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Review

Subcutaneous specific immunotherapy for seasonal allergic rhinitis: a review of treatment practices in the US and Europe

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Abstract

Background:

Subcutaneous specific immunotherapy (SCIT) is claimed to be successful both in the US and Europe, yet treatment methodology differs.

Methods:

The authors review current literature surrounding guidelines and clinical trials in Europe and the US and contrast the treatment approach to SCIT for allergic rhinitis. Search methodology employs MEDLINE and PubMed, selecting articles on SCIT and allergic rhinitis, limited between 1990–2009. They focus on the safety and efficacy of vaccines, and the differences in formulations. Also mentioned are: standardization, new approaches in SCIT and sublingual immunotherapy (SLIT).

Results:

SCIT treatment differs in many respects regarding availability of SCIT products, regulatory controls, guidelines (e.g. multiple allergen vaccines in US, single allergen vaccines in Europe) and in location of formulation (US, clinician's office; Europe, manufacturers).

Conclusions:

SCIT is an effective and safe therapy, but major evidence for efficacy is provided from European studies of single allergen extract vaccines; these vaccines may gain more acceptance because of increasing regulatory approval and lower numbers of injections. The potential impact upon public health (e.g. arrest of the 'allergic march') should not be overlooked.

Introduction

The practice of desensitization using pollen extract injections for the treatment of allergic rhinitis spans almost 100 years and was first pioneered by Noon and Freeman in London in 1911^{1,2}. Now referred to as subcutaneous specific immunotherapy (SCIT), the use of allergen specific desensitization involves the administration of gradually increasing quantities of an allergen to ameliorate the symptoms associated with subsequent exposure to the causative allergen^{3,4}. The main differences of specific immunotherapy compared with other treatments are the immunoregulation of the allergic response and the resolution of the early and late clinical manifestations of allergy via up-regulation of the Treg response to a specific allergen while minimizing the Th2 (allergic IgE-based) response⁵. This effect is achieved via several biological pathways, including early induction of the peripheral IL-10 response and later up-regulation of antigen-specific IgG4⁶. Antigen-specific IgG antibodies have a 'blocking' effect on

antigen-specific IgE-related mast cell activation which may also inhibit antigen capture and presentation to T cells⁷.

Clinical practice guidelines have been developed by different organizations in the US and Europe for the treatment of allergic rhinitis and for the use of SCIT^{3,8-12}. Whilst there are small differences in each of these guidelines, in general SCIT is recommended as a second-line treatment when there is a poor response to pharmacotherapy or allergen avoidance in patients with allergic rhinitis or allergic conjunctivitis mediated by IgE or when pharmacotherapy needs to be avoided in these same patients. SCIT has been associated with a beneficial effect on concurrent allergic asthma, although severe uncontrolled asthma remains a contraindication for SCIT. In addition, recommendations such as those devised by the WHO ARIA (World Health Organization Allergic Rhinitis and its Impact on Asthma) initiative^{4,13} have emphasized the link between rhinitis and asthma and acknowledged that SCIT can reduce the risk of asthma development, particularly in children. As a result, these recommendations suggest that SCIT might be considered as a treatment of choice in situations where a preventative management approach is desired^{4,13} (Table 1).

Despite the improvements in SCIT as a result of newer formulations and the existence of similar treatment guidelines in both Europe and the US there appear to be varying national views on the appropriate use of SCIT, and differences in the types of SCIT products available. Estimates of the usage of SCIT vary between and within countries, e.g. 8.6% (1996 Medical Expenditure Panel Survey¹⁴) and 2.2% (Healthcare Maintenance Organization data¹⁵) amongst patients with asthma or rhinitis in the US, and 7% in patients with asthma or rhinitis in Germany¹⁶.

This review aims to explore the similarities and differences that exist between the US and Europe in the rationale for treatment alignment in these developed countries and their clinical approaches to SCIT for allergic rhinitis. The authors have seen little published on this topic, which may help to clarify perceptions of

clinical practice by allergists in either geographical areas, and at least we hope this review will assist in medical education. The perspective is first set by describing the impact of allergic rhinitis. Next, of paramount importance is the issue of safety and efficacy of vaccines; all published allergen vaccine clinical trials cannot be individually reviewed, but there are recent reviews which should give an insight sufficient for the purposes of this paper. Guidelines are reviewed to find similarities and differences. The aspect of single versus multiple allergen vaccines is an important difference between the two areas in clinical allergy that needs highlighting. The availability of vaccines in Europe and the US is discussed, revealing a number of clear differences. There are now new approaches in SCIT, which it would be neglectful to ignore. Similarly, sublingual immunotherapy (SLIT) is rapidly becoming a 'rival' therapy to SCIT in Europe and requires comment.

Finally, patient surveys are discussed which reveal various points of concern.

Literature search methodology

Systematic MEDLINE and PubMed searches of scientific literature from 1990 to September 2009 were performed to identify all journal articles discussing the use of SCIT for the treatment of seasonal allergic rhinitis. The search was limited to the English language. Search terms included one of [subcutaneous specific immunotherapy], [SCIT], [uSCIT] or [sublingual] in conjunction with either [allergic rhinitis], [grass pollen allergy], [allergoid] or [standards]. Articles were selected by relevance to allergists' practice, by those known to the authors and those felt useful for medical education. A limitation of this review was that few references are quoted for literature dated earlier than 1990, owing to the search criteria. Reference lists of all the included articles were reviewed to identify additional relevant references.

Table 1. Guidelines for the use of subcutaneous immunotherapy in allergic rhinitis.

Source	Territory	Recommendation for patient selection
Joint Taskforce on practice parameters (AAAAI, ACAAI and JCAAI) ⁹	US	IgE-mediated allergy in patients who do not have unstable asthma and whose symptoms are unsatisfactorily managed with other medications
ARIA/GA ² LEN/WHO/AllerGen ⁴	Europe/worldwide	IgE-mediated allergy where pharmacotherapy has been unsuccessful
EAACI ¹¹	Europe	Following unsuccessful pharmacotherapy where 1–2 allergens involved
BSACI ⁵⁰	UK	Consider after exhausting other treatment options if sensitive to one or two allergens
Wonca, IPAG, IPCRG ⁸⁴	Worldwide (primary care)	Consider if moderate–mild or severe intermittent symptoms

AAAAI: The American Academy of Allergy, Asthma and Immunology. ACAAI: The American College of Allergy, Asthma and Immunology. JCAAI: Joint Council of Allergy, Asthma and Immunology. ARIA: Allergic Rhinitis and its Impact on Asthma. GA²LEN: Global Allergy and Asthma European Network. WHO: World Health Organization. EAACI: European Academy of Allergy and Clinical Immunology. BSACI: British Society for Allergy and Clinical Immunology. Wonca: World Organization of Family Doctors. IPAG: International Primary Care Airways Group. IPCRG: International Primary Care Respiratory Group. IgE: Immunoglobulin E.

Rationale for treatment alignment

Impact of allergic rhinitis on public health

Allergic rhinitis is a common global chronic disease with a similar impact in most Western countries. Various surveys have indicated prevalences of over 20% in both adults and children in developed countries such as the US and UK^{12,17–20}. Surveys have also highlighted an important rise in the prevalence of allergic rhinitis and asthma in developed countries in recent years^{18,21–24}, which has been linked to modern standards of hygiene and environmental pollution²⁵.

As none of the currently available symptomatic treatments alter the natural course of allergic rhinitis, the phenomenon of the ‘allergic march’, where allergic rhinitis gradually progresses to allergic asthma, largely goes unabated. Allergic rhinitis is a major risk factor for the development of asthma²⁶, and the potential impact of this disease could be much greater than current estimates show.

Allergic rhinitis has a significant impact on patients’ quality of life^{27,28}, although this effect may be routinely overlooked by clinicians due to the widespread availability of symptomatic therapies without prescription. SCIT has been shown to significantly improve quality of life for patients both short term and after repeated courses of treatment^{29,30}.

Specific immunotherapy: efficacy and safety

The protocols used for clinical trials of SCIT have varied considerably over past years and in an effort to develop a methodological standard for these trials the World Allergy Organization (WAO) has recently published guidelines for future immunotherapy studies³¹. These guidelines recommend a combined symptom plus medication score be used as the primary outcome measure. Useful secondary outcome measures can include changes in individual symptom scores and, in addition, demonstration of the effects of SCIT on quality of life of patients should be included; organ-related validated questionnaires for asthma and rhinitis are recommended. Updated guidelines on clinical testing of preparations for specific immunotherapy have recently been issued by the European Medicines Agency³².

Whilst many of the newer clinical trials that have been undertaken recently do follow these guidelines^{30,33,34}, older trials used more diverse assessment criteria thus making comparison of trials difficult. However, a recent Cochrane systematic review and meta-analysis has been undertaken in an effort to provide evidence-based data for the efficacy and safety of SCIT. This review has shown that SCIT improves the symptoms of seasonal allergic rhinitis, reduces the need for medication in these patients and improves disease-specific quality of life,

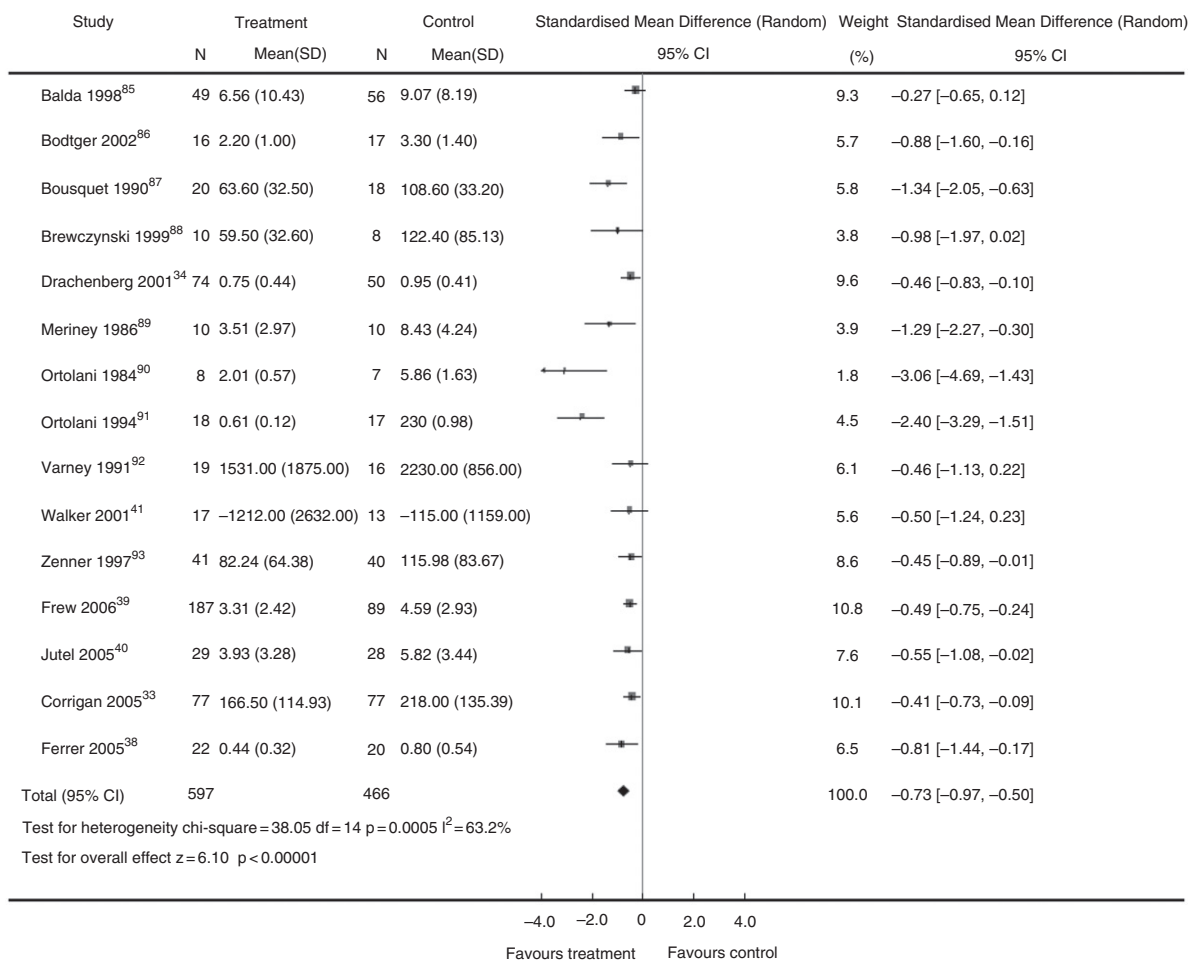
whilst remaining well tolerated³⁵. The review, which included data from 51 publications, concluded that in ‘suitably well selected patients’ with seasonal allergic rhinitis, SCIT results in a significant reduction in symptom scores and medication use. This conclusion was based on a meta-analysis of symptom score data from 15 clinical trials which showed a statistically significant reduction in overall symptom score in SCIT recipients compared with those receiving placebo (standardized mean difference [SMD] -0.73 [95% CI: -0.97 to -0.50], $p < 0.00001$) (Figure 1)³⁵ and a similar analysis from medication score data from 13 trials, which showed a reduction in the need for symptomatic medication in patients who received SCIT compared with those receiving placebo, (SMD -0.57 [95% CI: -0.82 to -0.33], $p < 0.00001$)³⁵ (Figure 2).

The efficacy of SCIT, both in terms of extent of symptom relief and proportion of patients experiencing benefit, appears to improve with longer periods of therapy either in terms of increased duration of maintenance therapy^{36,37}, or repeated courses of pre-seasonal SCIT^{30,33}. In a recent 2-year clinical trial in 154 grass pollen-allergic patients, pre-seasonal therapy with a preparation containing six grass pollen allergoids resulted in reduction of the combined symptom and medication score and improved quality of life. Importantly, the third course of SCIT further improved these measures compared with the first and second treatment years³⁰.

The systematic review³⁵ has also shown that the reported clinical benefits may translate into improvements in disease-specific quality of life: the most recent studies have reported on outcomes using validated rhinitis quality of life questionnaires. Five studies were included in the rhinoconjunctivitis quality of life meta-analysis, comprising over 300 active immunotherapy subjects and over 200 placebo recipients^{33,38–41}. The combined SMD for rhinoconjunctivitis quality of life following subcutaneous SCIT was -0.52 (95% CI: -0.69 to -0.34 , $p < 0.00001$) which indicates a clinically and statistically significant improvement in rhinoconjunctivitis quality of life in the immunotherapy-treated group compared with placebo³⁵.

The effectiveness of SCIT is not limited to pollen allergies and the development of various different formulations of SCIT has now made this an effective treatment for other similar IgE-mediated conditions; for example, in patients with asthma and allergic rhinoconjunctivitis sensitized to the dust mite⁴², SCIT significantly improved symptoms scores and reduced medication scores, compared with placebo. In addition, there was a significant improvement for those receiving desensitization as measured using the 20-item self-administered asthma quality of life questionnaire (AQLQ)⁴³.

SCIT has a relatively low risk of severe adverse events and side-effects generally resolve within a short time after



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SCIT: subcutaneous immunotherapy.

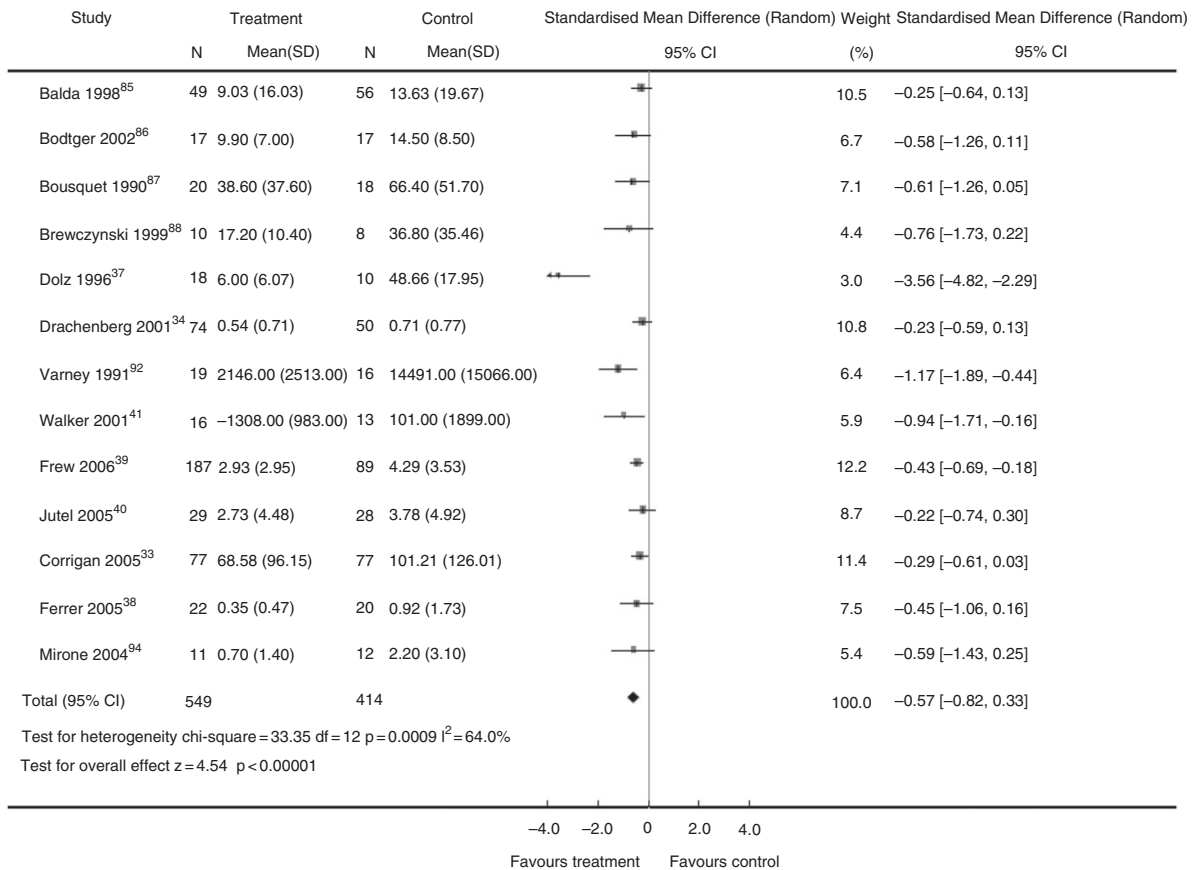
Figure 1. SCIT versus placebo for symptom score³⁵.

dose administration³⁵; some allergists routinely premedicate their patients with antihistamines in order to reduce the risk of occurrence of adverse events following each dose of SCIT. A total of 33 studies reported systemic adverse events in the systematic review³⁵, 1051 occurring in patients receiving active SCIT compared with 857 receiving placebo. These events included early (<30 minutes) grade 2, 3 and 4 events and late (>30 minutes) events. In 13 studies adrenaline use was reported; it was given following 0.13% of injections (19 of 14,085 injections) for those receiving active treatment, and following 0.01% of injections (1 of 8278 injections) in the placebo groups. There were no fatalities.

In an earlier, large retrospective analysis of data spanning 25 years and involving over 300,000 injections, systemic reactions were reported after 0.061% of injections

(134 of 6319 patients, 2.1%)⁴⁴. Of the systemic reactions reported, urticaria (59.3%) and mild asthma (23.9%) were the most common. There were no cases of anaphylactic shock and no hospital admissions, and it was concluded that SCIT could be considered as a first-line treatment⁴⁴.

A survey of fatal and near-fatal reactions to immunotherapy and skin prick testing between 1990 and 2001 estimated that fatal reactions occurred at a rate of 1 per 2.5 million injections⁴⁵. It was noted that most fatalities occurred in patients who had concurrent asthma which was not optimally controlled, or where immunotherapy was administered in an unsuitable setting i.e. not medically supervised or without rapid access to rescue epinephrine. Strict adherence to current practice guidelines would prevent such situations from occurring.



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SCIT: subcutaneous immunotherapy.

Figure 2. SCIT versus placebo for medication score³⁵.

European and US approaches to seasonal allergic rhinitis and the use of SCIT

Guidelines and similarities

There are many national and international guidelines for the management of allergic rhinitis (Table 1) which describe the place of SCIT in this condition^{3,9,11,46–50}. The majority of these guidelines are not directed at primary care even though general practitioners treat most of the patients with respiratory diseases in the majority of Western countries⁴⁸. General practitioners and non-allergy specialists may find the implementation of the guidelines problematic due to lack of specialized knowledge⁵¹. Yet, despite these issues, most European and US guidelines for allergic rhinitis are similar in their recommended management approaches. If pharmacological intervention fails to improve a patient's condition, referral

to an allergy/immunology specialist is recommended and SCIT may be considered. In addition, patients' attitudes to the available therapy, cost and quality of life are recommended considerations^{9,11}.

One common aim of many allergy organizations has been to simplify guideline recommendations, making them easier to follow and implement. For example, the International Primary Care Respiratory Group (IPCRG) published guidelines for the management of allergic rhinitis specifically written for primary-care physicians⁴⁸. Similarly in Europe, the EAACI consensus paper has included algorithms to aid physicians with their choices of therapy¹¹. In addition, an initiative by ARIA has led to the introduction of a classification system for disease severity (with a new subdivision of disease: intermittent and persistent) and depending upon the subdivision and severity of allergic rhinitis, they propose a stepwise approach to management similar to that seen in asthma guidelines^{4,14}.

These guidelines are in general agreement over SCIT and its place in the management of allergic rhinitis. In another example, primary-care physicians and allergists in the US are assisted by a joint task force publication from the three major allergy/immunology organizations (ACAAI, AAAAI, JCAAI) which has produced an annotated algorithm to highlight the major decision points¹⁰. Similarly, in Europe the EAACI has published standards for SCIT to ensure optimum quality in this avenue of treatment³.

Guidelines differences

An important difference between Europe and the US in their approach to allergen desensitization for seasonal allergic rhinitis with SCIT is in the number of allergen extracts used in the vaccination. In Europe, SCIT is used to treat the few most important allergen sensitizations. European guidelines recommend that SCIT is used for patients with evidence of clinically relevant IgE-mediated disease and only a limited spectrum of allergies (following the failure of pharmacotherapy and allergen avoidance)^{11,46}. European allergists select courses often based on single allergenic extract preparations and the concurrent treatment of multiple sensitizations is not recommended^{52,53}. Indeed, many consider it ineffective to use multiple unrelated allergens^{8,54,55}. The symptoms of allergic rhinitis result from an inflammatory response to allergen in the nasal mucosa and upper airways. However, in atopic patients inflammatory mediators (e.g. eosinophils, neutrophils and inflammatory modulators such as ICAM-1) remain elevated beyond the symptomatic period, and are present in response to subclinical exposure to low levels of pollen⁵⁶. The concept of minimal persistent inflammation (MPI)⁵⁶ emphasizes the importance of this background inflammation and asserts that allergic symptoms result when the airways are sufficiently inflamed. This low level of inflammation essentially primes the tissue for further response; atopic patients with a subclinical level of airways inflammation are therefore more likely to experience symptoms in response to stimuli which would be asymptomatic in non-atopic patients. Well-targeted specific allergen immunotherapy is particularly advantageous because by attenuating the inflammatory response to a dominant allergy, MPI is reduced. In this way, treating one allergy may have a beneficial effect on symptoms resulting from other type I hypersensitivities. There is clear evidence of SCIT resulting in the reduction of both cell numbers (e.g. eosinophils) and inflammatory mediators at sites of allergen exposure^{57,58}. The effect of immunotherapy resulting in tolerance to unrelated antigens (allergens) is sometimes described as bystander tolerance⁵⁹.

The reluctance to formulate multi-allergen vaccines has been described by an EAACI taskforce. Mixing unrelated allergens can lead to impotent vaccines by the interaction of enzymatic components. Furthermore, there is an inevitable dilution of individual components which could easily lead to suboptimal doses³. These reservations could be challenged suitably if there is good evidence that multi-allergen vaccines are successful. However, there is very little literature to provide evidence of efficacy with multi-allergen immunotherapy; literature, if anything, shows failures⁵⁵.

On the other hand, a more thorough approach could be argued by the US allergist. Vaccination with multiple allergens is common practice as all relevant allergies are considered for inclusion in the treatment course. Allergens are combined in a single mixture for the more typical patient with more than one sensitization⁹. To achieve an effective therapeutic concentration of each allergen, it may be necessary to prepare more than one allergen extract mixture. As described above, some allergens are incompatible in mixtures (e.g. mold/fungi and grass pollen) and so this may also necessitate preparation of more than one extract mixture and increase considerably the number of injections administered. The formulation of the vaccine prescription is generally composed and made up in the clinician's office; the efficacy (and safety) of the resulting vaccine(s) is therefore in part allied to the individual allergist's expertise in formulation.

Available formulations

In Europe there is a greater variety of SCIT products available than in the US, and regulatory procedures facilitate the registration of new products and formulations, further increasing the options for physicians and patients. Furthermore, the types of products registered differ between Europe and the US. In the US, allergen extracts are registered, regulated and approved by the FDA whereas in Europe, proprietary formulations of extract-containing products are registered; additionally allergen extracts are available on a named-patient basis. The European named-patient preparation (NPP) system involves a vaccine formulated by a vaccine manufacturer rather than the allergist, each vaccine bearing the name of a patient following an allergist's order. Claimed benefits of the system are (a) formulation to GMP standards; (b) a very wide range of specific allergens; and (c) the versatility to mix a small number of homologous allergens, e.g. two or at most three. NPP vaccines are not licensed, but are approved as 'specials' from licensed premises.

Conventionally, SCIT employs a build-up phase of escalating doses of allergen extract until a therapeutic maintenance dose is reached; weekly injections are given for a period of 2–3 months. Subsequently, the dose

frequency is reduced from weekly to twice monthly or monthly and sustained at this frequency for three to five years⁶⁰. Whilst effective, this process can be very inconvenient and therefore patients need to be highly motivated and committed to follow the regimen which involves significant burdens in terms of the patients' time and the number of injections. In order to make SCIT more convenient, accelerated (rush and cluster) immunotherapy regimens have been developed, which employ an accelerated build-up phase in order to reach the maintenance phase more rapidly and reduce the time period of intensive injections for the patient.

The use of unmodified, aqueous allergen extract SCIT is the standard practice in the US; sometimes, alum depot adjuvant is incorporated. However, in Europe, proprietary SCIT products with improved formulation technologies are more widespread; aqueous extracts are rarely used. Adsorbing extracts onto depot materials, such as alum or L-tyrosine, helps to reduce the frequency of maintenance injections by facilitating a slow presentation of antigen from the injection site (so a larger dose of maintenance allergen can be given in each maintenance dose, providing a prolonged interaction with the immune system). Another development is the use of chemically modified allergens (allergoids). Complexation of allergens with, for example, glutaraldehyde, produces a large allergoid molecule with reduced IgE binding (reduced allergenicity and therefore enhanced safety), while retaining immunogenicity⁶¹. Allergoids can therefore be used at higher concentrations which again allows lower numbers of injections.

New approaches

The ideal allergen vaccine would have high efficacy and safety with shorter than currently available injection regimens. There are interesting developments which may rival and erode current methodologies.

New adjuvants are now being exploited in recently licensed anti-infectious vaccines. Recently, in parallel with anti-infectious immunotherapy, the immunological adjuvant monophosphoryl lipid A (MPL) has been incorporated into SCIT formulations in order to skew the immune response to an allergen towards a beneficial Th1-type profile. MPL is derived from detoxified lipopolysaccharide from the cell wall of *Salmonella minnesota*, and is an agonist for Toll-like receptor 4, which enhances the development of type 1 dendritic cells, drivers of the Th1 response. This approach has enabled the development of an 'ultra short course SCIT' (uSCIT).

This particularly short regimen of four annual pre-seasonal injections over three weeks, with no subsequent maintenance, has been shown to provide clinical efficacy in patients with seasonal allergic rhinitis^{34,62–64}. Currently, this product is available on a NPP basis in

Europe and the grant of a license for a grass pollen formulation is anticipated soon.

Peptide immunotherapy is a particularly novel approach. T-cell epitope-containing peptides (typically 10–20 amino acids long) derived from allergens modulate T-cell responses while having little potential to cross-link IgE⁶⁵. As yet, there has been no strong evidence for efficacy; however, clinical phase II studies are now underway for cat, ragweed and house dust mite allergies.

Recombinant allergen vaccines are currently being trialed. These formulations involve major allergens of defined and constant composition, giving better confidence in efficacy and safety; moreover, some hypoallergenic allergens are now being examined^{40,66}.

Sublingual immunotherapy (SLIT) can be described as a relatively new innovation which is rapidly gaining ground. In 1998 a WHO position paper stated that "SLIT may be considered as a viable alternative to the injection route in adults"⁶⁷. Since then there have been many well-controlled studies in Europe involving single allergen preparations. Meta-analyses have shown that SLIT is significantly efficacious for both adults and children^{68,69}. European licenses have recently been granted for tablet-based grass pollen SLIT vaccines. However, each single allergen vaccine will need an individual license, which means some time will be taken to build up a range of licensed vaccines for the common allergens. Meanwhile, European patients can be prescribed more flexibly under the NPP system.

Sublingual immunotherapy offers the advantage of home administration due to its greater safety profile. In addition, it provides an alternative method for delivering immunotherapy for those who dislike injections and may have greater convenience compared with therapy that is administered in the clinic⁷⁰. Thus the use of SLIT has been rapidly gaining ground in Europe. Although there is relatively low US use of SLIT⁶⁰, US allergists have participated in their clinical evaluation⁷¹ and there is a possibility of FDA approval of licensed manufactured vaccines. There is, as yet, no FDA-approved SLIT formulation for preparation by allergists, which means that most insurers will not agree to reimbursement. Following the grant of a SLIT vaccine license, it is very likely there will be an interested response but this will be focused on (a) patients with sensitivity to the particular single allergen and (b) to allergic rhinitis patients who have a low number of sensitivities.

Standardization of SCIT products

The nature of allergen extracts makes the definition of universal purity and dosage recommendations a complex issue. In the US, the Center for Biologics Evaluation and Research (CBER) maintains reference standards for 19

Table 2. Comparison of subcutaneous immunotherapy in the US and Europe.

	US	Europe
Allergens used	Multiple	Mainly single
Standardization of products	CBER reference materials for standardized extracts	In-house reference
<i>In vivo</i> potency reference standard	Titrated intradermal tests measuring erythema	Titrated prick test compared with histamine
Up-dosing phase frequency	1–2 times a week	Weekly
Up-dosing phase duration	3–6 months	2–3 months
Maintenance phase frequency	Every 2–6 weeks	Every 4–6 weeks
Maintenance phase duration	Individualized, generally 3–5 years	3 years
Depot vaccines	Rarely	Yes
Allergoid preparations	No	Yes
Use of adjuvants	Rarely (e.g. alum depot adjuvant)	Yes
Recommended supervision after injection	30 minutes	30 minutes

CBER: Center for Biologics Evaluation and Research.

common allergens, and manufacturers use these to assess the potency of their products. Allergen extracts for which there is no reference standard are unstandardized⁷² and subject to general Good Manufacturing Process and raw material protocols.

In Europe, SCIT products are usually sold pre-formulated in graded treatment sets for each patient, or sold as standardized, licensed products⁶², rather than as raw extracts. Manufacturers usually standardize products against their own in-house reference standards, using a variety of units and procedures. In effect this means that while individual manufacturers can ensure the batch-to-batch consistency for their products, it is very difficult to compare products from different manufacturers^{3,73}. The European Union CREATE project recently aimed to produce recombinant reference standards for nine common allergen proteins, verified by a variety of physical, chemical and biological methods⁷⁴. Three allergens were successfully characterized, with partial success for five others.

A comparison of US and European SCIT products is shown in Table 2.

Barriers and misconceptions

Barriers to the use of SCIT are most likely related to the convenience and safety issues historically associated with conventional preparations; these issues have been considerably improved with the newer preparations. SCIT must still be carried out by a specialist allergist and should be offered in settings where appropriate personal emergency treatment and resuscitative facilities are available. SCIT should be administered by trained personnel experienced in the early recognition and treatment of severe adverse reaction and anaphylaxis^{9,35}. This can present problems since allergic patients' first medical contact is often their primary-care physician, who may be inclined to place more emphasis on quick symptom relief with medications than on SCIT⁷⁵. Indeed, most allergic patients are treated solely with symptomatic pharmacotherapy, which could be a result of both convenience and safety concerns

with SCIT⁶². Although use of symptomatic treatments such as antihistamines might be the first course of action in most countries there is evidence to suggest that there are important unmet needs and differences in perception between the patients and clinicians in terms of their levels of satisfaction with this kind of treatment⁷⁶. In a survey in the US, between 82% and 91% of healthcare providers believed that patients receive suitable cost-benefit from their prescription medication, while only 55% of patients agreed with this assessment. In addition, 72% of primary care physicians believed that patients would rate themselves as 'very satisfied' with their overall disease management and treatment; whereas only 58% of patients who had seen a healthcare practitioner in the past 12 months said that they were 'very satisfied' with their disease management.

A UK survey investigated adult hay fever sufferers who had been prescribed oral antihistamine or nasal corticosteroid therapy⁷⁷. Fewer than half (45.6%) of respondents experienced good symptom control, and only 25% were receiving maximal therapy (i.e. daily antihistamine and daily steroid). Sixty-two percent experienced troublesome residual symptoms and described symptom control as partial or poor⁷⁸. It is therefore clear that not only is symptomatic therapy not always properly prescribed, but also that patient compliance with symptomatic regimens is not guaranteed.

Amongst specialist physicians, barriers to the use of SCIT may be related to convenient access to trained allergists, risks of complications and concerns about effectiveness. A postal questionnaire in the UK amongst ear, nose and throat specialists showed that SCIT was used by only a small percentage of those involved⁷⁸; of the 304 replies that were evaluated in this survey, 79 advocated immunotherapy (26%) but only 18 (6.6%) actually used it. In comparison, the US medical climate is far more positive for immunotherapy. A retrospective database review of over 3300 otolaryngology patients referred for allergy skin testing between 1979 and 1999 found 80% had positive test results. Of these, 75.5% progressed onto immunotherapy⁷⁹.

The uptake of SCIT could be similar, if not higher, for patients who are directly referred to allergists.

The availability of allergists of course will influence SCIT uptake. In the US, there are over 4500 allergists whereas in the UK it is recognized that there are insufficient numbers⁸⁰. Europe embraces many countries with different circumstances, but it is fair to say that allergists are more widespread in the large countries of France and Germany.

There have been compliance issues amongst patients with conventional SCIT; since it carries a risk of anaphylaxis, patients are required to complete a 30 minute observation period after each injection^{3,9} and this can mean long attendance times at clinics in addition to the time spent travelling to and from the clinic. More importantly, with conventional SCIT, and particularly with the non-depot extracts which are ubiquitous in the US, optimal SCIT requires a three to five year commitment from the patient to regular maintenance injections, often on a monthly basis. Such a commitment can seriously limit adherence (especially for out-of-season maintenance when symptoms are not troublesome); compliance rates of >50% are unusual after one year with conventional SCIT^{81,82}. In one large survey, treatment compliance was dramatically reduced after the first course and only 16% of patients completed the minimum recommended three year treatment duration⁸³.

Summary

SCIT is an effective and well-tolerated treatment option in the management of allergic rhinitis which has been practiced for almost a century, during which methods for standardization and regulation have evolved. Despite agreement in guidelines for the use of SCIT there are clear differences between Europe and the US, principally in the types of product which are available. SCIT in the US is generally prepared from stock extracts and individually tailored to the patient's specific sensitizations. In Europe, proprietary products and allergen mixtures are the primary form of SCIT, and the use of depot substances and adjuvants has led to the design of novel and innovative SCIT formulations. A greater alignment of practices and sharing of SCIT techniques between the US and Europe might help to overcome some of the common barriers to the use of SCIT, which include convenience, acceptance and compliance; many of the compliance and convenience issues can be addressed with some of the newer advances in SCIT formulation. When practiced appropriately with adherence to current guidelines, SCIT remains an underutilized resource in the treatment of allergic rhinitis. SCIT has repeatedly been shown to be an effective and safe therapy, and its potential impact upon

public health, especially with respect to consequent effects in allergic asthma, should not be overlooked.

Transparency

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Declaration of financial/other relationships

L.C. has disclosed that she has acted as a consultant for Hollister-Stier, Stallergenes and Schering-Plough. M.C. has acted as a consultant for ALK-Abello and Schering-Plough, and a speaker for ALK-Abello, Allergy Therapeutics (UK) Ltd, MSD and GSK. He has appeared on advisory boards for Allergy Therapeutics (UK) Ltd and ActoGeniX, received honoraria from ALK-Abello, Allergy Therapeutics (UK) Ltd, Schering-Plough and MSD and research grants from ALK-Abello and GSK.

Peer reviewers may receive honoraria from CMRO for their review work. Peer Reviewer 1 has disclosed that he/she has received grant funding from, and acted as a consultant to, Dynova Labs, Dyax, and Flint Hills Resources; and that he/she is on the speakers bureau for AstraZeneca and Alcon. Peer Reviewer 2 has disclosed no relevant financial relationships.

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References

1. Freeman J. Further observations on the treatment of hay fever by hypodermic inoculations of pollen vaccine. *Lancet* 1911;2:814-17
2. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1:1572-3
3. Alvarez-Cuesta E, Bousquet J, Canonica GW, et al. Standards for practical allergen-specific immunotherapy. *Allergy* 2006;61(Suppl. 82):1-20
4. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63(Suppl. 86):8-160
5. Secrist H, Chelen CJ, Wen Y, et al. Allergen immunotherapy decreases interleukin 4 production in CD4+ T cells from allergic individuals. *J Exp Med* 1993;178:2123-30
6. Francis JN, James LK, Paraskevopoulos G, et al. Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG4 inhibitory antibody activity. *J Allergy Clin Immunol* 2008;121:1120-5
7. Wilcock LK, Francis JN, Durham SR. IgE-facilitated antigen presentation: role in allergy and the influence of allergen immunotherapy. *Immunol Allergy Clin North Am* 2006;26:333-ix
8. Bousquet J. Pro: Immunotherapy is clinically indicated in the management of allergic asthma. *Am J Respir Crit Care Med* 2001;164:2139-40
9. Cox L, Li JT, Nelson HS, et al. Allergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol* 2007;120(3 Suppl.):S25-S85
10. Joint Task Force on Practice Parameters. Allergen immunotherapy: a practice parameter. *American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol* 2003;90(1 Suppl. 1):1-40
11. van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis. *European Academy of Allergology and Clinical Immunology. Allergy* 2000;55:116-34

12. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;122(2 Suppl.):S1-84
13. Bachert C, van CP. The WHO ARIA (allergic rhinitis and its impact on asthma) initiative. *Chem Immunol Allergy* 2003;82:119-26
14. Law AW, Reed SD, Sundy JS, et al. Direct costs of allergic rhinitis in the United States: estimates from the 1996 Medical Expenditure Panel Survey. *J Allergy Clin Immunol* 2003;111:296-300
15. Donahue JG, Greineder DK, Connor-Lacke L, et al. Utilization and cost of immunotherapy for allergic asthma and rhinitis. *Ann Allergy Asthma Immunol* 1999;82:339-47
16. Schramm B, Ehlken B, Smala A, et al. Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. *Eur Respir J* 2003;21:116-22
17. Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 2003;90(1 Suppl. 1):1-40
18. ISAAC Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998;351:1225-32
19. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;24:758-64
20. Gupta R, Sheikh A, Strachan DP, et al. Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy* 2004;34:520-6
21. Jarvis D, Burney P. ABC of allergies. The epidemiology of allergic disease. *BMJ* 1998;316:607-10
22. Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. *BMJ* 1992;304:873-5
23. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001;108(1 Suppl.):S2-S8
24. Mygind N, Dahl R. Epidemiology of allergic rhinitis. *Pediatr Allergy Immunol*; 7(9 Suppl.):57-62
25. Garn H, Renz H. Epidemiological and immunological evidence for the hygiene hypothesis. *Immunobiology* 2007;2126:441-52
26. Guerra S, Sherrill DL, Martinez FD, et al. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol* 2002;109:419-25
27. Derebery MJ, Berliner KI. Allergy and health-related quality of life. *Otolaryngol Head Neck Surg* 2000;123:393-9
28. Blaiss MS. Important aspects in management of allergic rhinitis: compliance, cost, and quality of life. *Allergy Asthma Proc* 2003;24:231-8
29. Powell RJ, Frew AJ, Corrigan CJ, et al. Effect of grass pollen immunotherapy with Alutard SQ on quality of life in seasonal allergic rhinoconjunctivitis. *Allergy* 2007;62:1335-8
30. Williams A, Henzgen M, Rajakulasingam K. Additional benefit of a third year of specific grass pollen allergoid immunotherapy in patients with seasonal allergic rhinitis. *Eur Ann Allergy Clin Immunol* 2007;39:123-6
31. 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) task-force. *Allergy* 2007;62:317-24
32. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. EMEA CHMP, 2008. Available at: <http://www.emea.europa.eu/pdfs/human/ewp/1850406enfin.pdf> [Last accessed 14 July 2009]
33. Corrigan CJ, Kettner J, Doemer C, et al. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy* 2005;60:801-7
34. Drachenberg KJ, Wheeler AW, Stuebner P, et al. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. *Allergy* 2001;56:498-505
35. Calderon MA, Alves B, Jacobson M, et al. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007(1):CD001936
36. Giovannini M, Braccioni F, Sella G, et al. Comparison of allergen immunotherapy and drug treatment in seasonal rhinoconjunctivitis: a 3-years study. *Eur Ann Allergy Clin Immunol* 2005;37:69-71
37. Dolz I, Martinez-Cocera C, Bartolome JM, et al. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy* 1996;51:489-500
38. Ferrer M, Burches E, Pelaez 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
39. Frew AJ, Powell RJ, Corrigan CJ, et al. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:319-25
40. Jutel M, Jaeger L, Suck R, et al. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol* 2005;116:608-13
41. Walker SM, Pajno GB, Lima MT, et al. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;107:87-93
42. Ameal A, Vega-Chicote JM, Fernandez 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
43. Marks GB, Dunn SM, Woolcock AJ. A scale for the measurement of quality of life in adults with asthma. *J Clin Epidemiol* 1992;45:461-72
44. Luigi A, Senna G, Mezzelani P, et al. Safety of specific immunotherapy: a retrospective study. *J Investig Allergol Clin Immunol* 1994;4:250-4
45. Bernstein DI, Wanner M, Borish L, et al. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113:1129-36
46. Bousquet J, Van CP, Khaltayev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5 Suppl.):S147-S334
47. Dykewicz MS, Fineman S, Skoner DP, et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology. *Ann Allergy Asthma Immunol* 1998;81:478-518
48. Price D, Bond C, Bouchard J, et al. International Primary Care Respiratory Group (IPCRG) Guidelines: management of allergic rhinitis. *Prim Care Respir J* 2006;15:58-70
49. Scadding GK, Durham SR, Mirakian R, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy* 2008;38:19-42
50. Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 2003;90(1 Suppl. 1):1-40
51. Bonini S, Ansotegui IJ, Durham S, et al. Allergy and clinical immunology services in Europe. *Allergy* 2006;61:1191-6
52. Mari A, Scala E. Allergenic extracts for specific immunotherapy: to mix or not to mix? *Int Arch Allergy Immunol* 2006;141:57-60
53. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol* 2009;103:451-60
54. Abramson M, Puy R, Weiner J. Immunotherapy in asthma: an updated systematic review. *Allergy* 1999;54:1022-41
55. Adkinson Jr 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
56. Storms WW. Minimal persistent inflammation, an emerging concept in the nature and treatment of allergic rhinitis: the possible role of leukotrienes. *Ann Allergy Asthma Immunol* 2003;92:131-40
57. Wilson DR, Nouri-Aria KT, Walker SM, et al. Grass pollen immunotherapy: symptomatic improvement correlates with reductions in eosinophils and IL-5 mRNA expression in the nasal mucosa during the pollen season. *J Allergy Clin Immunol* 2001;107:971-6
58. Till SJ, Francis JN, Nouri-Aria K, et al. Mechanisms of immunotherapy. *J Allergy Clin Immunol* 2004;113:1025-34
59. Sehra S, Pynaert G, Tournoy K, et al. Airway IgG counteracts specific and bystander allergen-triggered pulmonary inflammation by a mechanism dependent on FcγR and IFN-γ. *J Immunol* 2003;171:2080-9

60. Plaut M, Valentine MD. Clinical practice. Allergic rhinitis. *N Engl J Med* 2005;353:1934-44
61. Wheeler AW, Woroniecki SR. Allergy vaccines – new approaches to an old concept. *Expert Opin Biol Ther* 2004;4:1473-81
62. Patel P, Salapatek AM. Pollinex Quattro: a novel and well-tolerated, ultra short-course allergy vaccine. *Expert Rev Vaccines* 2006;5:617-29
63. Kaiser HB, Keith PK, Casale TB, et al. Significant reduction in combined symptom and medication score compared with placebo with a ragweed uSCIT formulation for seasonal pollen allergy. *J Allergy Clin Immunol* 2009;123:731
64. Frew AJ, DuBuske LM, Amersdorffer J, et al. Significant benefit in combined symptom and medication scores for ultra short course subcutaneous immunotherapy compared with placebo in patients with grass pollen allergic rhinoconjunctivitis. *Allergy* 2009;64:s90
65. Larche M. Update on the current status of peptide immunotherapy. *J Allergy Clin Immunol* 2007;119:906-9
66. Kahlert H, Suck R, Weber B, et al. Characterization of a hypoallergenic recombinant Bet v 1 variant as a candidate for allergen-specific immunotherapy. *Int Arch Allergy Immunol* 2008;145:93-206
67. Bousquet J, Lockett R, Malling HJ, et al. World Health Organization position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998;53:933-44
68. Wilson DR, Torres L, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Allergy* 2005;60:3-8
69. Penagos M, Complatati E, Tarantini F, et al. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in children. Meta-analysis of randomized controlled trials. *Ann Allergy Asthma Immunol* 2006;97:141-8
70. Calderon MA, Penagos M, Durham SR. Sublingual immunotherapy for allergic rhinoconjunctivitis, allergic asthma, and prevention of allergic diseases. *Clin Allergy Immunol* 2008;21:359-75
71. Cox LS, Linnemann DL, Nolte H, et al. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006;117:1021-35
72. Allergens. FDA, 2008. Available at: <http://www.fda.gov/cber/allergens.htm> [Last accessed 16 October 2008]
73. Larenas-Linnemann D, Cox LS. European allergen extract units and potency: review of available information. *Ann Allergy Asthma Immunol* 2008;100:137-45
74. Chapman MD, Ferreira F, Villalba M, et al. The European Union CREATE Project: a model for international standardization of allergy diagnostics and vaccines. *J Allergy Clin Immunol* 2008;122:882-9
75. Wang DY, Chan A, Smith JD. Management of allergic rhinitis: a common part of practice in primary care clinics. *Allergy* 2004;59:315-19
76. Derebery JM. Satisfaction level with current treatments for allergic rhinitis. 2006. Available at: <http://www.medscape.com/viewarticle/549530> [Last accessed 8 July 2008]
77. White P, Smith H, Baker N, et al. Symptom control in patients with hay fever in UK general practice: how well are we doing and is there a need for allergen immunotherapy? *Clin Exp Allergy* 1998;28:266-70
78. Dhanasekar G, Izzat AB, D'Souza AR. Immunotherapy for allergic rhinitis – a United Kingdom survey and short review. *J Laryngol Otol* 2005;119:799-805
79. Lane A, Pine H, Pillsbury III H. Allergy testing and immunotherapy in an academic otolaryngology practice: a 20-year review. *Otolaryngol Head Neck Surg* 2001;124:9-15
80. Holgate ST, Ewan P. Allergy: the unmet need. A report of the Royal College of Physicians on the provision of allergy services in the UK. Available at: www.bsaci.org [Last accessed 7 March 2010]
81. Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. *J Allergy Clin Immunol* 1993;91:734-7
82. Lower T, Henry J, Mandik L, et al. Compliance with allergen immunotherapy. *Ann Allergy* 1993;70:480-2
83. 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* 2008;121:227-322
84. Bousquet J, Reid J, van WC, et al. Allergic rhinitis management pocket reference 2008. *Allergy* 2008;63:990-6
85. Balda BR, Wolf H, Baumgarten C, et al. Tree-pollen allergy is efficiently treated by short-term immunotherapy (SIT) with seven preseasonal injections of molecular standardized allergens. *Allergy* 1998;53:740-8
86. Bodtger U, Poulsen LK, Jacobi HH, et al. The safety and efficacy of subcutaneous birch pollen immunotherapy – a one-year, randomised, double-blind, placebo-controlled study. *Allergy* 2002;57:297-305
87. Bousquet J, Hejjajoui A, Soussana M, et al. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. IV Comparison of the safety and efficacy of two dosages of a high-molecular-weight allergoid. *J Allergy Clin Immunology* 1990;85:490-7
88. Brewczynski PZ, Kroon AM. Efficacy and safety of immunotherapy with modified grass pollen allergens. Results of a placebo-controlled study [Wirksamkeit und verträglichkeit einer immuntherapie mit modifizierten gras-pollenallergenen]. *Allergologie* 1999;22:411-20
89. Meriney DK, Kothari H, Chinoy P, et al. The clinical and immunologic efficacy of immunotherapy with modified ragweed extract (allergoid) for ragweed hay fever. *Ann Allergy* 1986;56:34-8
90. Ortolani C, Pastorello E, Moss RB, et al. Grass pollen immunotherapy: a single year doubleblind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. *J Allergy Clin Immunology* 1984;73:283-90
91. Ortolani C, Pastorello EA, Inconvaia C, et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of *Parietaria judaica* in patients with *Parietaria* hay fever. *Allergy* 1994;49:13-21
92. Varney VA, Gaga M, Frew AJ, et al. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *Brit Med J* 1991;302:265-9
93. Zenner HP, Baumgarten C, Rasp G, et al. Short-term immunotherapy: A prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. *J Allergy Clin Immunology* 1997;100:23-9
94. 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