

REVIEW

Specific immunotherapy in asthma: efficacy and safety

G. Passalacqua and G. W. Canonica

Allergy and Respiratory Diseases, University Of Genoa, Genoa, Italy

Clinical & Experimental Allergy

Summary

The use of specific immunotherapy (SIT) to treat asthma has been, and still is, a matter of debate, and there are no clear or unequivocal indications in the official documents. This is partly due to the fact that there are few studies specifically designed to assess asthma, that none of such studies had a formal sample size calculation, and that objective parameters of pulmonary function have been assessed only sporadically. Nonetheless, there are good quality studies for both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) where asthma symptoms were evaluated, and showing positive results. Moreover, several favourable meta-analyses are available, although their validity is limited by the great heterogeneity of the trials included. The disease modifying effect of SIT, that is the capacity of preventing asthma onset should be also taken into account. Concerning the safety, fatalities seem to be an exceptional event and in Europe no fatality has been reported over the last two decades. Uncontrolled asthma is universally recognized as the most important risk factor for severe adverse events. In conclusion both SLIT and SCIT can be used in asthma associated with rhinitis (which is the most common condition), provided that asthma is adequately controlled by pharmacotherapy. In such case, a measurable clinical benefit on asthma symptoms can be expected. On the other hand, SIT cannot be presently recommended as single therapy when asthma is the unique manifestation of respiratory allergy.

Correspondence:

Giovanni Passalacqua, MD, Allergy & Respiratory Diseases, Department of Internal Medicine, Padiglione Maragliano, L.go R. Benzi 10, 16132 Genoa, Italy.
E-mail: passalacqua@unige.it

Introduction

Although in guidelines it is clearly stated that allergen immunotherapy is not specific for the disease (rhinitis/asthma) but only for the allergen causing disease [1], the efficacy has been always maintained separate for the two disorders, and the issue of specific immunotherapy (SIT) in asthma is one of the most debated aspects in the field for several decades [2–7]. This is even more curious if we look at venom immunotherapy, where a distinction of its efficacy in urticaria, angioedema or anaphylaxis has never been made. In addition, we should consider that isolated allergic asthma without rhinitis is infrequent, whereas asthma is present in >30% of rhinitics (for review see [8]). This is the reason why the majority of the recent clinical trials have been conducted in allergic rhinitis (AR) (with or without allergic asthma), and very few trials were specifically designed to evaluate the effect of SIT in asthma. Another problem is that none of the trials evaluating asthma symptoms has been adequately designed and reported [9]. In other words, none of the trials had a sample size calculation and a power analysis based on asthma symptoms as primary outcome. In addition, there is no formal consensus on which measure-

ment parameters for asthma should be chosen. Asthma symptoms, rescue medications, combined scores, asthma-free days, forced expiratory volume in 1 s (FEV₁), and asthma exacerbations are all equally reasonable choices [10]. In this regard, objective functional pulmonary measurements were carried out only sporadically.

As such, all our knowledge on SIT in asthma is based on old clinical trials with injection subcutaneous immunotherapy (SCIT), and on few recent trials conducted with the sublingual immunotherapy route (SLIT). Despite the presence of these limitations and confounding factors, there is some evidence available to derive at least provisional conclusions.

Subcutaneous immunotherapy in asthma

Clinical trials

There are numerous clinical trials of SCIT in asthma, most of them published before 1990 and including small numbers of patients. The available largest reviews of clinical trials included 32 [1] and 33 [2] randomized placebo-controlled trials. Many of the studies were not specifically designed for asthma, but had asthma

symptoms reported. Although there are heavy methodological limitations (small samples, no power calculation, variable inclusion criteria) the aforementioned studies substantially agree on the clinical efficacy of SCIT in asthma induced by the most common allergens (grass, mite, pet dander), although 25% of the studies mentioned in the WHO position paper [1] failed to show a significant difference in clinical efficacy between placebo and active groups. In some studies an effect on specific and non-specific bronchial responsiveness (BR) was also clearly documented.

After 1998 several new randomized controlled trials [11–31] were published (Table 1). Also in this case none of the studies had a formal sample size calculation, the inclusion criteria and outcomes were largely variable, and the methodological quality was sometimes low. The number of patients ranged from approximately 20 to 120. Some trials reported totally or partially negative clinical results [11, 19, 20]. Nonetheless the majority of the recent trials were able to show an improvement of asthma

symptoms, and some of them also a reduction of anti-asthma drugs intake. Whereas lung function [either FEV₁ or peak expiratory flow rate (PEFR)] was measured only in few trials [11, 19, 22, 25, 30] and with controversial results, many trials consistently reported a significant decrease in bronchial non-specific and specific responsiveness [11, 12, 15, 17, 19, 21].

Meta-analyses

The first meta-analysis of SCIT in asthma was published in 1995 [32], included 20 studies (either controlled or not) and concluded that there was a significant effect of SCIT over placebo in reducing symptoms and drug intake. The authors updated the meta-analysis about 10 years later [33], and results supported a similar conclusion. The same meta-analysis was updated again very recently [34]. This latter review includes 88 randomized controlled trials (70 of which placebo-controlled) published between 1954 and 2009, with 13 new studies added. The methodological

Table 1. Randomized controlled trials of SCIT in asthma published after 1998

References	Allergen	Active/ placebo*	Duration	Jadad score	Main results
Tabar et al. [31]	Alternaria	14/14 A	1 year	5/5	↓ asthma symptom score and asthma severity; ↑ PEFR
García-Robaina et al. [30]	Mite	32/32 A	1 year	4/5	↓ asthma symptom score; ↓ specific-bronchial reactivity; ↓ inhaled steroids
Blumberga et al. [29]	Mite	27/27	3 years	4/5	↓ inhaled steroids at 1 and 2 year; no change asthma severity
Roberts et al. [28]	Grass	19/20 C	2 years	5/5	↓ asthma symptom score; ↓ specific-bronchial reactivity
Ferrer et al. [27]	Parietaria	21/20 A	20 months	3/5	Not placebo controlled. ↓ asthma symptom score and asthma severity; ↑ well days
Wang et al. [26]	Mite	64/65 A/C	1 year	3/5	↓ asthma symptom score and medication score; no change in PEFR
Ameal et al. [25]	Mite	29/26 A	1 year	2/5	↓ specific and non-specific bronchial reactivity; ↓ asthma symptoms; no change in medication score
Maestrelli et al. [21]	Mite	41/31 A	1 year	4/5	No change asthma symptoms; ↓ use salbutamol; ↓ specific-bronchial reactivity;
Mirone et al. [24]	Ragweed	16/15 A	1 year	4/5	↓ asthma symptoms and medication score; ↑ asthma-free days
Varney et al. [20]	Mite	15/13 A	1 year	4/5	No change asthma symptoms, medications, PEFR
Guerra et al. [19]	Olive 2 doses	15/15/15 A	12 months	2/5	↓ specific-bronchial reactivity only with the highest dose
Ferrer and García-Sellés [23]	Mite	22/11 A	6 months	1/5	Not placebo controlled. ↓ specific-bronchial reactivity; ↑ PEFR; no change in inhaled steroids and asthma symptoms
Arvidsson et al. [22]	Birch	10/9 A	6 months	3/5	↓ specific-bronchial reactivity (early and late phase); ↓ non-specific bronchial reactivity
González et al. [17]	Olive	23/23 A	1 year	2/5	↓ specific-bronchial reactivity and symptom score
Basomba et al. [18]	Mite (liposome)	28/27 A	1 year	3/5	↓ asthma symptom score and medications, ↑ well days; no change PEFR
Arvidsson et al. [16]	Birch	25/23 A	2 years	3/5	↓ asthma symptom score and medication score
Bødtger et al. [14]	Birch	17/18 A	10 months	5/5	↓ asthma symptom score and total medication score
Grembiale et al. [15]	Mite	42/42 A	2 years	3/5	↓ non-specific-bronchial reactivity
Hedlin et al. [11]	Mite/cat	14/15 C	3 years	3/5	↓ non-specific-bronchial reactivity; no change in inhaled steroids use
Paranos and Petrovic [12]	Mite	40/40 A	4 months	1/5	↓ skin reactivity; no change medications; ↑ FEV ₁ , PFR
Adkinson et al. [13]	seven allergen mix	61/60 C	2 years	4/5	No difference in clinical parameters between groups

*A, Adults; C, children. ↓, decrease/reduction; ↑, increase; FEV₁, forced expiratory volume in 1 s; PEFR, peak expiratory flow rate; QoL, quality of life.

quality, assessed by the Jadad score, was low to moderate, with only six trials receiving the maximum score of 5 points. Concealment of allocation was considered adequate in 16 trials and insufficient in 15. Symptom scores were reported in 35 studies and medication scores in 21, whereas only 20 studies had a pulmonary function measurement. There was only a borderline reduction of symptoms with mite allergens, whereas the effect was highly significant with pollens. No significant improvement with cat, dog or multiple allergen extracts was observed. The effect of SCIT on asthma medication was significant. No change in pulmonary function could be seen, whereas a significant reduction in allergen-specific bronchial responses was consistently shown. The heterogeneity of the studies was high, thus limiting the strength of the conclusions that could be drawn from the meta-analysis.

Additional effects of subcutaneous immunotherapy in asthma

Rhinitis is a risk factor for the development of asthma [8, 35]. Because SIT profoundly modifies the immune response to allergens it has been hypothesized that it may alter the natural history of the disease, specifically by reducing the risk of asthma onset. Thus, another possible evaluation criterion of efficacy is the capacity of immunotherapy to prevent the development of asthma. Indeed, the preventative effect of SIT was suggested >40 years ago in an observational open prospective study [36], but it was confirmed in a more rigorous trial only in the last decade [37, 38]. The Preventative Allergy Treatment study enrolled 205 children (aged 6–10 years) suffering from AR. They were randomized to either drug therapy alone or drugs plus SCIT. After 3 years, the SCIT-treated patients had developed significantly less asthma than the control group, with an odds ratio of 2.5. Interestingly, the beneficial effect of SCIT lasted several years after discontinuation, and also at the 10 year follow-up there were significantly less patients with asthma in the formerly SCIT-treated group.

Comparison with pharmacotherapy

The clinical effects of SIT are not immediate such as those of traditional drugs (i.e. bronchodilators or antihistamines), but the immunomodulation is profound and long-lasting. Based on this background, it is currently stated that SIT does not replace drugs but must be used in addition to them, in order to achieve the maximum benefit. Nevertheless, the direct comparison of the effects of drugs and SIT is still a matter of debate. The main problem in such comparison studies is that the clinical benefits of SIT can be appreciated only in the long-term, whereas pharmacotherapy has a prompt action that can be

measured within days. Another problem is that a rigorous head-to-head comparison would require a double-blind and double-dummy design that is difficult to do for long periods.

Very few studies compared SCIT and pharmacotherapy, and none specifically in asthma. Rak et al. [39] in a double-blind study showed that nasal steroids were more effective than SIT in controlling rhinitis in the short-term, although SIT decreased the seasonal bronchial hyperresponsiveness (BHR) in asthmatic patients. Shaikh [40] compared SIT and inhaled budesonide in an open study and found that the steroid produced a more rapid and relevant benefit than SIT, but SIT maintained its effects even after discontinuation. These studies, conducted in the short-term, overall failed to demonstrate a clear advantage of immunotherapy over drugs.

Safety

In the studies published so far, the frequency of SCIT-induced SRs is largely variable according to the allergen used, the administration schedule, the standardization of the extract, the maintenance dose given and the severity and type of disease before the treatment. Another problem in studying the safety of SIT is the lack of a universally accepted classification/grading of the adverse events. This problem has recently been addressed by the World Allergy Organization with a proposal of a new classification and grading system [41]. Finally, most data on systemic side-effects come from small controlled studies, whereas only large-scale surveys can assure reliable data on the prevalence, character and severity of side-effects.

The majority of the data we have available on the safety of SCIT come therefore from the large surveys performed in the United States [42–47]. They recorded about 50 deaths over a 50-year period with a risk of one death every 2 500 000 injections and one near-fatal reaction per million injections. In this regard, it is important to remember that the clinical practice of SCIT in the United States is partly different from Europe, as mixtures of multiple allergens are commonly used [48]. Thus, caution should be applied in transferring the USA data to other countries. There are less data available in European countries. In the well-known report of 26 deaths in UK over 30 years, published in 1986 [49], many were probably ascribable to incorrect practice, whereas it was established that the presence of asthma was a risk factor in most cases. Since that time fatalities have become extremely rare, and no report has been released in the last decade. Two Italian surveys [50, 51], reported an overall rate of systemic reactions of about 5% of patients. A Spanish survey including 423 patients [52] found a slightly lower prevalence of 3.7% reactions per patient. A recent multi-centre survey [53] suggested that systemic reactions are slightly more frequent in rhinitis with

asthma than in rhinitis alone, although another retrospective study [54] found no significant association between SRs and the presence of asthma.

Despite the overall rarity of deaths the surveys agreed on the fact that uncontrolled asthma is the most prominent risk factor for fatalities and severe adverse events, including asthma itself [1]. Thus, asthma is not an absolute contraindication to SCIT, provided that the patient is well controlled with pharmacotherapy.

Sublingual immunotherapy in asthma

Clinical trials

SLIT is more recent than SCIT and, therefore, its effects in asthma are still an important matter of debate. There are now >60 randomized controlled trials of SLIT [55], but none was formally sized and adequately powered for asthma. For this reasons it is not possible to be definitive about the role of SLIT in asthma at the present time. Nonetheless there are some trials which have been specifically designed to evaluate the effects in asthmatics [56–68] or which clearly reported asthma-related outcomes (Table 2). Most studies were performed in children.

Three studies [56, 57, 58] reported no effect on asthma symptoms. Nevertheless, in two of these studies [56, 57], all the patients (active and controls) had almost no symptoms of asthma at baseline and during the trial, therefore not leaving the possibility that an effect, if present, could be detected. When patients had measurable asthma symptoms at enrolment, the effect of SLIT could be demonstrated. This was clearly shown in three studies [59, 60, 61] with dust mite extracts. One involved 85 adults and the others 58 and 86 children with mite-induced asthma.

In these studies, in addition to clinical improvement an increase in functional spirometric parameters was seen. In the adult study FEV₁ increased from 95% to 102% of predicted, in one pediatric study non-specific bronchial reactivity was more than halved after SLIT [59], and in the other one FEV₁ increased from 83% to 92% of predicted [60]. In another pediatric study [62] a significant decrease in symptoms, but not medication intake, was seen. Pajno et al. [63] reported a significant clinical improvement of asthma symptoms in mite-allergic children, although no functional parameter was evaluated. Similar results were reported by Lue et al. [65] and Niu et al. [64], who evaluated nighttime and daytime symptoms and also FEV₁, showing a significant change vs. baseline and vs. placebo for all parameters. The most recent pediatric trial, specifically investigating asthma [66] reported a significant improvement in all clinical parameters. One of the recent 'big trials' assessed the effect of grass tablets on asthma in children 5–16 years of age [67]. All asthma symptoms were significantly reduced, whereas use of rescue medication was reduced not significantly. Finally, in a randomized double-blind placebo-controlled trial, it was shown that SLIT was capable of reducing the degree of non-specific BHR in children with parietaria allergy [68].

Meta-analyses

The number of randomized controlled trials is nowadays quite large and, therefore, some meta-analyses could be performed. The first meta-analysis specifically dedicated to the effect of SLIT in asthma was published in 2006 [69], and analyzed 25 trials with 1076 patients (adults and children). This meta-analysis reported a significant

Table 2. Randomized controlled trials of slit in asthma

References	Allergen	Active/ placebo*	Duration	Jadad score	Main results
Tari et al. [60]	Mite	30/28 C	18 months	4/5*	↓ asthma symptom score and total medication score; ↓ specific and non-specific bronchial reactivity
Bousquet et al. [59]	Mite	17/18 A	2 years	4/5	↓ asthma symptom score; ↑ FEV ₁ , PFR; ↑ QoL
Hirsch et al. [58]	Mite	13/14 C	1 year	5/5	↓ asthma symptom score; no change in bronchial reactivity
Vourdas et al. [62]	Olive	34/32 C	2 years	4/5	↓ dyspnea score; no change in medications
Pajno et al. [63]	Mite	12/12 C	2 years	5/5	↓ asthma symptom score only 2nd year; ↓ night asthma symptom and medication both years
Ippoliti et al. [61]	Mite	47/39 C	6 months	4/5	↓ asthma symptom score; ↑ FEV ₁
Pajno et al. [68]	Parietaria	20/20 C	2 season	5/5	↓ inseason non-specific bronchial reactivity
Niu et al. [64]	Mite	56/54 C	6 months	4/5	↓ asthma symptom score, daytime, nighttime symptoms and medication score; no change FEV ₁ and oral steroids
Lue et al. [65]	Mite	10/10 C	8 months	4/5	↓ nighttime symptoms, ↑ FEV ₁ vs. baseline; no change total symptom score, medications and FEV ₁ vs. placebo
Dahl et al. [56]	Grass	74/40 A	5 months	5/5	No change symptoms and medications
Pham Ti et al. [57]	Mite	55/56 C	18 months	4/5	No change symptoms, medications, FEV ₁ , well days
Stelmach et al. [66]	Grass	25/25 C	2 season	5/5	↓ asthma symptoms and medications
Bufe et al. [67]	Grass	126/127 C	6 months	5/5	↓ asthma symptoms; no change medications

*A, Adults; C, children. ↓, decrease/reduction; increase; FEV₁ ↑, forced expiratory volume in 1 s; PEFR, peak expiratory flow rate; QoL, quality of life.

difference between SLIT and placebo for categorical outcomes (better/unchanged/worsened), but no difference using the symptom or medication scores for asthma. On the other hand, the combined symptom score of asthma + rhinitis were clearly in favour of SLIT. Nonetheless, there was a high heterogeneity, which limits at some extent the positive conclusions. Another meta-analysis [70] dealt with pediatric asthma (patients < 18 years) and included nine trials with 441 patients. The results, according to the mean standardized difference demonstrated a significant reduction in both symptoms ($P=0.02$) and medication use ($P=0.007$) vs. placebo. Also in this case a high degree of heterogeneity was found, due to the different inclusion criteria, scoring systems and regimens.

One of the major problems of meta-analyses is that they pool together the different allergens (i.e. mites and pollens). Very recently, this aspect has been addressed by two analyses, one restricted to mite extracts [71] and one to grass extracts [72]. The meta-analysis for dust mites included nine trials with asthma symptoms/medications evaluated. The results showed a significant reduction vs. placebo in both symptom scores ($P=0.02$) and medication intake ($P=0.02$). Also in this case, there was a high heterogeneity ($I^2 > 90\%$) across studies. The meta-analysis for grasses did not report specific results for asthma.

Additional effects

Because rhinitis is a risk factor for the development of asthma [8], it is possible that SIT has the potential to modify the progression of allergic diseases. This was demonstrated previously in a randomized open trial with SCIT as mentioned above. Concerning SLIT there are two studies supporting the possible disease-modifying effect of the treatment. The first open controlled study [73] involved 113 children aged 5–14 years suffering from seasonal rhinitis due to grass pollen. They were randomly allocated to medications plus SLIT or medications only. After 3 years, 8/45 SLIT subjects and 18/44 controls had developed asthma, with a relative risk of 3.8 for untreated patients. Another randomized open controlled trial [74] involved 216 children (age 5–17 years) suffering from rhinitis with/without intermittent asthma. They were randomly allocated 2 : 1 to drugs plus SLIT or drugs only, and followed for 3 years for the presence of persistent asthma. The prevalence of persistent asthma was 2/130 (1.5%) in the SLIT group and 19/66 (30%) in the control group, with a number to treat of 4. These data support the need for further randomized blinded trials of the potential long-term benefits of SLIT in the development of asthma.

Comparison with pharmacotherapy

As occurs for SCIT, the comparison of efficacy between SLIT and medications remains an open problem. This is

due to the fact that SLIT is not a receptor agonist/antagonist but rather an immune-modifying treatment. Thus, the effects of immunotherapy can be appreciated only in the long-term (months). A trial [75] conducted in asthmatic children demonstrated that the clinical efficacy of SLIT plus fluticasone is equal to that of fluticasone alone, but that the addition of SLIT improved also on non-bronchial symptoms.

One head-to-head open randomized trial of SLIT vs. inhaled budesonide as add-on in asthmatic patients, showed in the long-term an overall superiority of immunotherapy [76], because SLIT provided an improvement also in nasal symptoms and nasal inflammation, whereas functional parameters were improved by both treatments. The same was shown by adding SLIT or montelukast to standard antiasthma treatment [77]. Both studies were randomized, but open, and with measurements carried out after 3 and 5 years, this limiting the methodological value of the observations.

Safety

It is generally agreed that the safety of SLIT is superior to that of SCIT [78]. No fatality has been so far reported with SLIT. In addition, the reports of anaphylaxis with SLIT so far available in the literature are only six [79–83] and four of these occurred with inappropriate off label use. A controlled dose finding study of safety [84] involved 48 grass-allergic patients outside pollen season. They received SLIT for 28-day periods at progressively increasing doses, up to 200 mcg Phl p 5 that is about 40 times the amount given with one injection. The overall incidence of side-effects was 74%, all of mild or moderate intensity. The most frequently reported events were irritation of the throat and oral itching. According to this study, the occurrence of side-effects seems to be dose-dependent, as occurs with SCIT. The study by Dahl et al. [56] specifically assessed the safety of SLIT in asthma. More than 100 grass-allergic asthmatics were enrolled and studied before the pollen season. The number of side-effects linked to asthma (wheezing cough, dry throat, dyspnoea and increased bronchial secretion) was similar between the active and placebo group, and there was no evidence of asthma aggravation. In general, SLIT induces asthma as side-effect only very rarely [55]. Thus, limited data available suggests that the presence of asthma may not increase the risk of adverse events. Despite this, at the present time it is prudent that SLIT is restricted to subjects with mild asthma and not be recommended in subjects with uncontrolled asthma.

Concluding remarks

In recent years, evidence-based medicine has become more and more important, and almost all guidelines and

recommendations are prepared according to well accepted evaluation systems such as the GRADE or the Shekelle's rules [85]. The evidence based criteria firstly require that the methodology of trials is adequate, and this is not always the case for SIT studies. In fact, almost all the available randomized controlled trials suffer from methodological limitations, mainly the small number of patients, the absence of a sample size calculation and the large variability of the outcomes and inclusion criteria. This applies also to asthma studies, where no trial was adequately powered.

It is also true that when multiple positive trials and meta-analyses, are available, as occurs with SCIT and SLIT, the evidence should be considered robust and the recommendations should be of high grade. Despite this, scientists and researchers are generally reluctant to definitely recommend the use of SIT in asthma. This is due to the fact that (a) the large heterogeneity of trials [34, 69, 70] limits the validity of meta-analyses; (b) with SCIT, most important, there are safety concerns; (c) with SLIT there are few clearly positive studies; and (d) no clear proof of an effect of SIT on pulmonary function has been so far provided. Another problem is that the majority of trials are not truly placebo-controlled, because rescue medications were allowed, and that there are very few direct comparisons of drug therapy and SIT in asthma.

On the other hand, it would not be reasonable to discard all the clinical data that have been produced until now, and also the likely disease-modifying and long-lasting effects of SIT in asthma prevention should be taken into

account. As such, on the basis of the available evidence we can say that SIT (either SLIT or SCIT) can be confidently used together with medications in asthma, when it is associated with rhinitis and when the causal role of the allergen (pollens, mite or pets) is clearly confirmed [86]. The recommendation of not giving SIT in patients with moderate-severe or uncontrolled asthma remains valid. When asthma is the only manifestation of allergic disease, SIT may exert a beneficial effect, at least by reducing the need for medications and reducing associated BR. This does not imply that SIT is to be used as the primary therapeutic approach in adults or indeed in children, where highly effective drugs (i.e. inhaled corticosteroids) are currently available.

Future studies should focus on mild-moderate asthma where asthma is the primary focus, and where long-term benefits after discontinuation are evaluated. There is also an urgent need to evaluate in a double-blind fashion the long-term preventive aspects of immunotherapy in children with rhinitis on future asthma development and the development of new sensitizations, as implied but not proven by currently available evidence.

Acknowledgements

A special thanks to Prof Stephen Durham for his precious advice and for editing the text.

Funding and conflict of interest:

None to declare.

References

- Bousquet J, Lockey RF, Malling HJ (eds). Allergen immunotherapy: therapeutical vaccines for allergic diseases. *Allergy* 1998; 54(Suppl 82):1–33.
- Bonifazi F, Bilò MB. Efficacy of specific immunotherapy in allergic asthma: myth or reality? *Allergy* 1997; 52: 698–710.
- Cox L. Allergen immunotherapy and asthma: efficacy, safety, and other considerations. *Allergy Asthma Proc* 2008; 29:580–9.
- Nelson HS. Allergen immunotherapy: where is it now? *J Allergy Clin Immunol* 2007; 119:769–79.
- Saltoun CA. Update on efficacy of allergen immunotherapy for allergic rhinitis and asthma. *Allergy Asthma Proc* 2002; 23:377–80.
- Bousquet J, Demoly P, Michel FB. Specific immunotherapy in rhinitis and asthma. *Ann Allergy Asthma Immunol* 2001; 87 (1 Suppl 1):38–42.
- Creticos PS. The consideration of immunotherapy in the treatment of allergic asthma. *J Allergy Clin Immunol* 2000; 105:S559–74.
- Cruz AA, Popov T, Pawankar R *et al.* Common characteristics of upper and lower airways in rhinitis and asthma: ARIA update, in collaboration with GA(2)LEN. *Allergy* 2007; 62 (Suppl 84):1–41.
- Bousquet PJ, Brozek J, Bachert C *et al.* The CONSORT statement checklist in allergen-specific immunotherapy: a GA2LEN paper. *Allergy* 2009; 64:1737–45.
- Canonica GW, Baena Cagnani C, Bousquet J *et al.* Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007; 62:317–24.
- Hedlin G, Wille S, Browaldh L *et al.* Immunotherapy in children with allergic asthma: effect on bronchial hyperactivity and pharmacotherapy. *J Allergy Clin Immunol* 1999; 103:609–14.
- Paranos S, Petrovic S. Early effects of rush immunotherapy with *Dermatophagoides pteronyssinus* in asthmatics. *J Investig Allergol Clin Immunol* 7: 588–95.
- Adkinson NF, Eggleston PA, Eney D *et al.* A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997; 336:324–31.
- Bødtger U, Poulsen LK, Jacobi HH, Malling HJ. The safety and efficacy of subcutaneous birch pollen immunotherapy – a one-year, randomised, double-blind, placebo-controlled study. *Allergy* 2002; 57:297–305.
- Grembale RD, Camporota L, Naty S, Tranfa CM, Djukanovic R, Marsico SA. Effects of specific immunotherapy in allergic rhinitic individuals with bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 2000; 162: 2048–52.

- 16 Arvidsson MB, Löwhagen O, Rak S. Effect of 2-year placebo-controlled immunotherapy on airway symptoms and medication in patients with birch pollen allergy. *J Allergy Clin Immunol* 2002; 109:777–83.
- 17 González P, Florido F, Sáenz de San Pedro B, de la Torre F, Rico P, Martín S. Immunotherapy with an extract of *Olea europaea* quantified in mass units. Evaluation of the safety and efficacy after one year of treatment. *J Investig Allergol Clin Immunol* 2002; 12:263–71.
- 18 Basomba A, Tabar AI, de Rojas DH *et al.* Allergen vaccination with a liposome-encapsulated extract of *Dermatophagoides pteronyssinus*: a randomized, double-blind, placebo-controlled trial in asthmatic patients. *J Allergy Clin Immunol* 2002; 109:943–8.
- 19 Guerra F, Daza JC, Almeda E. Immunotherapy with a depigmented, polymerized vaccine of *Olea europaea* pollen allergens. Significantly reduces specific bronchial and skin test reactivity in sensitized patients after one year of treatment. *J Investig Allergol Clin Immunol* 2003; 13:108–17.
- 20 Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy* 2003; 33:1076–82.
- 21 Maestrelli P, Zanolla L, Pozzan M, Fabbri LM. Regione Veneto Study Group on the “Effect of immunotherapy in allergic asthma”. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. *J Allergy Clin Immunol* 2004; 113:643–9.
- 22 Arvidsson MB, Löwhagen O, Rak S. Allergen specific immunotherapy attenuates early and late phase reactions in lower airways of birch pollen asthmatic patients: a double blind placebo-controlled study. *Allergy* 2004; 59:74–80.
- 23 Ferrer A, García-Sellés J. Significant improvement in symptoms, skin test, and specific bronchial reactivity after 6 months of treatment with a depigmented, polymerized extract of *Dermatophagoides pteronyssinus* and *D. farinae*. *J Investig Allergol Clin Immunol* 2003; 13:244–51.
- 24 Mirone C, Albert F, Tosi A *et al.* Efficacy and safety of subcutaneous immunotherapy with a biologically standardized extract of *Ambrosia artemisiifolia* pollen: a double-blind, placebo-controlled study. *Clin Exp Allergy* 2004; 34:1408–14.
- 25 Ameal A, Vega-Chicote JM, Fernández S *et al.* Double-blind and placebo-controlled study to assess efficacy and safety of a modified allergen extract of *Dermatophagoides pteronyssinus* in allergic asthma. *Allergy* 2005; 60:1178–83.
- 26 Wang H, Lin X, Hao C *et al.* Double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. *Allergy* 2006; 61:191–7.
- 27 Ferrer M, Burches E, Peláez A *et al.* Double-blind, placebo-controlled study of immunotherapy with *Parietaria judaica*: clinical efficacy and tolerance. *J Investig Allergol Clin Immunol* 2005; 15:283–92.
- 28 Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. *J Allergy Clin Immunol* 2006; 117:263–8.
- 29 Blumberg G, Groes L, Haugaard L, Dahl R. Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. *Allergy* 2006; 61:843–8.
- 30 García-Robaina JC, Sánchez I, de la Torre F, Fernández-Caldas E, Casanovas M. Successful management of mite-allergic asthma with modified extracts of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* in a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2006; 118:1026–32.
- 31 Tabar AI, Lizaso MT, García BE *et al.* Double-blind, placebo-controlled study of *Alternaria alternata* immunotherapy: clinical efficacy and safety. *Pediatr Allergy Immunol* 2008; 19:67–75.
- 32 Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995; 151:969–74.
- 33 Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003; 4:CD001186.
- 34 Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010; 8:CD001186.
- 35 Shaaban R, Zureik M, Soussan D *et al.* Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet* 2008; 372:1049–57.
- 36 Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children – a 14-year study. *Pediatrics* 1968; 42:793–802.
- 37 Möller C, Dreborg S, Ferdousi HA *et al.* Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; 109:251–6.
- 38 Jacobsen L, Niggemann B, Dreborg S *et al.* Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; 62:943–8.
- 39 Rak S, Heinrich C, Jacobsen L, Scheynius A, Venge P. A double-blinded, comparative study of the effects of short pre-season specific immunotherapy and topical steroids in patients with allergic rhinoconjunctivitis and asthma. *J Allergy Clin Immunol* 2001; 108:921–8.
- 40 Shaikh WA. Immunotherapy vs inhaled budesonide in bronchial asthma: an open, parallel, comparative trial. *Clin Exp Allergy* 1997; 27:1279–84.
- 41 Cox L, Larenas Linneman D, Lockey RF, Passalacqua G. Speaking a common language in immunotherapy. WAO grading of systemic reactions. *J Allergy Clin Immunol* 2010; 125:569–74.
- 42 Lockey RF, Benedicts LM, Turkeltaub PC, Platt-Mills TA. Fatalities from immunotherapy and skin testing. *J Allergy Clin Immunol* 1987; 76:660–77.
- 43 Reid MJ, Lockey RF, Turkeltaub PC, Platt-Mills TA. Survey of fatalities from skin testing and immunotherapy. *J Allergy Clin Immunol* 1993; 92:6–15.
- 44 Bernstein DI, Wanner M, Borish L, Liss GM. Immunotherapy Committee American Academy Allergy Asthma Immunology. Twelve years of survey of fatal reactions to allergen injections and skin testing 1990–2001. *J Allergy Clin Immunol* 2004; 113:1129–36.
- 45 Lin MS, Tanner E, Lynn J, Friday GA Jr. Non fatal systemic allergic reactions induced by skin test and immunotherapy. *Ann Allergy* 1993; 71:557–62.

- 46 Hetal S, Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006; 117:169–75.
- 47 Tinkelman DG, Cole WQ III, Tunno J. Immunotherapy: a one-year prospective study to evaluate risk factors of systemic reactions. *J Allergy Clin Immunol* 1995; 95:8–14.
- 48 Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol* 2009; 103:451–59.
- 49 Committee on the Safety of Medicines. Desensitizing vaccines. *BMJ* 1989; 293:948.
- 50 Nettis E, Giordano D, Pannofino A, Tursi A. Safety of inhalant allergen immunotherapy with mass units-standardized extracts. *Clin Exp Allergy* 2002; 32:1745–9.
- 51 Ragusa RF, Passalacqua G, Gambardella R *et al.* Nonfatal systemic reactions to subcutaneous immunotherapy: a 10 years experience. *J Invest Allergol Clin Immunol* 1997; 7:151–4.
- 52 Moreno C, Cuesta-Herranza J, Fernandez-Tavora L, Alvarez-Cuesta E. Immunotherapy safety: a prospective multicentric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. *Clin Exp Allergy* 2004; 34:527–31.
- 53 Schiappoli M, Ridolo E, Senna G *et al.* A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. *Clin Exp Allergy* 2009; 39:1569–74.
- 54 Rank MA, Oslie CL, Krogman JL, Park MA, Li JT. Allergen immunotherapy safety: characterizing systemic reactions and identifying risk factors. *Allergy Asthma Proc* 2008; 29:400–5.
- 55 Canonica GW. editor World Allergy Organization position paper on sublingual immunotherapy. *Allergy* 2009; 64 (Suppl 91):1–59.
- 56 Dahl R, Stender H, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006; 61:185–90.
- 57 Pham-Thi N, Scheinmann P, Fadel R, Combebias A, Andre C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. *Pediatr Allergy Immunol* 2007; 18:47–57.
- 58 Hirsch T, Sahn M, Leupold W. Double-blind placebo-controlled study of sublingual Immunotherapy with house dust mite extract (D.pt.) in children. *Pediatr Allergy Immunol* 1997; 8:21–7.
- 59 Bousquet J, Scheinmann P, Guinnepain MT. Sublingual swallow immunotherapy (SLIT) in patients with asthma due to house dust mites: a double-blind placebo-controlled study. *Allergy* 1999; 54:249–60.
- 60 Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double blind study. *Allergol Immunopathol (Madrid)* 1990; 18:277–84.
- 61 Ippoliti F, De Sanctis W, Volterrani A *et al.* Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol* 2003; 14:216–21.
- 62 Vourdas D, Syrigou E, Potamianou P *et al.* Doubleblind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy* 1998; 53:662–72.
- 63 Pajno GB, Morabito L, Barberio G. Clinical and immunological effects of long-term sublingual immunotherapy in asthmatic children sensitized to mite: a double-blind study. *Allergy* 2000; 55:842–9.
- 64 Niu CK, Chen WY, Huang JL, Lue KH, Wang YJ. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. *Respir Med* 2006; 100:1374–83.
- 65 Lue KH, Lin YH, Sun HL *et al.* Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. *Pediatr Allergy Immunol* 2006; 17:408–15.
- 66 Stelmach I, Kaczmarek-Woźniak J, Majak P, Oszlowski-Chlebna M, Jermyska A. Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen. *Clin Exp Allergy* 2009; 39:401–8.
- 67 Bufer A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009; 123:167–73.
- 68 Pajno G, Passalacqua G, Vita D, Permiani S, Barberio G. Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with *Parietaria*-induced respiratory allergy: a randomized controlled trial. *Allergy* 2004; 59:883–7.
- 69 Calamita Z, Saconato H, Bronhara Pelà A, Atallah AN. Efficacy of sublingual immunotherapy in asthma. Systematic review of randomized clinical trials. *Allergy* 2006; 61:1162–72.
- 70 Penagos M, Passalacqua G, Compalati E, Tarantini F, Canonica GW. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 2008; 133:599–609.
- 71 Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2 LEN meta-analysis. *Allergy* 2009; 64:1570–9.
- 72 Di Bona D, Plaia A, Scafidi V, Di Lorenzo G. Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2010; 126:558–66.
- 73 Novembre E, Galli E, Landi F *et al.* Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; 114:851–7.
- 74 Marogna M, Tomassetti D, Bernasconi A *et al.* Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008; 101:206–11.
- 75 Pajno GB, Vita D, Parmiani S, Caminiti L, La Grutta S, Barberio G. Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to *Parietaria* pollen treated with inhaled fluticasone propionate. *Clin Exp Allergy* 2003; 33:1641–7.
- 76 Marogna M, Spadolini I, Massolo A *et al.* Long-term comparison of sublingual immunotherapy vs inhaled budesonide in patients with mild persistent asthma due to grass pollen. *Ann Allergy Asthma Immunol* 2009; 102:69–75.

- 77 Marogna M, Colombo T, Spadolini I *et al.* Randomized open comparison of montelukast and sublingual immunotherapy as add-on treatment in moderate persistent asthma due to birch pollen. *J Investig Allergol Clin Immunol* 2010; **20**:146–52.
- 78 Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006; **117**:1021–35.
- 79 Dunskey E, Goldstein MF, Dvorin MJ, Belcanech GA. Anaphylaxis due to sublingual immunotherapy. *Allergy* 2006; **61**:1235.
- 80 Antico A, Pagani M, Crema A. Anaphylaxis by latex sublingual immunotherapy. *Allergy* 2006; **61**:1236.
- 81 Eifan AO, Keles S, Bahceciler NN, Barman IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy* 2007; **62**:567–8.
- 82 Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. *Allergy* 2008; **63**:374.
- 83 de Groot H, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 2009; **64**:963–4.
- 84 Kleine-Tebbe J, Ribel M, Herold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. *Allergy* 2006; **61**:181–4.
- 85 Brozek JL, Baena Cagnani C, Canonica GW *et al.* Methodology for development of the allergic rhinitis and its impact on asthma guideline 2008 update. *Allergy* 2008; **63**:38–46.
- 86 Brozek JL, Bousquet J, Baena-Cagnani CE *et al.* Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; **126**:466–76.