



REVIEW

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Allergen-specific immunotherapy provides immediate, long-term and preventive clinical effects in children and adults: the effects of immunotherapy can be categorised by level of benefit -the centenary of allergen specific subcutaneous immunotherapy

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Abstract

Allergen Specific Immunotherapy (SIT) for respiratory allergic diseases is able to significantly improve symptoms as well as reduce the need for symptomatic medication, but SIT also has the capacity for long-term clinical effects and plays a protective role against the development of further allergies and symptoms. The treatment acts on basic immunological mechanisms, and has the potential to change the pathological allergic immune response. In this paper we discuss some of the most important achievements in the documentation of the benefits of immunotherapy, over the last 2 decades, which have marked a period of extensive research on the clinical effects and immunological background of the mechanisms involved. The outcome of immunotherapy is described as different levels of benefit from early reduction in symptoms over progressive clinical effects during treatment to long-term effects after discontinuation of the treatment and prevention of asthma. The efficacy of SIT increases the longer it is continued and immunological changes lead to potential long-term benefits. SIT alone and not the symptomatic treatment nor other avoidance measures has so far been documented as the therapy with long-term or preventive potential. The allergic condition is driven by a subset of T-helper lymphocytes (Th2), which are characterised by the production of cytokines like IL-4, and IL-5. Immunological changes following SIT lead to potential curative effects. One mechanism whereby immunotherapy suppresses the allergic response is through increased production of IgG4 antibodies. Induction of specific IgG4 is able to influence the allergic response in different ways and is related to immunological effector mechanisms, also responsible for the reduced late phase hyperreactivity and ongoing allergic inflammation. SIT is the only treatment which interferes with the basic pathophysiological mechanisms of the allergic disease, thereby creating the potential for changes in the long-term prognosis of respiratory allergy. SIT should not only be recognised as first-line therapeutic treatment for allergic rhinoconjunctivitis but also as secondary preventive treatment for respiratory allergic diseases.

Keywords: Allergy, Rhinitis, Asthma, Specific immunotherapy, Immunological mechanisms, Antibodies, IgG, IgE, Long-term effect, Prevention

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Introduction

Allergy is a systemic disease with a local response following allergen exposure. Rhinitis, asthma and Bronchial Hyperresponsiveness (BHR) are closely related and a systemic pathway, involving the bloodstream and bone marrow, contributing to the cross-talk between the upper and lower airways [1].

The close relationship between allergic rhinitis and allergic asthma and the co-morbidity of upper and lower airway diseases has been carefully described elsewhere [2-4]. In asthmatic children it has been shown that asthma was more severe when in concomitance with allergic rhinitis and that increased asthma medication was required [5]. In asthmatic adults with concomitant allergic rhinitis asthma control is less manageable while there is a higher rate of asthma exacerbations and emergency room visits [6]. Allergic rhinitis is a major risk factor for the later development of asthma [3,7] and more than 20% of all rhinitis patients develop asthma later on in life [8]. Up to 50% of rhinitis patients have increased bronchial hyperresponsiveness during, as well as outside the pollen season [9] and an ongoing subclinical level of inflammation [10]. Allergic sensitivities usually increase with age [11] and being sensitised to one allergen source also increases the risk for developing new sensitizations over time [12]. The understanding of allergy as a chronic systemic immunological condition should be the platform for the choice of diagnostic, treatment as well as monitoring options in the allergic patient.

Allergen specific immunotherapy (SIT) produces a decrease in symptoms and in the need for medication, but SIT also has the capacity for long-term clinical effects and for the prevention of the development of further allergies and symptoms. The treatment acts on the basic immunological mechanisms responsible for causing symptoms and has the potential to change the immune response and the pathological pathways responsible for the allergic symptoms [13]. SIT is an anti-inflammatory, causal and preventive treatment for respiratory allergic diseases [14].

The year 2011 marked the 100th anniversary of the first publication on SIT by Leonard Noon [15]. Since then, SIT has been widely used in the treatment of respiratory allergic diseases - at first on a more or less empirical basis. For a number of years the treatment has progressively evolved along with greater medical and immunological insights. Basic immunological research, specific knowledge about allergic diseases and intensive research related to the allergenic molecules and the extracts used for diagnosis and therapy have been continuously developed and as a result improved the opportunities for specific treatment of respiratory allergic diseases [16,17].

More recently the regulatory environment has evolved and allergen extracts are regarded as pharmaceutical specialties with an increased need and request for documentation and clinical data on effectiveness and safety [18,19].

This paper highlights and examines some of the most important developments and information regarding the potential benefits of SIT achieved over the last 10-20 years - a period marked by much clinical activity, explorative as well as confirmative studies on SIT and the publication of international guidelines to support clinical practice [4,20-22]. Although the use of sublingual immunotherapy (SLIT) with the commercial availability of new products represents the most recent and well documented form for immunotherapy, the majority of explorative studies on basic immunology, mechanisms of application of allergen products and long-term clinical potential have been performed using the original subcutaneous immunotherapy (SCIT) treatment concept. All these studies which have been performed mainly based on scientific interest, have established a very important basis for the design of guidelines for production of the basic clinical documentation on efficacy and safety of new product. It is of paramount importance that in the new wider documentary immunotherapy studies we also seek confirmation of the knowledge we have achieved over the many years of investigator driven data exploration.

SIT - mechanism of action

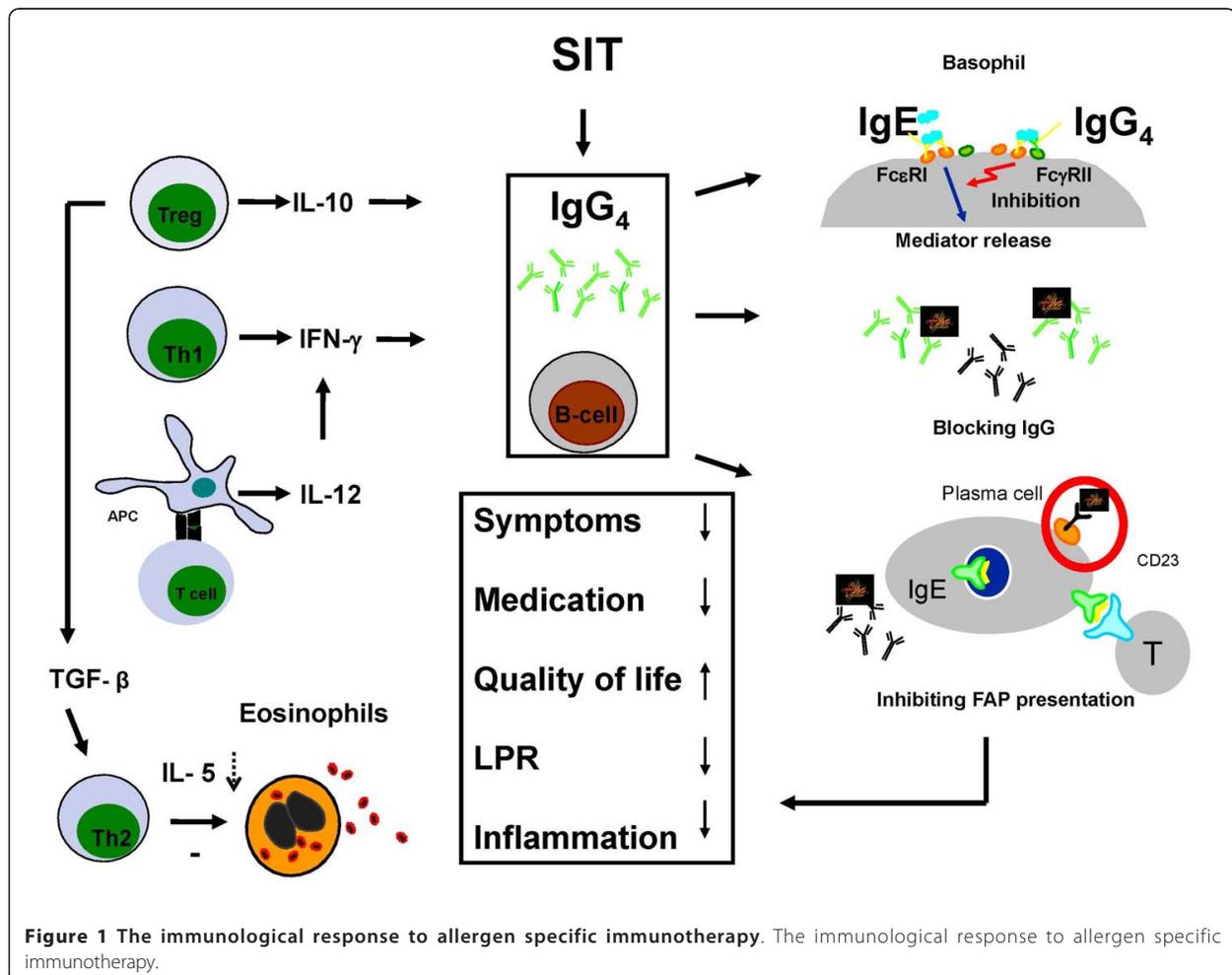
Different immunological effector cells are responsible for allergic inflammation [23-25]. The allergic disease is driven by a subset of T-helper lymphocytes (Th2), which are characterised by the production of cytokines like IL-4, IL-5 and IL-13 among others. These cells and their cytokines are responsible for the effects on other cells involved in the allergic response. The most important effector cells in the allergic immunological response are eosinophils, mast cells and basophils. Th2 cells play an essential role in the promotion of allergen-specific IgE synthesis by B cells.

The benefits and the clinical effects of SIT should be evaluated and analysed in terms of the immunological changes that follow the treatment. SIT acts by influencing basic immunological mechanisms [26] resulting in the suppression of the seasonal increase in eosinophilia [27], in reduction of the late-phase reactivity [28,29] and a shift from a Th2- to Th1-like response is initiated and maintained [30-33]. T regulatory cells play a central role in the mechanism of effective SIT with an important effect on the down regulation of the Th2 response [34]. One mechanism by which immunotherapy suppresses the allergic response is through an increase in the production of specific IgG antibodies, primarily of the IgG4

subtype. In the context of IgE-mediated allergy, the appearance of IgG4 antibodies is usually associated with a decrease in symptoms. This is likely to be due, at least in part, to an allergen-blocking effect at the mast cell level and/or at the level of the antigen-presenting cell (preventing IgE-facilitated activation of T cells) [35]. Because the production of IgE against normally harmless antigens is the cause of the allergic responses, the production of antigen specific IgG antibodies, can antagonise and block the allergic inflammatory cascade resulting from antigen recognition by IgE. Therefore, the shift in balance between IgE and IgG4 is essential to successful allergen SIT. It has been demonstrated that allergen-specific IgG4 antibodies with potent inhibitory activity against IgE persist after treatment discontinuation and could account for long-term clinical tolerance [36]. Induction of specific IgG4 has the capacity to influence the allergic response in different ways (Figure 1), and is related to immunological effector mechanisms, also responsible for the reduced late-phase hyperreactivity

and ongoing allergic inflammation. Details are described in Textbox 1.

Studies have shown that symptomatic improvement correlates with reductions in eosinophils and IL-5 expression in the nasal mucosa [32] during the pollen season, as well as with increased interferon-gamma (INF) production [37]. Immunotherapy induces an IL-12-response shown to be inversely related to IL-4 production and to promote a Th1-response estimated as interferon-gamma production which promotes B-cells into IgG production [31]. Several studies have shown that immunotherapy induces a new regulatory T-cell response characterised by induction of IL-10 [38,39] which precedes the inhibitory IgG4 antibody activity [40]. TGF- β is also a T-regulatory cell mediator induced by immunotherapy [41] which is responsible for the down regulation of the Th2 response - reducing IL-5 production [33] and preventing allergen-exposure-induced eosinophilia and inflammation [32]. The importance of T regulatory cells in allergy and in relation to immunotherapy has been carefully



reviewed [34,42,43]. The left side of Figure 1 summarises basic immunological changes during immunotherapy. The immunological mechanisms described here illustrate the close connection between the basic immunological response to immunotherapy and the humoral response, characterised by the induction of competitive specific antibodies accompanying and potentially leading to clinical benefits.

Textbox 1

Different IgG4 related immunological effects acting as a competitive response to that of specific IgE, result in clinical effects as reduction in symptoms and the need for medication, and a reduced inflammatory response to allergen presentation (Figure 1).

Inhibition of mediator release

- Inhibition of mediator release could be caused by direct inhibition of the allergen-IgE interaction or through co-aggregation of the inhibitory FcγRIIB and FcγRI [44]
- SIT-induced IgG inhibited histamine release from basophils [45]

Blocking antibody

- Specific IgG antibodies acts by a “dilution” of the antigen exposure to specific IgE antibodies by binding to epitopes on the surface of the allergen, and thereby directly reducing the antigen presenting capacity by the relevant cell types [46]

Facilitated Antigen Presentation (FAP)

- IgE-facilitated antigen presentation results in the activation and subsequent proliferation of allergen-specific T-cells at extremely low concentrations of allergen and activates Th2 cells which then produce important cytokines (IL-4, IL-13) inducing further IgE synthesis [47]
- Immunotherapy-induced specific IgG antibodies can also affect and inhibit IgE-facilitated antigen presentation (FAP) and activation of Th2-cells, and thereby significantly reduce the allergic response [23,45,48]

There is a time dependence in serum inhibitory activity of Facilitated Antigen Binding which seem to be consistent with the continued increase in clinical benefits following prolonged treatment with immunotherapy [49]

Clinical effectiveness of SIT

The first priority for respiratory allergic patients is usually the treatment of allergic symptoms as these appear as a consequence of allergen exposure. Different symptomatic drugs have the capacity to reduce the symptoms either on a rescue basis or when taken daily [4,22]. From a regulatory point of view the primary focus on the benefit from anti-allergic treatments is usually on the potential reduction in symptoms. Together with the potential range of benefits following SIT, reduction in symptoms is mandatory. Recently, an overview of how

effective SIT is in reducing symptoms including a comparison to the effectiveness of symptomatic treatment options was published [50]. The data support that already during the first seasonal exposure after initiation of SCIT a reduction in symptoms at least as potent as the reduction following treatment with symptomatic drugs can be achieved.

Together with the significant reduction in allergic symptoms, several studies on SIT have documented a significant reduction in the need for symptomatic drugs on short term as well as during long-term treatment [51-54] even in patients with severe allergic rhinoconjunctivitis, who fail to respond adequately to symptomatic treatment [55]. The reduction in symptomatic medication achieved early after initiation of treatment with SIT has been shown for pollens [52] as well as perennial allergens [56]. Also, the long-term benefit even after termination of SIT has been shown [57,58]. The most comprehensive overview of the outcome on reduction of the need for symptomatic medication is provided by the recent Cochrane reviews covering SIT studies with subcutaneous and sublingual application of SIT for rhinoconjunctivitis as well as asthma [59-61]. If patients were sensitised to other allergens, this did not influence the response to the treatment for their grass allergy [55], suggesting that SIT can be efficiently used even in polysensitised patients. Both adults and children with house dust mite-induced allergic asthma, benefit from SIT which results in a steroid-sparing effect by following guideline-defined asthma control [62,63]. This is of particular importance as allergic asthma is frequently associated with rhinitis [64] with the consequent need of simultaneous nasal steroid therapy as well as some concern arising from possible adverse effects of long-term treatment with inhaled steroids in children [65].

Endpoints and combined symptom and medication score in SIT trials

The World Allergy Organization has proposed a model for the standardisation of clinical trials of allergen specific immunotherapy for respiratory allergic symptoms [21]. They suggest defining the primary outcome of immunotherapy trials as the total clinical score, calculated as the sum of symptom score plus drugs usage calculated as one score. The European Medicines Agency (EMA guideline “Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases”) has also described the issues that the use of rescue medication has a direct impact on symptom severity [18]. An estimate of the power as well as the number of subjects to be included is mandatory to the outcome of clinical studies and the primary endpoint of a clinical study should be the variable capable of providing the most clinically relevant and convincing evidence

directly related to the primary objective of the trial. It is also mandatory in confirmative clinical trials to define the endpoint up front. It may sometimes be desirable to use more than one primary variable, each of which could be sufficient to cover the range of effects of the therapies. For clinical trials on allergen specific immunotherapy this could be the use of symptom score as well as medication score reduction [66]. The extent of inter correlation among the proposed primary variables may be considered.

Different methods for combining symptom score and intake of rescue medication have been described [66,67] but there is no guideline for how this combined score should be established, and from case to case the method used must be pre-specified and justified. In order to further develop the methods for one and only one final endpoint for trials on SIT, new methods to establish a clinical relevant score evaluating the potential reduction in allergic symptoms in combination with the potential reduced need for symptomatic medication have been assessed [51,68,69]. Recently, the first validation of a combined symptom/medication score strategy was published as the "Allergy-Control-SCORE™". Based on a comparison of the symptoms and need for medication during the pollen season between allergic subjects and healthy controls, they proved a reliable instrument in distinguishing between allergic patients and controls, which is also able to assess the severity of disease [70]. After the final endpoint has been defined and the results obtained, it is possible to look for secondary parameters and explorative outcomes which are extremely useful for the establishment of new hypotheses and future research [66,71].

Clinical effect levels

In this paper the effects of immunotherapy are categorised into the following levels of benefit whose immunological characteristics are explained above.

- Early effect - reduction in symptoms/need for medication
- Progressive effect - further reduction in symptoms/need for medication and reduction in hyperresponsiveness/late-phase response
- Persistent effect - long-term reduced symptoms/need for medication long-term reduced hyperresponsiveness/late phase response after end of treatment period
- Preventive effect - prevention of new sensitivities and progression of disease (rhinitis into asthma)
- Immunological effect - immune modulation and tolerance - immunological changes that lead to a potentially curative effect

These correspond to the different levels of clinical effects which can be claimed for the registration of

products for SIT as defined by the EMA [18] (Textbox 2). Evidence for the different claims is summarised below.

Textbox 2

Depending on the clinical documentation available and study duration different claims for efficacy are possible:

- Treatment of allergic symptoms: Short term clinical trials conducted to show efficacy in the first pollen season after commencing specific immunotherapy or to show efficacy in perennial allergies after some months of treatment
- Sustained clinical effect: Maintenance of significant and clinically relevant efficacy over two to three treatment years
- Long-term efficacy and disease modifying effect: Sustained significant and clinically relevant efficacy in post-treatment years
- Curing allergy: Sustained absence of allergic symptoms in post-treatment years

Early effect -reduction in symptoms/need for medication

It is evident that very early on and during the first seasonal exposure after initiation of immunotherapy -or alternatively when patients have reached the top or maintenance dosage [30,55,72,73], they experience an improvement in allergy symptoms (rhinoconjunctivitis and/or asthmatic symptoms) and a need for rescue medication. The early effect of SIT on rhinoconjunctivitis symptom scores has been confirmed in the so-called "big trials" which recruited hundreds of grass pollen allergic patients [55,74,75]. In sublingual tablet studies the positive effects of at least 16 weeks of treatment have been documented [74,75] and a single study using an adjuvant (MPL) in combination with a grass allergen extract also indicate efficacy after only 4 weeks with 4 injections [76,77].

Pre-seasonal short-term therapy normally including six weeks of treatment has been shown to be clinically effective as early as in the first season [51,78-80]. A six-month treatment period with recombinant grass pollen major allergens has also proved effective [81]. A combined symptom/medication score strategy has recently been used and confirmed the clinical efficacy for short term injection therapy [51,68], as well as for sublingual tablet treatment [66].

Progressive effect - further reduction in symptoms/need for medication and reduction in hyperresponsiveness/late-phase response

During a long-term treatment period of up to four years, persistent effects and further increased clinical and immunological benefits are achieved. This has been shown for grass, cat and dog, and house dust mites

[28,82,83]. In a study using two consecutive pre-seasonal short-courses of a grass pollen allergoid, using a combined symptom medication score it was clear that although the treatment was clinically effective in the first season, its clinical efficacy was even better in the second seasonal [51]. An open continuation of this study including a third pre-seasonal treatment period confirmed the increased efficacy potential which prolonged immunotherapy treatment provides [54]. When continuing the treatment for more than 12 months it is possible to introduce non-specific efficacy parameters, seen as a decrease in the patient's non-specific bronchial hyper responsiveness as an indicator of inflammation. This was shown in patients suffering from house dust mite related allergic asthma, who increased their tolerance to bronchial challenge with house dust mite allergen after six months, but it was only after 18 months of SIT that a persistent reduced bronchial inflammation and hyperresponsiveness measured by bronchial challenge with metacholine was found [84]. It has also been observed that two years of immunotherapy prevented the seasonal onset of bronchial hyperresponsiveness in grass pollen allergic patients with rhinitis and asthma [29]. According to a meta-analysis on asthma, SCIT significantly reduced allergen specific bronchial hyperresponsiveness, which was evaluated in the majority of the studies done after one year of treatment [61]. The finding that SIT is able to improve specific bronchial hyperreactivity is important from a clinical point of view. Indeed, patients with brittle allergic asthma are at risk of sudden deterioration when exposed to increased levels of an aeroallergen to which they are sensitive, as in the case of mould allergic patients. Currently, the measurement of BHR is the only accurate method of assessing such a risk and any intervention which reduces the risk of an acute episode of asthma under these circumstances would be clinically useful. Moreover, a high percentage of children and adults also develop a late asthmatic response after an allergen specific bronchial challenge [85], the presence of which is considered an experimental model close to resembling chronic bronchial allergic inflammation. Subcutaneous SIT is able to decrease not only early, but also late asthmatic responses following allergen specific bronchial challenge, thus confirming the anti-inflammatory effect of the treatment in the lung [53].

A Th2/Th1 response towards normal balance is usually associated with a positive clinical effect of immunotherapy. In grass pollen allergic patients undergoing injection immunotherapy it has been shown that a significant change towards a Th1 response measured by the level of interferon-gamma in peripheral blood was achieved after a 12-month treatment period, but not after just three months treatment -despite a well-documented symptomatic effect being found after three months [30]. Administering a short

four-week therapy with a grass allergen extract together with an MPL adjuvant showed that specific IgG and IgG4 levels increased only slightly in year one of SIT, but which became highly significant in year two [86]. A progressive immunological change as indicated by the significant induction of non-IgE competitive antibodies was also observed in year two of treatment with a sublingual tablet for grass pollen allergy whose clinical efficacy comparable to the benefits of year one [87]. In a three-year long-term SIT study in grass allergic patients with both rhinoconjunctivitis and asthma the asthma symptoms had completely cleared after 3 years with a general progression in clinical effect over the years. Symptoms and the need for medication was generally reduced from the beginning although nasal symptoms were not reduced during the first season - again indicating that continuing the treatment will increase the benefits [88].

Persistent effect -long-term reduced symptoms/need for medication -long-term reduced hyperresponsiveness/late-phase response after end of treatment period

Recently, wider studies have confirmed the long-term clinical potential of SIT after termination of treatment. In the Preventive Allergy Treatment Study (PAT) children treated for 3 years with pollen immunotherapy (grass and/or birch) showed a consistent reduction in their symptom score rated by Visual Analogue Score (VAS) and by objective measures of conjunctival sensitivity (CPT). The children were tested respectively two and seven years after discontinuation of treatment [89,90]. The sustained long-term and disease-modifying effects of immunotherapy have also been confirmed in a large-scale randomised, double-blind, placebo-controlled sublingual trial with a two-year follow-up after three consecutive years of treatment with a sublingual grass allergen tablet [58,91]. The key study which confirms the long-term persistent clinical and also immunological effect measured on late-phase skin response to an allergen, is the double blind randomised study where patients treated for grass pollen allergy with SCIT over a three-to-four year span were followed up to three years after cessation of therapy and compared to a SCIT naive matched group of patients [57]. Other studies have shown up to eight years persistent long-term clinical effects after termination of two to three years of SIT for grass pollen, tree pollen, animal hair and dander and house dust mites [92-96]. In cat allergic patients with mild to moderate asthma not only was the reactivity to cat allergen reduced following immunotherapy, but also a reduction in specific as well as non-specific hyperresponsiveness occurred during the five-year follow up period [94]. In a small open controlled three year consecutive pre-seasonal treatment study with an allergoid persistent clinical efficacy in children for as long as up to 12 years after discontinuation of the treatment was shown [97,98].

Preventive effect -prevention of new sensitivities and progression of disease (rhinitis into asthma)

Evidence for prevention of asthma - the PAT study and background

The Preventive Allergy Treatment study (PAT) [9] was the first large prospective randomised controlled long-term follow-up study designed to show whether SIT can prevent the development of asthma in children suffering from seasonal allergic rhinoconjunctivitis caused by allergy to birch and/or grass pollen. SIT was administered for three years, after which the children were evaluated for the development of asthma. Metacholine bronchial provocation tests were carried out during the relevant season(s) and during winter. Unexpectedly, as a consequence of the careful study examination at baseline, before commencing SIT, it was found that 20% of the children had undiscovered mild asthmatic symptoms during the pollen season (s), and that more than a third had significant seasonal ongoing bronchial hyperresponsiveness as revealed by metacholine challenge. Among those without asthma at baseline, the group treated with SIT showed a significant positive odds ratio for reducing the risk for development of asthma (odds ratio 2.52; $p < 0.001$). Another study using sublingual immunotherapy with grass allergen extract for 3 consecutive years also showed potential for the prevention of developing new asthma in children during the treatment period [99]. In this open randomised trial in children aged 5-14 years, patients were treated with a standardised mixture of 5 grasses. The PAT study initiative was based on a list of clinical studies which had all shown preventive potential. Among these, the classic 14-year long-term follow up study in children by Johnstone and Dutton who investigated SIT for the prevention of exacerbation and development of asthma. A highly significant reduction in the number of patients with asthma was reported at the time of follow-up which corresponded to the date of the children's 16th birthday. Only 22% of the placebo treated children were free of asthma compared to 72% of the SIT treated children. The children were initially treated for four years with individual mixtures of allergens and the clinical effect as well as the potential prevention of asthmatic symptoms was dose related - the strongest being in children who received the highest doses of allergen [100]. In a two-year placebo controlled study on the effect of immunotherapy in patients with allergic rhinoconjunctivitis caused by house dust mite allergy, the authors had selected children and adults with coexisting BHR. Besides the finding that immunotherapy reduced the provocative dose of metacholine 4-fold, they also reported that none of the SIT treated patients had developed symptoms of asthma during the 2 year study period [101].

Evidence for the prevention of new allergies

An early study by Johnstone showed that SCIT could reduce the risk of development of new allergic

sensitisations as they found that no children during a 4 year course of high dose immunotherapy developed new IgE sensitisations compared to 25% of those in the control group [102]. In the last two decades several studies using SIT have confirmed such findings. Two studies have shown the reduction in new sensitisations in children who were treated for house dust mite allergy.

In one study, monosensitised children treated for three years with SIT compared to non-treated controls, showed a significant reduction in the development of new allergic sensitivities (45% developed no new sensitisations at all) although none of the control patients remained free of the development of one or more new sensitisations [103]. In the other study measuring sensitisations to inhalant allergens three years after termination of house dust mite immunotherapy, two thirds of the control group children had developed one or more new sensitisations revealed by skin prick testing and specific IgE compared to only a quarter with new sensitivities in the SIT group [104].

A very large follow-up study including more than 7182 monosensitised patients with different allergies and with allergic rhinitis and/or asthma were treated with SCIT for four years and compared to 1214 open controls treated only with symptomatic drugs. Sixty-eight percent of controls had developed one or more new sensitisations compared to 27% in immunotherapy treated patients and at a follow-up visit three years after termination of the treatment period, 75% of controls had developed new sensitizations compared to 25% in the active group [105]. In a group of children with grass allergy followed up for 12 years the data revealed fewer new allergies in the active group treated with a consecutive three year pre-seasonal short-term treatment compared with controls [98,99]. Most studies on prevention of new sensitizations have been performed using SCIT, but SLIT has also shown its potential for reducing the risk for new allergies from 38% of control group patients to 5.9% of actively treated patients [106].

Evidence for long term prevention

The long term asthma preventive potential of SIT was first described in a tree pollen immunotherapy study in which 36 adult patients received immunotherapy. During the long-term six year follow-up period after the termination of treatment with standardised tree pollen allergen extracts for two years, none of the patients initially suffering from rhinitis alone had developed asthma during the eight-year study period [94]. The five and ten year follow-up of the PAT study are the first prospective follow-up studies testing whether SIT can prevent the long-term development of asthma and whether the clinical effects persist in children suffering from seasonal allergic rhinoconjunctivitis caused by allergy to birch and/or grass pollen as these children mature. After the total SIT

period of three years, the children were evaluated for development of asthma and then re-evaluated after a total of five years. The evaluation showed that immunotherapy reduces progression from allergic rhinoconjunctivitis to asthma after three years of SIT [9] and at the five year follow-up two years after SIT termination [89]. The actively treated children had persistently significantly less asthma at the five year follow-up (odds ratio 3.1; $p < 0.01$). The significant improvements in allergic rhinoconjunctivitis symptom and medications scores as well as in the conjunctival sensitivity to birch and grass observed to persist at five-year follow-up, also persisted at the ten-year follow-up. As at the five-year follow-up, fewer actively treated subjects had developed asthma at the ten-year follow-up (odds ratio 2.5 (1.1-5.9) [90]. After the complete study, the longitudinal treatment effect including all observations at three-, five- and ten-year follow-up was highly statistically significant ($p = 0.0075$) and the odds ratio for not developing asthma was 4.6 (95% CI (1.5; 13.7)) in favour of SIT over the ten-year period. The study also showed that bronchial hyperresponsiveness at baseline was associated with an increased risk of later development of asthma ($p = 0.002$) and in children with seasonal allergic rhinitis evaluation of BHR should be recommended in the indication for immunotherapy.

Only SIT has a long term and preventive potential

Neither symptomatic treatment nor different avoidance measures for allergy have so far documented the long-term or preventive benefits. Various strategies for the prevention of the development of allergic rhinoconjunctivitis and asthma have been proposed including allergen avoidance, pharmacological treatment (antihistamines and steroids) and SIT. Allergen avoidance is hardly applicable for many allergen sources and only a limited reduction in exposure can be achieved by modification of life habits (Prevention of Allergy and Allergic Asthma -WHO/WAO Geneva, 2002) [107]. Secondary prevention addressing children suffering from atopic dermatitis to prevent respiratory symptoms and further disease progression into asthma involves traditional pharmacotherapy with antihistamines. While treatment with antihistamines does provide symptomatic relief, it does not modify long term outcomes in children as the natural course of the disease is not altered. A recent large multi-centre trial in which children with atopic dermatitis were given cetirizine, failed to reduce the development of asthma [108].

A potential tertiary preventive measure for worsening of asthma through early treatment with inhaled steroids in children with episodic wheezing has been suggested, but recent studies on the capacity of inhaled steroid therapy during early symptomatic episodes of wheezing to delay progression to persistent disease have failed to show any preventive potential [109,110].

Conclusion

Allergen specific immunotherapy is the only treatment that interferes with the basic pathophysiological mechanisms of the allergic disease and thereby carries the potential for changes in the long-term prognosis of respiratory allergy. SIT should be recognised not only as first-line therapeutic treatment for allergic rhinoconjunctivitis but also as secondary preventive treatment for respiratory allergic diseases. Together with the long term clinical experience available, SIT is an important treatment for prevention of asthma in patients with allergic rhinitis and it makes asthma control easier to accomplish. Immunotherapy seems to reduce the development of new allergic sensitivities as measured by skin prick test as well as specific IgE measurements, and long term follow-up on immunotherapy studies demonstrate that specific immunotherapy with modern pharmaceutically standardised allergen extracts shows persistent long term effect on clinical symptoms after termination of treatment and long-term, preventive effect on later development of asthma in children with seasonal rhinoconjunctivitis. These are important added benefits to the immediate clinical effect which is comparable to other treatment options and has shown to progressively improve during treatment periods. It is so far the only treatment for allergic diseases which has shown to be able to prevent worsening of disease and development of asthma. In these years, a number of large ongoing clinical studies with the primary purpose of establishing the EMA guideline documentation needed for registration of pharmaceutical products will certainly add further to our basic knowledge about the potential immunological modifications and long-term options. This is of great importance for the optimization of the future treatment of the increasing number of patients suffering from respiratory allergic diseases.

Abbreviations

SIT: Allergen Specific Immunotherapy; SCIT: Subcutaneous Immunotherapy; SLIT: Sublingual Immunotherapy; BHR: Bronchial Hyperresponsiveness; CPT: Conjunctival Provocation Test; VAS: Visual Analogue Scale.

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Authors' contributions

LJ wrote the manuscript. MB revised and added to the manuscript. UW revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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