



Subcutaneous allergen immunotherapy for allergic disease: examining efficacy, safety and cost-effectiveness of current and novel formulations

Subcutaneous immunotherapy (SCIT) is a unique therapy for allergic disease because it provides symptomatic relief while modifying the allergic disease by targeting the underlying immunological mechanism. Its efficacy and safety have been established in the treatment of asthma, allergic rhinitis/rhinoconjunctivitis and stinging insect hypersensitivity in numerous controlled clinical trials. This review evaluates a spectrum of clinical factors, ranging from efficacy to cost-effectiveness, which should be considered in evaluating SCIT. The evidence for SCIT safety and efficacy for these conditions is reviewed in an evaluation of the systematic reviews and meta-analyses. The evidence for the persistent and preventive effects of SCIT is also examined. An overview of the SCIT outcomes measures utilized in clinical trials is presented. The cost-effectiveness of SCIT compared with conventional medication treatment, novel indications and formulations for SCIT are also explored in this review.

KEYWORDS: specific allergen immunotherapy • subcutaneous immunotherapy • sublingual immunotherapy

Linda Cox^{*1},
Moisés Calderón²
& Oliver Pfaar³

¹Department of Medicine, Nova Southeastern University, 5333 North Dixie Highway, Fort Lauderdale, FL 33334, USA

²Section of Allergy & Clinical Immunology, Imperial College London, National Heart & Lung Institute, Royal Brompton & Harefield Foundation Trust, London, UK

³Center for Rhinology & Allergology, Wiesbaden, Germany

*Author for correspondence:
lindawolfcox@msn.com

Subcutaneous immunotherapy (SCIT) has been employed in the treatment of allergic conditions for over a century, in a manner largely unchanged from the practice established by Noon and Freeman, the pioneers who first described successful treatment of grass pollen-induced hay fever with grass pollen inoculations [1–3]. Noon had been influenced by the work of William Dunbar, who believed a pollen ‘toxin’ was the cause of allergic rhinitis (AR) [4]. Unfortunately, Dunbar’s experiments with passive immunization utilizing serum from immunized rabbits and horses produced poor results and serious adverse events. Noon also believed a pollen ‘toxin’ was the cause of hay fever but, unlike Dunbar, was able to demonstrate effective treatment of hay fever patients with a protocol of increasing doses of grass pollen extract administered via subcutaneous injections. Using conjunctival allergen challenge, he established objective proof of SCIT efficacy by demonstrating that an immunotherapy-treated patient could tolerate an increase of up to 100-fold of allergen exposure before experiencing a conjunctival reaction [3]. He also showed that anaphylaxis may be induced by SCIT allergen ‘overdose’. These early studies suggested that SCIT’s clinical benefits may persist for at least 1 year after treatment cessation [2]. Subsequent clinical trials confirmed SCIT’s persistent clinical benefits as well its possible preventive effect in terms of progression of the allergic disease

from rhinitis to asthma or the development of new allergen sensitivities. In the ensuing century, multiple randomized controlled trials (RCTs) have demonstrated that SCIT is clearly effective and safe in the treatment of allergic asthma, rhinitis and stinging insect hypersensitivity and may be beneficial in other clinical conditions such as atopic dermatitis.

Although it has been over 100 years since SCIT’s efficacy was first established, the mechanisms responsible for its efficacy are still being elucidated (Box 1). Despite this, multiple studies have demonstrated that both the efficacy and safety of SCIT are largely dependent on dose regardless of the specific allergen used. This paper will review the evidence for SCIT safety and efficacy beginning with an evaluation of the systematic reviews and meta-analyses for the approved indications discussed above. This evaluation will include a review of how SCIT outcomes are assessed and reported and novel formulations and indications for SCIT. The evidence for persistent and preventive effect of SCIT, as well as the cost-effectiveness of SCIT compared with conventional medication treatment, will also be examined.

Assessment of immunotherapy outcomes

In performing clinical studies on allergen-specific immunotherapy (SIT), a variety of clinical outcome parameters are utilized for the

Future
Medicine  part of 

Box 1. Allergen immunotherapy landmarks in the past 101 years: bench to bedside.

- 1911–1930: Noon and Freeman reported successful immunization of hay fever patients with timothy grass pollen extract [1,3,97]
- 1921: Prausnitz and Kustner demonstrated that anaphylaxis sensitivity could be passively transferred by the serum of the sensitive patient (known as the Prausnitz–Kustner reaction) [98]
- 1935: Cooke demonstrated that blocking antibodies from patients treated with ragweed extract can confer protection on unvaccinated ragweed-allergic patients [98]
- 1954: Franklind and Augustin carried out the first placebo-controlled immunotherapy study of patients with grass pollen-induced hay fever [99]
- 1957, 1968: Johnstone demonstrated a preventive and dose–response effect of immunotherapy in terms of bronchial hypersensitivity and development of asthma [100,101]
- 1965: Lowell and Franklin demonstrated the specificity of immunotherapy in ragweed-allergic hay fever patients [102]
- 1967: Ishizaka identified IgE as the reaginic antibody [103,104]
- 1997: Des Roches *et al.* demonstrated that immunotherapy may prevent new allergen sensitizations [75]
- 1999: Durham *et al.* demonstrated the persistent benefits of immunotherapy after discontinuation of immunotherapy in grass pollen hay fever [54]
- 2002: Moller *et al.* demonstrated that immunotherapy may prevent progression of allergic rhinitis to asthma [70]
- 2003, 2004: Ewbank *et al.* and Nanda *et al.* demonstrated immunotherapy dose–response effect on immunological changes associated with cat SCIT with the effect at 5 weeks being predictive of the response at 1 year [105,106]
- 2006: Creticos *et al.* demonstrated efficacy of six weekly injections of vaccine containing CpG conjugated to the major ragweed allergen Amb a 1 [92]
- 2007: Jacobsen *et al.* demonstrated that the asthma-preventive effect of SCIT was still significant 7 years after treatment discontinuation [69]
- 2008: Francis *et al.* demonstrated SCIT immunological changes occurred at different time points and allergen doses: IL-10 production at 2–4 weeks associated with low allergen doses and inhibition of late-phase skin responses [107]

SCIT: Subcutaneous immunotherapy.

evaluation of the clinical efficacy of the therapy [5,6]. It is common practice to define ‘primary’ as well as ‘secondary’ outcome parameters before initiation of the SIT trial.

‘Primary outcome measures’ include the daily severity of symptoms as well as the daily consumption of antiallergic concomitant medication as documented in patients’ (paper or electronic) diaries. The EMA guidance on statistical principles for clinical trials states that “The primary variable (‘target’ variable, primary endpoint) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial” [201]. The 2008 guidance of the EMA indicated that, to date, there has been no validated symptom and medication scoring method for clinical trials for SIT [202]. However, the guidance points out that “measurement of symptoms on a 4-point rating scale ... is generally accepted,” which should include itching, sneezing, rhinorrhea, nasal obstruction for nasal symptoms and, furthermore, itching/grittiness/redness and ocular tearing for conjunctival symptoms. Each symptom can be scored by patients between 0 (absent symptoms) and 3 (severe symptoms) (Box 2). All symptoms together may sum between 0 and 18 points as Rhinoconjunctivitis Total Symptom Score. A World Allergy Organization (WAO) Taskforce

position paper on recommendations for standardization of clinical trials with SIT suggests that pulmonary symptoms, such as chest tightness, shortness of breath, cough and wheezing, may also be included in the symptom score [7].

An important consideration in assessing outcomes is that there is an interdependence between allergic symptoms and the use of antiallergic medication. The WAO Taskforce recommendation clearly states that both scores should not be evaluated separately but be calculated in a combined score [7]. The use of a combined score was endorsed by the EMA guidance, which stated that “a weighted sum of the symptom and medication score” shall be used [202]. Again, currently there is no standardized and widely accepted method for the reporting of combined symptom and medication scores [8].

One approach used to report combined symptom–medication scores is the Adjusted Symptom Score, which is primarily based on the Rhinoconjunctivitis Total Symptom Score calculated forward (‘last observation carried forward’) [9], with an adjustment in the symptoms score if the patient had taken an allergy medication the subsequent day [10]. A novel instrument, the Allergy-Control-SCORE™, designed to assess patients’ allergy severity by recording symptoms and rescue medication, has recently been validated [11].

The Allergy-Control-SCORE, which takes into account the global allergy severity, allergy-related consultations and the validated Rhinoconjunctivitis Quality of Life Questionnaire [12], was found to be a “valid and reliable instrument to assess allergy severity in clinical trials and observational studies of respiratory allergic diseases” [11].

Secondary outcome parameters may also be evaluated as important outcome measures in clinical trials on SIT. These include Rhinoconjunctivitis Quality of Life, ‘well/hell days’, allergen provocation tests and other surrogate markers, such as allergen-specific IgG antibodies or inflammatory parameters [7].

Systematic reviews & meta-analyses

Systematic reviews and meta-analyses have been conducted to evaluate the efficacy and safety of SCIT for AR and asthma [13]. Well-conducted systematic reviews and meta-analyses are still considered powerful instruments for synthesizing clinical trial data, providing a straightforward answer to a specific pre-established question: is there a beneficial effect between the therapeutic intervention (such as SCIT) and the placebo [14]?

In this statistical analysis, researchers have conducted systematic reviews of SCIT, which have included studies with small numbers of patients. One potential problem with small studies is that they may not be sufficiently powered to establish a positive effect when one is present, which is referred to as a type II error. A meta-analysis can combine the results of individual studies and increase the power of the analysis providing the interventions and outcomes in the various studies are sufficiently similar. However, because of the significant clinical and methodological heterogeneity of SCIT studies, it may be difficult to directly compare studies unless the results of each study are standardized by calculating the standardized mean difference (SMD). The SMD is the difference of the means of both treatment arms divided by the pooled standard deviation. In this way, the treatment effect in each study is expressed in standard units (instead of the original units). “Efficacy can be expressed as ‘numbers needed to treat’ (NNT), which is the number of people who need to be treated to benefit one additional person over placebo and can be calculated by the following formula:

$$NNT = \frac{1}{(\% \text{ responders}_{\text{active}} - \% \text{ responders}_{\text{placebo}})}$$

The ideal NNT is 1, where everyone improves with treatment and there is no improvement in any of the control group. Generally, the higher the NNT, the less effective is the treatment” [15].

The heterogeneity of studies is reflected in the I^2 , which provides an estimate of the variability across studies that is likely due to a true difference in treatment effect and not chance. A higher I^2 (>0.5) correlates with greater heterogeneity.

■ Allergic rhinitis

Three meta-analyses have been published evaluating the efficacy of SCIT for AR. Klimek *et al.* published in 1999 the first so-called “meta-analyses of SCIT on clinical and immunologic treatment used in patients with allergic rhinoconjunctivitis” [16]. They included 43 RCTs published between 1980 and 1997. In this thorough literature review, the authors found that SCIT was effective in the treatment of allergic rhinoconjunctivitis, decreasing symptoms, the need for medication, and reactivity in specific nasal and conjunctival provocation tests, as well as inflammatory markers. The authors concluded that the efficacy of SCIT is dependent on certain characteristics of the allergen to which the patient is sensitized, these being:

- The allergen itself
- Its quality
- The amount used during SCIT
- The schedule used

In 2000, Ross *et al.* published a second analysis of SCIT for treating AR [17]. Sixteen prospective, single-blind or double-blind, placebo-controlled studies published between 1966 and 1996 were included. The experimental designs varied considerably from one study to another; therefore, it was not possible to reduce the entire database to a single format for statistical analysis. However, odds ratios (ORs) and 95% CIs were calculated using a random-effects model for a variety of clinical outcomes. All but one study

Box 2. Evaluation of symptoms using a 4-digit score system as given by the Committee for Medicinal Products for Human Use.

- 0 = absent symptoms (no sign/symptom evident)
- 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated)
- 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable)
- 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)

Reproduced with permission from [202] and [206].

concluded that SCIT was effective in terms of reducing the symptoms of AR compared with placebo (OR: 1.81; 95% CI: 1.48–2.23).

In 2007, Calderón and colleagues published the first Cochrane systematic review and meta-analysis evaluating the effect of allergen injection immunotherapy on seasonal AR [18]. The following are the characteristics of the studies included in this systematic review:

- Fifty-one RCTs published between 1984 and 2006 were included;
- A total of 2871 patients (1645 active and 1226 placebo);
- Each patient received on average 18 injections;
- The seasonal allergens used in these included studies were ragweed (12 trials), mixed grass (16 trials), timothy (five trials), *Parietaria* (six trials), birch (four trials), orchard (two trials), cedar (three trials), bermuda (one trial), *Juniperus ashei* (one trial) and *Cocos nucifera* (one trial);
- Twenty-seven studies included patients with mild-to-moderate seasonal allergic asthma, six studies had no coexistent asthma and in 18 studies the status of asthma was not specified;
- The types of vaccines used were extracts (38 studies), allergoids (12 studies) and nonspecified (one study);
- The duration of maintenance treatment and the period of follow-up varied considerably between studies, largely reflecting preseasonal, coseasonal and postseasonal administration;
- The duration of immunotherapy varied from 3 days (minimum duration) to 3 years (maximum duration). Six studies did not mention the duration of treatment;
- It was not possible from most of the studies to determine accurately the dose of allergen given in terms of micrograms of major allergen. Doses given were quantified in many different proprietary units including BU, PNU, SQ-U, mg Ag, SE-U, AUeq, SU/ml, TU, wt/vol and HEP.

Meta-analyses were performed for the symptom and medication scores (TABLE 1):

- Symptom score (data from 15 trials): there was an overall reduction in the immunotherapy group with a SMD of -0.73 (95% CI: -0.97 to -0.50); $I^2 = 63\%$ (moderate heterogeneity);
- Medication score (data from 13 trials): there was an overall reduction in the immunotherapy

group with a SMD of -0.57 (95% CI: -0.82 to -0.33); $I^2 = 64\%$ (moderate heterogeneity).

■ Asthma

The clinical efficacy of SCIT in allergic asthma has been evaluated by Abramson and colleagues in three systematic reviews and meta-analyses, all of them are the consecutive updates.

The first review was a systematic review and meta-analysis of 20 trials in asthma published between 1954 and 1990 [19]. Subsequently, this systematic review was updated as a Cochrane meta-analysis to include 75 trials published between 1954 and 2001 [20]. The following are the characteristics of the studies included in the last systematic review [21]:

- Eighty-one RCTs published between 1950 and 2005 were included;
- A total of 3792 patients (3459 with asthma) were involved;
- The allergens used were house mite (42 trials; *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*), pollen (27 trials; bermuda grass, orchard grass/cockfoot, timothy grass, velvet grass, sweet vernal grass, perennial rye grass, birch, olive or ragweed pollen), animal dander (ten trials; cat and dog), *Cladosporium* mold (two trials), latex (two trials) and multiple allergens (six trials);
- The types of vaccines used were natural extracts and allergoids.

The results of these meta-analyses on the effect of SCIT on asthma showed that (TABLES 2–5):

- There was a significant reduction in asthma symptoms and medication and improvement in bronchial hyper-reactivity following immunotherapy;
- There was a significant improvement in asthma symptom scores (SMD: -0.59; 95% CI: -0.83 to -0.35);
- It would have been necessary to treat three (95% CI: 3–5) patients with immunotherapy to avoid one deterioration in asthma symptoms;
- It would have been necessary to treat four (95% CI: 3–6) patients with immunotherapy to avoid one requiring increased medication;
- Allergen immunotherapy significantly reduced allergen-specific bronchial hyper-reactivity, with some reduction in nonspecific bronchial hyper-reactivity as well;

- There was, however, no consistent effect on lung function. The investigators stated that the benefits of allergen immunotherapy could be overestimated because of unpublished negative studies, and suggested that additional studies would be necessary to overturn these results.

It was concluded that allergen immunotherapy is a treatment option in highly selected patients with extrinsic ('allergic') asthma.

Ross *et al.* also evaluated the effect of SCIT in asthmatics from 24 prospective trials published between 1966 and 1998 [22]. A random-effects model was used. The SCIT group showed an improvement compared with the placebo group for symptoms of asthma (OR: 2.76; 95% CI: 2.22–3.42), pulmonary function (OR: 2.87; 95% CI: 1.82–4.52), protection against bronchial challenge (OR: 1.81; 95% CI: 1.32–2.49) and reduced need for medications (OR: 2.00; 95% CI: 1.46–2.72).

■ Venom immunotherapy

Systemic reactions (SRs) to Hymenoptera stings, both flying and imported fire ants, especially when associated with respiratory symptoms, cardiovascular symptoms, or both, and positive skin test or *in vitro* test results for specific IgE, are an indication for allergen immunotherapy [23]. In the USA, patients aged older than 16 years with a SR limited to the skin are also candidates for allergen immunotherapy. Patients 16 years or younger who present with only a cutaneous reaction to Hymenoptera stings might not require immunotherapy.

Ross *et al.* conducted a meta-analysis, published in 2000, in which they compared the effects of SCIT in the treatment of Hymenoptera venom hypersensitivity [24]. Eight studies published between 1966 and 1996 were included (total of 453 patients). The authors found that the symptoms of Hymenoptera venom hypersensitivity

Table 1. Injection allergen immunotherapy for seasonal allergic rhinitis: summary of outcomes.

Outcome parameter	Number of studies	Participants (active/placebo)	SMD (95% CI)
Nasal symptoms	9	396/276	-1.28 (-2.03 to -0.54)
Bronchial symptoms	5	266/163	-0.59 (-1.06 to -0.11)
Ocular symptoms	3	226/119	-1.80 (-3.28 to -0.31)
RQLQ	5	332/239	-0.52 (-0.69 to -0.34)

RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; SMD: Standardized mean difference. Adapted with permission from [18].

were prevented in 79% of the 101 patients receiving SCIT versus 36% of the 136 comparison patients (OR: 2.20; 95% CI: 1.72–2.81).

Safety of SCIT

Systematic reviews have shown that SCIT is a safe therapeutic intervention when it is prescribed to well-selected patients, and given in a specialist clinic with adequate facilities and by trained medical personnel.

SCIT is associated with a risk of systemic side effects and anaphylaxis. SCIT can produce both local and systemic adverse reactions; however, in the majority of cases these symptoms are readily reversible if recognized early and with prompt treatment. The risk is greater in subjects with asthma [25,26] and with accelerated dosing schedules.

Adverse effects may occur with all allergen preparations whether using standardized extracts, allergoids or recombinant allergens [13].

The safety of SCIT was evaluated in a Cochrane systematic review of 51 RCTs for seasonal AR [18]. Following the European Academy of Allergy and Clinical Immunology Systemic Reactions Grading System [27], the authors found that:

- A total of 22% of SCIT versus 8% of placebo recipients had mild (grade 2) reactions;

Table 2. Injection allergen immunotherapy for asthma: asthma symptoms and medication scores by allergen.

Allergen	Asthma symptoms scores		Asthma medication scores	
	Studies (participants)	SMD (95% CI)	Studies (participants)	SMD (95% CI)
Mite	12 (408)	-0.48 (-0.96 to 0.0)	12 (424)	-0.61 (-1.04 to -0.18)
Pollen	18 (663)	-0.61 (-0.87 to -0.35)	8 (324)	-0.52 (-0.9 to -0.13)
Others	5 (213)	-0.83 (-1.92 to -0.26)	1 (121)	-0.26 (-0.62 to 0.10)
Total	34 (1284)	-0.59 (-0.83 to -0.35)	20 (869)	-0.53 (-0.80 to -0.27)

SMD: Standardized mean difference. Adapted with permission from [21].

Table 3. Injection allergen immunotherapy for asthma: summary of allergen-specific bronchial hyper-reactivity indices.

Allergen-specific BHR index	Studies (participants)	SMD (95% CI)
Log PD ₂₀ mite	6 (148)	-0.98 (-1.39 to -0.58)
Log PD ₂₀ pollen	5 (202)	-0.55 (-0.84 to -0.27)
Log PD ₂₀ animal dander	6 (153)	-0.61 (-0.95 to -0.27)
Log PD ₂₀ /PC ₁₀₀ other allergens	2 (61)	-0.18 (-0.70 to 0.33)
Total	19 (564)	-0.61 (-0.79 to -0.43)

BHR: Bronchial hyper-reactivity; PC₁₀₀: Concentration required to produce a 100% increase in lung resistance; PD₂₀: Provocative dose required to produce a 20% fall in forced expiratory volume in 1 s; SMD: Standardized mean difference.
Adapted with permission from [21].

- A total of 7% of SCIT versus 1% of placebo recipients had moderate-to-severe (grade 3) reactions;
- Anaphylaxis (grade 4) was reported in only three cases in the SCIT group (0.72%) versus one case in the placebo group (0.33%);
- Adrenaline was used in 3.4% of participants (19/557 patients; 0.13% of 14,085 injections) in the SCIT group versus 0.25% (1/404 patients; 0.01% of 8278 injections) in the placebo group;
- This review suggests that adverse reactions serious enough to require treatment with adrenaline (epinephrine) occur approximately once in every 770 immunotherapy injections;
- There were no fatalities associated with SCIT for seasonal AR.

Pretreatment with oral H₁-antihistamines during the induction and maintenance phases seems to reduce the frequency and severity of systemic side effects [28].

Recently, a universal terminology and grading system for SCIT-related adverse events has been published and should be implemented when reporting adverse reactions due to SCIT [29].

Table 4. Injection allergen immunotherapy for asthma: summary of allergen-nonspecific bronchial hyper-reactivity indices.

Nonspecific BHR index	Studies (participants)	SMD (95% CI)
Log PD ₂₀ methacholine	12 (453)	Not evaluable
Log PC ₂₀ histamine	4 (76)	-0.55 (-1.37 to 0.28)
Log PC ₃₅ acetylcholine	1 (21)	-1.29 (-2.28 to -0.31)
ΔFEV ₁ % cold air	1 (26)	-0.52 (-1.31 to 0.26)
Total	18 (576)	-0.35 (-0.59 to -0.11)

BHR: Bronchial hyper-reactivity; FEV₁: Forced expiratory volume in 1 s; PC₂₀: Concentration required to induce a 20% fall in forced expiratory volume in 1 s; PC₃₅: Concentration required to produce a 35% decrease in specific airway conductance; PD₂₀: Provocative dose required to produce a 20% fall in forced expiratory volume in 1 s; SMD: Standardized mean difference.
Adapted with permission from [21].

In a 3-year collaborative American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Immunotherapy Safety Surveillance study, there were no fatalities reported in the approximately 8.1 million injections administered by 1922 SCIT prescribers in the period from June 2008 until July 2009 [30]. A total of 82% of 806 practices reported a total of 8502 SCIT SRs (SR rate: 10.2 SRs per 10,000 [0.1%] injection visits) [30]. Most of these SRs were categorized as grade 1 (74%) or grade 2 (23%) SRs and occurred within 30 min. However, 3% of the reported SRs were grade 3, which was defined as “severe, life-threatening anaphylaxis: severe airway compromise due to severe bronchospasm or upper airway obstruction with stridor or hypotension.” This would translate into three severe SRs per 100,000 injection visits. A total of 14% of the SRs were delayed in onset (>30 min after the injection) [31]. Most delayed-onset SRs were grade 1 but 3% were grade 3 reactions.

Other indications for SCIT

SCIT is currently indicated for patients with symptoms of AR, rhinoconjunctivitis and/or asthma after natural exposure to allergens who demonstrate specific IgE antibodies to relevant aeroallergens, and patients who have experienced SRs to Hymenoptera and/or imported fire ant stings [23,32]. Factors to consider in the decision to prescribe allergen immunotherapy include the severity and duration of symptoms, response to pharmacotherapy, quality of life and responsiveness to other forms of therapy (e.g., allergen avoidance or medication) and indirect effects of the allergic disease, such as lost time from work or school (see Box 3 for SCIT indications). Although relative contraindications for SCIT may vary according to different guidelines (e.g., pregnancy and β-blockers), virtually all agree that SCIT should be avoided in patients with medical conditions that would reduce their ability to survive a SCIT systemic allergic reaction and/or the resultant treatment.

■ SCIT for large local venom reaction: potential indication

Although large local insect sting reactions have not been shown to be predictors of future SR, they may cause significant morbidity and impairment of quality of life, particularly in individuals who may experience frequent stings due to their occupation (e.g., beekeeper or landscaper) or avocation (e.g., gardener). One 4-year controlled pilot study suggested that venom immunotherapy (VIT)

may significantly reduce the size and duration of large local reactions [33]. In the 29 patients with a history of large local sting reactions (≥ 16 cm) confirmed on sting challenge who received VIT, there was a 42% reduction in the size and a 53% reduction in the duration of the large local sting reactions after 7–11 weeks of VIT compared with an 18% reduction in both size and duration in the untreated control group ($p < 0.01$ for both) [33]. Further studies are needed to establish the safety and efficacy of VIT for large local reactions, but recent practice guidelines suggest it may be “considered in patients who have frequent and disabling large local reactions, particularly those with occupational exposure” (e.g., beekeepers) [32]. Further study would also be needed to evaluate the cost–efficacy and most appropriate patients for VIT directed at treating large local reactions.

■ SCIT for atopic dermatitis: potential indication

There are some data indicating that SCIT may be effective for atopic dermatitis when this condition is associated with aeroallergen sensitivity [34–37]. In one systematic review of immunotherapy for atopic dermatitis, SCIT was associated with a statistically significant improvement in dermatitis symptoms in the four comparable placebo-controlled studies [36]. One randomized, double-blind, dose–response study demonstrated a dose-dependent response in atopic dermatitis severity, as measured by the Scoring Atopic Dermatitis (SCORAD) score ($p = 0.0378$) and topical corticosteroid use ($p = 0.0007$) [34]. In addition, one open-label study demonstrated serological and immunological changes consistent with tolerance, as well as significant reductions in objective and subjective SCORAD scores in dust mite allergic patients with atopic dermatitis [37].

■ SCIT for food hypersensitivity & oral allergy syndrome

In addition to the above indications, SCIT has been investigated in several other clinical conditions, including food allergy. SCIT provided some clinical tolerance against peanut anaphylaxis with an aqueous peanut extract but was associated with an unacceptable rate of systemic allergic reactions, such that the investigators recommended discontinuation of clinical trials until a modified extract was available [38]. At present, investigations with SCIT for food hypersensitivity have largely been abandoned. However, studies with alternative immunotherapy routes have

Table 5. Injection allergen immunotherapy for asthma: summary of lung function parameters.

Lung function parameter	Studies (participants)	SMD (95% CI)
Peak expiratory flow	11 (524)	0.14 (–0.33–0.61)
FEV ₁	7 (199)	–0.32 (–0.96–0.31)
Thoracic gas volume	2 (81)	Not evaluable

FEV₁: Forced expiratory volume in 1 s; SMD: Standardized mean difference.
Adapted with permission from [21].

demonstrated potential efficacy in the treatment of IgE-mediated food reactions. Increased tolerance on food challenge was demonstrated with hazelnut [39] and milk [40] sublingual immunotherapy (SLIT) and with peanut [41], egg [42,43] and milk [44] oral immunotherapy. In peanut-sensitized mice, epicutaneous immunotherapy was found to be as effective as SCIT in inducing favorable immunological and physiological responses compared with sham-treated mice [45].

Clinical trials examining the benefits of SCIT for oral allergy syndrome utilizing the cross-reacting pollen(s) have produced conflicting results. One controlled prospective study demonstrated that birch pollen SCIT was effective in decreasing oral allergy symptoms related to apple or hazelnut birch tree [46]. Another double-blind, double-dummy, placebo-controlled study demonstrated no significant effect on the severity of apple allergy symptoms with either birch pollen SCIT or SLIT compared with the placebo group, despite a significant effect of both SIT routes on seasonal hay fever symptoms and medication use as well as a decrease in IgE reactivity [47]. More investigation is required to determine whether SCIT is effective in the treatment of oral allergy symptoms related to cross-reacting pollens.

■ SCIT for indications with limited or no supporting evidence for efficacy and/or safety: latex, urticaria & angioedema

Clinical trials with SCIT for latex-induced respiratory disease have produced conflicting results in terms of clinical efficacy [48–50]. Moreover, latex SCIT was associated with frequent and severe SRs, including hypotension, compared with placebo treatment [48,50]. At the present, much of the focus of latex immunotherapy has been on the sublingual route, for which there appears to be a more favorable efficacy–safety profile [51].

There is no allergic basis for the majority of chronic urticaria and angioedema patients or clinical trial evidence to support treatment of these conditions with any route of SIT [32].

Box 3. Clinical indications for allergen immunotherapy.**Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis or asthma**

Allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy may depend on a number of factors, including but not limited to:

- Patient preference/acceptability
- Adherence
- Medication requirements
- Response to avoidance measures
- Adverse effects of medications
- Coexisting allergic rhinitis and asthma
- Possible prevention of asthma in patients with allergic rhinitis
- Potential indication: atopic dermatitis if associated with aeroallergen sensitivity

Indications for allergen immunotherapy in patients with reactions to Hymenoptera stings

- Patients with a history of a systemic reaction to a Hymenoptera sting (especially if such a reaction is associated with respiratory symptoms, cardiovascular symptoms or both) and demonstrable evidence of clinically relevant specific IgE antibodies
- Patients older than 16 years with a history of a systemic reaction limited to the skin and demonstrable evidence of clinically relevant specific IgE antibodies (patients ≤ 16 years of age who present with a history of only cutaneous reactions to Hymenoptera stings usually do not require immunotherapy)
- Adults and children with a history of a systemic reaction to imported fire ant stings and demonstrable evidence of clinically relevant specific IgE antibodies
- Potential indication: for large local reactions in patients who have frequent and disabling large local reactions

Adapted with permission from [32].

Therefore, chronic urticaria and/or angioedema are not considered indications for SIT.

Persistent effect of SCIT

At present, there are no specific tests or clinical markers that can distinguish which patients will remain in long-term clinical remission after discontinuing effective SIT [52], but there is a growing body of evidence supporting its persistent efficacy. In contrast to pharmacotherapy, which appears to provide benefits only during treatment [53], the clinical benefits associated with SIT may persist long after treatment cessation [54–57].

The duration of SCIT efficacy has been most extensively studied in venom hypersensitivity with long-term follow-up studies suggesting that a 5-year VIT treatment course may be sufficient for most allergic individuals [58–60]. Although relapse rates as high as 15% of patients in the 10-year period after discontinuing VIT have been reported [59,60], these post-VIT SRs were generally much milder than the pretreatment reactions and rarely severe.

In a double-blind, placebo-controlled study of patients with severe grass pollen AR who received 3–4 years of SCIT, followed by 3 years of continued SCIT or placebo, there was no significant

difference in medication and symptom scores between the group that continued and the group that discontinued SIT [54]. There was a tendency for immediate skin test sensitivity to allergen to return, but there was a sustained reduction in the allergen late-phase skin response and associated immunological responses.

A prospective, controlled, follow-up study of children with AR $\pm$ asthma treated with 3 years of preseasonal grass SCIT or pharmacotherapy alone evaluated symptoms, medication use and objective parameters 6 and 12 years after treatment discontinuation [55,56]. Compared with the pharmacotherapy-alone group, the SCIT-treated patients had significantly lower medication use and symptoms during grass pollen season at both time points. Similar to the previously discussed study, skin prick test reactivity returned to the majority of the control group at 12 years after treatment cessation. The percentage of new allergy sensitizations, however, continued to be significantly smaller in patients with previous SIT (58%) compared with the controls (100%; $p < 0.05$) and there was a tendency for a lower prevalence of seasonal asthma in the post-SIT group ($p = 0.08$).

A controlled prospective study followed 40 asthmatic patients, who received 12–96 months

of dust mite SCIT, for signs of relapse after discontinuation of treatment [61]. Relapse was defined as signs of asthma and/or rhinitis or impaired pulmonary function tests. Within 3 years of discontinuing SCIT, 55% of the patients were considered to have relapsed. A significantly higher relapse rate was seen among those who received SCIT for less than 35 months compared with those who received treatment for longer than 36 months (relapse in 62% of the <35-month treatment group vs 48% of >36-month treatment group; $p < 0.04$).

A study designed to assess the duration of efficacy of a 3-year course of SCIT on cat- or dog-induced asthma found that, although there was a significant increase in allergen-induced bronchial sensitivity (i.e., an objective SCIT outcome), almost all patients felt that they had improved cat tolerance with natural exposure compared with prior to their SCIT treatment (i.e., a subjective SCIT outcome) [62].

In general, the few studies specifically designed to evaluate the duration of SCIT efficacy for aeroallergen sensitivity have demonstrated long term clinical efficacy despite the apparent return of immediate hypersensitivity. Recently, a large clinical trial involving 257 patients demonstrated that the clinical and immunological changes associated with SLIT persist at least 2 years after treatment discontinuation [63].

Preventive effect of SCIT on asthma development & new allergen sensitizations

SIT's unique disease-modifying effect may translate into reduced direct and indirect costs associated with AR and asthma. These savings may be a result of reduced current and long-term medication requirements and healthcare utilization as well as reduced progression of the allergic disease. This progression is often called the 'atopic march', which refers to the progression of AR to asthma and/or the development of new allergen sensitizations. AR is an identified risk factor for the development of asthma, with up to 40% of individuals with AR developing asthma later in life [64–67].

The preventive benefit of SIT on asthma development was suggested as early as 1968 in a 14-year study that investigated the dose–response relationship of SCIT in asthmatic children randomized to receive either one of three doses of an allergen mixture or placebo [68]. At the age of 16 years, a dose-dependent difference in terms of being 'free of asthma' was demonstrated with the lowest incidence being in

the group receiving the highest dose. There was essentially no difference between the lowest-dose and placebo groups.

One prospective, randomized, controlled, open-label study of 147 children, aged 16–25 years, evaluated the effect of a 3-year course of grass and/or birch pollen SCIT on the development of asthma compared with pharmacotherapy alone (referred to as the Preventive Allergy Treatment or PAT study) [69–71]. SCIT was associated with a significantly lower incidence of asthma compared with pharmacotherapy alone at the end of treatment and at 5 and 7 years after discontinuation (OR: 2.5; 95% CI: 1.1–5.9 at 7 years) [69]. The authors concluded that SCIT administered for 3 years results in a long-term preventive effect on the development of asthma.

The asthma-preventive effect of SCIT has also been demonstrated in the adult AR population. A 3-year, double-blind, RCT of 30 nonasthmatic AR adults assigned to receive *Parietaria* SCIT or placebo suggested that SCIT may prevent progression from AR to asthma [72]. At the end of the study, a time-dependent progression of asthmatic symptoms and asthma medication scores was apparent with nine of the 29 participants who completed the 3-year study developing asthma symptoms; of these, seven (47%) belonged to the placebo group whereas only two (14%) belonged to the SCIT-treated group ($p = 0.056$). In a subsequent 10-year retrospective study of 1104 nonasthmatic adults designed to investigate the natural history of AR and the potential effect of SCIT in reducing the incidence of asthma, the same authors found that the lowest risk factor for development of asthma was treatment with SCIT (OR: 0.53; 95% CI: 0.32–0.86) [73]. AR at baseline was the highest risk factor associated with an asthma diagnosis at the end of follow-up (OR: 7.8; 95% CI: 3.1–20.00) [73].

A similar preventive effect was seen in a 3-year open-label study of 113 children, aged 5–14 years, with grass pollen rhinitis, who were randomized to receive coseasonal SIT for 3 years or standard symptomatic therapy [74]. There was a significantly higher incidence of new-onset asthma in the control group compared with the group who received SLIT. After 3 years, the frequency of asthma was 3.8-times greater for control subjects than for those receiving SIT (95% CI: 1.5–10.0).

In addition to preventing progression to asthma, several randomized, controlled and open-label studies have demonstrated that

SCIT [56,75–77] may reduce the development of new allergen sensitizations. Three studies demonstrated a significantly lower incidence of new allergen sensitizations in monosensitized patients who received SCIT compared with matched controls who did not receive SCIT. New allergies developed in 23, 24 and 54% of those who received SCIT compared with 68, 67 and 100% of those who did not, respectively [75–77]. Similar results were found in a 3-year open-label study of 511 patients with AR ± asthma randomized to either SLIT or pharmacological treatment [78]. New allergen sensitizations developed in 38% of the control patients and in 5.9% of the SIT patients ($p = 0.01$).

Cost-effectiveness of SCIT compared with pharmacotherapy alone

Allergic conditions represent some of most common, chronic and costly diseases seen in westernized societies. In the USA, more than 50 million US residents are affected by an allergic disease. It is estimated that the cost of allergic disease to the US healthcare system is in excess of US\$18 billion annually [79]. The majority of these costs are attributable to asthma and AR.

Asthma is the leading chronic illness of children in the USA. With a prevalence of approximately 8%, asthma currently affects over 7 million children and 16 million adults in the USA [203]. Total US direct medical care costs for asthma in 2010 were estimated at \$15.6–18 billion [80,203]. The burden of asthma, in terms of direct medical costs, is substantially borne by the US public healthcare system: Medicaid, a government insurer that provides healthcare coverage for low-income individuals, covered 30% of the US adult asthma population, whereas only 10% of the general population was covered by Medicaid [80].

In 2005, approximately 7.3% of the US population (22 million people) reported experiencing AR-related symptoms, visiting a physician or obtaining a prescription drug to treat AR [204]. Direct medical expenses for AR nearly doubled in the 5-year period from 2000 to 2005, from \$6.1 billion to \$11.2 billion (all in 2005 US dollars and exclusive of costs for over-the-counter medications) [204]. Outpatient visits account for approximately one-third (36%) of AR-related direct costs and prescription medications account for nearly the entire remainder (59%) [81]. Allergen immunotherapy accounts for a small percentage (~2%) of AR-related costs, probably because only a small percentage of allergic patients (~5%) are

prescribed this treatment in Europe and the USA [82]. Inconvenience caused by the necessity for this treatment to be administered in a medical facility is the most likely reason for the low use of SCIT. SCIT's potential to alter the course of allergic disease, thereby reducing the need for long-term treatment in contrast to symptomatic drug treatment, which only temporarily relieves allergy symptoms, suggests that the clinical benefits of SIT may lead to economic benefits. This premise was confirmed in a review of allergen immunotherapy pharmacoeconomics, which found that SCIT was associated with substantial healthcare cost savings [83]. In a prospective 6-year study of 30 adults with *Parietaria* pollen-induced rhinitis and asthma randomly assigned to 3 years of SCIT plus standard drug treatment or standard drug treatment alone, there was a significant progressive reduction in cost associated with SCIT beginning in the third year of treatment [84]. Annual costs were 80% lower in the SCIT group at the end of the study, 3 years after discontinuation of treatment.

Two large-scale, retrospective, US-based studies have examined whether SCIT confers economic benefits among children with AR [85,86]. In the first, researchers conducted a 7-year (1997–2004) retrospective claims analysis of 354 Florida Medicaid-enrolled children with newly diagnosed AR to examine short-term (6-month) pre-SIT versus post-SIT healthcare costs [86]. There were significant reductions in the use of outpatient ($p < 0.001$), pharmacy ($p < 0.001$) and inpatient ($p = 0.02$) services in the 6 months after termination of SCIT compared with the 6 months preceding SCIT initiation. This reduction in healthcare utilization resulted in a 6-month, per-patient, total weighted cost saving of \$401.

In the second study, these investigators examined 10 years (1997–2007) of Florida Medicaid data to compare healthcare costs between children with newly diagnosed AR who subsequently received SIT versus a control group of patients who did not receive SCIT [85]. Patients were matched by age at first AR diagnosis, sex, race/ethnicity and diagnosis of asthma, conjunctivitis and atopic dermatitis. Children with AR who received SCIT had significantly lower 18-month, median, per-patient total healthcare costs (33%; \$3247 vs 4872), outpatient costs (29%; \$1829 vs 2594) and pharmacy costs (16%; \$1108 vs 1316) compared with matched controls ($p < 0.001$ for all). The differences in outpatient, pharmacy

and total healthcare costs were significant ($p < 0.001$) within 3 months of SIT initiation, and increased through to the study end.

A similar retrospective (1997–2008), matched cohort, claims analysis of adults (>18 years) with newly diagnosed AR with and without allergic conjunctivitis demonstrated similar findings in terms of cost savings with SCIT [87]. At 18 months, there were significant cost reductions for inpatient (\$10,352 vs 14,796; $p = 0.003$), outpatient (\$2668 vs 4101; $p < 0.0001$), pharmacy (\$5636 vs 6321; $p < 0.0001$) and total healthcare (\$10,626 vs 17,912; $p < 0.0001$) services in the SCIT-treated patients versus the non-SCIT group. The total healthcare cost savings were realized within 3 months of SCIT initiation and resulted in an 18-month mean per-patient total cost saving of 41% (\$7286 divided by 17,912).

Collectively, these studies provide considerable support for the cost-effectiveness of SIT compared with pharmacotherapy alone during the treatment. This effect is even greater when one considers the persistent clinical benefits of SIT after discontinuation of treatment, an effect not seen with pharmacotherapy [53,88].

Novel approaches for SCIT

Efforts to develop safer and more effective allergen immunotherapy have resulted in several modifications to allergen extracts. These modifications include alteration of the allergen (e.g., peptides and allergoids) and the addition of substances that can enhance the immunogenicity of the allergen extract (e.g., adjuvants).

Allergoids are chemically modified extracts that reduce IgE-binding capacity. The modification is intended to improve safety by reducing the extract's allergenicity while retaining its immunogenicity. T-cell-directed peptide immunotherapy utilizing major T-cell epitopes demonstrated efficacy in terms of reduction of late-phase skin response and safety comparable to placebo with a single vaccination in cat-allergic subjects [89]. In addition to cat allergy, peptides have been used to treat bee venom allergy in small open-label studies that have demonstrated favorable effects in terms of immunological changes, late-phase skin response and live bee stinging challenge response [90].

Adjuvants enhance the effectiveness of allergen immunotherapy primarily by shifting the immune response toward Th1 production via their action on Toll-like receptors. The receptor for CpG DNA, TLR9, can lead to production of IL-10, IgG isotope switching and inhibition

of other immune responses mediated by activated Th2 cells [91]. TOLAMBA™ (Dynavax Technologies, CA, USA) is a CpG adjuvant covalently linked to the major ragweed allergen, Amb a 1. A randomized, double-blind, placebo-controlled Phase II trial of 25 adults with ragweed-induced AR randomized to receive six increasing doses of TOLAMBA or placebo before the ragweed season demonstrated a significant reduction in total nasal symptom scores during the peak season in the TOLAMBA group compared with the placebo-treated patients in both the first and second ragweed season with a comparable safety profile to placebo [92]. However, there was no difference in the primary outcome, which was nasal allergen provocation response. The development of a CpG ragweed vaccine was discontinued by the company, Dynavax, after interim analysis of a subsequent large trial indicated that neither the placebo nor the CpG groups developed symptoms during the ragweed season, making it impossible to assess the therapeutic efficacy of the CpG vaccine [205].

Another adjuvant used in allergen immunotherapy is monophosphoryl lipid A (MPL), a TLR4 agonist derived from the lipopolysaccharide of *Salmonella minnesota* that induces Th1 cytokines in human and animal studies. In addition to allergen immunotherapy, it has been used for many years in licensed vaccines: Melacine® (Corixa/Schering Canada, WA, USA) and the human papillomavirus, Ceravarix® (GlaxoSmithKline, Brentford, UK) [93]. MPL is used in an allergen vaccine product composed of a tyrosine-absorbed (delays absorption), glutaraldehyde-modified allergoid (Pollinex® Quattro or MATA MPL, Allergy Therapeutics Ltd, Worthing, UK), which is administered as four injections given at 1–2-week intervals ending 2–4 weeks before the start of season. In a double-blind placebo-controlled trial of 1028 subjects with grass pollen-induced AR, who were randomized to receive Grass MATA MPL ($n = 514$; 300–2000 standardized units/injection) or placebo ($n = 514$) before the grass pollen season, Grass MATA MPL treatment afforded a 13.4% benefit over placebo in the 4 peak pollen weeks ($p = 0.0038$) [94]. “More significant benefits over placebo were observed in subjects with severe symptoms (17.1%; $p = 0.0023$), in those who had a history of allergic rhinoconjunctivitis for up to 35 years (up to 37.2%; $p = 0.0059$) and at sites with a higher burden of disease (38.3%; $p < 0.0001$)” [94].

Other novel immunotherapy approaches have shown promise for injection therapy utilizing currently available allergen extracts. A study that compared the combination of SCIT in the build-up phase followed by SLIT in the maintenance phase with SCIT or SLIT alone found similar improvement in asthma attacks and inhaled corticosteroid use in the two SCIT groups but significant improvement in rhinitis scores only in the SCIT plus SLIT group [95]. An open-label study compared the efficacy of 3 years of conventional SCIT with three low-dose intralymphatic injections administered over 2 months [96]. At 3 years, there was no difference between the groups in terms of clinical efficacy, despite the intralymphatic group having received only 8 weeks of treatment.

These investigations suggest that, in the future, SCIT may involve short courses with

modified extracts or be used in combination with or replaced by other SIT routes deemed more effective, convenient and/or safe.

Conclusion

Subcutaneous allergen immunotherapy has been shown in numerous clinical trials, systematic reviews and meta-analyses to be effective in reducing the clinical symptoms associated with asthma, AR/rhinoconjunctivitis and venom hypersensitivity. There is emerging evidence that it may be effective in other allergic conditions such as atopic dermatitis and venom sting large local reactions. Its benefits may persist long after treatment discontinuation and include prevention of allergic disease progression. Overall, if administered in an appropriate setting, SCIT is safe and well tolerated. However, systemic allergic reactions may occur and these have

Executive summary

Assessment of immunotherapy outcomes

- The most accepted primary outcome is evaluation of improvement in symptoms and medication use or a combined symptom–medication score.
- No validated method for assessing symptoms or medication but 4-point rating scale (3 = most severe) widely accepted for symptoms; Rhinoconjunctivitis Total Symptom Score (range 0–18).
- Recognizing the interdependence between allergic symptom and use of antiallergy medication, guidelines recommend evaluating both outcomes separately but calculating a combined score (i.e., weighted sum of symptoms and medication scores).
- Secondary outcomes include Quality of Life questionnaires, allergen provocation tests and immunological parameters such as specific IgG and IgE.

Systematic reviews & meta-analyses

- Efficacy: systematic reviews and meta-analyses are instruments for synthesizing clinical trial data to determine if there is a beneficial effect of a treatment over placebo:
 - Allergic rhinitis: significant reductions in symptoms scores (standardized mean difference: -0.73) and medication scores (standardized mean difference: -0.57);
 - Asthma: significant reductions in symptoms scores (standardized mean difference: -0.59), numbers needed to treat to prevent deterioration in asthma symptoms and increased medication use; 3 and 4, respectively. No consistent effect on pulmonary function;
 - Venom hypersensitivity: symptoms prevented in 79% of patients receiving venom immunotherapy versus 36% of those who did not.
- Safety:
 - Mild systemic reaction: 22% of subcutaneous immunotherapy (SCIT) versus 8% of placebo;
 - Moderate to severe: 7% of SCIT versus 1% of placebo;
 - Adverse reaction severe enough to require epinephrine occurred in one in 770 injections.

Potential indications for SCIT in addition to allergic rhinitis, asthma & Hymenoptera sensitivity

- Frequent and disabling large local venom insect sting reactions and atopic dermatitis.
- Conflicting evidence on efficacy in oral allergy syndrome.
- SCIT therapeutic safety index for food allergy not favorable with currently available unmodified extracts.

Preventive & persistent effect of SCIT

- Prevention of progression from allergic rhinitis to asthma has been demonstrated in some open-label and randomized controlled trials.
- Prevention of the development of new allergen sensitivities has been demonstrated in monosensitized individuals.

Cost-effectiveness of SCIT

- Studies comparing the healthcare costs between patients treated with SCIT and pharmacotherapy alone have demonstrated that SCIT may be associated with significant cost savings (as high as 80%).

Novel SCIT formulation

- Novel approaches to SCIT such as T-cell-directed peptide fragments or adjuvants conjugated to modified vaccines may offer shorter, more effective and safer treatment, which in turn may increase the number of allergic individuals subscribing to this treatment.

the potential to be life threatening. Studies suggest the incidence of SCIT SRs is approximately 0.1% of injections, with most being of a grade 1 severity. The financial burden of allergic disease to both society and patients is considerable. Studies comparing healthcare costs between SCIT and pharmacotherapy alone have demonstrated that SCIT may be associated with significant cost savings (as high as 80%). Only a small percentage of allergic patients subscribe to SCIT, probably due to the inconvenience and time involved in receiving this treatment in a medical facility. Investigations aimed at developing safer and more effective SCIT therapies have demonstrated promising results, which indicate that, in the near future, a single or ultrashort course SCIT vaccine may provide a 'cure' or long-term remission for allergic disease.

Future perspective

In the next 5–10 years it is likely that SCIT will involve more modified formulations, such as peptide fragments or modified extracts in conjunction with immune-stimulatory adjuvants. In addition to improved efficacy and safety, these modified extracts/vaccines may allow for shorter courses of treatment (e.g., four to six injections). The short-course treatments may

be more 'attractive' to patients who find it difficult to adhere to a 3–5-year SCIT regimen that requires regular office visits or to those who dislike taking daily sublingual tablets or solution. This may result in a much larger percentage of allergic patients subscribing to allergen immunotherapy than the small percentage that currently receives it (~5% of the allergic population) [82].

Financial & competing interests disclosure

M Calderón has received consulting fees, honoraria for lectures and/or research funding from ALK-Abelló and Stallergenes. L Cox has received consulting fees, honoraria for lectures and/or research funding from Stallergenes, Teva, Baxter and Thomas-Fisher. O Pfaar has received research grants from ALK-Abelló, Denmark; Allergopharma, Germany; Stallergenes, France; HAL and ArtuBiologicals, The Netherlands; Allergy-Therapeutics/Bencard, UK/Germany; Hartington, Spain; Lofarma, Italy; Novartis/Leti, Germany/Spain, and Roxall, Germany. He has also served as advisor to and on the speakers' bureaus for some of the aforementioned pharmaceutical companies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
■ of considerable interest

- Freeman J. Further observations of the treatment of hay fever by hypodermic inoculations of pollen vaccine. *Lancet* 2, 814–817 (1911).
- Freeman J. Vaccination against hay fever: report of results during the last three years. *Lancet* 183(4730), 1178–1180 (1914).
- Noon L. Prophylactic inoculation against hay fever. *Lancet* 1, 1572–1573 (1911).
- Ancestors of Allergy*. Simons FER (Ed.). Global Medical Communications Ltd, New York, USA (1994).
- Jacobsen L. Primary and secondary endpoints in clinical trials. *Arb. Paul Ehrlich Inst. Bundesamt Sera Impfstoffe Frankf. AM* 96, 96–104; discussion 104–105 (2009).
- Pfaar O, Kleine-Tebbe J, Hörmann K, Klimek L. Allergen-specific immunotherapy: which outcome measures are useful in monitoring clinical trials? *Immunol. Allergy Clin. North Am.* 31(2), 289–309 (2011).
- **Comprehensive review of allergen immunotherapy outcomes.**
- Canonica GW, Baena-Cagnani CE, 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* 62(3), 317–324 (2007).
- Pfaar O, Anders C, Klimek L. Clinical outcome measures of specific immunotherapy. *Curr. Opin Allergy Clin. Immunol.* 9(3), 208–213 (2009).
- Clark J, Schall R. Assessment of combined symptom and medication scores for rhinoconjunctivitis immunotherapy clinical trials. *Allergy* 62(9), 1023–1028 (2007).
- Grouin JM, Vicaut E, Jean-Alphonse S *et al.* The average Adjusted Symptom Score, a new primary efficacy end-point for specific allergen immunotherapy trials. *Clin. Exp. Allergy* 41(9), 1282–1288 (2011).
- Häfner D, Reich K, Matricardi PM, Meyer H, Kettner J, Narkus A. Prospective validation of 'Allergy-Control-SCORE(TM)': a novel symptom–medication score for clinical trials. *Allergy* 66(5), 629–636 (2011).
- Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin. Exp. Allergy* 21(1), 77–83 (1991).
- Calderón MA, Casale TB, Togias A, Bousquet J, Durham SR, Demoly P. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. *J. Allergy Clin. Immunol.* 127(1), 30–38 (2011).
- Calderón MA, Boyle RJ, Penagos M, Sheikh A. Immunotherapy: the meta-analyses. What have we learned? *Immunol. Allergy Clin. North Am.* 31(2), 159–173, vii (2011).
- Cox L. Allergen immunotherapy and asthma: efficacy, safety, and other considerations. *Allergy Asthma Proc.* 29(6), 580–589 (2008).
- Klimek L, Malling HJ. Specific immunotherapy (hyposensitization) in allergic rhinoconjunctivitis. Meta-analysis of effectiveness and side effects. *HNO* 47(7), 602–610 (1999).
- Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: an analysis of randomized, prospective, single- or double-blind, placebo-controlled studies. *Clin. Ther.* 22(3), 342–350 (2000).
- Calderón MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst. Rev.* 1, CD001936 (2007).

- **Cochrane meta-analysis on subcutaneous immunotherapy (SCIT) for allergic rhinitis.**
- 19 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.* 151(4), 969–974 (1995).
- 20 Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst. Rev.* 4, CD001186 (2003).
- 21 Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst. Rev.* 8, CD001186 (2010).
- **Most recent Cochrane meta-analysis on SCIT for asthma.**
- 22 Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. *Clin. Ther.* 22(3), 329–341 (2000).
- 23 Golden DB, Moffitt J, Nicklas RA *et al.* Stinging insect hypersensitivity: a practice parameter update 2011. *J. Allergy Clin. Immunol.* 127(4), 852–854.e23 (2011).
- 24 Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of Hymenoptera venom hypersensitivity: a meta-analysis. *Clin. Ther.* 22(3), 351–358 (2000).
- 25 Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J. Allergy Clin. Immunol.* 102(4 Pt 1), 558–562 (1998).
- 26 Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J. Allergy Clin. Immunol.* 79(4), 660–677 (1987).
- 27 Position paper: immunotherapy. (EAACI) The European Academy of Allergology and Clinical Immunology. *Allergy* 48(14 Suppl.), 7–35 (1993).
- 28 Nielsen L, Johnsen CR, Mosbech H, Poulsen LK, Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *J. Allergy Clin. Immunol.* 97(6), 1207–1213 (1996).
- 29 Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J. Allergy Clin. Immunol.* 125(3), 569–574.e7 (2010).
- 30 Bernstein DI, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. *Ann. Allergy Asthma Immunol.* 104(6), 530–535 (2010).
- **First-year SCIT safety surveillance study data on US prescribers (~8 million injections per year).**
- 31 Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Immediate and delayed-onset systemic reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy – year 2. *Ann. Allergy Asthma Immunol.* 107(5), 426–431.e1 (2011).
- **Second-year SCIT safety surveillance study data on US prescribers (~8 million injections per year).**
- 32 Cox L, Nelson H, Lockey R *et al.* Allergen immunotherapy: a practice parameter third update. *J. Allergy Clin. Immunol.* 127(1 Suppl.), S1–S55 (2011).
- **Most recent US practice parameter on SCIT.**
- 33 Golden DB, Kelly D, Hamilton RG, Craig TJ. Venom immunotherapy reduces large local reactions to insect stings. *J. Allergy Clin. Immunol.* 123(6), 1371–1375 (2009).
- **Pilot study looking at the effect of venom immunotherapy on large local reactions.**
- 34 Werfel T, Breuer K, Rueff F *et al.* Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. *Allergy* 61(2), 202–205 (2006).
- 35 Glover MT, Atherton DJ. A double-blind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema. *Clin. Exp. Allergy* 22(4), 440–446 (1992).
- 36 Bussmann C, Böckenhoff A, Henke H, Werfel T, Novak N. Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis? *J. Allergy Clin. Immunol.* 118(6), 1292–1298 (2006).
- 37 Bussmann C, Maintz L, Hart J *et al.* Clinical improvement and immunological changes in atopic dermatitis patients undergoing subcutaneous immunotherapy with a house dust mite allergoid: a pilot study. *Clin. Exp. Allergy* 37(9), 1277–1285 (2007).
- 38 Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J. Allergy Clin. Immunol.* 99(6 Pt 1), 744–751 (1997).
- 39 Enrique E, Malek T, Pineda F *et al.* Sublingual immunotherapy for hazelnut food allergy: a follow-up study. *Ann. Allergy Asthma Immunol.* 100(3), 283–284 (2008).
- 40 de Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. *Allergy* 61(10), 1238–1239 (2006).
- 41 Jones SM, Pons L, Roberts JL *et al.* Clinical efficacy and immune regulation with peanut oral immunotherapy. *J. Allergy Clin. Immunol.* 124(2), 292–300.e97 (2009).
- 42 Buchanan AD, Green TD, Jones SM *et al.* Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J. Allergy Clin. Immunol.* 119(1), 199–205 (2007).
- 43 Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 62(11), 1261–1269 (2007).
- 44 Narisety SD, Skripak JM, Steele P *et al.* Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. *J. Allergy Clin. Immunol.* 124(3), 610–612 (2009).
- 45 Mondoulet L, Dioszeghy V, Vanoirbeek JA, Nemery B, Dupont C, Benhamou PH. Epicutaneous immunotherapy using a new epicutaneous delivery system in mice. *Int. Arch. Allergy Immunol.* 154(4), 299–309 (2011).
- 46 Bucher X, Pichler WJ, Dahinden CA, Helbling A. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. *Allergy* 59(12), 1272–1276 (2004).
- 47 Hansen KS, Khinchi MS, Skov PS, Bindslev-Jensen C, Poulsen LK, Malling HJ. Food allergy to apple and specific immunotherapy with birch pollen. *Mol. Nutr. Food Res.* 48(6), 441–448 (2004).
- 48 Leynadier F, Herman D, Vervloet D, Andre C. Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. *J. Allergy Clin. Immunol.* 106(3), 585–590 (2000).
- 49 Sastre J, Fernandez-Nieto M, Rico P *et al.* Specific immunotherapy with a standardized latex extract in allergic workers: a double-blind, placebo-controlled study. *J. Allergy Clin. Immunol.* 111(5), 985–994 (2003).
- 50 Tabar AI, Anda M, Bonifazi F *et al.* Specific immunotherapy with standardized latex extract versus placebo in latex-allergic patients. *Int. Arch. Allergy Immunol.* 141(4), 369–376 (2006).
- 51 Bernardini R, Pecora S, Milani M, Burastero SE. Natural rubber latex allergy in children: clinical and immunological effects of 3-years sublingual immunotherapy. *Eur. Ann. Allergy Clin. Immunol.* 40(4), 142–147 (2008).

- 52 Cox L, Cohn JR. Duration of allergen immunotherapy in respiratory allergy: when is enough, enough? *Ann. Allergy Asthma Immunol.* 98(5), 416–426 (2007).
- 53 Guilbert TW, Morgan WJ, Zeiger RS *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N. Engl. J. Med.* 354(19), 1985–1997 (2006).
- 54 Durham SR, Walker SM, Varga EM *et al.* Long-term clinical efficacy of grass-pollen immunotherapy. *N. Engl. J. Med.* 341(7), 468–475 (1999).
- 55 Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy* 61(2), 198–201 (2006).
- 56 Eng PA, Reinhold M, Gnehm HP. Long-term efficacy of preseasonal grass pollen immunotherapy in children. *Allergy* 57(4), 306–312 (2002).
- 57 Jacobsen L. Preventive aspects of immunotherapy: prevention for children at risk of developing asthma. *Ann. Allergy Asthma Immunol.* 87(1 Suppl. 1), 43–46 (2001).
- 58 The discontinuation of Hymenoptera venom immunotherapy. Report from the Committee on Insects. *J. Allergy Clin. Immunol.* 101(5), 573–575 (1998).
- 59 Golden DBK, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. *J. Allergy Clin. Immunol.* 105(2), 385–390 (2000).
- 60 Lerch E, Müller UR. Long-term protection after stopping venom immunotherapy: results of re-stings in 200 patients. *J. Allergy Clin. Immunol.* 101(5), 606–612 (1998).
- 61 Des Roches A, Paradis L, Knani J *et al.* Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of the efficacy of immunotherapy after its cessation. *Allergy* 51(6), 430–433 (1996).
- 62 Hedlin G, Heilborn H, Lilja G *et al.* Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. *J. Allergy Clin. Immunol.* 96(6 Pt 1), 879–885 (1995).
- 63 Durham SR, Emminger W, Kapp A *et al.* Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J. Allergy Clin. Immunol.* 125(1), 131–138.e7 (2010).
- 64 Guerra S, Sherrill DL, Baldacci S *et al.* Rhinitis is an independent risk factor for developing cough apart from colds among adults. *Allergy* 60(3), 343–349 (2005).
- 65 Lombardi C, Passalacqua G, Gargioni S *et al.* The natural history of respiratory allergy: a follow-up study of 99 patients up to 10 years. *Respir. Med.* 95(1), 9–12 (2001).
- 66 Leynaert B, Neukirch C, Kony S *et al.* Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J. Allergy Clin. Immunol.* 113(1), 86–93 (2004).
- 67 Toren K, Olin AC, Hellgren J, Hermansson BA. Rhinitis increase the risk for adult-onset asthma – a Swedish population-based case–control study (MAP-study). *Respir. Med.* 96(8), 635–641 (2002).
- 68 Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children – a 14-year study. *Pediatrics* 42(5), 793–802 (1968).
- 69 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* 62(8), 943–948 (2007).
- ■ Preventive effect of SCIT on asthma.
- 70 Moller 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.* 109(2), 251–256 (2002).
- 71 Niggemann B, Jacobsen L, Dreborg S *et al.* Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy* 61(7), 855–859 (2006).
- 72 Polosa R, Li Gotti F, Mangano G *et al.* Effect of immunotherapy on asthma progression, BHR and sputum eosinophils in allergic rhinitis. *Allergy* 59(11), 1224–1228 (2004).
- 73 Polosa R, Al-Delaimy WK, Russo C, Piccillo G, Sarva M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. *Respir. Res.* 6, 153 (2005).
- 74 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.* 114(4), 851–857 (2004).
- 75 Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J. Allergy Clin. Immunol.* 99(4), 450–453 (1997).
- 76 Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin. Exp. Allergy* 31(9), 1392–1397 (2001).
- ■ Preventive effect of SCIT on development of new allergen sensitization.
- 77 Purello-D'Ambrosio F, Gangemi S, Merendino RA *et al.* Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin. Exp. Allergy* 31(8), 1295–1302 (2001).
- 78 Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: clinical efficacy and more. *Allergy* 59(11), 1205–1210 (2004).
- 79 American Academy of Allergy, Asthma and Immunology (AAAAI). *The Allergy Report: Science Based Findings on the Diagnosis and Treatment of Allergic Disorders, 1996–2001.* American Academy of Allergy, Asthma and Immunology (AAAAI), Milwaukee, WI, USA (2001).
- 80 Sullivan PW, Ghushchyan VH, Slejko JF, Belozeroff V, Globe DR, Lin SL. The burden of adult asthma in the United States: evidence from the Medical Expenditure Panel Survey. *J. Allergy Clin. Immunol.* 127(2), 363–369.e3 (2011).
- 81 Soni A. *Allergic Rhinitis: Trends in Use and Expenditures, 2000 to 2005. Statistical Brief #204.* Agency for Healthcare Research and Quality, Bethesda, MD, USA (2008).
- 82 Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann. Allergy Asthma Immunol.* 103(6), 451–459; quiz 459–461, 495 (2009).
- 83 Lockey RF, Hankin CS. Health economics of allergen-specific immunotherapy in the United States. *J. Allergy Clin. Immunol.* 127(1), 39–43 (2011).
- ■ Good review of health economics of SCIT.
- 84 Ariano R, Berto P, Tracci D, Incorvaia C, Frati F. Pharmacoeconomics of allergen immunotherapy compared with symptomatic drug treatment in patients with allergic rhinitis and asthma. *Allergy Asthma Proc.* 27(2), 159–163 (2006).
- 85 Hankin CS, Cox L, Lang D *et al.* Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. *Ann. Allergy Asthma Immunol.* 104(1), 79–85 (2010).

- 86 Hankin CS, Cox L, Lang D *et al.* Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. *J. Allergy Clin. Immunol.* 121(1), 227–232 (2008).
- 87 Wang Z, Hankin CS, Cox L, Bronstone A. Allergen immunotherapy significantly reduces healthcare costs among U.S. adults with allergic rhinitis: a retrospective matched cohort study jointly funded by the AAAAI and ACAAI. Presented at: *Annual Meeting of the American Academy of Allergy, Asthma, and Immunology*. San Francisco, CA, USA, 18–22 March 2011 (Poster presentation).
- 88 Strunk RC, Sternberg AL, Szeffer SJ, Zeiger RS, Bender B, Tonascia J. Long-term budesonide or nedocromil treatment, once discontinued, does not alter the course of mild to moderate asthma in children and adolescents. *J. Pediatr.* 154(5), 682–687 (2009).
- 89 Worm M, Lee HH, Kleine-Tebbe J *et al.* Development and preliminary clinical evaluation of a peptide immunotherapy vaccine for cat allergy. *J. Allergy Clin. Immunol.* 127(1), 89–97.e14 (2011).
- 90 Larché M. Peptide and recombinant immunotherapy. *Immunol. Allergy Clin. North Am.* 31(2), 377–389, xi (2011).
- 91 Casale TB, Stokes JR. Immunomodulators for allergic respiratory disorders. *J. Allergy Clin. Immunol.* 121(2), 288–296 (2008).
- 92 Creticos PS, Schroeder JT, Hamilton RG *et al.* Immunotherapy with a ragweed-Toll-like receptor 9 agonist vaccine for allergic rhinitis. *N. Engl. J. Med.* 355(14), 1445–1455 (2006).
- 93 Cox LS. How safe are the biologicals in treating asthma and rhinitis? *Allergy Asthma Clin. Immunol.* 5(1), 4 (2009).
- 94 DuBuske LM, Frew AJ, Horak F *et al.* Ultrashort-specific immunotherapy successfully treats seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy Asthma Proc.* 32(3), 239–247 (2011).
- 95 Keles S, Karakoc-Aydiner E, Ozen A *et al.* A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes. *J. Allergy Clin. Immunol.* 128(4), 808–815.e7 (2011).
- 96 Senti G, Prinz Vavricka BM, Erdmann I *et al.* Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. *Proc. Natl Acad. Sci. USA* 105(46), 17908–17912 (2008).
- 97 Freeman J. ‘Rush inoculation’, with special reference to hay fever treatment. *Lancet* 1, 744–747 (1930).
- 98 Norman PS. Immunotherapy: past and present. *J. Allergy Clin. Immunol.* 102, 1–10 (1998).
- 99 Frankland AW, Augustin R. Prophylaxis of summer hay-fever and asthma: a controlled trial comparing crude grass-pollen extract with isolated main protein component. *Lancet* 1, 1055–1057 (1954).
- 100 Johnstone DE. Study of the role of antigen dosage in the treatment of pollenosis and pollen asthma. *J. Dis. Child.* 94(1), 1–5 (1957).
- 101 Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children – a 14-year study. *Pediatrics* 42, 793–802 (1968).
- 102 Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. *N. Engl. J. Med.* 273, 675–679 (1965).
- 103 Ishizaka K, Ishizaka T, Terry WD. Antigenic structure of gamma-E-globulin and reaginic antibody. *J. Immunol.* 99, 849–858 (1967).
- 104 Ishizaka K, Ishizaka T. Identification of gamma-E antibodies as a carrier of reaginic activity. *J. Immunol.* 99, 1187–1199 (1967).
- 105 Ewbank PA, Murray J, Sanders K, Curran-Everett D, Dreskin S, Nelson HS. A double-blind placebo-controlled immunotherapy dose–response study with standardized cat extract. *J. Allergy Clin. Immunol.* 111, 155–161 (2003).
- 106 Nanda A, O’Connor M, Anand M *et al.* Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. *J. Allergy Clin. Immunol.* 114, 1339–1344 (2004).
- 107 Francis J, James L, Paraskevopoulos G *et al.* Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG4 inhibitory antibody activity. *J. Allergy Clin. Immunol.* 121, 1120–1125.e2 (2008).

■ Websites

- 201 Note for Guidance on Statistical Principles for Clinical Trial (CPMP/ICH/363/96). September 1998.
www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf
- 202 Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases (CHMP/EWP/18504/2006). November 2008.
www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf
- 203 American Lung Association, Epidemiology and Statistics Unit, Research and Program Services Division. Trends in Asthma Morbidity and Mortality. February 2010.
www.lungusa.org/finding-cures/our-research/trend-reports/asthma-trend-report.pdf
- 204 Medical Expenditure Panel Survey. Statistical Brief #204: Allergic Rhinitis: Trends in Use and Expenditures, 2000 and 2005. May 2008.
www.meps.ahrq.gov/mepsweb/data_files/publications/st204/stat204.pdf
- 205 Dynavax Reports Interim TOLAMBATM Ragweed Allergy Results from DARTT Trial 01/08/2007 press release.
<http://investors.dynavax.com/releasedetail.cfm?ReleaseID=231013>
- 206 Guidance for Industry. Allergic Rhinitis: Clinical Development Programs for Drug Products. Draft Guidance. US Department of Health and Human Services. FDA. Center for Drug Evaluation and Research (CDER). April 2000.
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071293.pdf