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BSACI GUIDELINES

Immunotherapy for allergic rhinitis

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Summary

Allergic rhinitis (AR) affects more than 20% of the population in the United Kingdom and western Europe and represents a major cause of morbidity that includes interference with usual daily activities and impairment of sleep quality. This guidance prepared by the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI) is for the management of AR in patients that have failed to achieve adequate relief of symptoms despite treatment with intranasal corticosteroids and/or antihistamines. The guideline is based on evidence and is for use by both adult physicians and paediatricians practising allergy. During the development of these guidelines, all BSACI members were included in the consultation process using a web-based system. Their comments and suggestions were carefully considered by the SOCC. Where evidence was lacking, consensus was reached by the experts on the committee. Included in this guideline are indications and contraindications for immunotherapy, criteria for patient selection, the evidence for short- and long-term efficacy of subcutaneous and sublingual immunotherapy, and discussion on safety and the different modes of immunotherapy including, pre-seasonal and co-seasonal treatments. There are sections on children, allergen standardization, vaccines used in the United Kingdom, oral allergy syndrome, cost effectiveness of immunotherapy and practical considerations of undertaking immunotherapy including recommendations on who should undertake immunotherapy and dosing schedules. Finally, there is discussion on potential biomarkers of response to immunotherapy, the use of component-resolved diagnostics, novel approaches, alternative routes and potential areas for future research.

Keywords aeroallergens, allergen, allergic rhinitis, allergen standardization, allergy to animals, allergy to house dust mites, asthma, BSACI, cat allergy, component-resolved diagnostics, cost effectiveness, dosing schedules, grass pollen, guideline, immunotherapy, oral allergy syndrome, perennial rhinitis, pollinosis, ragweed allergy, SAR, seasonal pollen induced rhinitis, subcutaneous immunotherapy, sublingual immunotherapy, tree pollen
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Executive summary

- Untreated rhinitis represents a major cause of morbidity that includes interference with usual daily activities and impaired sleep quality.
- Immunotherapy, both subcutaneous and sublingual, is an effective treatment for adults and children with severe allergic rhinitis (AR) that does not respond to conventional pharmacotherapy and allergen avoidance measures.
- The efficacy of immunotherapy depends on correct patient selection, the type of allergen and the product chosen for treatment. Each vaccine requires individual assessment before recommendation for routine use.

- In asthma, the risk benefit is less favourable than for rhinitis and therefore immunotherapy for asthma is not routinely recommended in the United Kingdom.
- Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) has been shown to give long-lasting benefit for some years after stopping treatment.
- Single allergen vaccines are more effective than vaccines containing mixtures of allergens.
- Selection of patients for immunotherapy requires accurate identification of an underlying allergic trigger through a combination of clinical history and skin and/or blood tests for allergen specific IgE.
- SCIT is safe when undertaken in selected individuals in a specialist allergy clinic by trained health professionals – in a setting with access to immediate treatment for anaphylaxis and resuscitation if required.
- The safety profile of SLIT appears to be superior to SCIT although there have been no head to head comparisons of efficacy.
- Cost effectiveness for immunotherapy has been shown but only in vaccines that provide long-term benefit.
- Patients receiving immunotherapy should be carefully monitored for at least 1 h (UK recommendation) and systemic reactions treated promptly.

Introduction

Allergen immunotherapy involves the repeated administration of allergen extracts with the aim of reducing symptoms on subsequent allergen exposure, improving quality of life (QoL) and inducing long-term tolerance. In order to be effective immunotherapy requires careful patient selection. Immunotherapy is safe provided adequate precautions are taken. A decision whether to treat with immunotherapy will depend on a variety of personal and organizational factors which determine whether one type of immunotherapy is more suitable than another (e.g. SCIT vs. SLIT).

AR affects more than 20% of the population in the United Kingdom and western Europe [1]. Rhinitis represents a major cause of morbidity that includes interference with usual daily activities and impaired sleep quality [2]. The majority of patients respond adequately to pharmacotherapy, provided that it is taken properly and regularly. Nevertheless, a substantial proportion of patients report inadequate relief of symptoms despite treatment with intranasal corticosteroids and oral or topical antihistamines [3]. It is also reasonable to offer allergen immunotherapy to those unable to tolerate pharmacotherapy,

The main indications for immunotherapy in the United Kingdom are

1. IgE-mediated seasonal pollen induced rhinitis, if symptoms have not responded adequately to optimal pharmacotherapy [4, 5].
2. Systemic reactions caused by hymenoptera venom allergy [see separate British Society for Allergy and Clinical Immunology (BSACI) guideline]
3. Selected patients with animal dander or house dust mite (HDM) allergy in whom rigorous allergen avoidance and reasonable pharmacotherapy fail to control symptoms.

The selection, initiation and monitoring of all patients for immunotherapy should be supervised by specialists in allergy. Immunotherapy should only be administered by physicians and nurses with specialist knowledge of allergy and specific immunotherapy (SIT) [6].

Rationale for use

What is the evidence for the use of immunotherapy in seasonal allergic rhinitis (SAR)?

Subcutaneous immunotherapy

A recent Cochrane systematic review of SCIT in SAR [7] demonstrated efficacy as shown by reductions in seasonal symptoms and rescue medication compared with placebo treatment. Data from large randomized trials have also supported dose-dependent efficacy in seasonal rhinitis. For example in a UK multi-centre trial of an alum-based grass pollen vaccine (Alutard SQ *Phleum pratense*) in 410 patients with severe seasonal rhinitis there was a mean 30% reduction in symptoms and $>40\%$ reduction in rescue medication during the summer [8]. There have been few direct comparisons of the effectiveness of SCIT and regularly administered pharmacotherapy and further trials are needed. Evidence for efficacy of the subcutaneous route in perennial rhinitis is less robust, with no current systematic review and meta-analysis, although individual studies report efficacy. One trial [9] found that HDM immunotherapy resulted in a 58% reduction in symptoms ($P<0.002$) and a 20% reduction in the use of rescue medication despite a large placebo effect. Another DBPC study of HDM immunotherapy for rhinitis found significant reduction in a clinical index derived from symptom and drug scores, visual analogue score, nasal challenge and skin prick test (SPT) ($P<0.01$) and also in each parameter [10]. One possible reason for the apparent lower success rate of HDM immunotherapy for perennial rhinitis is that perennial rhinitis and rhinosinusitis have a multitude of causes and, even in patients sensitized to HDM it is often difficult to be certain that allergy is contributing significantly to symptoms. It is evident from the variety of studies with each allergen that the degree of efficacy is allergen and product-specific such that each vaccine requires individual assessment before recommendation for routine use.

Many controlled studies have also shown that SCIT and SLIT exerts beneficial effects on asthma symptoms in atopic, asthmatic adults and children clinically sensitized

to seasonal and perennial allergens [11–13]. Meta-analyses [14–16] of placebo-controlled trials for asthma suggest a small but significant improvement in symptoms and lung function with active therapy as compared with placebo. The problem is that there are very few studies addressing whether and in what circumstances immunotherapy adds to conventional anti-asthma therapy in terms of reduced drug consumption, improved lung function or indeed any other outcome measure. In one such study [17], HDM SCIT administered for 3 years to adult atopic asthmatics sensitized to mite slightly but significantly reduced 'as required' bronchodilator usage and increased peak flow as compared with placebo, although cumulative inhaled corticosteroid dosages, symptoms, lung volumes and bronchial responsiveness to methacholine were unchanged. A more recent study [18] has suggested that HDM SCIT, when added to conventional asthma therapy may be corticosteroid sparing in children.

Although the incidence of severe systemic reactions with subcutaneous allergen immunotherapy is low, asthmatics are particularly susceptible to severe bronchospasm during such reactions [11]. In view of this risk and the uncertainty of benefit, immunotherapy is not currently recommended for the treatment of perennial asthma in the United Kingdom. In contrast, the presence of seasonal asthma in those with severe seasonal pollinosis is not a contra-indication. One long-term randomized controlled open study of SCIT in pollen-allergic children provided evidence that immunotherapy may modify the natural history of asthma with a two- to threefold reduction of physician-diagnosed asthma that persisted for 10 years after the initiation of treatment and was accompanied by a parallel reduction in rhinitis symptoms [20]. However, pending confirmation from randomized, blinded, controlled trials immunotherapy is not currently recommended for asthma prevention.

Sublingual immunotherapy

SLIT involves the regular self-administration and retention of allergen extract under the tongue for 1–2 min before the extract is swallowed. A Cochrane meta-analysis [19] that has been recently updated [20] to include a total of 42 double-blind, placebo-controlled studies showed a significant reduction in rhinitis symptoms and medication requirements. There are also recent systematic reviews with meta-analyses that demonstrate efficacy of SLIT in children (Table 1) [21, 22].

It is not yet clear from these studies whether SCIT and SLIT are of equivalent efficacy. Optimal regimens for administration of both types of treatment may be refined in the future and therefore comparison of their relative effectiveness will continue to evolve. As with other meta-analyses, limitations include heterogeneity between studies, and a lack of standardization of immunotherapy protocols and outcome measures [23]. Negative publication bias is also possible although less likely following the introduction of regulatory requirements to register all clinical trials on a public database. In support of the conclusions of recent meta-analyses, recent data from large multi-centre trials of SLIT for seasonal rhinitis in adults (reviewed in [24]) and in children [25, 26] have provided further evidence for the efficacy of SLIT at least for grass pollen-induced SAR (Table 1).

Table 1. Efficacy of immunotherapy in allergic rhinitis (summary of cochrane meta-analyses)

	Subcutaneous immunotherapy for seasonal allergic rhinitis [7]	Sublingual immunotherapy for seasonal and perennial rhinitis [14]
Participant numbers (Active/Placebo)	597/466	2333/2256
Symptom scores SMD random (95% CI)	−0.73 (−0.97, −0.50)	−0.49 (−0.64, −0.34)
P-value	<0.00001	<0.00001
Heterogeneity (I^2)	63%	81%
Medication scores SMD random (95% CI)	−0.57 (−0.82, −0.33)	−0.32 (−0.43, −0.21)
P-value	<0.00001	<0.00001
Heterogeneity (I^2)	64%	50%

Heterogeneity:
Low = I^2 25%.
Moderate = I^2 50%.
High = I^2 75%.

Summary statement of efficacy for sublingual and subcutaneous immunotherapy in allergic rhinitis

In summary, there is category 1a evidence [grading according to Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/)] for efficacy in adults and children to support both SCIT and SLIT for AR. Patients report improvements in symptom control and QoL although may continue to require concomitant pharmacotherapy after SIT. The sublingual route, particularly for seasonal pollinosis, represents a viable alternative to SCIT that is suitable for home use [27]. The indications are similar so patient choice is important in the decision whether to use the subcutaneous or sublingual route [27]. There, however, is a particular need for more definitive large studies of immunotherapy with perennial allergens and long-term studies that include a pharmaco-economic evaluation compared with anti-allergic drugs. Head-to-head trials that compare SLIT with SCIT are also needed.

Duration of immunotherapy treatment and its long-term effectiveness

Subcutaneous immunotherapy

Few studies have examined the long-term efficacy of SCIT with aeroallergens. There is one randomized,

double-blind, placebo-controlled cessation study of grass pollen immunotherapy [28]. After 3–4 years of SCIT, there was no significant difference in symptom or medication scores in the subsequent three pollen seasons. The others are open studies. In a study that monitored 40 patients with asthma treated with HDM SCIT for 1–8 years, half relapsed in the subsequent 3 years [29] but how far this reflects possible loss of, and subsequent re-acquisition of clinical allergy to house dust mite cannot be determined. These data suggest that 3 years of grass pollen SCIT has benefits that persist for a further 3 years after discontinuation, whereas the potential long-term benefits after discontinuation of SCIT using perennial allergens remains to be determined.

Sublingual immunotherapy

There is evidence that SLIT may also have long-term effects. A double-blind randomized controlled trial of grass allergen tablet immunotherapy in adults with moderate/severe persistent SAR demonstrated that 3 years treatment resulted in an approximate 30% reduction in symptoms and 40% decrease in use of anti-allergic drugs that was maintained for 1 year after stopping treatment, supporting a disease-modifying effect [30].

What is the evidence for pre-seasonal immunotherapy?

The use of immunotherapy as a pre-seasonal or co-seasonal therapy is more convenient, given the fewer visits required for patients and staff, and therefore potentially more cost-effective. Pre-seasonal SCIT with modified allergens (allergoids) [31, 32] have been shown to be efficacious whereas long-term benefits following withdrawal have yet to be evaluated. Allergoids, which have reduced binding affinity for IgE compared with the native allergen may be safer, although this would be difficult to demonstrate in controlled trials. Although four to seven pre-seasonal injections of allergoids appear to be efficacious, the optimal number of injections has yet to be defined. In the case of SLIT one study of sublingual grass tablet immunotherapy suggested that treatment should start at least 8 weeks before the season and be continued for at least 16 weeks [24]. There are only limited data on the long-term benefits of pre-seasonal immunotherapy but there is a single report of a placebo-controlled study of 3 years' treatment with SLIT which demonstrated persistent benefit for at least 1 year following cessation of immunotherapy [33].

Is there evidence of efficacy for immunotherapy using multiple allergens?

The clinical benefit of allergen immunotherapy is specific for the allergen species used for immunotherapy. For example, Norman and Lichtenstein [34] showed that ragweed SCIT in dual ragweed- and grass-allergic subjects was effective only in relieving symptoms during the ragweed season. Frew et al. [8] studied participants with seasonal hayfever whose symptoms were largely confined to the grass pollen season. In subjects selected in this way grass pollen immunotherapy using an alum-based single species grass vaccine was equally effective in subjects with multiple positive skin tests compared with those monosensitized to grass pollen. Lowell and Franklin [35] demonstrated that ragweed allergen was effective as a constituent of a multi-allergen mix in treating seasonal ragweed-induced symptoms. Taken together this evidence demonstrates that SCIT using a single allergen is allergen-specific, that single allergen immunotherapy may be effective against the relevant allergen in polysensitized patients and that a single allergen used for immunotherapy as part of a multi-allergen mixture may retain efficacy against the relevant allergen.

In contrast, evidence in favour of the use of a cocktail of allergens in a mixture simultaneously to treat multiple allergies is not convincing. For the subcutaneous route, one double-blind trial of a multi-allergen mix in children with perennial asthma and multiple allergies showed no difference compared with placebo [36]. However, in patients with dual sensitivity to grass and olive pollen, SCIT with a mixture of modified grass and olive extracts was effective [37]. For the sublingual route, an open study of simultaneous administration of grass and birch allergens reduced seasonal symptoms to both allergens, although the absence of a placebo meant that results could have been explained by a placebo effect alone [38]. In contrast, in a blinded controlled single centre study, sublingual grass allergen as part of a multi-allergen mix did not affect thresholds for titrated nasal challenge or levels of serum-specific IgG4 whereas the sublingual grass extract alone increased both [39].

Currently available commercial products contain only mixtures of related and cross-reacting allergen; for grass a mixture of four to six individual grasses and for dust mite, *Dermatophagoides pteronyssinus and Dermatophagoides farinae*. Mixing of unrelated allergens is technically feasible although in view of potential interactions between enzymatic components, detailed quality control and stability assessments are required [40]. For example, grass allergens were unstable after mixing with fungal or cockroach extracts [41].

Further controlled trials that employ an inclusive mix of relevant allergens in effective concentrations in defined allergic populations are needed. However, at present, allergen immunotherapy with allergen mixtures in multi-allergic patients cannot be recommended either via subcutaneous or sublingual routes.

Indications for allergen immunotherapy

Selection of patients for immunotherapy requires accurate identification of an underlying allergic trigger through a

combination of clinical history and skin and/or blood tests for allergen specific IgE. While IgE sensitization to additional inhalant allergens is not a contraindication, immunotherapy for one allergen is less likely to be effective where exposure to other allergens is contributing to ongoing symptoms. Initial management should focus on pharmacotherapy and allergen avoidance measures. Where these measures achieve adequate symptom control there is no proven medical advantage in proceeding to immunotherapy. A clearer mandate for immunotherapy emerges when patients have persistent symptoms despite best use of antiallergic medication.

The decision of patient and clinician to embark on immunotherapy should be founded on an understanding of the necessary commitment involved as well as the scope and effectiveness of immunotherapy for their disease. Patients should be aware that immunotherapy with any allergen is unlikely to be curative with clinical trials typically demonstrating a 30–40% reduction in symptoms and similar reduction in medication use in the first year of treatment, although pharmacotherapy is likely to be able to control symptoms much more effectively after immunotherapy. The available data also suggests that immunotherapy may offer long-term benefits after its discontinuation, particularly where treatment has been continuously administered for several years. The benefit of immunotherapy for AR triggered by perennial allergens, particularly HDM, is less well established than with seasonal allergens. Nevertheless, clinical trials have shown a definite benefit provided subjects are appropriately selected [42]. Clearer evidence of efficacy has been established in animal dander, especially cat allergy [43–46].

Immunotherapy is conventionally given for 3 years, either continuously or pre-seasonally. Cessation of immunotherapy should be considered if clinical improvement is not apparent after 2 years of treatment.

Contraindications to allergen immunotherapy

Very rare serious and fatal adverse reactions to SCIT have occurred in patients with uncontrolled or unstable asthma [47]. Asthma is therefore a relative contraindication for immunotherapy although seasonal asthma is not, because many patients with seasonal pollen asthma respond well to immunotherapy and this is safe provided updosing is undertaken out of season. BSACI recommends that immunotherapy for rhinitis is not indicated in perennial asthma, except for those patients with mild intermittent asthma symptoms controlled with occasional bronchodilator use [step 1 the SIGN/British Thoracic Society (BTS) (http://www.brit-thoracic.org.uk/) asthma guidelines [48]]. This recommendation is in contrast to US practice where asthma is not considered to be such an important contraindication. Patients with asthma should be referred for treatment to a tertiary centre. Allergen immunotherapy for rhinitis should not be initiated in patients receiving β-blockers as these drugs may enhance the end organ cardiac, respiratory and cutaneous effects of type-1 hypersensitivity reactions and make anaphylaxis difficult to treat [49–52]. Relative contraindications for immunotherapy include underlying chronic disorders causing impaired tolerance of hypotension or bronchospasm, immunodeficiency, malignancy, autoimmune diseases and immunosuppressive agents. A careful risk-benefit assessment should be undertaken in these patients. Although allergen immunotherapy has no known teratogenic effects, immunotherapy must not be initiated during pregnancy. However, patients who have not had systemic events during maintenance therapy may be allowed to continue their course of treatment [53].

Allergen immunotherapy in children

Specific allergen immunotherapy is effective in children with moderate to severe AR who do not respond to environmental control and optimal medication. SLIT with grass pollen extract is licensed in the United Kingdom for children aged 5 years and above [54]. However, there is only limited published evidence to support the use of immunotherapy in children under 5 years of age although both SCIT and SLIT have been used in this age group [55].

SCIT [56–59] and SLIT [33, 60–63] improve the symptoms of AR. In children, there is also evidence that immunotherapy can prevent or at least delay the onset of asthma. In a controlled trial of subcutaneous pollen immunotherapy, improvement in AR symptoms lasted for at least 7 years after discontinuation of treatment [57, 58]. In the same study, there was a reduction in the progression from rhinitis to physician-diagnosed asthma (OR 2.5 in favour of active treatment) which also persisted for 7 years. Two trials of subcutaneous HDM immunotherapy in monosensitized children provided further evidence for a disease-modifying effect, with prevention of onset of new allergic sensitizations [64, 65]. In a single open study, sublingual grass pollen immunotherapy was associated with reduction in development of seasonal asthma during the 3-year active treatment period with reduced risk of new sensitizations [66].

Pre-seasonal and pre-co-seasonal treatment for seasonal allergens is also effective [67]. Subcutaneous cluster up dosing is a safe alternative to conventional regimens for HDM and grass pollen achieving clinical efficacy sooner [68, 69]. Ultra-rush updosing with sublingual drops and also immunotherapy with tablets containing pollen extracts may be well tolerated and effective [62, 70–72].

Immunotherapy for allergic rhinitis and oral allergy syndrome

Birch-induced AR is commonly associated with oral allergy symptoms after eating raw fruit, vegetables and

Box 1. General considerations for the administration of allergen immunotherapy

- Allergen immunotherapy must be performed in specialist allergy centres with adequate facilities including drugs used for the treatment of anaphylaxis. Equipment for resuscitation must be immediately available.
- Allergen immunotherapy must be performed by health professionals with adequate knowledge and experience and the ability to recognize and treat early symptoms and signs of anaphylaxis.
- Before initiating immunotherapy patients must receive adequate information and counselling about their planned immunotherapy schedule.
- Written informed consent must be obtained from all patients (or parent/guardian in paediatric practice) and filed in the patient's hospital record
- Before each injection, patients should be identified by name, date of birth and the vaccine to be administered
- Injection Immunotherapy must be under the direct supervision of a physician experienced in treating anaphylaxis and trained in resuscitation.
- The allergen immunotherapy dose and shelf-life should be double-checked with a second health professional who has adequate experience and knowledge.
- The patient should be asked about any local or general side-effects following the previous injection – any side-effects should be noted and if necessary dosage adjustment made.
- The interval since the previous injection should be checked, any delay from the planned schedule recorded and if necessary dosage adjustment made.
- Any intercurrent infection, other new illness or feelings of malaise or tiredness should be noted. If present, postponement of the immunotherapy injection should be considered.
- Any change in the patient's clinical status should be recorded including any new medications, pregnancy, etc.
- In patients with coexisting asthma, it is essential to ensure that their asthma has been stable and optimally controlled before administration of immunotherapy. Routine peak flow monitoring before and after injections is advisable so that poorly controlled asthma is never missed.
- In patients with seasonal allergic rhinitis, the maintenance subcutaneous dose may be reduced or postponed if the patient is symptomatic, either during the relevant pollen season, during co-seasonal exposure to an overlapping pollen or to a relevant perennial allergen.
- Patients should remain under supervision within the clinic for at least an hour after their last injection
- In patients with hayfever, allergen immunotherapy must not be initiated during the pollen season.

certain nuts [73]. This condition is believed to reflect the presence of IgE cross-reactivity between epitopes in pollen allergens and homologous proteins in these foods. Although some studies have shown limited improvement of oral allergy symptoms following immunotherapy with birch pollen extracts [74–79] others have disagreed. Improvements appear more likely to occur in patients over 20 years who are monosensitized to birch pollen and with more intense oral symptoms. Resolution is less likely in patients treated with combined grass and tree pollen immunotherapy [75]. Symptoms may become worse [75, 80] and new sensitizations may develop while on treatment [81]. Symptoms may also recur once treatment has been discontinued. On the basis of current evidence, the presence of oral allergy syndrome is neither an indication nor a contra-indication to birch pollen SCIT or SLIT. Component resolved analysis to individual birch allergens may throw further light on the variable response of individuals with oral allergy syndrome.

Preparations available in the United Kingdom

Two immunotherapy vaccines are currently licensed for treatment of AR in the United Kingdom. The only licensed SCIT product is Pollinex®, available for grass or tree pollen, produced by Allergy Therapeutics (Worthing, UK). The only licensed sublingual product is the grass pollen vaccine Grazax®, produced by ALK Abelló (Horsholm, Denmark). However, a large number of unlicensed vaccines may be prescribed to individual, 'named patients' according to clinical need. The characteristics of the vaccines most commonly used in United Kingdom immunotherapy clinics, as determined by a BSACI survey in the Summer 2010, are summarized in Table 2. Although producers estimate content of certain major allergens in vaccines using in-house assays, the sole purpose of these measurements is internal standardization during manufacture. In the absence of agreed methods for external allergen standardization (see 'Allergen standardization') comparison of these values among different vaccines is of limited value.

Allergen standardization

There is some evidence that the efficacy of allergen immunotherapy is related to the cumulative allergen dose administered. This is confirmed in relation to pollen immunotherapy [8, 42, 82, 83], although information for a dose–response relationship for other allergens is limited and largely derived from provocation tests [43, 44, 46]. Allergen standardization should minimize qualitative and quantitative variation in the composition of a vaccine in order to maintain both reproducible efficacy and high standards of safety. The WHO [84] and European Pharmacopoeia [85] published guidelines on allergen standardization. In Europe, current guidelines dictate that manufacturers use in-house reference preparations to ensure standardization between product batches [86–88]. A major aspect of allergen standardization is to control for total allergenic potency, which is achieved at least in part by international collaboration between manufacturers and control authorities using the same standards

Table 2. Characteristics of the vaccines commonly used in the United Kingdom immunotherapy clinics*

	Nature of vaccine	Dosing Schedule	Content	UK Licence	Min Age	Cost (excl. VAT)	Estimated major allergen content	Information relating to allergen content estimation**
Grass pollen subcutaneous injection vaccines								
Allergovit (Allergopharma, Reinbek, Germany)	Allergoid+aluminium hydroxide	Minimum seven pre-seasonal injections each year for 3 years	Six species of grass	No	6 years	£195 per year	Approximately 50 μg group 5 allergen per course (i.e. per year)	Based on manufacturer estimate of 4.2 μg/mL Group 5 allergens in 'Strength A' and 42 μg/mL Group 5 allergen in 'Strength B'. Figures are for allergen content before denaturation step to produce allergoid
Alutard SQ (ALK Abelló)	Allergen Extract+alum	Continuous for 2–3 years (approximately 25 injections in first year, 12 maintenance injections per year thereafter)	Six species of grass	No	5 years	1st year £1359.10 (one initiation and two maintenance kits); subsequent years require two to three maintenance kits per year (£893.50–£1340.25)	Approximately 240 μg group 5 allergen first year (assume 40% dose reduction during pollen season)	Based on manufacturer estimate of 20 μg group 5 allergen per 100 000 SQ-U
Pollinex (Allergy Therapeutics)	Allergoid+L-tyrosine	Six pre-seasonal injections	12 species of grass+Rye	Yes	6 years	£450 per year	Approximately 38 μg group 1 allergen per course (i.e. per year)	Based on manufacturer estimate of 16.8 μg group 1 allergen per mL
Pollinex Quattro (Allergy Therapeutics)	Allergoid+L-tyrosine+mono-phosphoryl lipid A	Four pre-seasonal injections	12 species of grass+Rye	No	6 years	£695 per year	Approximately 22 μg group 1 allergen per course (i.e. per year)	Based on manufacturer estimate of 16.8 μg group 1 allergen per mL
Grass pollen sublingual vaccines								
Grazax (ALK Abelló)	Allergen extract (tablet)	Daily tablet for up to 3 years, starting 4 months before pollen season	Single grass species (*Phleum pratense*)	Yes	5 years	£823.50 per year (based on using 37 packs over 3 years)	Approximately 15 μg group 5 allergen per dose (5.5 mg per year)	Based on manufacturer estimate of 15 μg *Phleum pratense* group 5 allergen per 75 000 U tablet
Oralvac (Allergy Therapeutics)	Allergen extract (solution administered by pump)	Two alternative regimens: (1) Seven pumps of top dose (No. 3 bottle) per day for 3 months, or (2) three pumps per day for 8 months	12 species of grass	No	2 years	3-month regimen: £430 per year (two sets) or 8-month regimen: £629 per year (three sets)	3-month regimen: Approximately 3.9 μg group 5 allergen per dose (0.36 mg per year). 8-month regimen: 1.7 μg group 5 allergen per day (total dose per year 0.41 mg)	Based on manufacturer estimate of 8 μg/mL of group 5 allergen in top dose (No. 3 bottle; 1 'pump 'contains 70 μL)
Staloral^{300} (Stallergenes)	Allergen extract (solution administered by pump)	Nine to 11 day updosing followed by daily treatment for 4 months starting 2 months before pollen season, or; thrice weekly maintenance regimen at higher dose. Company recommend 3–5 years treatment.	Five species of grass	No	5 years	Both daily and thrice weekly regimen require two kits: total cost £394.20	Daily regimen (120 IR): Approximately 8 μg group 5 allergen per dose (0.98 mg per year). Thrice weekly regimen (240 IR): 16 μg group 5 allergen per dose (0.84 mg per year).	Based on manufacturer estimate of 20 μg/mL of group 5 allergens in 300 IR

Table 2. continued

	Nature of vaccine	Dosing Schedule	Content	UK Licence	Min Age	Cost (excl. VAT)	Estimated major allergen content	Information relating to allergen content estimation**
Tree pollen subcutaneous injection vaccines								
Allergovit (Allergopharma)	Allergoid+aluminium hydroxide	Minimum 7 pre-seasonal injections each year for 3 years	Three tree species (Birch/Alder/Hazel)	No	6 years	£195 per year	Approximately 16 μg Bet v 1 major Birch allergen per course (i.e. per year). Alder/Hazel major allergen content not available.	Based on manufacturer estimate of 1.3 μg/mL Bet v1 major Birch allergen in 'Strength A' and 13 μg/mL Bet v1 in 'Strength B'. Figures are for allergen content before denaturation step to produce allergoid. Alder/Hazel represent an additional 30% and 35% of vaccine content, respectively
Alutard SQ (ALK Abelló)	Allergen extract+alum	Continuous for 2–3 years (approximately 25 injections in first year, 12 injections per year thereafter)	Single tree species (Birch)	No	5 years	1st year £1359.10 (1 initiation and 2 maintenance kits); subsequent years require two to three maintenance kits per year (£893.50-£1340.25)	Approximately 145 μg Bet v 1 allergen first year (assume 40% dose reduction during pollen season)	Based on manufacturer figure of 12 μg Bet v1 allergen per 100 000 SQ-U
Pollinex (Allergy Therapeutics)	Allergoid+L-tyrosine	Six pre-seasonal injections	Three tree species (Birch/Alder/Hazel	Yes	6 years	£450 per year	Approximately 34 μg major allergen (Bet v1 equivalent) per course (i.e. per year)	Based on manufacturer estimate of 14.75 μg major allergen (Bet v1 equivalent) allergen per mL
Pollinex Quattro (Allergy Therapeutics)	Allergoid+L-tyrosine+mono-phosphoryl lipid A	Four pre-seasonal injections	Three tree species (Birch/Alder/Hazel	No	6 years	£695 per year	Approximately 19 μg major allergen (Bet v1 equivalent) per course (i.e. per year)	Based on manufacturer estimate of 14.75 μg major allergen (Bet v1 equivalent) allergen per mL
Tree pollen sublingual vaccines								
Staloral[300] (Stallergenes)	Allergen extract (drops administered by pump)	Nine to 11 day updosing followed by daily treatment for 4 months starting 2 months before pollen season, or; thrice weekly maintenance regimen at higher dose. Company recommend 3–5 years treatment.	Betula-ceae (four species: birch, alder, hazel, horn-beam)	No	5 years	Both daily and thrice weekly regimen require two kits: total cost £394.20 per year	Daily regimen (120 IR per dose): Approximately 2.4 mg Bet v1 major allergen each year (19.6 μg Bet v 1 allergen each dose) Thrice weekly regimen (240 IR): 2.0 mg Bet v1 major allergen each year (39.2 μg Bet v 1 allergen each dose).	Based on manufacturer estimate of 49 μg/mL of Bet v 1 family allergens in 300 IR
House dust mite (HDM) subcutaneous injection vaccines								
Alutard SQ (ALK Abelló)	Allergen extract+alum	Continuous for 2–3 years (approximately 25	HDM (Der)	No	5 years	1st year £1359.10 (one initiation and two maintenance kits);	Approximately 90 μg Der p 1 allergen per year	Based on manufacturer estimate of 7 μg Der p 1

		injections in first year, 12 injections per year thereafter)				subsequent years require two to three maintenance kits per year (£893.50–£1340.25)		major allergen per 100 000 SQ-U
HDM sublingual vaccines								
Oralvac Compact (Allergy Therapeutics)	Allergen extract (solution administered by pump)	Three pumps per day for 8 months	*D. pteronyssinus*	No	2 years	£629 per year (three sets)	Approximately 2.9 μg major allergen per day (total dose per year 0.71 mg)	Based on manufacturer estimate of 13.8 μg/mL of Der p 1 major allergen in top dose (No. 3 bottle; 1 'pump 'contains 70 μL).
Staloral300 (Stallergenes)	Allergen extract (drops administered by pump)	Nine to 11 day updosing followed by daily treatment, or; thrice weekly treatment at higher dose all year. Company recommend 3–5 years treatment.	*D. pteronyssinus and D. farinae*	No	5 years	Both daily and thrice weekly regimens require five kits: total cost £985.50 per year	Daily regimen (120 IR): Approximately 84 μg group 1 allergens per dose (30.7 mg per year). Thrice weekly regimen (240 IR): 168 μg group 1 allergen per dose (61.3 mg per year).	Based on manufacturer estimate of 20 μg of Der p 1 and 50 μg/mL Der f 1 in 100 IR Awaiting correction by company
Cat subcutaneous injection vaccines								
Alutard SQ (ALK Abelló)	Allergen extract+alum	Continuous for 2–3 years (approximately 25 injections in first year, 12 injections per year thereafter)	Cat dander	No	5 years	1st year £1359.10 (one initiation and two maintenance kits); subsequent years require two to three maintenance kits per year (£893.50-£1340.25)	Approximately 200 μg Fel d 1 allergen per year	Based on manufacturer estimate of 15 μg Fel d 1 major allergen per 100 000 SQ-U
Cat sublingual vaccines								
Oralvac Compact (Allergy Therapeutics)	Allergen extract (solution administered by pump)	Three pumps per day for 8 months	Cat dander	No	2 years	£629 per year (three sets)	Approximately 0.59 μg major allergen per day (total dose per year 144 μg)	Based on manufacturer estimate of 2.8 μg/mL of Fel d1 in top dose (No. 3 bottle; 1 'pump 'contains 70 μL).

*According to a BSACI survey of UK immunotherapy clinics performed during the Summer 2010. A survey was performed by the BSACI of UK immunotherapy clinics during the Summer 2010: 42 clinics that responded to the survey were performing immunotherapy with inhalant allergens. Those vaccines used by two or more of these clinics are represented.

**Inhouse measurements not subject to external standardization.

(available from the National Institute of Biological Science and Control, Hertfordshire, UK [88]). Inhouse reference preparations used by individual laboratories are compared with international standard and 'batch-to-batch' control involves monitoring quantity and allergenic potency of major allergens.

Recently Chapman et al. [89] in their CREATE project have produced a panel of recombinant inhalant allergens indistinguishable from their purified natural counterparts together with several standardized enzyme-linked immunoassays for their accurate measurement. This represents a major step forward towards standardization to provide reference materials and tests and allow future measurement and comparison of allergen preparations world-wide.

Safety

Safety of subcutaneous immunotherapy

SCIT is safe when undertaken in selected individuals in a specialist clinic with adequate facilities and trained health professionals. Patients treated with SCIT are at risk of both local and systemic adverse reactions but, in the vast majority of cases, symptoms are readily reversible if they are recognized early and treated promptly. Recently a standardized grading system for the reporting of systemic allergic reactions during SCIT has been developed by the World Allergy Organisation [90]. This should facilitate more standardized reporting of systemic reactions globally in the future. Side-effects may occur with all allergen preparations whether using standardized extracts [8], allergoids [31] or recombinant allergens [91, 92].

In the Cochrane meta-analysis of 2007 patients undergoing SCIT for SAR [7], 22% on immunotherapy vs. 8% on placebo had mild, grade II allergic reactions at some time during their course of immunotherapy and 7% of immunotherapy vs. 1% of placebo-treated patients had grade III allergic reactions [European Academy of Allergy and Clinical Immunology (EAACI); http://www.eaaci.net/] [93]. 0.72% of patients, (three in the immunotherapy-treated group) vs. 0.33% (one in the placebo group) suffered grade IV reactions. Adrenaline (epinephrine) was used in 3.4% of participants (19/557 patients, equivalent to 0.13% of 14 085 injections) in the treated group vs. 0.25% (1/404 patients equivalent to 0.01% of 8278 injections) in the placebo group. There were no fatalities. Pre-treatment with oral H1-antihistamines during the induction phase reduced the frequency and severity of systemic side-effects [94]. However, antihistamines are not routinely advised in view of the theoretical risk that they may mask or delay the onset of systemic reactions (particularly during updosing) such that their risk-benefit ratio in the large numbers of patients necessary for such an evaluation remains unproven. Antihistamines may be considered in those who experience repeated mild local or systemic reactions to immunotherapy during their maintenance phase of treatment

Fatalities that have previously been reported with SCIT have occurred almost exclusively in patients with co-existing asthma (16 of 17 in one report) that was frequently poorly controlled [42, 47]. In a North American survey of events from 1990 to 2001 and involving 646 practices, 41 fatal (20 directly and 21 indirectly reported by physicians) and 273 near-fatal reactions to SCIT were reported. This survey estimated fatal reactions at a rate of 1 per 2.5 million injections [95] (Box 2).

Safety of sublingual immunotherapy

The safety profile of SLIT appears superior to that of subcutaneous therapy in terms of the incidence of severe systemic reactions, the caveat being that such incidents typically occur away from expert care. Reported serious adverse effects such as anaphylaxis during sublingual treatment have been infrequent, with six reported events to date [96–103]. In clinical trials as well as post-marketing surveys over the last 2 decades, adverse reactions have occurred in 10–15% of patients receiving SLIT and have been classified as mainly local non-life-threatening, self-remitting episodes [61, 62, 100–107]. Most patients develop discomfort in the early phase of treatment including oropharyngeal pruritus and angio-oedema. These symptoms may respond to antihistamines on an *ad hoc* or prophylactic basis and often settle with continued administration of the vaccine [100–103, 107]. Uncommonly, local reactions are severe enough to discontinue treatment. Other relatively rare adverse reactions include nausea and/or abdominal pain particularly in children, rhinitis, conjunctivitis, headache, urticaria, cough and bronchospasm [100–103, 107].

As SLIT is self-administered, it is important to give patients and their carers clear information about the nature and likelihood of unwanted events and simple, written instructions on the steps to take if they arise, as well as advice on the storage of sublingual vaccines securely out of the reach of children. All patients should

Box 2. Factors associated with severe adverse reactions during subcutaneous immunotherapy are as follows

Co-existing asthma
Poorly controlled asthma
History of previous systemic reaction(s) to immunotherapy
Delay or omission of the use of adrenaline in treating anaphylaxis
Inappropriate selection of candidates for injection immunotherapy
Dosing errors
Changeover between batches of allergen; reaction to the first dose of a new vial
Lack of cardio-respiratory resuscitation facilities
Commencing an updosing immunotherapy regimen during the pollen season

have access to telephone advice and the opportunity to be seen at short notice. Antihistamines should be available to all patients (see Appendix A). Where primary care practitioners agree to share care of patients undergoing SLIT, they too should be fully briefed about side effects and how to manage them.

Cost effectiveness of immunotherapy

When evaluating the cost effectiveness of a drug, the costs of all resources including the cost of the drug itself and the costs of emergency physician visits, acute ward visits and hospitalization must be taken into account, both during the period of treatment and possibly into the future if the drug has effects which endure for longer. It is also important to consider societal costs such as productivity loss and time off work. National Institute for Health and Clinical Excellence (NICE) use 'quality adjusted life years' or QALYs to appraise new drugs as a generic measure comparable across disease areas that combine two dimensions of health: life expectancy and QoL [108]. If a new treatment is more cost effective than standard therapy then the cost per QALY gained should be below an acceptable threshold (currently set at £20–30 000) [109]. Thus, medical interventions can be compared regardless of whether they increase life expectancy or QoL.

Using these methods Grazax was reported in three studies to demonstrate an acceptable cost per QALY gained [110–112]. Since in each of these studies, however, the pharmaco-economic analysis assumed benefits from treatment for at least 6 years after cessation of 3 years of treatment, and comparison was with oral antihistamine and nasal corticosteroid therapy taken as required for intolerable symptoms rather than prophylactically, these data are difficult to interpret.

A number of studies, which have evaluated the cost effectiveness of immunotherapy did not employ a generic QoL measure, precluding a calculation of cost per QALY gained and allowing only comparison between immunotherapy and medical therapy. Using these methods there is evidence that both SCIT [113] and SLIT [114] reduce drug costs with fewer inpatient and outpatient episodes, although it is not clear that comparison was with optimally delivered, regular prophylactic medical therapy.

A 6-year prospective observational study of Italian adults treated with high dose SCIT for *Parietaria* (Alustal®, Stallergenes, Antony, France) [115], showed a significant cost benefit with 3 years of treatment with SCIT compared with drugs alone. As for all such studies, the cost benefit was realized only because of the prolonged clinical benefits of SCIT beyond the period of treatment. In this particular case, the cost reduction was maintained for at least 3 years after discontinuation of SCIT with a net saving of €623/patient/year. High dose SLIT (Staloral®, Stallergenes) was also considered cost effective in a retrospective analysis of 135 Italian children with AR and asthma (46 had perennial and 89 seasonal allergies). The average annual cost/patient was €2672 in the year before initiation of SLIT and €629/year during the 3 years of treatment when both direct and indirect costs were taken into account [116].

More recent studies have attempted to evaluate cost effectiveness of immunotherapy compared to symptomatic treatment alone. An Italian study of SLIT (Staloral®, Stallergenes) in adults with seasonal rhinitis and asthma [117] evaluated the cost per patient without asthma at the end of an observation period of 6 years. In this study, the break-even point in favour of SLIT was achieved in the fourth year when only healthcare costs were taken into account but was achieved in the second year when societal costs were also evaluated. A French study in children and adults treated with SLIT or SCIT (Alustal® and Staloral®, Stallergenes), for both seasonal and perennial rhinitis and asthma [118] reported similar findings, with immunotherapy most cost effective in dust mite allergy in adults and pollen allergy in children. One study [119] reported that SLIT may be a less expensive choice of immunotherapy than SCIT (Phostal™, Stallergenes) from all study perspectives (society, patient and NHS).

Practical aspects of immunotherapy

Recent position papers that address practical aspects of immunotherapy in detail are those from the European Academy of Allergy and Clinical Immunology [6] and the American Academy of Allergy, Asthma and Immunology [120]. General considerations are listed in Box 1.

Who should undertake immunotherapy?

SCIT should be carried out only by specialists with experience and knowledge of immunotherapy and in centres undertaking SCIT in significant numbers of patients and where the team has expertise and experience in the recognition and treatment of acute allergic reactions including asthma and anaphylaxis.

The decision to prescribe SCIT or SLIT should be undertaken by a consultant with specialist training in allergy diagnosis and immunotherapy. Physicians and nurses undertaking immunotherapy should have received specialist training in its use. In particular, they must be familiar with the indications and contra-indications for immunotherapy, the assessment of a patient before commencement of the therapy, the practicalities of using this approach and the expected adverse effects.

To undertake immunotherapy successfully and safely, space is required for the consultation. Immunotherapy should be performed with at least two people present, one of whom being a physician. A staff team should be in place for observation following the injection and an area,

including a couch, should be available to manage and treat patients with unwanted effects. Treatment for anaphylaxis and resuscitation equipment should be available at all times [34].

The following equipment is required:

- Adrenaline (1 : 1000) should be drawn up or immediately available.
- Antihistamines and corticosteroids (intravenous and oral preparations).
- β-agonist (with facilities for inhalation with or without a spacer and nebulization),
- Saline/colloids for intravenous infusion.
- Oxygen and suction equipment should be immediately available.
- Equipment for monitoring blood pressure and oxygen saturation.
- Nebulizer and masks.
- Peak flow meter and mouthpieces.
- Syringes, needles and intravenous cannulae.

Dosing schedules for subcutaneous immunotherapy

A number of updosing schedules are used for children and adults including the conventional one injection per week [28] and cluster regimens [8]. Schedule selection will depend on the product, time to reach maintenance, patient choice, particularly with respect to side-effect profiles and convenience, and staff availability and local expertise. Generally, more rapid induction is likely to cause more adverse effects. Any updosing schedule is not fixed and must be tailored according to patient response and exposure to relevant perennial or overlapping co-seasonal allergens. The usual target maintenance dose is between 5 and 20 μg purified major allergen [42] but the maintenance dose and interval may also need to be modified as some patients only tolerate smaller doses.

Pre-seasonal immunotherapy is an alternative approach that involves administration of four to seven incremental dosages at weekly intervals, before the start of the specific pollen season for three consecutive years [31, 121]. In patients receiving immunotherapy to both tree and grass pollens, injections should be given separately with a minimum interval of 30 min between injections.

Dosing schedules for sublingual immunotherapy

SLIT involves placing the vaccine either as a tablet or in solution under the tongue for 1–2 min without swallowing. Allergen extracts must not be administered if there are raw areas or bleeding in the oral cavity or following dental procedures until the wound is completely healed. A patient information sheet about SLIT can be found in Appendix A. The optimum dosage, duration of treatment and frequency of administration of SLIT have not yet been established. Much higher doses of allergen are used than for SCIT with cumulative monthly doses typically 30–50 times greater than conventional SCIT [101]. Details of products currently available for use in the United Kingdom are summarized in Table 2.

Several regimens have been employed including daily dosing [82, 122–132] with or without an initial updosing phase, three times per week [133] and weekly [134]. With seasonal allergens such as pollen, various regimens including pre-seasonal, co-seasonal, pre- or co-seasonal followed by perennial have been investigated. It has been shown [23] for grass pollen that SLIT is more effective if commenced daily a minimum of 8 weeks before the onset of the pollen season and clear efficacy was achieved in two large controlled trials of grass allergen tablets when administered for 4 months before and during the pollen seasons [81, 82]. It has also been shown that, when SLIT treatment is continued perennially, clinical and immunological changes occur in successive years of treatment [135] although whether this requires daily as opposed to less frequent treatment is unknown. With some products, if there is a gap in vaccine administration, treatment must be re-initiated at a lower dose according to previously published guidelines [6, 93] and the experience of the clinical team.

Monitoring after treatment

Baseline blood pressure and pulse should be recorded before a course of immunotherapy is commenced. In the United Kingdom, it is a requirement that all patients remain under observation for 60 min after SCIT injections [136]. Peak expiratory flow rate should be measured in all patients before and at 30–60 min after injections. The size of the local weal and flare response and any local swelling around the injection site after 1 h is recorded. Large local reactions may require a dosage adjustment or pre-medication before subsequent injections. Eye symptoms, sneezing, scratching, restlessness, sensation of generalized heat, erythema or urticaria or a 'feeling of doom' are early indications of possible early systemic symptoms. Peak flow, blood pressure and oximetry should be monitored continuously by a separate member of the team. Severe symptoms or rapid progression of symptoms is an indication for early use of adrenaline. Adrenaline should be given *immediately* in all cases complicated by hypotension or acute respiratory distress due to asthma or angio-oedema of the upper airway.

SLIT is more convenient from the patient's perspective because only the first dosage needs administration under medical supervision. Similar observations should be used as with SCIT with additional examination of the mouth and pharynx. Subsequent dosages are administered by the patient and provided by the primary care physician, although it is customary for allergists to monitor progress,

Box 3. Reported biomarkers of clinical response to immunotherapy

Increase in allergen-specific serum IgG4 [123, 126, 138–142].
Increase in serum functional IgG responses: Inhibition of basophil histamine release [143]; inhibition of IgE-facilitated allergen binding (IgE-FAB) [144].
Reduction in immediate and late-phase skin test responses to allergen [131, 138, 140, 145].
Suppression of rise in ECP [132, 146–148] and tryptase [149] concentrations in nasal lavage during the pollen season
Increased *in vitro* IL-10 production by peripheral blood mononuclear cell (PBMC) following stimulation with allergen [150, 151]
Reduction in allergen-induced *in vitro* PBMC proliferative responses [152].
Reduction in bronchial responses to allergen and methacholine challenge [153, 154]

say every 6 months to a year. Examples of patient information sheets for sublingual and SCIT are included in Appendices A and B, respectively.

Predicting the response to immunotherapy

The current best way to engineer a favourable outcome of SCIT or SLIT is to ensure that patients are desensitized to those allergens that are responsible for their symptoms as identified in the history and with objective confirmation of IgE sensitivity. Even when this is done, however, patients show a spectrum of clinical response, and while the majority report improvements in symptoms and QoL, few lose their symptoms altogether, while a minority fail to respond. A number of end-points of immunotherapy have been described based on theories of the underlying mechanism of action (see Box 3). However, so far none of these markers have been shown to predict clinical response to immunotherapy in individual patients. The use of functional antibody assays of IgG have been shown to correlate more effectively than serum immunoreactive IgG levels [137] although still only account for a small proportion of the variance of the clinical response. Future studies are likely to focus on tracking antigen-specific T cell responses in peripheral blood and monitoring changes in target organs using non-invasive methods. Whether gene screening in blood or target tissues or more extensive and sophisticated monitoring of local antibodies or cytokine or mediator pathways at protein level will be predictive remains to be determined.

Alternative routes of immunotherapy

In addition to the sublingual route as an alternative to SCIT there have been attempts to use other routes in order to improve safety while maintaining efficacy. The inhaled route proved ineffective in two clinical trials but was limited by bronchospasm [155, 156]. The oral route has also been studied although results were disappointing [157–159]. Nasal immunotherapy, in contrast, has been shown to be efficacious in several well-designed clinical trials (category of evidence, 1b according to SIGN methodology) [104]. Although encouraging, the nasal route is limited by poor patient acceptability, largely due to persistent local adverse effects that require topical nasal premedication for their prevention. Nasal immunotherapy is limited to the treatment of AR and there is no information regarding its long-term efficacy or prophylactic effects. The use of intralymph node injections of allergen [159] and more recently of allergen-containing patches for transdermal use [160] has stimulated great interest although data are currently preliminary.

Novel approaches to allergen immunotherapy

An overview of new approaches to allergen immunotherapy is provided in Box 4. Most of the present new strategies are based on the perceived need to modify allergen-specific T cell function (by skewing the cytokine profile of Th2 effector cells or inducing allergen-specific T regulatory cells) while abolishing or reducing binding of the injected substance to IgE. This not only reduces or abolishes the risk of anaphylaxis, but also allows much higher quantities of allergen to be administered safely, which may be an important factor for tolerance induction. Strategies include fusion, polymerization, refolding or fragmentation of allergens to alter their structure while preserving T cell epitopes, or immunization with identified T cell epitopes. This latter strategy is problematic in that many allergenic substances (such as grass pollen) contain a mixture of many proteins to which most individuals (major allergens) or only a minority of individuals (minor allergens) may respond. Epitope vaccination has been most successful with substances containing one or a few major allergens, such as cat dander, but even then there will be rare individuals whose MHC haplotype precludes their T cells from recognizing the particular epitopes in the vaccine. A compromise is simply to fragment the allergens into small peptides.

Because each batch of allergen produced by any given manufacturer has to be biologically standardized, units of 'biological activity' of allergens are not compatible between manufacturers. This effectively means that switching between vaccines in the course of immunotherapy is very difficult. An obvious solution is to produce recombinant allergens that can be used at defined concentrations and in complete purity to produce vaccines which would then be universally standardized. While this has been achieved successfully for some mixtures of allergens (Box 4), it is still problematic when extracts comprise

Box 4. Novel approaches to allergen immunotherapy

New approach	Rationale	Reference
Strategies to alter the shape of intact allergens		
Fusion of major allergens	Several major allergens are fused and expressed as a recombinant protein, thus altering the shape of the individual allergens and reducing IgE binding while preserving T cell epiotpes	[168]
Chimeric allergens	Fragments of major allergens are fused and expressed as a single protein, thus reducing IgE binding but preserving T cell epitopes (provided the fragments are sufficiently large)	[169]
Polymeric allergens	Major allergens are polymerized, reducing IgE binding but preserving T cell epitopes	[143]
Unrefolded allergens	Major recombinant allergens are denatured and then allowed to refold but in a manner different to the native conformation, reducing or abolishing IgE binding but preserving T cell epitopes	[170]
Strategies to fragment allergens		
Allergen fragments	Major allergens are divided into fragments, thus abolishing IgE binding but preserving T cell epitopes	[143]
Allergen peptides	Treatment is with a mixture of allergen-derived peptides covering the entire molecule or identified T cell epitopes, thus abolishing IgE binding	[171]
Conjugation of allergens to immune response modifiers		
Conjugation to CpG oligonucleotide	Major allergen is bound to a Toll-like receptor ligand (in this case TLR9), thus skewing the induced innate and adaptive immune responses away from the Th2 phenotype	[172]
Conjugation to virus-like particles	Allergens or allergen-derived peptides are coupled to virus capsid-like recombinant proteins, thus skewing the adaptive immune response and enhancing immunogenicity	[173]
Miscellaneous strategies		
Mixtures of recombinant allergens	An attempt to rationalize allergen concentrations in vaccines by using mixtures of recombinant allergens of complete purity and known concentrations	[92]
Combination immunotherapy with anti-IgE therapy	The rationale is to improve the safety of allergen immunotherapy by pre-treatment with anti-IgE, thus reducing or abolishing the possibility of anaphylaxis; safety and efficacy are still under investigation	[161, 174]
Intralymphatic vaccination	Administration of immunotherapy vaccines directly into lymph nodes under ultrasound guidance, the aim being to deliver high concentrations of allergen directly into the secondary lymphoid system; safety and efficacy are currently being explored	[159]

many major and minor allergens, each of which has to be produced in pure, recombinant form and then added back to the final vaccine in predetermined proportions. This is likely to be a relatively expensive procedure. Eventually it may be possible to 'tailor make' vaccines for individuals according to their particular patterns of recognition of major and minor allergens as determined by *in vitro*, extended IgE measurement. Although attractive in terms of allergen standardization, this strategy is again likely to be expensive and not necessarily of therapeutic advantage.

Immunotherapy has been used (Box 4) in conjunction with anti-IgE therapy. The clearest rationale for this is to improve safety, particularly in asthmatic patients. In addition, removal of allergen-specific IgE by anti-IgE therapy before immunotherapy results in it no longer being available to facilitate 'capture' of injected allergens when bound to the surface of antigen-processing cells such as B cells and dendritic cells, which could result in alternative processing and presentation of the allergen to T cells and, in theory, improved efficacy of the immunotherapy [161].

Immunotherapy vaccines are conventionally injected adsorbed to adjuvants such as aluminium hydroxide (alum) that enhances their immunogenicity and skews T cell responses [162]. Although alum is the most commonly used adjuvant for vaccines world-wide, and has been safe in millions of patients, both adults and children, there are some reports that a very small proportion of patients develop persistent cutaneous nodules when treated with alum-containing immunotherapy vaccines [163, 164] and even suggestions [165] that such injections may cause subsequent contact allergy to aluminium. Attempts have been made to improve these adjuvants so as to enhance the therapeutic effects of vaccination. Most of these approaches have involved chemical conjugation of the allergen to so-called 'immune response modifiers' (Box 4), which typically target Toll-like receptors on the surface of antigen-presenting cells, thus increasing the

immunogenicity of the allergen and, at least in theory, skewing the balance of the resulting T cell response away from the Th2 phenotype. As an alternative to chemically modifying the allergen, another approach is to inject it adsorbed onto a modified conventional adjuvant containing bacterial cell wall analogues such as monophosphoryl lipid A, which is again postulated to act as an immune response modifier [166, 167]. Time will tell whether or not these approaches are safe, more efficacious and more cost effective.

The use of component testing to improve patient selection for pollen immunotherapy

Traditionally, the choice of pollen immunotherapy relies on the time of year clinical symptoms occur and response to skin testing and/or measurement of specific IgE using whole grass or birch allergen. However, rather than using whole pollen for allergy testing, advances in molecular biology have led to identification of IgE binding proteins which have been synthesized using recombinant technology. This 'component resolved diagnosis' has the potential to reveal individual patterns of IgE sensitization in individuals with higher resolution.

Many 'allergens' are mixtures of various proteins to which individuals are variably sensitized. The formation of IgE antibodies to some of these proteins appears to be associated with a greater risk of developing clinical symptoms of rhinoconjunctivitis than others. For example, IgE directed against the Phl p 1 and Phl p 5 determinants of Timothy grass and Bet v 1 of birch pollen are associated with a relatively high risk of symptoms. Sensitization to other allergenic determinants, such as profilins (in Timothy grass, Phl p12 and in birch pollen Bet v 2) and procalcins (in grass Phl p 7 and in birch Bet v 4) on the other hand appears to carry a lower risk. This may partly underlie the poor ability of SPT to predict clinical responsiveness to the majority of allergen 'mixes'.

In pollen extracts used for SIT, disease relevant allergens generally exist in large amounts, while the content of less relevant allergens may vary [175, 176]. A retrospective assessment of the efficacy of SIT demonstrated 73% efficacy in patients sensitized to major allergens as compared with 16% efficacy when given to patients sensitized exclusively to minor allergens [177]. Consequently immunotherapy is more likely to be effective in patients sensitized to disease-relevant allergens, and component resolved diagnosis may facilitate identification of better responders and perhaps even 'tailor making' of vaccines for individuals [178].

Future research

Although the propensity of allergen immunotherapy to modify the immune system in terms of down-regulation of Th2-mediated T lymphocytes, immune deviation of T cell responses towards the Th1, induction of T regulatory cells and 'protective' non-inflammatory antibodies of IgG, IgG4 and IgA isotypes and the potential of regulatory B cells to regulate basophil responsiveness, it remains a challenge to understand what contribution each of these phenomena makes to the end result of immunotherapy which is to reduce or abolish acute and chronic responsiveness of the target organ to allergen exposure. In fact immunotherapy is an attempt to achieve the situation observed naturally in many atopic individuals who remain asymptomatic despite making IgE antibodies to allergens. Perhaps a full understanding of how immunotherapy works will require complete understanding of this natural phenomenon.

An important aspect of future research is to identify biomarkers which predict and echo responsiveness to immunotherapy and indicate when relapse is imminent. This will require adequately powered, controlled trials in which clinical end-points and persistence of responses in individuals are related to immunologic changes. Whereas traditionally the focus has been on T cell and B cell responses and changes in effector cells and antibodies, an alternative untested approach, unbiased by pre-conceptions of disease mechanisms will be to study the transcriptome and epigenome of immune effector cells in the periphery as well as target organs. Furthermore, it will be of interest to relate these changes to the individual's micro-profile of allergen sensitization. This approach is potentially achievable in phase II–III clinical trials but likely to be limited by the numbers needed to demonstrate efficacy with the crude end-points in current use. An alternative is to use surrogate clinical end-points in simulated conditions such as allergen challenge in target organs or exposure in pollen chambers.

Much of our knowledge of immunotherapy strategies is based on studies of seasonal pollinosis. Within the United Kingdom there is an increasing need to treat subjects with dual allergy to both tree pollens and grass pollens. Future clinical trials that incorporate the use of both tree and grass allergen extracts administered either separately or using combined updosing protocols are needed.

The concept of long-term benefits including suppression of new sensitizations and prevention of disease progression should be confirmed in further large clinical trials with pollen allergens and extended to perennial aeroallergens including domestic pets, HDM and cockroach allergy. Research into QoL benefits and pharmacoeconomic evaluation of long-term benefits will be essential if we are to convince funders to support widespread use of immunotherapy.

Research into alternative novel approaches that are safer, more effective and more acceptable to patients than traditional SCIT are in progress. Phase III trials of allergoids, different adjuvants and combination with anti-IgE are examples. Peptide immunotherapy represents an

attractive alternative testable approach. There is a real need to develop the sublingual approach with head-to-head trials with subcutaneous treatment, and to study long-term effects in children and adults with both pollens and perennial allergens. The use of recombinant allergens that are quantifiable, reproducible and available in large quantities is a major advance. Apart from the potential for 'tailor-made' immunotherapy, recombinant allergens are amenable to the manufacture of hypoallergenic variants that reduce the risk of anaphylaxis. As these strategies advance towards phase III 'definitive' clinical trials, there is the need for parallel improvements in the quality and reproducibility of clinical trials, with consistency in trial design, methodology, analysis and reporting of results. This will require research into trial methodology, expert statistical input and ongoing co-operation between academia, industry and the regulatory authorities.

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These *guidelines* inform the application of immunotherapy for AR. Adherence to these guidelines does not constitute an automatic defense for negligence and conversely non-adherence is not indicative of negligence. It is anticipated that these guidelines will be reviewed 5 yearly.

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References

1 Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004; **24**:758–64.
2 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.
3 Smith H. Asthma, inflammation, eosinophils and bronchial hyperresponsiveness. *Clin Exp Allergy* 1992; **22**: 187–97.
4 Dahl R, Kapp A, Colombo G *et al*. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; **118**:434–40.
5 Keles N. Treatment of allergic rhinitis during pregnancy. *Am J Rhinol* 2004; **18**:23–8.
6 Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. *Allergy* 2006; **61** (Suppl. 82):1–20.
7 Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007: CD001936.
8 Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; **117**:319–25.
9 Varney VA, Tabbah K, Mavroleon G, Frew AJ. Usefulness of specific immunotherapy in patients with severe perennial allergic rhinitis induced by house dust mite: a double-blind, randomized, placebo-controlled trial. *Clin Exp Allergy* 2003; **33**:1076–82.
10 Ewan PW, Alexander MM, Snape C, Ind PW, Agrell B, Dreborg S. Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. *Clin Allergy* 1988; **18**:501–8.
11 Bousquet J, Hejjaoui A, Michel FB. Specific immunotherapy in asthma. *J Allergy Clin Immunol* 1990; **86**:292–305.
12 Cantani A, Arcese G, Lucenti P, Gagliesi D, Bartolucci M. A three-year prospective study of specific immunotherapy to inhalant allergens: evidence of safety and efficacy in 300 children with allergic asthma. *J Investig Allergol Clin Immunol* 1997; **7**:90–7.
13 Peroni DG, Piacentini GL, Martinati LC, Warner JO, Boner AL. Double-blind trial of house-dust mite immunotherapy in asthmatic children resident at high altitude. *Allergy* 1995; **50**:925–30.
14 Olaguibel JM, Alvarez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. *J Investig Allergol Clin Immunol* 2005; **15**:9–16.

15 Calamita Z, Saconato H, Pela AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 2006; **61**:1162–72.
16 Abramson M, Puy R, Weiner J. Immunotherapy in asthma: an updated systematic review. *Allergy* 1999; **54**: 1022–41.
17 Maestrelli P, Zanolla L, Pozzan M, Fabbri LM. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. *J Allergy Clin Immunol* 2004; **113**: 643–9.
18 Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2010; **126**: 942–9.
19 Wilson DR, Torres LI, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2003: CD002893.
20 Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010; **12**:CD002893.
21 Penagos M, Compalati E, Tarantini F *et al*. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006; **97**:141–8.
22 Calderon MA, Birk AO, Andersen JS, Durham SR. Prolonged preseasonal treatment phase with Grazax sublingual immunotherapy increases clinical efficacy. *Allergy* 2007; **62**:958–61.
23 Nieto A, Mazon A, Pamies R, Bruno L, Navarro M, Montanes A. Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. *J Allergy Clin Immunol* 2009; **124**:157–61.
24 Durham SR. Sublingual immunotherapy: what have we learnt from the 'big trials'? *Curr Opin Allergy Clin Immunol* 2008; **8**:577–84.
25 Larenas-Linnemann D. Sublingual immunotherapy in children: complete and updated review supporting evidence of effect. *Curr Opin Allergy Clin Immunol* 2009; **9**:168–76.
26 Larenas-Linnemann D. Sublingual immunotherapy in children: more optimism today. *Pediatr Allergy Immunol* 2009; **20**:399–400.
27 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.
28 Durham SR, Walker SM, Varga EM *et al*. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999; **341**:468–75.
29 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* 1996; **51**:430–3.
30 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* 2010; **125**: 131–8.e7.
31 Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy* 2005; **60**:801–7.
32 Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. 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.
33 Ott H, Sieber J, Brehler R *et al*. Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. *Allergy* 2009; **64**: 1394–401.
34 Norman PS, Lichtenstein LM. The clinical and immunologic specificity of immunotherapy. *J Allergy Clin Immunol* 1978; **61**:370–7.
35 Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injecton therapy in ragweed hay fever. *N Engl J Med* 1965; **273**: 675–9.
36 Adkinson NF Jr, Eggleston PA, Eney D *et al*. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997; **336**:324–31.
37 Alvarez-Cuesta E, Aragoneses-Gilsanz E, Martín-Garcia C, Berges-Gimeno P, Gonzalez-Mancebo E, Cuesta-Herranz J. Immunotherapy with depigmented glutaraldehyde-polymerized extracts: changes in quality of life. *Clin Exp Allergy* 2005; **35**:752–8.
38 Marogna M, Spadolini I, Massolo A *et al*. Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. *Ann Allergy Asthma Immunol* 2007; **98**: 274–80.
39 Amar SM, Harbeck RJ, Sills M, Silveira LJ, O'Brien H, Nelson HS. Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. *J Allergy Clin Immunol* 2009; **124**: 150–6.
40 Valenta R, Kraft D. From allergen structure to new forms of allergen-specific immunotherapy. *Curr Opin Immunol* 2002; **14**:718–27.
41 Grier TJ, LeFevre DM, Duncan EA, Esch RE. Stability of standardized grass, dust mite, cat, and short ragweed allergens after mixing with mold or cockroach extracts. *Ann Allergy Asthma Immunol* 2007; **99**:151–60.
42 Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998; **102**:558–62.
43 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* 1995; **96**:879–85.
44 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* 2004; **114**:1339–44.
45 Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. *Clin Exp Allergy* 1997; **27**:860–7.
46 Arvidsson MB, Lowhagen O, Rak S. Early and late phase asthmatic response in lower airways of cat-allergic asthmatic patients – a comparison between experimental and environmental allergen challenge. *Allergy* 2007; **62**: 488–94.

47 Desensitising vaccines: an allergist's view. *Br Med J (Clin Res Ed)* 1986; **293**:1169–70.

48 British Thoracic Society (BTS). Guideline on the management of asthma. *Thorax* 2008; **63** (Suppl. 4):iv1–121.

49 Javeed N, Javeed H, Javeed S, Moussa G, Wong P, Rezai F. Refractory anaphylactoid shock potentiated by beta-blockers. *Cathet Cardiovasc Diagn* 1996; **39**:383–4.

50 Kivity S, Yarchovsky J. Relapsing anaphylaxis to bee sting in a patient treated with beta-blocker and Ca blocker. *J Allergy Clin Immunol* 1990; **85**:669–70.

51 Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. *Ann Intern Med* 1991; **115**:270–6.

52 Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. *Ann Allergy* 1981; **47**:35–7.

53 Blaiss MS. Management of rhinitis and asthma in pregnancy. *Ann Allergy Asthma Immunol* 2003; **90**:16–22.

54 Ibanez MD, Kaiser F, Knecht R *et al*. Safety of specific sublingual immunotherapy with SQ standardized grass allergen tablets in children. *Pediatr Allergy Immunol* 2007; **18**:516–22.

55 Finegold I. Immunotherapy: when to initiate treatment in children. *Allergy Asthma Proc* 2007; **28**:698–705.

56 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* 2002; **109**:251–6.

57 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* 2006; **61**:855–9.

58 Jacobsen L, Niggemann B, Dreborg S *et al*. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; **62**:943–8.

59 Kuehr J, Brauburger J, Zielen S *et al*. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002; **109**:274–80.

60 Moller C, Dreborg S, Lanner A, Bjorksten B. Oral immunotherapy of children with rhinoconjunctivitis due to birch pollen allergy. A double blind study. *Allergy* 1986; **41**:271–9.

61 Bufe A, Eberle P, Franke-Beckmann E *et al*. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009; **123**:167–73.

62 Wahn U, Tabar A, Kuna P *et al*. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009; **123**:160–6.

63 Halken S, Agertoft L, Seidenberg J *et al*. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. *Pediatr Allergy Immunol* 2010; **21**:970–6.

64 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* 1997; **99**:450–3.

65 Pajno GB, Barberio G, De LF, 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* 2001; **31**:1392–7.

66 Novembre E, Galli E, Landi F *et al*. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; **114**:851–7.

67 Caffarelli C, Sensi LG, Marcucci F, Cavagni G. Preseasonal local allergoid immunotherapy to grass pollen in children: a double-blind, placebo-controlled, randomized trial. *Allergy* 2000; **55**:1142–7.

68 Zhang L, Wang C, Han D, Wang X, Zhao Y, Liu J. Comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus* in the treatment of persistent allergic rhinitis. *Int Arch Allergy Immunol* 2009; **148**:161–9.

69 Serrano P, Justicia JL, Sanchez C *et al*. Systemic tolerability of specific subcutaneous immunotherapy with index-of-reactivity-standardized allergen extracts administered using clustered regimens: a retrospective, observational, multicenter study. *Ann Allergy Asthma Immunol* 2009; **102**:247–52.

70 Stelmach I, Kaczmarek-Wozniak J, Majak P, Olszowiec-Chlebna M, Jerzynska J. Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen. *Clin Exp Allergy* 2009; **39**:401–8.

71 Ariano R, Incorvaia C, La GS *et al*. Safety of sublingual immunotherapy started during the pollen season. *Curr Med Res Opin* 2009; **25**:103–7.

72 Seidenberg J, Pajno GB, Bauer CP, La GS, Sieber J. Safety and tolerability of seasonal ultra-rush, high-dose sublingual-swallow immunotherapy in allergic rhinitis to grass and tree pollens: an observational study in 193 children and adolescents. *J Investig Allergol Clin Immunol* 2009; **19**:125–31.

73 Ma S, Sicherer SH, Nowak-Wegrzyn A. A survey on the management of pollen-food allergy syndrome in allergy practices. *J Allergy Clin Immunol* 2003; **112**:784–8.

74 Kelso JM, Jones RT, Tellez R, Yunginger JW. Oral allergy syndrome successfully treated with pollen immunotherapy. *Ann Allergy Asthma Immunol* 1995; **74**:391–6.

75 Baumann K, Roessler F, Müllner G, Pichler WJ, Helbling A. Effect of the specific, subcutaneous immunotherapy with pollen extracts on the pollen-associated food allergy. A retrospective analysis on 72 patients. *Allergologie* 2002; **25**:326–32.

76 Modrzynski M, Zawisza E, Rapiejko P, Przybylski G. Specific-pollen immunotherapy in the treatment of oral allergy syndrome in patients with tree pollen hypersensitivity. *Przegl Lek* 2002; **59**:1007–10.

77 Asero R. Effects of birch pollen-specific immunotherapy on apple allergy in birch pollen-hypersensitive patients. *Clin Exp Allergy* 1998; **28**:1368–73.

78 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* 2004; **59**:1272–6.

79 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* 2004; **48**:441–8.

80 Czarnecka-Operacz M, Jenerowicz D, Silny W. Oral allergy syndrome in patients with airborne pollen allergy treated with specific immunotherapy. *Acta Dermatovenerol Croat* 2008; **16**:19–24.
81 Modrzynski M, Zawisza E. Possible induction of oral allergy syndrome during specific immunotherapy in patients sensitive to tree pollen. *Med Sci Monit* 2005; **11**:CR351–5.
82 Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; **117**:802–9.
83 Didier A, Malling HJ, Worm M *et al*. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007; **120**:1338–45.
84 Allergen immunotherapy: therapeutic vaccines for allergic dieseases. *Allergy* 1998; **53** (Suppl. 44):1–42.
85 Council of Europe. 2001; *Strasbourg. European Pharmacopoeia; European Series 50*. Strasbourgh, France: Council of Europe.
86 Larsen JN, Houghton CG, Lowenstein H, Lombardero M. Manufacturing and standardizing allergen extracts in Europe. *Clin Allergy Immunol* 2004; **18**: 433–55.
87 Lowenstein H. Purification and characterization of allergens. Summing up. *Allergy* 1980; **35**:210–1.
88 Spangfort MD, Larsen JN. Standardization of allergen-specific immunotherapy vaccines. *Immunol Allergy Clin North Am* 2006; **26**:191–206.
89 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.
90 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* 2010; **125**: 569–74.
91 Pauli G, Larsen TH, Rak S *et al*. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2008; **122**:951–60.
92 Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol* 2005; **116**:608–13.
93 Malling HJ, Weeke B. Immunotherapy (Position Paper). *Allergy* 1993; **48**:9–35.
94 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* 1996; **97**:1207–13.
95 Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. *J Allergy Clin Immunol* 2004; **113**:1129–36.
96 Andre C, Fadel R. Anaphylaxis caused by allergen sublingual immunotherapy? *Allergy* 2007; **62**:1220–1.
97 Dunsky EH, Goldstein MF, Dvorin DJ, Belecanech GA. Anaphylaxis to sublingual immunotherapy. *Allergy* 2006; **61**:1235.
98 Eifan AO, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy* 2007; **62**:567–8.
99 de Groot H., Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 2009; **64**:963–4.
100 Gidaro GB, Marcucci F, Sensi L, Incorvaia C, Frati F, Ciprandi G. The safety of sublingual-swallow immunotherapy: an analysis of published studies. *Clin Exp Allergy* 2005; **35**:565–71.
101 Cox LS, Larenas LD, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006; **117**:1021–35.
102 Lombardi C, Gargioni S, Cottini M, Canonica GW, Passalacqua G. The safety of sublingual immunotherapy with one or more allergens in adults. *Allergy* 2008; **63**:375–6.
103 Passalacqua G, Pawankar R, Baena-Cagnani CE, Canonica GW. Sublingual immunotherapy: where do we stand? Present and future. *Curr Opin Allergy Clin Immunol* 2009; **9**:1–3.
104 Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005; **60**:4–12.
105 Radulovic S, Calderon M, Wilson S, Durham S. Sublingual immunotherapy for allergic rhinitis: an updated Cochrane systematic review and meta-analysis. *Allergy* 2007; **62** (Suppl. 83): 263; Abstract.
106 Passalacqua G, Durham SR. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. *J Allergy Clin Immunol* 2007; **119**:881–91.
107 Rodriguez-Perez N, mbriz-Moreno MJ, Canonica GW, Penagos M. Frequency of acute systemic reactions in patients with allergic rhinitis and asthma treated with sublingual immunotherapy. *Ann Allergy Asthma Immunol* 2008; **101**: 304–10.
108 Drummond M, Dubois D, Garattini L *et al*. Current trends in the use of pharmacoeconomics and outcomes research in europe. *Value Health* 1999; **2**:323–32.
109 Sculpher M. The use of quality-adjusted life-years in cost-effectiveness studies. *Allergy* 2006; **61**:527–30.
110 Bachert C, Vestenbaek U, Christensen J, Griffiths UK, Poulsen PB. Cost-effectiveness of grass allergen tablet (GRAZAX) for the prevention of seasonal grass pollen induced rhinoconjunctivitis – a Northern European perspective. *Clin Exp Allergy* 2007; **37**:772–9.
111 Canonica GW, Poulsen PB, Vestenbaek U. Cost-effectiveness of GRAZAX for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe. *Respir Med* 2007; **101**:1885–94.
112 Nasser S, Vestenbaek U, Beriot-Mathiot A, Poulsen PB. Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma. *Allergy* 2008; **63**:1624–9.
113 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**: 227–32.
114 Berto P, Frati F, Incorvaia C *et al*. Comparison of costs of sublingual immunotherapy and drug treatment in grass-pollen induced allergy: results from the SIMAP database study. *Curr Med Res Opin* 2008; **24**:261–6.
115 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* 2006; **27**:159–63.
116 Berto P, Bassi M, Incorvaia C *et al*. Cost effectiveness of sublingual immu-

notherapy in children with allergic rhinitis and asthma. *Eur Ann Allergy Clin Immunol* 2005; **37**:303–8.
117 Berto P, Passalacqua G, Crimi N *et al*. Economic evaluation of sublingual immunotherapy vs symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study. *Ann Allergy Asthma Immunol* 2006; **97**:615–21.
118 Omnes LF, Bousquet J, Scheinmann P *et al*. Pharmacoeconomic assessment of specific immunotherapy versus current symptomatic treatment for allergic rhinitis and asthma in France. *Eur Ann Allergy Clin Immunol* 2007; **39**:148–56.
119 Pokladnikova J, Krcmova I, Vlcek J. Economic evaluation of sublingual vs subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol* 2008; **100**:482–9.
120 Cox L, Nelson H, Lockey R *et al*. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011; **127**:S1–55.
121 Gawchik SM, Saccar CL. Pollinex quattro tree: allergy vaccine. *Expert Opin Biol Ther* 2009; **9**:377–82.
122 Bowen T, Greenbaum J, Charbonneau Y *et al*. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2004; **93**:425–30.
123 Bufe A, Ziegler-Kirbach E, Stoeckmann E *et al*. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004; **59**:498–504.
124 Casanovas M, Guerra F, Moreno C, Miguel R, Maranon F, Daza JC. Double-blind, placebo-controlled clinical trial of preseasonal treatment with allergenic extracts of Olea europaea pollen administered sublingually. *J Investig Allergol Clin Immunol* 1994; **4**:305–14.
125 Clavel R, Bousquet J, Andre C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. *Allergy* 1998; **53**:493–8.
126 Lima MT, Wilson D, Pitkin L *et al*. Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis: a randomized controlled trial. *Clin Exp Allergy* 2002; **32**:507–14.
127 Nelson HS, Oppenheimer J, Vatsia GA, Buchmeier A. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. *J Allergy Clin Immunol* 1993; **92**:229–36.
128 Passalacqua G, Albano M, Riccio A *et al*. Clinical and immunologic effects of a rush sublingual immunotherapy to Parietaria species: a double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 1999; **104**:964–8.
129 Pradalier A, Basset D, Claudel A *et al*. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy* 1999; **54**: 819–28.
130 Sanchez PA, Schamann F, Garcia JA. Sublingual immunotherapy with cat epithelial extract. Personal experience. *Allergol Immunopathol (Madr)* 2001; **29**:60–5.
131 Tonnel AB, Scherpereel A, Douay B *et al*. Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004; **59**:491–7.
132 Vourdas D, Syrigou E, Potamianou P *et al*. Double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized olive pollen extract in pediatric patients with allergic rhinoconjunctivitis and mild asthma due to olive pollen sensitization. *Allergy* 1998; **53**:662–72.
133 Bordignon V, Parmiani S. Variation of the skin end-point in patients treated with sublingual specific immunotherapy. *J Investig Allergol Clin Immunol* 2003; **13**:170–6.
134 Lombardi C, Gargioni S, Venturi S, Zoccali P, Canonica GW, Passalacqua G. Controlled study of preseasonal immunotherapy with grass pollen extract in tablets: effect on bronchial hyperreactivity. *J Investig Allergol Clin Immunol* 2001; **11**:41–5.
135 Dahl R, Kapp A, Colombo G *et al*. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. *J Allergy Clin Immunol* 2008; **121**:512–8.
136 BSACI Working Party. Position paper on allergen immunotherapy. Report of a BSACI working party. January-October 1992. *Clin Exp Allergy* 1993; **23**:1–44.
137 James LK, Shamji MH, Walker SM *et al*. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol* 2011; **127**: 509–16.
138 La Rosa M., Ranno C, Andre C, Carat F, Tosca MA, Canonica GW. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999; **104**:425–32.
139 Smith H, White P, Annila I, Poole J, Andre C, Frew A. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004; **114**:831–7.
140 Tari MG, Mancino M, Madonna F, Buzzoni L, Parmiani S. Immunologic evaluation of 24 month course of sublingual immunotherapy. *Allergol Immunopathol (Madr)* 1994; **22**: 209–16.
141 Tari MG, Mancino M, Monti G. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. *Allergol Immunopathol (Madr)* 1990; **18**:277–84.
142 Till SJ, Francis JN, Nouri-Aria K, Durham SR. Mechanisms of immunotherapy. *J Allergy Clin Immunol* 2004; **113**:1025–34.
143 Niederberger V, Horak F, Vrtala S *et al*. Vaccination with genetically engineered allergens prevents progression of allergic disease. *Proc Natl Acad Sci USA* 2004; **101** (Suppl. 2):14677–82.
144 Shamji MH, Wilcock LK, Wachholz PA *et al*. The IgE-facilitated allergen binding (FAB) assay: validation of a novel flow-cytometric based method for the detection of inhibitory antibody responses. *J Immunol Methods* 2006; **317**:71–9.
145 Durham SR, Varney VA, Gaga M *et al*. Grass pollen immunotherapy decreases the number of mast cells in the skin. *Clin Exp Allergy* 1999; **29**:1490–6.
146 Gozalo F, Martin S, Rico P, Alvarez E, Cortes C. Clinical efficacy and tolerance of two year Lolium perenne sublingual immunotherapy. *Allergol Immunopathol (Madr)* 1997; **25**:219–27.

147 Ippoliti F, De SW, Volterrani A *et al*. Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol* 2003; **14**:216–21.
148 Passalacqua G, Albano M, Fregonese L *et al*. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. *Lancet* 1998; **351**: 629–32.
149 Marcucci F, Sensi L, Frati F *et al*. Effects on inflammation parameters of a double-blind, placebo controlled one-year course of SLIT in children monosensitized to mites. *Allergy* 2003; **58**:657–62.
150 Nouri-Aria KT, Wachholz PA, Francis JN *et al*. Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. *J Immunol* 2004; **172**:3252–9.
151 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.
152 Fanta C, Bohle B, Hirt W *et al*. Systemic immunological changes induced by administration of grass pollen allergens via the oral mucosa during sublingual immunotherapy. *Int Arch Allergy Immunol* 1999; **120**:218–24.
153 Cirla AM, Cirla PE, Parmiani S, Pecora S. A pre-seasonal birch/hazel sublingual immunotherapy can improve the outcome of grass pollen injective treatment in bisensitized individuals. A case-referent, two-year controlled study. *Allergol Immunopathol (Madr)* 2003; **31**:31–43.
154 Rak S, Lowhagen O, Venge P. The effect of immunotherapy on bronchial hyperresponsiveness and eosinophil cationic protein in pollen-allergic patients. *J Allergy Clin Immunol* 1988; **82**:470–80.
155 Crimi E, Voltolini S, Troise C *et al*. Local immunotherapy with Dermatophagoides extract in asthma. *J Allergy Clin Immunol* 1991; **87**:721–8.
156 Tari MG, Mancino M, Monti G. Immunotherapy by inhalation of allergen in powder in house dust allergic asthma – a double-blind study. *J Investig Allergol Clin Immunol* 1992; **2**:59–67.
157 Valovirta E, Passalacqua G, Canonica WG. Non-injection routes for immunotherapy of allergic diseases. *Clin Allergy Immunol* 2004; **18**:607–23.
158 Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. *J Allergy Clin Immunol* 2003; **111**: 437–48.
159 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* 2008; **105**:17908–12.
160 Senti G, Graf N, Haug S *et al*. Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy. *J Allergy Clin Immunol* 2009; **124**:997–1002.
161 Klunker S, Saggar LR, Seyfert-Margolis V *et al*. Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: inhibition of IgE-facilitated allergen binding. *J Allergy Clin Immunol* 2007; **120**:688–95.
162 Wilcock LK, Francis JN, Durham SR. Aluminium hydroxide down-regulates T helper 2 responses by allergen-stimulated human peripheral blood mononuclear cells. *Clin Exp Allergy* 2004; **34**:1373–8.
163 Garcia-Patos V, Pujol RM, Alomar A *et al*. Persistent subcutaneous nodules in patients hyposensitized with aluminum-containing allergen extracts. *Arch Dermatol* 1995; **131**:1421–4.
164 Jones SK, Lovell CR, Peachey RD. Delayed onset of inflammatory nodules following hay fever desensitization injections. *Clin Exp Dermatol* 1988; **13**:376–8.
165 Netterlid E, Hindsen M, Bjork J *et al*. There is an association between contact allergy to aluminium and persistent subcutaneous nodules in children undergoing hyposensitization therapy. *Contact Dermatitis* 2009; **60**:41–9.
166 Baldrick P, Richardson D, Woroniecki SR, Lees B. Pollinex Quattro Ragweed: safety evaluation of a new allergy vaccine adjuvanted with monophosphoryl lipid A (MPL) for the treatment of ragweed pollen allergy. *J Appl Toxicol* 2007; **27**:399–409.
167 Puggioni F, Durham SR, Francis JN. Monophosphoryl lipid A (MPL) promotes allergen-induced immune deviation in favour of Th1 responses. *Allergy* 2005; **60**:678–84.
168 Kussebi F, Karamloo F, Rhyner C *et al*. A major allergen gene-fusion protein for potential usage in allergen-specific immunotherapy. *J Allergy Clin Immunol* 2005; **115**:323–9.
169 Karamloo F, Schmid-Grendelmeier P, Kussebi F *et al*. Prevention of allergy by a recombinant multi-allergen vaccine with reduced IgE binding and preserved T cell epitopes. *Eur J Immunol* 2005; **35**:3268–76.
170 Akdis CA, Blaser K. Bypassing IgE and targeting T cells for specific immunotherapy of allergy. *Trends Immunol* 2001; **22**:175–8.
171 Larche M. Immunoregulation by targeting T cells in the treatment of allergy and asthma. *Curr Opin Immunol* 2006; **18**:745–50.
172 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* 2006; **355**:1445–55.
173 Kundig TM, Senti G, Schnetzler G *et al*. Der p 1 peptide on virus-like particles is safe and highly immunogenic in healthy adults. *J Allergy Clin Immunol* 2006; **117**:1470–6.
174 Casale TB, Busse WW, Kline JN *et al*. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006; **117**:134–40.
175 Focke M, Marth K, Flicker S, Valenta R. Heterogeneity of commercial timothy grass pollen extracts. *Clin Exp Allergy* 2008; **38**:1400–8.
176 Focke M, Marth K, Valenta R. Molecular composition and biological activity of commercial birch pollen allergen extracts. *Eur J Clin Invest* 2009; **39**: 429–36.
177 Schmid-Grendelmeier P. Recombinant allergens. For routine use or still only science? *Hautarzt* 2010; **61**:946–53.
178 Valenta R, Ferreira F, Focke-Tejkl M *et al*. From allergen genes to allergy vaccines. *Annu Rev Immunol* 2010; **28**:211–41.

Appendix A: example of a patient information sheet for sublingual immunotherapy

What is sublingual immunotherapy?
Sublingual immunotherapy or 'SLIT' is a course of treatment given to reduce allergy symptoms caused by a specific allergen. This course of treatment lasts for a period of about 3 years. Depending on the allergy it is either given as a liquid preparation or a tablet. While SLIT for hayfever is commenced a few months before the pollen season, the treatment for perennial allergens (e.g. HDM) can be started at any time of year.

The first dose of SLIT is administered under medical supervision and you will be observed for a period of 1 h before being allowed to leave. After this visit you will administer the treatment yourself at home but will be required to attend the allergy clinic for review to monitor your progress.

What types of allergies can be treated?
In the United Kingdom, we offer this treatment mainly for AR caused by grass or tree pollen, HDM or animals such as cats and dogs. SLIT is not available for treating severe reactions to insects, eczema or food allergies.

How do I take sublingual immunotherapy?
You take SLIT by placing the medication under your tongue for 1–2 min depending on the product, before you swallow. You must not eat or drink anything for the next 5 min.

For the treatment to be successful and long-term benefits maximized, it is important to take your medication regularly as prescribed for the entire treatment period.

When should treatment be stopped?
Because this treatment is working on your immune system, there are certain situations when you should not take your treatment and these are listed as follows:

- Any current illness, e.g. coughs, colds, flu or if you feel unwell. If in doubt, please contact a member of staff in the allergy clinic.
- Any mouth ulcers or if you have a tooth removed; usually you should wait for 1 week after dental extractions or until the wound in your mouth has healed before re-starting your treatment.
- Any serious or life-threatening illnesses: In this situation, please contact the allergy clinic to discuss whether you should continue with treatment.

What are the alternative treatments?
Injection immunotherapy (desensitization) may be an alternative treatment. Please discuss this with your allergy specialist if you would prefer to be considered for this treatment.

What are the possible risks of the treatment?
The most commonly reported side-effects include a tingling or itching sensation under the tongue, mouth or in your ears, this may happen immediately after you have taken the medication. This is only temporary and usually does not last more than 5–10 min. These symptoms usually improve after about a week, however if they continue and are troublesome please discuss this with us.

If you experience any of the following less common side-effects, you must stop the treatment immediately, seek medical attention via your GP or local accident and emergency department and report to your allergy specialist as soon as possible:

- Swelling of the face, mouth or throat.
- Difficulty swallowing.
- Difficulty breathing.
- Worsening of existing asthma.
- Nettle rash.
- Voice changes.
- Tummy pain, nausea and/or vomiting.

What are the benefits of treatment?
Clinical trials have shown that SLIT is beneficial and safe in patients with hayfever and HDM allergy. However, benefit cannot be guaranteed in everyone. SLIT is a convenient treatment option as hospital visits are minimized.

Pregnancy and breastfeeding
SLIT will not be started during pregnancy. If you become pregnant during the course, the treatment may be continued but only after discussion with your consultant. This also applies to breastfeeding.

What about other medication?
Please inform your consultant if you are taking, or have recently taken any other medication, including that bought at your local chemist or supermarket without a prescription. Also, if you have developed a new illness, please report this to your allergy specialist so they can advise you about continuation of SLIT.

Appendix B: example of a patient information sheet for subcutaneous immunotherapy using grass pollen

What is desensitization?
Desensitization (or immunotherapy/hyposensitization) is a form of treatment for summer hayfever and related allergies. It consists of a series of injections in which increasing amounts of an extract of the substance causing the allergy (e.g. grass pollen) are injected under the skin. It has the effect of preventing or reducing allergic symptoms.

What does it involve?
It involves regular injections into the arm. Initially these are given weekly. At each visit the dose is gradually increased so that by 12–16 weeks patients can tolerate

very large amounts of the allergen extract. Monthly 'top-up' injections are required for a further 3 years.

How long does it take at each visit?
The injection itself only takes a few minutes but as a precaution it is necessary to remain in the clinic under observation for a period of 1 h. If a reaction occurs (which is very rare) it can be treated rapidly.

Are there unpleasant side-effects?
The most common side-effect of desensitization is transient tiredness, which sometimes occurs after the first few injections. The injection site may also itch slightly, rather like an allergy skin test. Very rarely, a mild rash or wheeze occurs, which is easily treatable.

You will be given a prescription for oral antihistamine tablets and an asthma inhaler (salbutamol). These are for use if you develop a rash or become wheezy or short of breath after leaving the clinic. You should carry these drugs with you to all your visits to the hospital. What to do if this occurs is discussed overleaf.

Can it be dangerous?
The risk of a serious reaction is very small indeed if the procedure is carried out in a specialized hospital allergy clinic, by staff trained in desensitization procedures and where 'high-quality' vaccines are used.

How effective is it?
The treatment is very effective. Most (around 80%) patients have some benefit after an initial 6–8-month course of injections. In many the improvement is very substantial indeed. However, the longer the course of injections is maintained (up to 3 years) the more likely the benefit. Generally speaking 80% of sufferers improve following one full year of treatment, and this figure may increase after 2–3 years treatment.

Does it last?
This varies between individuals although generally speaking the longer the initial course the less likely symptoms are to return. In a recent study, 3 years treatment with grass pollen immunotherapy provided significant benefit for 3 years after stopping. If symptoms do subsequently return, they usually do so in a mild form.

Is desensitization advised for all hayfever sufferers?
Desensitization is usually considered only when patients have responded poorly to the combination of antihistamines and nasal sprays. In other words, desensitization is a 'last resort' for the hayfever patient because most sufferers respond well to anti-allergy drugs.

Are there any contraindications to hayfever desensitization?
The most important contraindication is asthma requiring treatment all year round.

Can I take other drugs during the course of injections?
Yes. The only exception is β-blockers, which are normally used for high blood pressure and some heart conditions. You must tell a member of staff if you start taking a new drug during your treatment.

Is there anything that I cannot do after an injection?
Vigorous exercise is not recommended after an injection as this can speed up absorption of the vaccine into the body and may cause side-effects.

Are there any times when I should not have an injection?
Your injection should be postponed if you are feeling unwell from a cold, 'flu' or if you feel unwell for any other reason. Similarly, if you have severe hayfever symptoms at the time of your injection, treatment may be postponed. If you are unwell when you arrive at the hospital you may not receive an injection. This is for your safety.

Pregnancy
It is not advisable to start desensitization during pregnancy. However, if the maintenance dose has been reached then desensitization may be continued. You should discuss any planned or suspected pregnancies with us as soon as possible.

How the clinic is run

- Please make an appointment either by ringing the appointments office or by arranging one before you leave the hospital each time. It does not matter what time you make the appointment for as the clinic is run on an open basis, and each patient is treated as they arrive
- Appointments should always be made for a _____ day morning. Please register with the appointments desk when you arrive
- Come straight to Room _____ where the clinic is held. If the door is shut, please knock
- The clinic is run by _____ and managed by _____
- Please telephone _____ if you experience any reactions after leaving the hospital, or if you have any queries regarding the treatment. If you have a reaction later on, outside working hours, advice may be obtained by calling (provide emergency contact details). This should only be used when the other numbers are not answered or in an emergency.
- Please make sure that you cancel your appointment with the appointments office if you are unable to attend
- Remember, do not come to the clinic if you are ill. If you are in any doubt as to what is 'ill' then please telephone _____ beforehand to check

I _____ have read and understood the information given on this sheet and understand the risks and limitations of immunotherapy treatment. I have received a copy of this sheet.

Signature: _____ Date: _____

Date of birth: _____

Appendix C

Who should undergo immunotherapy? When should treatment be started?