

SPECIFIC IMMUNOTHERAPY IN CHILDREN: THE EVIDENCE

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Specific immunotherapy (SIT) is the only treatment able to not only act on the symptoms of allergy but also act on the causes. At present, SIT may be administered in two forms: subcutaneous (SCIT) and sublingual immunotherapy (SLIT). SCIT represents the standard modality of treatment while SLIT has recently been introduced into clinical practice and today represents an accepted alternative to SCIT. The main advantages of SIT that are lacking with drug treatment are long-lasting clinical effects and alteration of the natural course of the disease. This prevents the new onset of asthma in patients with allergic rhinitis and the onset of new sensitizations. The mechanism of action of both routes is similar; they modify peripheral and mucosal Th2-responses into a prevalent Th1-polarization with subsequent reduction of the allergic inflammatory reaction. Both have long-term effects for years after they have been discontinued, although for SLIT these evidences are insufficient. To date several guidelines have defined indications, contraindications, side-effects, and clinical aspect for SCIT and SLIT. New forms of immunotherapy, allergen products and approaches to food allergy and atopic eczema represents the future of SIT.

Specific immunotherapy (SIT) is the only treatment able to not only act on the symptoms of allergy but also act on the causes. Allergen specific immunotherapy (SIT) was introduced on an empirical basis about one hundred years ago (1), with the supposed rationale of vaccinating against "airborne toxins" which were considered to be the cause of seasonal rhinitis. After the discovery of Immunoglobulin E (IgE), the rationale for the use of SIT became clearer, the mechanisms were investigated, and clinical efficacy began to be assessed in double-blind placebo-controlled trials starting from the 1960's. SIT remained an empirical treatment for more than 40 years, but the first controlled trial in 1954 paved the way for the scientific era. From the 1960's until the end of the 1980's there was no significant change in the practice of SIT apart from the introduction of chemically modified allergens (allergoids). Twenty years later, the World Health Organization published a position paper which stated the indications, contraindications, risks and benefits of SCIT and, from this point, SIT was recognized as an effective treatment for respiratory allergy

and Hymenoptera venom allergy (2). At present, SIT may be administered in two forms: subcutaneous (SCIT) and sublingual immunotherapy (SLIT). SLIT is considered a useful alternative to SCIT widely used in many countries, except in USA where no product has been licensed. A large number of trials, globally analyzed in several meta-analyses, have showed a solid evidence of efficacy of both SCIT and SLIT in allergic rhinitis and asthma. Providing the recommended doses and administration schedules are adhered to, the safety and tolerability are very good for both route of administration although adverse systemic reactions remain a drawback for SCIT. However after one century of use, accumulating evidence surrounds SIT and the central role in the management of respiratory allergy.

RATIONALE FOR PRESCRIBING IMMUNOTHERAPY

Respiratory allergy is an evolving disease in which a strong link between asthma, rhinitis, and bronchial

Key words: Specific immunotherapy, allergy, subcutaneous immunotherapy

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0394-6320 (2011)

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hyperactivity (BHR) exists. In general it is documented a comorbidity between the upper and lower respiratory tracts and it has been also demonstrated that rhinitis is a risk factor for the later development of asthma (3,4). Corticosteroid therapy act against tissue inflammation but even if used in the earliest phases and in children at risk, have not been demonstrated to be effective in preventing asthma and the remodeling of the bronchial mucosa (5,6,7).

The use of a vaccine in an allergic pediatric patient on one hand proposes to improve the pediatric patient's quality of life through an improvement in symptoms and a reduction in the use of medication. On the other hand, it also proposes to substantially modify the natural history of the allergic disease. Sufficient evidence currently exists to support the use of vaccines for allergies in children with rhinitis and/or bronchial asthma (8).

In 1968 Johnston had already found a dose-dependent effect of ITS in the prevention of the occurrence of asthma (9). In more recent years, the PAT study randomized 200 children with or without asthma who had allergic rhinitis caused by birch or grass pollen (10). The studied children either underwent a 3-year cycle of SIT or placebo. After the study period the patients have been followed-up for a total of 10 years (11,12) and the placebo group have been found to develop asthma at a statistically significant higher rate than the treated group. On 2004 Novembre *et al's* in an open-randomized study was the first one on SLIT of a preventative nature (13). Apart from the efficacy on symptoms (in the second year) and on use of pharmaceuticals (second and third year), the study documented a significantly increased in risk of developing asthma after three years in the control group.

Various studies demonstrate the preventative effect of ITS on new sensitivities. Both Des Roches (14) and Pajno (15) observed this effect of ITS on new sensitivities in patients who had undergone SCIT for mites and were re-evaluated three years later. In 2001 Purello d'Ambrosio (16), in a retrospective study, verified that subjects (primarily adults) treated with SCIT demonstrated a clear reduction in new sensitivities 8 years after suspension of therapy when compared to a control group. In an open, randomized, controlled study Marogna *et al* (17) demonstrated that in children treated with SLIT and then followed for 3 years, the appearance of new sensitivities were found in 5.9% compared to 38% of controls.

Today the level of evidence for the prevention of new allergies is Ib for SCIT and IIa for SLIT.

However it has been underlined by several Authors that until today clinical trials involving immunotherapy are extremely heterogeneous and further studies that adhere to the CONSORT criteria are recognized as being necessary.

ECONOMIC ASSESSMENT

The economic performance of treatments is of primary relevance. An optimal treatment must be clinically effective but should also have a measurable impact on the costs of disease. A number of studies reported a cost reduction in respect to drug treatment for traditional, subcutaneous immunotherapy (SCIT) (18). It has been suggested that, being self-managed by the patient at home, SLIT can obtain substantial savings over subcutaneous IT (19).

Concerning the cost comparison between SCIT and SLIT, the first study was conducted in France in 2007 (20). In adults, the savings with subcutaneous IT were 393 € for dust mite and 1327 € for pollen allergy over a 6-year period. In children, the savings were 583 € for dust mite and 597 € for pollen allergy over a 7-year period. The data from SLIT showed – as expected because of no need of visits for injections – higher savings, corresponding to 3158 € for dust mite and 1708 € for pollen allergy in adults, and to 3938 € for dust mite and 824 € for pollen allergy in children. A recent study on patients with allergic rhinoconjunctivitis receiving SLIT, SCIT, or only drugs for 3 years (21) showed that the total average direct cost per patient was 416 € for SLIT and 482 € for SCIT. A SLIT-treated patient paid less than a SCIT-treated patient for all out-of-pocket costs (176 € vs. 255 €), but paid more for allergen extracts (72 € vs. 55 €). The sum of direct and indirect costs gave, over the 3-year treatment, 684 € for SLIT and 1004 € for SCIT. In conclusion, there are clear data indicating that SLIT, and SCIT as well, may be very beneficial to the healthcare system, in that either it could bring more clinical effectiveness at a reduced cost versus standard drug treatment.

MECHANISMS OF ACTION

The balance between Th1 and Th2 response plays a crucial role in the pathogenesis of allergic inflammation.

In fact Th2-derived cytokines, such as IL-4 and IL-13, are the primary pathogenic factors in inducing, maintaining, and amplifying inflammatory allergic inflammation. IL-4 and IL-13 orchestrate allergic inflammation promoting IgE synthesis, up-regulating adhesion molecules selective for eosinophil recruitment, and causing increased mucus production and airway hyperreactivity (22).

On the other hand, there is an increasing evidence that Th1-related cytokines, such as IFN-gamma and IL12, may suppress and counteract this Th2 response and vice-versa, as there is functional dichotomy between Th1 and Th2 cells (23).

The exact mechanism of action of SIT on this balance

Table 1. *Safety Measures for allergen immunotherapy.*

Select a proper patient
Attention if it presents severe asthma
Check clinical status during treatment
Check concomitant intake of other/new drugs
Choose a proper dose
Adjust the dose during allergy season
Evaluate patient's compliance
Adjust the dose for newly prepared vaccines
Recognize and treat adverse reactions
Consider discontinuing therapy
Be vigilant for adverse reactions

Table 2. *Mechanism of action of immunotherapy.*

Reduction of Ig-E synthesis.
Increase of IgG specific allergen-related
Reduction of tissue inflammatory cells
Reduction of secretion of mediators
Switch Th2/Th1

Table 3. *Considerations for the prescription of immunotherapy.*

Ig-E mediated mechanism
Role of allergen in related-disease
Time of duration of disease
Age of patient
Response to pharmacological treatment
Expected response
Possibility to use standardized vaccine
Contraindications to use of vaccine
Safety of vaccine
Costs
Compliance of patient and parents

is not completely understood. Several studies have shown that subcutaneous administration of the allergen induced hypo-sensitization by modifying peripheral and mucosal Th2-responses into a prevalent Th1-polarization (24,25). However, regarding SLIT, only two studies have demonstrated that it was able to increase allergen-driven IFN-gamma production (26,27). Recently regulatory T cells (Tregs) seems to play an important role in controlling the Th2-biased responses (28) in patients treated with SCIT for grasses and house dust mites (29, 30). Moreover,

the role of IL-10 as an early marker of successful immunotherapy has been further evidenced (31). On the basis of these findings, it has been pointed out that SIT generates regulatory T cells secreting both IL-10 and TGF-gamma and specifically suppresses allergen-induced responses (32). This issue appears crucial, as a defect of Tregs was demonstrated by an experimental study in allergic subjects (33). Very recently, also regarding SLIT, it has been shown the appearance of an induction of allergen-specific tolerance, as documented by restored allergen-specific IL-10 and IFN-gamma production (34,35). On the other hand, SIT, both concerning SCIT and SLIT, is a long-term treatment, as it should last for 3-5 years; nevertheless, on the whole, a discrete percentage of allergic patients (about 20-30%) do not respond to the treatment (36,37). In this regard, no predictive markers of response are available (38). Previously, it has been indicated that a rapid increase in IL-10 production, such as after the maintenance dose was reached, is crucial for the beneficial outcome of the SCIT in AR patients (31). However, IL-10 production has been evaluated in patients treated with SLIT only 1 year or 3 years after its beginning (34,35). SIT is the only treatment which leads to a prolonged tolerance against previously disease-causing allergens, resulting from the restoration of normal immunity (39) by a modification of balance Th1/Th2 (table1). SCIT seems to be associated with a decrease in IL-4 and IL-5 production by CD4+ Th2 cells, and a shift towards increased IFN-gamma production by Th1 cells (24,25). Few data concerning the immunologic changes induced by SLIT (40) are known and these studies have shown a relevant effect on the IgG4 response thus it could seem that SLIT does not consistently reduce the IgE production and increase the IgG4 synthesis (41,42). On the contrary, a decrease of serum IL-13 and of T-cell proliferative response (43) was demonstrated after SLIT therapy (44). Regarding the balance between Th1-Th2 cells, some studies have shown a shift from a Th2 towards a Th1 response (26,27,35), whereas others have failed to demonstrate it (28,45).

SAFETY

The range of reported systemic reactions with SCIT can vary greatly depending on allergen dose and induction schedule. The occurrence of systemic reactions with SCIT is in general about 0.05-0.6% of doses administered (46). Near fatal and fatal events are rare, when SCIT is correctly prescribed and given, but fatalities continue to be occasionally reported (47).

In 1986, the British Committee for the Safety of Medicines officially reported 26 fatalities provoked by subcutaneous immunotherapy (SCIT) and the risk/benefit

ratio of immunotherapy began to be seriously questioned (48). Severe adverse events (AE) with SCIT were often caused by avoidable errors (incorrect administration, dose errors) (49). Notably, an e-mail survey of more than 17,000 physicians in the USA reported a high rate of errors in administration (wrong patient or wrong dose). The latest survey conducted in Italy in more than 2,000 patients reported a rate of systemic side effects of 4% of patients and 0.1% of doses, with no fatality and only 4 episodes of anaphylaxis. Thus, when SCIT is correctly prescribed and administered, it can be considered a safe treatment. Nonetheless, a remote risk of severe (even fatal) reactions still remains, and it is clear that a fraction of those severe events are not predictable or avoidable. In contrast, neither dose nor induction schedule seem to influence the adverse reaction rate with SLIT.

The importance of non-injection routes was growing, and many studies with positive results were published with SLIT, which soon entered the official guidelines as a viable alternative to SCIT (2,50).

Currently, SLIT is routinely used in several European countries, where standardized extracts for the relevant allergens are available.

In the case of SLIT, which was proposed with the specific rationale of improving the safety, a description of AE is available in the majority of the studies. The majority of AEs involves the digestive system, such as: itching, swelling, burning of the lip or oral mucosa or tongue, nausea, diarrhea, and abdominal pain. Most of AEs can be easily managed by dose modification or, in case of disturbing gastrointestinal reaction, by momentarily swallowing avoidance, i.e. spitting the extract after having kept it under the tongue (51).

The safety of SLIT did not differ between children below the age of 5 years and older ones (52,53,54).

A review of the published studies (55) evaluated the occurrence of AEs according to the dose expressed as the ratio between SLIT and the equivalent SCIT. This review concluded that local side effects are even more frequent with the "low" doses of allergen (less than 50 times the corresponding SCIT), than with higher ones. On the contrary, gastrointestinal complaints (nausea, stomach-ache and vomiting) were described to occur more frequently with higher doses.

Careful adherence to guidelines and coordination of doctor, staff and patient roles are crucial to minimize adverse reactions, especially associated with SCIT. The safety measures to reduce the risk of an adverse reaction to immunotherapy are summarized in Table 2.

Nowadays, the safety profile of SLIT has to be considered as satisfactory and, in general, more favorable than SCIT. Though, extemporaneous mixtures of multiple and not standardized extracts still must be avoided. No fatal

reaction has ever been reported, thus no certain risk factor for fatality can be identified. Yet, severe asthma, mostly if not controlled, seems to be a contraindication to sublingual immunotherapy, as it is for SCIT too.

EFFICACY: THE CUMULATIVE DOSE AND THE DURATION OF TREATMENT

It is commonly accepted from allergists that the clinical efficacy of immunotherapy is dose-dependent (56,57) and cumulative dose administered by subcutaneous route (SCIT) is critical for efficacy, especially in house dust mite allergy.

Much less is known for SLIT. Vaccination by the sublingual route requires much more allergen to reach similar levels of efficacy compared to SCIT (58). The effective doses of allergen for SLIT range between approximately 3 and 375 times the dose of SCIT and it seems that too low doses are ineffective (59).

In children, it is unclear whether the cumulative dose influences efficacy. Double-blind controlled studies on SLIT for dust mites (60) show that low cumulative doses can be less effective (61) on asthma symptoms than higher doses (60). The same seems to happen for rhinitis due to dust mites (61). Regarding symptoms due to pollen allergy in children, there is a paucity of studies which compared the efficacy of different cumulative doses (62,63).

Recently, in a large prospective study with sublingual grass-tablets, adults were randomized to 2,500, 25,000, or 75,000 standardized quality grass allergen tablets or placebo during 18 weeks. Daily doses around 15 µg of the major allergen (Phl p5) are required to achieve optimal efficacy in terms of symptom and medication use reduction, as well as QoL improvement balanced with side effects (64). Similar conclusions were drawn from another study with grass-tablets, where a standardized mixture of 5 grass pollens demonstrated a significant efficacy compared to placebo when administered at dose of approximately 25 µg but not of 5 µg of major allergens (65).

A low starting dose and the escalation phase is considered useful for reducing side effects of SCIT. However, it may affect the compliance.

A prospective study comparing the long-term efficacy of SLIT according to different regimens of treatment (66) showed three years after discontinuation, greater improvement in patients who had received the 3 year of SLIT as compared to the 2 year regimen.

SLIT can be administered either pre-seasonally (stop at the beginning of the season), pre-coseasonally (stop at the end of the season) or continuously. Pre-seasonal and pre-coseasonal schedules, starts 2-3 months before the

expected pollen season. In the pre-coseasonal regimen, no dose reduction during the pollen season is usually applied. On the other hand, for nearly-perennial or perennial allergens, a continuous treatment is preferred. A recent study evaluated in patients allergic to dust mites the possibility to use a SLIT schedule with intermittent (i.e. 2-month treatment alternate to 2-month suspension) administration of the mite extract, with comparable safety in respect to the continuous daily administration (67).

There is no published randomized controlled study on the optimal duration of a SLIT treatment, although long lasting clinical effects were reported with a 4-5 year course of treatment both in children (68) and adults (69). Since these evidences are insufficient, the recommendation for the duration of SLIT must necessarily derive from the SCIT experience as reported in consensus documents (70,15). This implies that a SLIT course should be continued for 3 to 5 years to expect long lasting efficacy, but discontinued if there is no benefit after 2 years of treatment.

COMPLIANCE

The first studies on compliance with SIT were conducted when only the subcutaneous route was available and reported low compliance, ranging from 45% to 60%, (71). More recent studies using less aggressive schedules reported a better compliance, estimated at 75% to 90%, inconvenience remaining the major cause of noncompliance, followed by the cost of the treatment (72).

SLIT has different compliance issues than SCIT, because it is administered at home by patients themselves. Some studies reported that treatment withdrawal is frequently caused by repeated local reactions in the mouth or at the gastrointestinal level (73) or as noted in SCIT studies, by the erroneous perception that once allergic symptoms are improved, SLIT is no more needed (13). Concerning specific compliance and adherence studies, the available data indicate quite satisfactory results (74). The approach of evaluating the adherence by measuring the consume of allergen extracts was used in other 3 studies, which were facilitated by the fact that preparations in tablets or in liquid monodoses were employed (75,76,77). In the first of these the adherence value comprised between 75% and 97%, in the second 76.3% of the patients after 3 months and 74.8% of the patients after 6 months had compliance higher than 90%, in the third study on children a compliance rate higher than 75% was found in 85% of the children at the third month and in 84% of the children at the sixth month and the major cause of withdrawal (5.6% of the cases) was the cost of the treatment, while side effects accounted for 1.4% of stopping.

In a study comparing compliance to SLIT, SCIT and

local nasal immunotherapy (LNIT) in children, the data on SLIT concerned 806 patients, 173 of whom (21.4%) were noncompliant, with a highly significant difference ($p < 0.0001$) for better compliance in hospital setting (90.5%) compared to private office setting (61.2%); the most common reason of withdrawal was the cost of the treatment, reported globally in 36.4% of the patients, compared with 39.6% of the patients undergoing SCIT and 13.3% of the patients undergoing LNIT, followed by inconvenience (17.9% of the patients vs. 24.2% of the patients undergoing SCIT and 3.5% of the patients undergoing LNIT), feeling of inefficacy (24.9% of the patients vs. 13% of the patients undergoing SCIT and 18.3% of the patients undergoing LNIT), and side effects (5.8% of the patients vs. 8.7% of the patients undergoing SCIT and 56.6% of the patients undergoing LNIT) (78).

In a survey on the allergist's opinion about the factors positively influencing the adherence to SLIT, the issues judged most important were the patient's perception of efficacy, reimbursability, tolerability, and the patient's education (79). Today this latest aspect is likely to be of pivotal importance, as showed in a recent study reporting a clear difference in compliance between the patients receiving a complete educational course on SLIT and those receiving only standard instructions (80).

THE FUTURE

Immunotherapy in the last decade has produced several studies on alternative approaches to traditional subcutaneous immunotherapy (SCIT). Newer forms of allergen immunotherapy are designed to lessen TH2 responses to allergens and provide a safer alternative to SCIT. One therapeutic option is the addition of an anti-IgE recombinant humanized mAb agent (omalizumab), approved for use in patients with moderate-to-severe perennial allergic asthma, to SCIT (81). Alternative strategies to improve the immunological responses and clinical outcomes in SIT treated allergic patients are the activation of the innate immune system through Toll-like receptor (TLR) agonists, innate immune receptors designed to respond to a variety of pathogens and induce TH1 and regulatory T-cell responses. Another therapeutic option involves packaging CpG ISSs (inhaled CpG immunostimulatory sequences) into virus-like particles (VLPs), allergoids, recombinant allergens, peptides, hybrid molecules, IgE-reactive haptens and mimotopes (81,82,83,84,85).

An innovative, but yet purely experimental treatment option is gene therapy, in which allergens could be transfected into cells and sites where immune tolerance is induced (mainly bone marrow, thymus, spleen, lymph nodes, or liver). Given the development of safe vectors

and generation of suitable hypoallergens, gene therapy might be suitable especially for prophylactic treatment of patients at risk (83).

Oral immunotherapy has been used in small trials for food desensitization to common foods, such as egg, milk, and peanut. Although there are promising results in several oral immunotherapy trials for food allergy, more data are needed to define the correct dosing regimen and ultimately clinical utility in routine clinical practice. Probable future indications are atopic dermatitis and latex allergy, but current evidence suggests to keep immunotherapy treatment for these indications in experimental settings, at least for next few years (86,87,88,89). Of the alternative routes for SCIT, SLIT has been studied the most and is an approved treatment in many countries. Additional improvement should derive from the introduction of mucoadhesive formulation. In an experimental model, a mucoadhesive maltodextrin formulation of ovalbumin enhanced priming of the local mucosal immune system and tolerance induction via the sublingual route, and offers promising opportunities to improve SLIT by further simplifying immunization schemes (81,83,90). Although initially designed for drug delivery purposes, microneedle arrays are more and more frequently used in epicutaneous immunization studies. This novel technology might therefore bear the potential to design the ideal vaccine for desensitization conferring protection after a single administration. Last but not least, encapsulation of allergen into nanoparticles or liposomes might be an additional strategy to enhance treatment efficacy. The two outstanding characteristics of epicutaneous allergen specific immunotherapy (EPIT) consist in its favourable safety profile and its needle-free administration mode enabling self-administration. These two features might also allow its application in two 'niche situations': treatment of food allergy and promotion of SIT in children (91).

CONCLUSIONS

In order to obtain more reliable results that could be compared with each other as well as to ensure that even meta-analyses are of constantly improving quality, it is necessary that new studies be conducted using more rigid (CONSORT) criteria. In the future, it will be important to acquire data differentiated by allergen, pathology, dosage, and administration method from pediatric patients.

It will be necessary to define when therapy should begin, and also to evaluate the real importance of recombinant molecular allergens. Pharmaceutical companies will have to be required to standardize their products in a way that gives unequivocal assurance as to what a vial does and does not contain, and exactly

how much there is of it, just as all other pharmaceutical companies are required to do.

Until that day, any experimental data obtained using the extract of a company and given at a dosage according to that company's internal standards cannot be automatically extended to the same extract produced by another company.

Considerations for a better prescription of immunotherapy are reported in table 3. In light of the current evidence, ITS can be suggested for use in children with allergic rhino-conjunctivitis, especially if they are mono-sensitive, for a duration of not less than three years. The earlier treatment begins, the better. The presence of light asthma or aspecific bronchial reactivity is a further reason to use ITS given its efficacy in reducing the risk of developing persistent asthma. As regards the choice between the method of administration (the traditional SCIT or the innovative SLIT), it is up to the physician to find the right equilibrium. SCIT with conventional extracts is efficacious as a therapy for respiratory IgE-mediated allergic diseases. Furthermore, it can also have long-term effects after its suspension. SLIT is the most efficacious and secure method that does not require injection and is useful for the prescription of ITS for patients that either reside far away from treatment centers or prefer to self-administer their own immunotherapy treatment.

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