in some but not all patients; a later phase begins several hours later. The early phase corresponds with the release of various mediators from local tissue mast cells and circulating basophils, including histamine, prostaglandin D2, kinins, cysteinyl leukotrienes (LTC4, D4, and E4), cytokines, and chemokines. These mediators can be measured in nasal secretions during nasal challenges. Some of the mediators stimulate cell recruitment to the area of challenge, leading to a secondary influx of inflammatory cells, including T lymphocytes, eosinophils, and additional basophils. The newly arrived cells release specific inflammatory mediators that perpetuate the underlying inflammation and contribute to persistent allergic symptoms.[10]

Unlike drug treatments, which mask or suppress allergic reactions, allergen-specific immunotherapy (SIT) "resets" the immune system to prevent these reactions and hence can be termed hyposensitization or desensitization therapy. SIT is the repeated administration of increasing amounts of purified allergen vaccines to allergic individuals with the aim of inducing immunologic tolerance. So, it is the only immune-modifying and probable etiological therapy for allergy.[11]

SIT is a highly cost-effective treatment strategy which results in an improved quality of life, reduction in days off school/work, long-term remission of allergic symptoms, reduction of severity of asthma, reduction of the need for medication and reduction of the chances of new sensitizations to allergens developing.[12] It is highly effective in IgE-mediated diseases as in allergic rhino-conjunctivitis and allergic asthma and in patients who develop systemic anaphylactic reactions to wasp/bee venom.[13] In addition, it is most effective specifically for pollen, dust, and animal dander allergies.[14]

After several months of immunotherapy, patients undergoing nasal allergen challenge demonstrate a significantly blunted early response; although complete inhibition is uncommon. The late phase reaction is even more effectively reduced.[15]

Mechanism of action of SIT

Allergen-specific immunotherapy induces marked increase in "blocking" IgG antibodies and blunts the seasonal increases in allergen specific IgE concentrations in patients with seasonal pollinosis. There is inhibition of the recruitment and activation of effector cells including mast cells, eosinophils, and basophils in the allergic respiratory mucosa of the nose and bronchi. These "effector" mechanisms are modified as a consequence of altered T-lymphocyte responses following high dose allergen exposure during immunotherapy.[16] There is immune deviation from a "Th2-type" response with dominant production of interleukin (IL)-4 and IL-5 in favour of "Th1-type" responses with production of interferon gamma and IL-2. Moreover, it was found that osteopontin produced by $CD14^+$ cells induced IL-12 in antigen presenting cells to activate Th1 responses.[17]

Immunotherapy also has been shown to induce a subset of "T-regulatory" cells with allergen-specific increases in the production of IL-10 [18] and transforming growth factor beta (TGF-β).[19] These cytokines inhibit T responses and avert antibody production in favor of IgG4 – especially in bee or wasp venom immunotherapy – and, possibly, IgA synthesis with downregulation of IgE responses. The end result is a global decrease in the secretion of Th2 (i.e., IL-4, IL-5, IL-9 and IL-13) and Th1 cytokines (i.e., IFN-γ and IL-2), and T-cell hyper-responsiveness. These events are accompanied by suppression of allergen-induced T cell-dependent late responses in the skin and lung and long term disease suppression which is apparent following discontinuation.[20]

Allergen Extracts and Vaccines

Allergens are substances that are perceived by the immune system mistakenly as threats. Most allergens are proteins of low molecular weight; 10-70 kd. Molecules smaller than 10 kd cannot bridge adjacent IgE molecules on the surface of mast cells or basophils, to activate and induce degranulation of these cells, and those larger than 70 kd cannot cross mucosal surfaces to reach the antigen-presenting cells.[21]

The historical term allergen extract was changed to allergen vaccine to reflect the fact that allergen vaccines are used in medicine as immune modifiers. So, allergen vaccines are extract preparations that are approved by the FDA as therapeutic allergens or immune modifiers for treatment of allergic diseases. When possible, standardized vaccines of known potency and shelf-life should be used.[22] They are provided as aqueous, glycerinated, lyophilized or alum-precipitated formulations. There are 4 standardized extracts; Cat, Dust Mite, Grass and Ragweed. Some of these vaccines are standardized regarding the available concentration as those extracts for cat hair, cat pelt, Dermatophagoides pteronyssinus and farinae, and Hymenoptra venoms.[23]

Adjuvants used in conjunction with allergen extracts may contribute to further improvement in SIT immunogenicity and efficacy, and to shortening of treatment duration. Conventional adjuvants including aluminium hydroxide or calcium phosphate are used by most producers. Novel generations of adjuvants – derived from cholera toxin and Escherichia coli enterotoxin for mucosal priming and boosting[24] – may direct the immune response more specifically toward a Th1 switch or toward T-cell tolerance.[25]

Recombinant Allergens are considered as effective as purified natural allergens or whole allergen extracts. If they are folded in their native configuration, they might induce the same adverse reactions as the usual extracts because they can then bind IgE as natural allergens. They were reportedly well tolerated in most patients.[26]

Hypoallergenic polymerized formulations of whole allergen extracts have been developed for this reason. They include the so-called *allergoid preparations*. Site-directed mutagenesis of IgE-binding sites led to the expression of allergens with variable, but significantly decreased IgE-binding capacity. That is why hypoallergenic recombinant allergen fragments may be administered safely to hypersensitive patients at a markedly higher concentration than SIT with whole allergen extract would allow.[27]

Immunotherapy Protocols

Conventional Immunotherapy:

This involves weekly subcutaneous injections for 8-16 weeks during an updosing phase till reaching a maintenance dose; a dose that is, in principle, well tolerated by the patient or induces only limited-to-minimal local or systemic side effects. Once the maintenance dose is reached, the injections are administered every two to four weeks (some centers empirically extend this interval to 6-8 weeks) for a period of 3-5 years. In general, the longer the treatment and the higher the dose, the greater is the therapeutic benefit. In addition, SIT needs to be started 2 – 4 months before the start of the allergen season in case of seasonal allergies.[28]

Cluster Immunotherapy:

Accelerated schedules involve two to three injections administered per treatment day (with an

interval of 30 minutes between the injections) in weekly intervals. So, the individual maximum dose can be reached after 1–4 weeks depending on the depot-allergen preparations or chemically modified allergen preparations ('allergoids') used.[29] Principles of accelerated schedules in SCIT have been described first by Freeman[30] in the thirties (1930) as *'intensive desensitization'*. These schedules have not been widely used in Europe and in the USA, likely due to safety concerns.[31] The first controlled cluster protocols were described by Norman *et al.* in the 1980s with 11 injections given in 5 treatment days and therapy intervals of 3 weeks in between.[32]

A large survey by Mellerup *et al.* with 650 allergic patients demonstrated a significantly reduced rate of adverse events using a cluster schedule with depot-allergens compared to a cluster protocol with native aqueous extracts.[33]

In a recently published trial, allergic children sensitized to house dust mites (HDM) were randomized to two groups: 20 children were treated with a cluster protocol, whereas 10 children were randomized to a *'conventional'* protocol to reach a maintenance dose within 13 weeks. There was no significant difference in the incidence of adverse events though the time needed for the dose increment in the 'cluster group' was more than half lower than in the 'conventional group'. During the study, significant immunological effects (increase of mite-specific IgG and IgG4 levels) were observed in the eighth week after the beginning of the cluster schedule while they were demonstrated in the conventional group not earlier than 12 weeks after the beginning of therapy. These data were confirmed by blocking CD63 expression as well as release of cysteinyl leukotrienes after in-vitro basophil stimulation.[34]

So, there is an increasing evidence for convincing safety profile of cluster protocols with both (native) depot allergens and chemically modified allergen preparations ('allergoids'). Allergoids were also examined in recently published cluster studies such as the study of Subiza et al. in which they used a grass mixture modified by glutaraldehyde. Large local reactions were found after 5.1% of all injections, whereas systemic reactions were not observed.[35]

As an alternative option for the up-dosing phase of SCIT, these protocols account for the desire of patients to abbreviate the total length of SCIT without a higher risk of adverse reactions. This issue is of high importance as inconvenience is likely the most common reason for not beginning or discontinuing the conventional (or 'leisurely') form of SCIT.[29]

Cost-effectiveness of cluster protocols was also an important issue to assess and preliminary data suggest that cluster SIT definitely spares lots of money per capita as shown by some studies concerned with pharmaco-economics.[36]

Rush Immunotherapy:

This involves repeated updosing injections in order to achieve maintenance doses within several hours. This protocol is applicable to venom sensitive patients, although unsuitable for patients with inhalant allergies due to marked increase of side effects.[37]

Routes of Immunotherapy

Subcutaneous Immunotherapy (SCIT):

Subcutaneous injection immunotherapy is the only approved route in the USA and in general, it is the only established form of SIT.[38] SCIT proved its efficacy in the management of allergic rhinitis and asthma, even in multi-allergen mixes. It demonstrated effective prevention of new sensitizations and progression of rhinitis to asthma. The effective doses and duration are well established and the persistence of efficacy after stopping administration was demonstrated in several randomized controlled trials.[39] All the SIT protocols (discussed before) involve this route of SIT administration.[40] It is to be noted that patients must remain under medical observation for 30 minutes after an immunotherapy injection in case an allergic reaction occurs.[41]

Sublingual Immunotherapy (SLIT):

This is administered under the tongue for two minutes and then swallowed[46]. There is convincing evidence that the mechanisms of action of SLIT are partially similar to those of SCIT. In particular, SLIT is capable of inducing the production of IL-10 from regulatory T cells, thus modifying the balance between Th1 and Th2 cells.[42]

Confirmation of the clinical efficacy and satisfactory safety of SLIT has been achieved in several meta-analyses, large randomized controlled trials and post-marketing surveys.[43]

In respect to the prevention of asthma in children with rhinitis, a randomized open prospective study in children receiving SLIT or drugs only was published in 2004. This trial demonstrated that SLIT can reduce significantly the onset of asthma over a 3-year period of observation. It was reported to be more effective in AR to grass pollen, but not to mites.[44]

Another large prospective randomized open trial, involving more than 200 children treated with SLIT or drugs alone for 3 years, demonstrated that

SLIT reduced significantly the onset of persistent asthma and the onset of new skin sensitizations.[45]

Finally, a long-term follow-up of children with mite allergy, showed that SLIT – again – reduced the onset of asthma, and that this effect was maintained for 5 years after discontinuation.[46]

Moreover, all the present studies agree that one of the advantages of SLIT over SCIT is greater safety in children < 5 years.[47]

Many years ago; in 1998, the World Health Organization concluded that sublingual immunotherapy was a viable alternative to the injection route and that its use in clinical practice is justified[28]. In addition, recent studies ascertained that SLIT has a shorter escalation phase, equal or greater efficacy for rhinitis, and an improved safety profile.[48]

On the other hand, in a recent review of all studies on SLIT by the American Academy of Allergy, Asthma and Immunology published in Journal of Allergy and Clinical Immunology, 35% of studies resulted in significant reductions in medications and symptom scores but 38% of studies found no significant benefit from SLIT. When SLIT did work, it was typically less effective than with conventional subcutaneous injection immunotherapy and sometimes SLIT took two years to show significant clinical benefit.[49]

It is clear that more information is needed concerning the preventive effect of SLIT, although the available data are consistent with a preventive capacity of the treatment.

Advantages of SLIT[42, 50]

SLIT has favorable effects on several features of airway inflammation, as follows:

1) It decreases bronchial hyper-responsiveness
2) It is efficient in preventing asthma development in children
3) It is efficient in preventing the occurrence of novel sensitizations
4) Milder adverse events than SCIT and they are mainly local in mouth
5) Compliance is a key factor for success of SLIT

Disadvantages of SLIT[51]

Weaknesses still compromise the development of SLIT, as follows:

- Only rare dose-ranging studies have been performed
- Unclear benefit in polysensitized patients
- The optimal duration is not definitely characterized
- Patients' selection criteria are largely undefined
- Partially defined formulation and mode of delivery (tablets versus drops)

Oral Immunotherapy

Researchers at Hopkins Children's center evaluated the efficacy and safety of consuming increasingly higher doses of the offending food; either milk or egg protein, by children with allergies. They reported encouraging results although they recommended long-term monitoring of studied patients and implementation of these trials only by a trained pediatric allergist. Children who received that kind of immunotherapy had lower blood levels of IgE antibodies and even when symptoms did occur, they were mild to moderate in the form of itching and swelling of the mouth and throat. In another study at the same center, they compared SLIT – by placing small amounts of milk protein under the tongues of allergic children – to oral consumption of milk as before. They found that oral therapy was slightly more effective than SLIT, but the latter was safer with lower risk for severe allergic reactions.[52]

OIT was not only studied for foods, but it was also tried in allergic rhinitis using – for instance – either sublingual tablets of grass pollen or enteric and microencapsulated preparations of ragweed pollen extract.[53]

Local Nasal Immunotherapy

A double-blind randomized multicenter trial for assessment of the efficacy and safety of specific local nasal immunotherapy (LNIT) in patients with allergic rhinitis was done in Italy in the year 2000. The researchers identified allergens with the skin prick test (SPT) and sensitization threshold dose with the specific nasal provocation test, and then they started self-administered treatment using insufflators. They evaluated the patients after 32 weeks of treatment subjectively through self-reported symptoms and objectively by analysis of nasal provocation test, nasal resistance by anterior rhinomanometry, and mucociliary clearance time. They concluded that specific LNIT is effective for allergic rhinitis and appears to offer considerable advantages over other hyposensitization methods. It can be done at home, patient compliance is good, and the treatment is safe.[54]

Another study was done by Passàli and colleagues[55] in Italy also underlined the efficacy and quickness of LNIT in the treatment of perennial allergic rhinitis. In the same year, another group of research workers tested the low-dose LNIT in children with perennial allergic rhinitis due to Dermatophagoides ascertained the ease of use and lack of serious side-effects.[56]

In a more recent Egyptian study, 1000 patients from 6 Egyptian governorates were enrolled for assessment of LNIT. The study showed significant

improvement of skin tests, blood, nasal and sputum eosinophilia, total IgE levels and nasal symptoms. The researcher concluded that LNIT is a simplified, self-administrable method with high compliance being used at home.[57]

Novel modes of delivery

Apart from the conventional subcutaneous or sublingual application, there is place for other variants, including intradermal injections, transdermal applications, nanotechnologies as well as the previously mentioned novel mucosal strategies (oral and nasal). The mucosal approach is probably the domain where needs for improvements to the immunotherapeutic formulations are the most acute.[28]

Another novel route for SIT is the *intralymphatic immunotherapy* (ILIT).[58] This administers allergens directly into a subcutaneous lymph node enhancing the immune responses to protein, peptide, and naked DNA vaccines. Animal studies demonstrated a more than 10-fold higher IgG2 response with 100-fold lower allergen doses than SCIT. Human trials suggest better compliance, lower doses and shorter duration of treatment.[59]

Indications of Immunotherapy

The treatment of allergic diseases is based on allergen avoidance, pharmacotherapy, allergen immunotherapy, and patient education. Physicians should know the local and regional aerobiology and be aware of the potential allergens in the patient's indoor and outdoor environments. Only physicians trained in allergology can select the clinically relevant allergen vaccines for therapy. Immunotherapy, when appropriate, should be used in combination with other forms of therapy with the hope that the patient will become as symptom-free as medically possible.[22]

So, SIT is indicated in the following conditions:

- IgE-mediated disease (symptoms on exposure to relevant allergen supported by a positive SPT/RAST to that allergen)
- Inability to avoid allergen(s)
- Inadequacy of drug treatment
- Limited spectrum of allergies
- Patients who understand risks and limitations of treatment
- In venom immunotherapy, an absolute indication is a history of severe allergic systemic reactions with respiratory symptoms, cardiovascular symptoms, or both and positive diagnostic tests (skin tests, serum-specific IgE, or both).[22]

Unfortunately, there are no definite criteria for the indication of SLIT versus SCIT and no consensus on the degree of severity of asthma still compatible with SLIT.[60]

Immunotherapy for treatment of allergic rhinitis/conjunctivitis is indicated:

(1) when antihistamines and topical drugs insufficiently control symptoms, (2) in patients who do not wish to receive pharmacotherapy, (3) when pharmacotherapy produces undesirable side effects (4) when the patient is concerned about long-term pharmacologic therapy, and (5) if the season is prolonged or polysensitized patients are exposed to several subsequent pollen seasons (i.e., tree, grass, and weed pollen sensitivity) The risk/benefit ratio should be considered in every case. In addition, avoidance is the treatment of choice for animal dander–induced allergic diseases and SIT is only indicated when complete avoidance is difficult.[22]

Contraindications

Contraindications for inhalant allergen and venom immunotherapy may be absolute or relative. Sublingual immunotherapy is *contraindicated* in patients who have systemic diseases of the immune system, inflammatory conditions of the oral cavity with associated severe symptoms (e.g. oral lichen planus with ulcers or severe oral mycosis) or individuals with severe and uncontrolled asthma. Immunotherapy tablets are also contraindicated in individuals who are allergic to any of the addition constituents of the tablet.[12]

So, SIT is generally contraindicated in the following conditions:[61]

- Co-existent uncontrolled asthma (within the UK, presence of asthma is considered a relative contraindication).
- Patients with other medical/immunological disease
- Small children (less than 5 years)
- Pregnancy (maintenance injections may be continued during pregnancy)
- Patients unable to comply with the immunotherapy protocol
- Patients on some heart and blood pressure medications such as beta-blockers (relative)

How to ensure success?[28]

- Full and precise diagnosis of allergic sensitivities by a trained allergologist should be documented.
- Patients' compliance should be optimal.
- Polysensitized patients usually fail to benefit and allergen avoidance is crucial for them. However, a recent study in Italy evaluated SLIT in a group of polysensitized children with AR and/or mild to moderate asthma. The

researchers reported significant improvement of allergic symptoms and drug use and they concluded that polysensitization is not an obstacle for prescribing SLIT.[62]

- The quality of the allergen extract is a key to SCIT success. Non-standardized allergen extracts should be, thus, under close scrutiny by regulatory authorities.[63]
- Exclude intrinsic asthma.
- Only select patients with mild-to-moderate persistent asthma and not with severe uncontrolled conditions, as recommended by most of the international guidelines.[64]
- Patients with a forced expiratory volume in one second (FEV_1) lower than 70% of predicted (under anti-inflammatory systemic or topical treatment) should not be eligible for SCIT.
- Treatment should start 10 – 14 weeks before the start of the grass pollen season. This early start results in a 34% reduction of rhino-conjunctivitis symptoms.

Drawbacks of SIT [65]

1. The long duration of treatment.
2. The unsatisfactory standardization of allergen extracts.
3. A questionable safety level.
4. Being injectable in its conventional form; SCIT.

Side effects of SIT

The major risk of SIT is anaphylaxis and asthma appears to be a significant risk factor for systemic reactions. Itching, swelling, and redness at the site of injection are almost constant features.[66]

Recently, a *new classification* for systemic reactions related to SCIT has been developed by the World Allergy Organization (WAO) which uses a 5-stage grading system and will allow better comparisons of systemic reactions between different immunotherapy formulations and schedules in the future (table 1).[67]

Management of side-effects

In general, local swelling following injections is to be expected. No treatment is required other than reassurance, although occasional use of an antihistamine may be indicated. Some doctors may advise the patient to take an antihistamine a few hours before each injection to reduce the likelihood of local discomfort and other side-effects.[28]

Systemic reactions should be recognized and treated promptly, according to recommended guidelines. In general, mild rhinitis or wheezing may be treated by an antihistamine or bronchodilator with continued observation. More severe reactions, including moderate asthma, urticaria, or angio-oedema require intravenous hydrocortisone and antihistamine. Adrenaline 0.5 mg by the intramuscular route is indicated in rapidly evolving systemic reactions which do not respond to these measures and in all patients where there is associated moderate/severe respiratory impairment or hypotension. In general, if in doubt, give adrenaline which is more effective when administered early during a systemic reaction. Delayed systemic reactions are almost always mild, involving mild urticaria or asthma and respond to antihistamines and/or inhaled bronchodilator therapy. Afterwards, the dose should be adjusted to a safe level. In the case of SLIT, there is no need to do a titrated graduated updose and therapy is generally started at the usual clinical dose.[68]

Side effects can be avoided if:

- Patients avoid exercising or overheating for a few hours before and after the procedure
- The first sublingual tablet is administrated whilst under observation of a medical doctor and observed for 30 minutes for any signs of serious side effects.[68]

Practical Immunotherapy

- SCIT should only be administered by trained persons in specialist clinics and with immediate access to adrenaline and other resuscitative measures. All patients should be observed in the clinic for at least 30 minutes following injections. There should be facilities for vaccine storage at 4ºC. In general, injections are given in the upper outer surface of the arm half way between the shoulder and elbow (figure 1) by the deep subcutaneous route**.** A sterile technique should be ensured.[16]
- At each immunotherapy visit, a record should be made of the date, dose, and volume of allergen vaccine given. Peak flow should be recorded before and after injections and any immediate (0-30 minutes) local or systemic reactions must be recorded. Moreover, any delayed local or systemic reactions following the previous injection should be recorded at the next visit. The patient should be well, without concomitant allergen exposure, suspected viral illness or recent immunization. The time interval since the last immunotherapy injection, any reaction to previous injections and, if indicated, premedication with antihistamine should also be checked. Dosage reduction according to standard guidelines should be performed in relation to previous systemic or large local reactions, during increased allergen exposure and if there is an extended time

interval since the previous injection. With the use of small hypodermic syringes pain could be alleviated.[69]

- In a German study published in 2010, Zielen et al. showed that adding a mite allergoid (a hypoallergenic mite preparation) SCIT to pharmacologic treatment (inhaled fluticasone propionate) is an effective and safe strategy to reduce corticosteroid doses while maintaining disease control in children with mite-induced allergic asthma.[70] On the other hand, some researchers observed that the combined administration of an inhaled corticosteroid drug and allergen extract suppressed the early clinical and immunological effects of SIT and that vitamin D3 prevented this 'adverse' influence of steroids.[71]
- Similarly, intervention with montelukast during the build-up phase of SIT significantly impairs the induction of regulatory T lymphocytes.[72]

Table (1). WAO Subcutaneous Immunotherapy Systemic Reaction Grading System[75].

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of 1 organ system present* **Cutaneous** Generalized pruritus, urticaria, flushing, or sensation of heat or warmth† or **Angioedema** (not laryngeal, tongue or uvular) or **Upper respiratory** Rhinitis - (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) or **Throat-clearing** (itchy throat) or **Cough** perceived to originate in the upper airway, not the lung, larynx, or trachea or **Conjunctival** Erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	Symptom(s)/sign(s) of more than 1 organ system present or **Lower respiratory** Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV_1 drop, responding to an inhaled bronchodilator) or **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea or **Other** Uterine cramps	**Lower respiratory** Asthma (eg, 40% PEF or FEV_1 drop NOT responding to an inhaled bronchodilator) or **Upper respiratory** Laryngeal, uvula, or tongue edema with or without stridor	**Lower or upper respiratory** Respiratory failure with or without loss of consciousness or **Cardiovascular** Hypotension with or without loss of consciousness	**Death**

- Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4.
- Children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis, as becoming very quiet or irritable and cranky.
- Scoring includes a suffix that denotes if and when epinephrine is or is not administered in relationship to onset of symptom(s)/sign(s) of the SR:a, ≤ 5 minutes; b, >5 minutes-to ≤10 minutes; c: >10 to ≤20 minutes; d:>20 minutes; z, epinephrine not administered.
- The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection and a suffix reflecting if and when epinephrine was or was not administered. e.g. Grade 2a; rhinitis:10 minutes.

Efficacy

SIT is potentially able to target all mucosa-associated lymphoid tissues affected by abnormal hypersensitivity to allergens. It is highly effective in seasonal allergic rhinitis, particularly in patients with seasonal pollinosis due to grass, tree, and weed pollens and patients with a limited spectrum of sensitivities.[69]

Regarding asthma, specific aspects of its pathogenesis may explain the questionable effectiveness of SIT compared to its efficacy in rhinoconjunctivitis. The bronchial remodeling of upper and lower airways, as a consequence of chronic bronchial inflammation, may be a key modulator of response. That is why the prognosis of immunotherapy in asthma depends on its severity and duration, and on the onset of SIT.[73] However, evaluation of SIT benefit in asthmatic children is somehow difficult because asthmatic subjects have often been considered in clinical studies as an at risk subgroup among rhinitis patients, rather than a target group by itself.[28]

However, some studies stated that immunotherapy is effective in allergic asthma, particularly seasonal asthma, whereas it is less effective in perennial asthma.[69]

A Cochrane meta-analysis on the efficacy of SIT on asthma was published online in 2003. A total of 75 trials were selected with allergy to house dust mites, pollen, animal dander, Cladosporium, latex, and multiple allergens. There was a significant reduction in asthma symptoms and medication and an improvement in bronchial hyper-reactivity following immunotherapy. The authors recognized that lung-function test results were only – partially – reported in 16 studies and hence their affection by SIT couldn't be analyzed.[74]

The beneficial effect of SIT on the allergy march in children is undoubtedly the most important feature of this therapeutic approach. In clinical trials, one year of treatment resulted in up to 75% reduction in symptoms and medication requirement for severe hay fever. For bee and wasp venom, there was a 90% or more reduction in the risk for anaphylaxis if stung.[28]

In the largest clinical program ever conducted with grass allergen-SIT in Italy, over 2000 adults and more than 500 children have been exposed to Grazax; tablets for sublingual use. The new product proved to be efficacious and safe both in adults and children. Interestingly, continued treatment over 2 years in the case of grass allergy shows progressive desensitization with up to 73 % reduction in symptomatology and research in children aged from 5 to 16 years old shows similar effectiveness in the treatment of grass allergy as seen in adults.[75]

Another study in Turkey ascertained the effectiveness of both SLIT and SCIT in asthma/rhinitis children sensitized to HDM.[76]

Long term benefit

Allergen immunotherapy has been shown, in several studies, to maintain long term benefit following discontinuation. For example, in one double blind placebo-controlled withdrawal study, 3-4 years grass pollen immunotherapy was shown to result in sustained reduction in symptoms and rescue medication for at least 3 years after discontinuation.[28]

Another convincing study on the preventive effect of SIT on asthma in children with seasonal rhinitis (with or without asthma) is the longitudinal Preventive Allergy Treatment (PAT) study; the first controlled prospective trial to address the question of long term benefit. The authors followed the patients for 7 years after the 3-year treatment period and they demonstrated the crucial influence of starting SIT early in the course of AR in order to limit the risk of progression to asthma.[77]

Safety

A limitation of the subcutaneous injection route of immunotherapy is the risk of potential side effects, which include systemic allergic reactions, occasional anaphylaxis and, even, fatalities. Risk factors for systemic reactions include extremely high sensitivity, co-seasonal allergen exposure, a history of previous systemic reactions, and, importantly, the presence of bronchial asthma.[78]

A major analysis of the incidence of adverse events in 912 patients between 1977 and 1987 revealed a frequency of adverse events of 2.2% with 8.67% of these documented as systemic reactions.[79] In a double-blind, placebo-controlled study on 40 grass pollen allergic patients, Walker *et al.* found 1.31% local reactions and 0.42% systemic reactions of all injections.[80] Moreover, a higher rate of both local and systemic reactions was found in the up-dose phase (2.5% and 1% of all injections, respectively). Another large review of 38 SCIT studies with conventional build-up schedules revealed a rate of systemic reactions between 0.05 and 3.2% of all injections and between 0.8 and 46.7% of allergic patients (mean 12.92%)[81]

Life-threatening reactions due to SCIT are very rare. The German Paul-Erich-Institute (PEI) registered an incidence of 0.002–0.0076% in not modified allergen preparations and of 0.0005–

0.01% in modified allergen preparations ('allergoids') between 1991 and 2000.[82]

Regarding SIT in cases of mold allergy, its safety and efficacy are not known in children and adolescents. A recent study in Poland evaluated 50 children and adolescents with Alternaria alternata-induced seasonal AR and/or bronchial asthma using a standardized allergen extract in a randomized, double-blind, placebo-controlled, 3-year prospective study. They found that the combined symptom medication score decreased; not significantly except in the years 2 and 3, and sensitivity after nasal challenge also decreased without serious side effects. The most common side effect was edema at the site of injection only in 11 injections.[83]

Venom immunotherapy (VIT)

Insect VIT is a potent tool for preventing sting anaphylaxis. Controlled studies demonstrate that immunotherapy with vespid, honey bee and jack jumper ant venoms are highly effective. Once subjects are receiving maintenance doses of yellow jacket or jumper ant venom, the risk of an immediate generalized reaction to a sting is approximately 5% per sting. Honey bee VIT is less effective by that criterion (the risk of a generalized reaction is of the order of 20% per sting), but needs to be assessed against an adverse natural history without immunotherapy. Many of the documented "failures" have involved mild systemic reactions. Although a statistical assessment of the effect of VIT on the risk of death is difficult if not impossible, studies in yellow jacket-sensitive subjects have shown a marked improvement in quality of life.[84]

The earliest markers for protective mechanisms against allergic reactions in the peripheral blood during the build-up phase of VIT were studied in Germany by Bussmann et al. and they found that tryptophan depletion, ILT3/4-mediated inhibition, higher IL-10 production as well as intracellular cAMP were the best markers.[85]

In summary, allergen-specific immunotherapy is a promising cure for allergic children that have the disadvantage of repeated injections; in its conventional form. Well designed and adequately powered trials in children are still needed to assess the efficacy of SLIT in pediatric asthma and allergic rhinitis.

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