REVIEW ARTICLE

One hundred years of allergen immunotherapy European Academy of Allergy and Clinical Immunology celebration: review of unanswered questions

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Keywords
allergen immunotherapy; efficacy; new developments; safety

treatment regimens

Abstract

Allergen immunotherapy was introduced by Leonard Noon 100 years ago and is the only disease-modifying treatment for allergic individuals. Improved understanding of immunology has taught us a great deal about the underlying mechanisms involved in allergen immunotherapy; however, despite these developments, a number of important questions remain unanswered. Several of these questions relate to the practice of allergen immunotherapy in the clinic, such as: Is it possible to unify units of allergen potency? Which treatment schedules are best? Is allergen immunotherapy effective in all patient groups? Is there a dose–response relationship for efficacy and safety?, and Is there evidence for long-term effects following allergen immunotherapy? Others are related to new developments, such as new indications, or developments in the production of allergens. On the centenary of Noon’s discovery, European experts in the field of immunotherapy met in Geneva under the aegis of the EAACI to discuss these controversial issues. This study presents outcomes and conclusions from these discussions.
considerable advances, there are a number of questions that remain unanswered. Several of these relate to recent developments in the practice of allergen immunotherapy, such as efficacy in polysensitized patients, the most effective treatment schedules, new indications and new modes of allergen administration, while other points for discussion relate to the recently introduced European Medicines Agency (EMA) guidelines on the quality of allergen products for human use and the clinical development of products for allergen immunotherapy (1, 2). For many years, allergen immunotherapy has been practised on a named patient basis; however, new requirements for marketing authorization from competent authorities require that clinical studies demonstrate dose–response data for clinical efficacy and safety, and long-term benefits of treatment after discontinuation of immunotherapy, which require the ability to draw comparisons between clinical studies, raising the issue of the need to standardize units of allergen potency.

On the 24th of February 2011, a group of European experts in the field of immunotherapy met in Geneva to discuss these controversial issues, which are outlined in Table 1. Designated experts presented the main arguments for and against each of the topics to the general audience. The audience then split into separate working groups, chaired by the presenters to discuss each of the topics. Arguments for and against each topic and the outcomes of these discussions are presented as follows.

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<td>Is there evidence for long-term efficacy and preventive effect of allergen immunotherapy?</td>
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### Is it really possible to unify allergen units?

In Europe, each allergen manufacturer uses proprietary units to express the potency of their allergen preparations. These units are established in different ways, and there is considerable variation between extracts from different manufacturers in terms of their protein content and composition. Comparison of the potency of preparations derived from same allergen sources is therefore presently impossible.

Table 2 presents allergen product units used by different European manufacturers and illustrates the considerable heterogeneity in the definitions used to describe potency. Meta-analyses and systematic reviews of clinical studies involving allergen immunotherapy are hampered by this use of different units. Unification of the units used to describe allergen potency would enable a better understanding of the heterogeneity of results between clinical studies and, in addition, might also help in establishing the optimal maintenance dose for patients who are allergic to a given allergen source.

This problem has been recognized for some time: almost 10 years ago, the CREATE project set out to develop candidate reference materials for important major allergens (single proteins) and to validate these recombinant allergens in immunoassays for the detection of their natural counterparts and isoforms in commercial allergen preparations, which represent complex mixtures (3, 4). However, when the same allergen preparations were tested using different assays (involving different antibodies and/or different standards), different results were obtained. As allergenic proteins exist in several different isoforms, and antibodies can display an intrinsic preference for one isoform over another, it was not possible to identify a standard assay that would work well with allergen preparations from different laboratories or manufacturers. Following on from the CREATE project, the biological standardization programme (BSP090), supported by the European Directorate for the Quality of Medicines (EDQM), the European Pharmacopeia, and the Centre for Biologics Evaluation and Research (CBER), has set out to establish robust assays for two candidate molecules, Bet v 1 and PhI p 5b, and to validate these in different laboratories by vigorous ring trials with a view to becoming part of the European Pharmacopeia (5).

### Outcomes of the discussion

- The group agreed that, presently, it is not possible to combine information from potency testing, biological testing and quantitative information on composition into one unit.
- There is inherent variability in the source materials and extraction methods employed by different allergen manufacturers, as well as among patients in terms of exposure, sensitizations, response to skin testing, polyclonal immunoglobulin (Ig) E responses, etc. Although variations in
Table 2 Definitions of allergen preparation units used by some European allergen manufacturers

<table>
<thead>
<tr>
<th>Allergen manufacturer</th>
<th>Website</th>
<th>Units</th>
<th>Definitions (given by allergen manufacturers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK-Abelló, D</td>
<td><a href="http://www.alk-abello.com">http://www.alk-abello.com</a></td>
<td>SQ-U</td>
<td>100 000 Standardized Quality – Units is the optimal maintenance dose of allergen extract administered, to the average patient during SCIT.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SQ-T</td>
<td>75 000 Standardized Quality – Tablet units is the optimal maintenance dose of grass allergen extract administered to the average patient during SLIT.</td>
</tr>
<tr>
<td>Allergopharma*, G</td>
<td><a href="http://www.allergopharma.com/">http://www.allergopharma.com/</a></td>
<td>TU</td>
<td>Therapeutic units: demonstration of clinical efficacy and safety in clinical studies determines an appropriate dose of the product, and TU are assigned accordingly. TU reflect the quality and consistency of the product on the basis of a comparison with the IHRP as well as the clinical efficacy and safety.</td>
</tr>
<tr>
<td>Allergy Therapeutics*, UK; Bencard, G</td>
<td><a href="http://www.allergytherapeutics.com/">http://www.allergytherapeutics.com/</a></td>
<td>TU</td>
<td>TU is derived from the corresponding ODC prick test strength. ODC = concentration with the lowest rate of false positive and false negative results at a specified cut-off. CET = $\sqrt{\frac{(FP)}{(TPP)} + \frac{(FN)}{(C0)}}$ (see also 62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SU</td>
<td>Standardized Units (SU) is the specified reactivity of specific IgG (not IgE) with the allergoid; in the case of grasses, Phl p 1, and in case of birch, Bet v 1.</td>
</tr>
<tr>
<td>Bial-Aristegui†, S</td>
<td><a href="http://www.bial.com/es/">http://www.bial.com/es/</a></td>
<td>DBU/TSU</td>
<td>Diagnostic Biological Units/Treatment Standardized Units (based on SPT using histamine 10 mg/ml as reference).</td>
</tr>
<tr>
<td>Diater Laboratorios, S</td>
<td><a href="http://www.diater.com/en.html">http://www.diater.com/en.html</a></td>
<td>HEP/ml (10 000 UB/ml)</td>
<td>Extract provokes a specific skin reaction in the median sensitive patient with a wheal of the same size as a wheal provoked by a positive reference solution consisting of histamines 54.3 mM (for example histamine dihydrochloride 10 mg/ml), when both solutions are administered using the same technique (SPT) on at least 20 individuals who are clinically allergic and cutaneously reactive to the allergen concerned.</td>
</tr>
<tr>
<td>HAL*, NL</td>
<td><a href="http://www.hal-allergy.com/">http://www.hal-allergy.com/</a></td>
<td>AU†</td>
<td>Erythema size total of two diameters, arithmetical mean of 50 mm = D50. Intradermal test in 15 highly allergic patients, chosen from a pool of patients with no controls.</td>
</tr>
</tbody>
</table>
|                                        |                                               | AUM   | HEP-BU are calculated according to the Nordic Guidelines: ‘the activity of an allergen extract is 10 000 BU or 10 HEP per ml when the extract provokes a specific skin reaction in the median sensitive patient with a wheal of the same size as a wheal provoked by a positive reference solution consisting of histamine 54.3 mM (histamine dihydrochloride 10 mg/ml), when both solutions are administered using the same technique (SPT) on at least 20 individuals who are clinically allergic and cutaneously reactive to the allergen concerned’.


The patient response must be accepted, developments in recombinant allergens may reduce variability between allergen preparations. In general, it is more important to demonstrate the clinical effect of an individual product than to have one unit to describe potency and insufficient clinical data.

Table 2 (continued)

<table>
<thead>
<tr>
<th>Allergen manufacturer</th>
<th>Website</th>
<th>Units</th>
<th>Definitions (given by allergen manufacturers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LETI†, S</td>
<td><a href="http://www.leti.com/eng/Index.asp">http://www.leti.com/eng/Index.asp</a></td>
<td>HEP</td>
<td>'An allergen extract is defined as having 10 HEP when it causes a specific reaction on the skin consisting of a wheal of the same average size as a positive reference consisting in histamine 54.3 mM (histamine HCl at a concentration of 10 mg/ml), when both solutions are used with the same technique (SPT) in a minimum of 20 individuals who are sensitized and who have a skin reaction to the allergen in question.'</td>
</tr>
<tr>
<td>Lofarma³, I</td>
<td><a href="http://www.lofarma.it/en/index.html">http://www.lofarma.it/en/index.html</a></td>
<td>AU</td>
<td>Biological unit that is equivalent to 1/40 of the corresponding unmodified allergen challenge dose assessed by nasal challenge test in volunteers suffering from allergic rhinitis.</td>
</tr>
<tr>
<td>Roxall, G</td>
<td><a href="http://www.roxall.com/">http://www.roxall.com/</a></td>
<td>TU (therapeutic units): 1 TU = 1 BU (same protein content)</td>
<td>HEP-BU are calculated according to the Nordic Guidelines: 'the activity of an allergen extract is 10 000 BU or 10 HEP per ml when the extract provokes a specific skin reaction in the median sensitive patient with a wheal of the same size as a wheal provoked by a positive reference solution consisting of histamine 54.3 mM (histamine dihydrochloride 10 mg/ml), when both solutions are administered using the same technique (SPT) on at least 20 individuals who are clinically allergic and cutaneously reactive to the allergen concerned'. [Correction added after online publication 1 March: the initial for Roxall was changed from 'S' to 'G'. The units were changed from 'AU', 'BU/ml' and '10 000 U/ml' to 'TU (therapeutic units): 1 TU = 1 BU (same protein content)']. The Definitions were changed, please see footnote below].</td>
</tr>
<tr>
<td>Stallergenes*, F</td>
<td><a href="http://www.stallergenes.com/">http://www.stallergenes.com/</a></td>
<td>IR</td>
<td>The IR unit has been defined to measure the allergenicity of an allergen extract. The allergen extract contains 100 IR/ml when, on a SPT using a Stallerpoint®, it induces a wheal diameter of 7 mm in 30 patients sensitized to this allergen (geometric mean). The cutaneous reactivity of these patients is simultaneously demonstrated by a positive SPT to either 9% codeine phosphate or 10 mg/ml histamine.</td>
</tr>
</tbody>
</table>

BU, biological units; HEP, histamine equivalent prick-testing; IHRP, in-house reference preparation; ODC, optimal diagnostic concentration; SPT, skin prick test; SQ, standardized quality; TU, therapeutic units.

*Full Member.
†Associate Member of the European Allergen Manufacturers Group (EAMG; http://www.eamg.com).
‡information based on (62).

The following definitions were changed to those now included in the table: 'Biological unit that is equivalent to 1/40 of the corresponding unmodified allergen challenge dose assessed by nasal challenge test in volunteers suffering from allergic rhinitis. BU is equivalent to 1/100 of the concentration of extract, which, before being chemically modified, induces at SPT testing a mean wheal equivalent to histamine 10 mg/ml. Corresponds to 4 g Equivalent/ml of Group 1'.

The inherent variability associated with biological testing, such as skin prick tests (SPT) and intra-dermal tests, as well as between patient cohorts from different geographical regions, highlights the limitations of these methods for comparing the potency of allergen preparations.

Another limitation of biological tests and potency assays that use ELISA or cell-based assays is that they do not provide information on the composition of an extract.

Qualitative analysis of active products (e.g. using mass spectrometry) could identify the components of a preparation that are responsible for its activity; quantitative methods based on mass spectrometry technology are currently being developed.

Even if there was a unified unit for allergen potency (such as US allergy units, which are related to total potency), the composition of extracts from different companies are different, making it impossible to switch from one company’s product to another in the clinic.

The group concluded that at present it is not possible to unify allergen units from different companies.

Is there a real dose–efficacy and dose–safety relationship?

To date, several clinical studies have been performed to compare different doses of the same allergen source and relate these to efficacy and safety outcomes. Several studies have observed a dose–response relationship. A recent report from the EAACI immunotherapy Task Force reviewed published dose-ranging SCIT and SLIT studies and observed that thirteen of the fifteen identified studies reported a dose–response relationship for clinical efficacy, with eight also reporting a dose–response effect for immunological endpoints and two for safety outcomes (6). Several of the studies reporting a dose–response effect for efficacy had a high quality of evidence as assessed by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) scoring system (7). However, as clinical endpoints vary widely between studies and there is currently no universally accepted standard for the measurement of allergen content, comparisons between studies or a meta-analysis were not possible.

Nevertheless, despite this evidence for a dose–response relationship, the currently available data have some shortcomings, which relate to the qualitative and quantitative differences in allergen compositions used in the different studies, the use of different adjuvants, different adjuvant/allergen ratios in SCIT studies, the use of sublingual tablets vs drops and the different volumes of solutions administered in SLIT studies (6).

Outcomes of the discussion

- The group agreed that there was evidence from individual SCIT and SLIT studies to support a dose–response effect for efficacy.
- In view of the current regulatory requirements for allergen products to demonstrate a dose–response relationship for efficacy in phase II clinical studies, communication between academic researchers, allergen manufacturers and regulatory authorities is vitally important.
- The logistical and financial implications of gathering dose–response data make it impossible to do this for all currently available allergen sources. Therefore, choices will have to be made – the group identified grass pollen, birch pollen, mite and venom as the principal allergen sources for which dose–response data should be obtained.
- The group agreed that it is worthwhile to measure the allergen content of the aforementioned preparations and to relate this to clinical efficacy. Owing to variations in allergen content and formulation between products from individual manufacturers, preparations should be studied individually.
- Rigorous standards must be applied to these studies, and the same measurement techniques should be used in each. Endpoints, such as combined symptom and rescue medication scores, must be clearly defined and standardized across studies.
- Despite only 2 of the 15 studies in the EAACI Task Force Report reporting a dose–response relationship for safety, the group was convinced that a dose–response relationship for safety exists and is evident during SCIT up-dosing in clinical practice. The panel concluded that the lack of a dose–response relationship for safety in clinical studies reflects the need for standardized reporting of adverse events; this should apply not only in the context of clinical trials, but also in routine clinical practice.
- Guidelines are available for assessing systemic adverse events during SCIT. Similar guidelines are needed for the reporting of adverse events in SLIT, especially local reactions, which occur most frequently.
- The group concluded that surrogate antigen challenges in the eye and nose would be useful to perform in parallel with phase II dose–response studies, as there is presently little data to correlate these tests with actual symptoms during the allergen season. Their relationship to clinical efficacy could be evaluated.
- It is presently not possible to identify a marker that is predictive of a clinical response to allergen immunotherapy. Such a marker should be serum- or plasma-based, as it is not feasible to perform complex T cell-based assays in the context of multicenter clinical trials. Candidate markers are as follows: sIgE, IgG1, IgG4, facilitated allergen binding (FAB) inhibition, ratio of sIgE to total IgE, ratio of sIgG4 to sIgE, and basophil sensitivity.
- At present, the utility of pollen chambers in dose–response studies has not been adequately studied.

Is a particular schedule better than another?

Induction and maintenance schedules for SCIT and SLIT vary widely in dosing interval, treatment duration and whether treatments are administered pre-seasonally, pre-co-seasonally or perennially. Published randomized controlled trials (RCTs) of allergen immunotherapy have employed many different treatment schedules, and no direct compari-
sons have been made. Some schedules may be preferable to others regarding the following: efficacy, including long-term efficacy; safety and risk reduction; patient convenience; cost; adherence; and the allergen extracts that are available.

The induction regimen is of minor importance to the long-term clinical efficacy of allergen immunotherapy and represents a titration to the dose essential for an immunological response (8). Conventional dose-increase schedules for SCIT imply one, or rarely two, weekly injections until the maintenance dose is reached. A slow induction of immune tolerance results in a lower frequency of adverse effects compared with more aggressive regimens (9). An alternative to conventional dose-increase regimens is rush immunotherapy; this regimen may save time, as the maintenance dose can normally be reached in 3–5 days (10), with some schedules reaching a maintenance dose within 2.5 h. However, the risk of inducing severe adverse effects is high, and this regimen should be limited to hospitalized patients (11). A compromise between these two extremes is cluster immunotherapy, which involves administration of two to four injections spaced at 30-minute intervals in weekly sequences. The advantage is a reduction in the time needed to reach the maintenance dose without jeopardizing patient safety, at the expense of a slightly increased risk of inducing adverse effects compared with conventional immunotherapy (11, 12). A pharmacoeconomic analysis concluded that a cluster regimen resulted in a global saving of USD 244.95 per patient compared with a conventional protocol (13). The situation is slightly different for SLIT, where very short build-up phases or the omission of the build-up do not result in an increased occurrence of adverse effects (14).

The length of the maintenance phase is an important issue and mainly depends on the specific allergen and the clinical allergic reaction encountered (15). Traditionally, a treatment duration of 3 years is recommended; however, scientific data to support this are scarce (16). The optimal duration has not been investigated in clinical studies, and no international guidelines exist. It has been shown that 3 years of 75 000 SQ-T grass SLIT tablets [correction added after online publication 1 March: SLIT changed to ‘75 000 SQ-T grass SLIT tablets’] gives a beneficial effect that lasts for a further 2 years after stopping treatment (17). In addition, results from a study with a 300IR 5–grass pollen SLIT tablet demonstrated a significant sustained efficacy after three seasons of 2- and 4-month pre- and co-seasonal treatment (18), as well as during the first treatment-free year after three seasons (19).

Outcomes of the discussion

- The group concluded that it was impossible to compare between schedules. The optimal method to identify the best schedule for allergen immunotherapy was to discern schedules where treatment was safe and effective.
- Safety should be the first consideration in the choice of schedule, followed by efficacy, convenience to the patient, cost and long-term benefit of treatment.
- The use of allergoids necessitates fewer injections, but shows no advantage in terms of efficacy and safety.
- The initial phase of the schedule should consider primarily the safety of, and convenience to the patient. At this point, it is not necessary to consider efficacy, which is related to the maintenance phase and duration of treatment.
- For SCIT, there is evidence that pre-medication with antihistamines can reduce the severity of adverse reactions and allow a higher maintenance dose to be reached, which is decisive for the efficacy of the treatment.
- For venom SCIT, treatment duration should be at least 3 years to lifelong. In aeroallergen SCIT, treatment duration should probably be at least 3 years. It is not yet clear whether longer treatment improves efficacy.
- Not all currently approved preparations for SLIT require up-dosing. [Correction added after online publication 1 March: the text ‘In SLIT, up-dosing is not necessary for all currently approved preparations, but may improve tolerability’ was replaced with ‘Not all currently approved preparations for SLIT require up-dosing’]. Preseasonal treatment should last at least 8 weeks. It is unclear whether efficacy is improved with up to 16 weeks of pre-seasonal treatment. The effect of pre-medication on adverse effects of SLIT has not been investigated.

Is allergen immunotherapy effective and safe in polysensitized patients?

Epidemiological and clinical trial data show that 51–81% of allergic patients are polysensitized (according to SPT and/or IgE assay results) (20–22). Among allergists, there are a variety of strongly held opinions on the best way to perform allergen immunotherapy in polysensitized patients. In the United States, allergists tend to treat for all sensitivities identified as individually important by skin testing, using mixtures of extracts prepared from bulk vials, whereas in Europe, patients, even those with multiple sensitivities, are normally only treated with one or few single-allergen sources, deemed to be the most clinically relevant, which are supplied direct from the manufacturer. Mixed allergen extracts are, however, available and are used in some parts of Europe as individual prescriptions (named patient products) or as custom mixes from manufacturers.

The prevailing view in Europe is that (i) a polysensitized subject is not necessarily polyallergic and (ii) multiple allergies do not always constitute a clinical problem (15, 23); the most troublesome allergy is treated with a single-allergen source preparation. The opposing view (which predominates in North America) is that, as long as multi-allergen therapy is effective and does not induce new sensitizations, there is an advantage in treating as many of the patient’s actual or potential allergies as possible.

In considering whether allergen immunotherapy is effective and safe in polysensitized patients, two quite separate questions arise:

1. Is monovalent allergen immunotherapy efficacious and safe in patients who are polysensitized?
2. Is polyvalent allergen immunotherapy efficacious?

Most recent clinical trials of allergen immunotherapy have been designed to demonstrate the efficacy of monovalent products. To maximize the power of the study, it is usual to
Outcomes of the discussion

- The key question for practitioners faced with a polysensitized patient is how the physician should decide on appropriate treatment?

- The group identified the need to clearly define polysensitization; patients with grass pollen allergy may be sensitized to multiple components of grass pollen but are referred to as monosensitized. Patients who cross-react to several allergens should not be considered polysensitized.

- Before starting treatment, it is necessary to determine the importance of a demonstrated sensitization in causing clinical symptoms.

- The group questioned the suitability of SPT to identify clinically relevant sensitizations and concluded that in rare cases, when clinical history is strong with negative SPT or/and sIgE, the use of specific allergen challenge test may help to identify the responsible allergen for local allergy.

- Regarding monovalent allergen immunotherapy, a post hoc analysis of clinical trials identified no data that enabled comparison of the efficacy of allergen immunotherapy in polyallergic vs monovalergic patients and concluded that, because of the need for very large and long studies, there was limited scope for large-scale clinical trials to address this question as a primary outcome.

- In patients with both seasonal and perennial sensitizations, the group concluded that it is worthwhile to treat the most severe and clinically relevant allergy, which is likely to be the seasonal component of seasonal allergic rhinitis.

**Table 3** New indications for allergen immunotherapy

<table>
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<tr>
<th>State of the art</th>
<th>References</th>
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<td><strong>Food allergy</strong></td>
<td>Two controlled trials of SCIT in peanut allergy have shown a significant increase in the peanut threshold and reduction in skin reactivity in nine actively treated patients. Systemic reactions occurred in 23% of the rush build-up doses and 39% of the maintenance doses. Mucosal routes of administration have been investigated in an attempt to improve the safety profile. SLIT with hazelnut and peach in double-blind, placebo-controlled (DBPC) trials have shown an increase in the food threshold and a good safety profile with mild systemic reactions in &lt;0.5% of doses. Local oral reactions were reported in 7% and 87% of patients treated with hazelnut and peach, respectively. Controlled and noncontrolled trials of specific oral tolerance induction (SOTI) with milk, egg and peanut have shown that 50–100% of patients are able to tolerate a normal serving or a substantial amount that protects them from accidental exposures. Systemic reactions were frequent, mostly in the build-up phases in the hospital, but also during the maintenance phase at home.</td>
</tr>
<tr>
<td><strong>Nickel allergy</strong></td>
<td>Open, noncontrolled, observational studies have reported positive results for efficacy (reduction in symptoms, need for medication, reduction in epicutaneous or intra-dermal test with nickel, increase in orally tolerated nickel, tolerance of nickel containing foods). Two trials failed to demonstrate efficacy. DBPC studies are needed to establish the usefulness of allergen immunotherapy in nickel allergy.</td>
</tr>
<tr>
<td><strong>Urticaria</strong></td>
<td>There are some open, non-controlled studies and case reports on the use of house dust mite (HDM) allergen immunotherapy in chronic urticaria, although a causal relationship between HDM sensitization and chronic urticaria has not been established. DBPC clinical trials are needed to evaluate this therapeutic approach.</td>
</tr>
<tr>
<td><strong>Atopic dermatitis</strong></td>
<td>Analysis of seven combined observational studies and five combined placebo-controlled trials involving SLIT and SCIT showed a significant improvement of atopic dermatitis. SOTI failed to demonstrate efficacy.</td>
</tr>
</tbody>
</table>
Epicutaneous

Intralymphatic IT (ILIT) An open

ment consists in avoidance of the offending food

tion for allergen immunotherapy. Current standard manage-

and is aimed at improving the specificity and efficacy

which is driven by recent advances in protein engineering

new recombinant or chemically modified allergens (Table 5),

safety of allergen immunotherapy; and the development of

tralymphatic routes, which aim to improve the efficacy and

administration (Table 4), including oral, epicutaneous and in-

caria and atopic dermatitis; new routes of allergen

New modalities of allergen immunotherapy include new clini-

realistic?

include self

the case of accidental reactions, rescue medication that may

complete avoidance is difficult to achieve and severe acciden-

tal reactions are frequent. There is therefore a need for an

active therapy to induce tolerance. Some SCIT studies have
demonstrated efficacy in allergen immunotherapy of peanut
allergy, but with a poor safety profile (27, 28). Alternative
routes of allergen administration, such as SLIT, specific oral
tolerance induction (SOTI) (29–40) and epicutaneous admin-
istration, are being investigated in an attempt to improve the
safety profile. Clinical trials of SLIT and SOTI are promising
and have shown a disease-modifying effect, although further
studies are needed to establish the balance between efficacy
and safety, the optimal dosing and duration, whether perma-
nent tolerance is developed and the immunological mecha-
nisms involved.

Some clinical studies of allergen immunotherapy in atopic
dermatitis have shown an acceptable balance of efficacy and
safety, but it is still a matter of debate whether atopic derma-
titis alone is an indication for allergen immunotherapy. Nickel
and house dust mite (HDM) allergen immunothera-
pies have been investigated in nickel allergy and chronic urti-
caria, respectively in open noncontrolled studies, which have
so far not provided evidence of clinical efficacy (Table 3).

Research into new routes of allergen administration has
mainly been aimed at improving convenience as well as the
risk/benefit profile of allergen immunotherapy. Although sev-
eral of the studies involving new routes, summarized in
Table 4, have reported fewer adverse effects compared with
traditional SCIT, further studies are needed to confirm these
findings and to establish if efficacy is comparable.

Another important area of development is the use of new
 technological approaches to improve the efficacy/risk profile
of the allergen/antigen preparation itself. One approach is
through the use of recombinant allergen molecules and
hypoallergenic allergen derivatives. Several of these new
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<th>Advantages/disadvantages</th>
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<td></td>
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<tr>
<td>targeting allergen-specific</td>
<td>Advantages: lack IgE reactivity and therefore cannot induce IgE-mediated adverse effects. Disadvantages/problems: 1) T-cell epitope-containing peptides can activate allergen-specific T cells, leading to T cell-mediated late-phase adverse effects, 2) Owing to major histocompatibility complex diversity among patients, it is impossible to perform treatment with one or few peptides, 3) Treatment seems to reduce T-cell activation, but the effects on IgE-mediated symptoms are unclear.</td>
<td>Trials of allergen-derived peptides containing T-cell epitopes without IgE reactivity showed no relevant clinical improvement and patients experienced considerable late-phase adverse effects. Further studies were performed to optimize the treatment, and trials, performed by Circassia, are ongoing.</td>
<td>85, 86</td>
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<td><strong>Recombinant wild-type allergens for SCIT, SLIT</strong></td>
<td>Advantages: allow the formulation of well-defined products containing specified amounts of each allergen. Can be easily produced under defined conditions that should satisfy regulators and health authorities. Disadvantages/problems: induce the same adverse effects as natural allergens.</td>
<td>Clinical efficacy has been demonstrated for recombinant wild-type allergen-based products in birch and grass pollen allergy using SCIT. Trials are ongoing to prepare tablets based on recombinant major birch pollen allergen, Bet v 1 for SLIT and a mix of recombinant grass pollen allergens for SCIT.</td>
<td>87, 88</td>
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<td><strong>Recombinant hypoallergenic allergen derivatives for SCIT</strong></td>
<td>Advantages: can be manufactured as defined molecules under defined conditions and thus fulfill requirements of modern allergen products. Do not induce IgE-mediated adverse effects and therefore can be given in higher doses than natural allergens. Disadvantages/problems: can induce T cell-dependent adverse effects.</td>
<td>Clinical efficacy has been demonstrated for SCIT with recombinant hypoallergenic Bet v 1 derivatives up to phase III.</td>
<td>89-93</td>
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<tr>
<td><strong>CpG-adjuvanted allergens</strong></td>
<td>Advantages: the approach is applicable to every purified allergen and may reduce IgE reactivity and enhance immunogenicity. Disadvantages/problems: chemical coupling of CpGs is difficult to control, and it is not clear whether comparable results can be obtained for different allergens. Enhancement of immunogenicity and Th1 bias was modest in humans.</td>
<td>A SCIT trial performed with CpG-conjugated Amb a 1 showed that the allergen preparation induced allergen-specific blocking IgG antibodies, and, similar to effects observed in the first SCIT trial with recombinant hypoallergenic derivatives of the major birch pollen allergen Bet v 1, reduced seasonal boosts of IgE production.</td>
<td>94</td>
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<tr>
<td><strong>Virus-like particles</strong></td>
<td>Advantages: allergens or allergen-derived peptides that induce allergen-specific IgG. Disadvantages/problems: difficult to manufacture.</td>
<td>Peptides from the house dust mite allergen Der p 1 coupled to the viral carrier protein induced allergen-specific IgG antibodies in non-allergic persons.</td>
<td>95, 96</td>
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modalities have shown promising results in clinical trials (Table 5).

Outcomes of the discussion

- The group agreed that basic research has produced several products that have shown promising results in proof-of-concept and phase I studies. Successful phase III trials have so far only been conducted with recombinant hypoallergenic Bet v 1.
- Development of new allergen products for allergen immunotherapy should begin with a sound scientific basis; there is a need to identify and define the clinically relevant allergen molecules and efficacy markers for use in clinical studies.
- There is a need for health economic studies to illustrate to political authorities that treatment of allergic diseases with allergen immunotherapy is economically favourable compared with symptomatic treatment, with the aim of increasing research funding for studies on new modalities of immunotherapy.
- Using recombinant technology, allergen/antigen preparations can be produced under carefully controlled and reproducible conditions that fulfil manufacturing requirements set out by regulators.
- Recombinant technology also brings the possibility to modify allergens or to produce peptide or allergen derivatives, with a view to minimize IgE- and T cell-mediated adverse effects and to increase immunogenicity.
- There is a need for new modified allergen molecules to enter clinical studies. It is hoped that promising results obtained with a recombinant hypoallergenic rBet v 1 derivative, which has reached phase III clinical trials, will pave the way.

Is there evidence for long-term efficacy and preventive effect of allergen immunotherapy?

In addition to alleviating allergic symptoms, one of the goals of allergen immunotherapy is to induce long-term tolerance that persists after discontinuation of treatment.

The EMA defines long-term efficacy in allergen immunotherapy as the documented capacity to significantly reduce symptoms and medication use compared with placebo for at least two years after termination of treatment in a RCT. Some controlled trials have suggested that the effect of SCIT may last for several years after discontinuation of treatment (41–44); however, only one of these studies is randomized and controlled. Moreover, the aforementioned studies do not include markers that correlate with a long-term effect on symptoms and medication. Two recent SLIT studies with grass pollen tablets have shown sustained efficacy after discontinuation of treatment (17, 19).

Several clinical studies have reported that allergen immunotherapy prevents new sensitizations (45–50), although the

<table>
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<td><strong>Advantages/disadvantages</strong></td>
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<tr>
<td>Recombinant fusion proteins containing allergen-derived peptides</td>
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<td>Genetic immunization</td>
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design of these studies offers differing strengths of evidence. Several studies have also reported prevention of the progression of allergic rhinitis to asthma (25, 42, 44, 51–55). An observational study of children aged 6–12 years with seasonal allergic rhinoconjunctivitis induced by both birch and grass pollen who were followed for 10 years after termination of treatment found that the incidence of seasonal asthma was significantly reduced by early SCIT intervention (44). Similar results were obtained in another open controlled trial in children, where 3 years of SLIT significantly reduced the occurrence of persistent asthma (56).

Candidates for a preventive approach are the following:

- Infants or toddlers with a positive family history of allergy, atopic dermatitis or food allergy in infancy (secondary prevention).
- Young infants with a positive family history before any manifestation of atopy (primary prevention).
- School children with allergic manifestations of the upper airways without asthma (secondary prevention).

A double-blind, placebo-controlled study on asthma prevention in high-risk infants, funded by the NIH, has treated a pilot cohort of children with a liquid extract of grass pollen, dust mite and cat allergens (57). The ongoing pan-European GAP trial aims to investigate the prevention of asthma in grass rhinitic children (58). The outcomes of these preventive intervention studies will provide evidence as to whether or not allergen immunotherapy can play a role in the primary or secondary prevention of atopic diseases.

If a clear preventive effect of allergen immunotherapy is observed, the question of when to start treatment to achieve maximum efficacy arises. A minimal age limitation of 5 years is still a usual recommendation in SCIT guidelines, although this is based on a single study with a rush induction protocol (59). Trials are currently underway to address this question (57). An additional question is whether to restart treatment in case of relapse; however, it is first necessary to determine when a sufficient level of efficacy has been achieved (60).

Outcomes of the discussion

- Data from older studies provide a moderate quality of evidence for the long-term efficacy of allergen immunotherapy. These studies, however, provide useful information for the design of new studies.
- To date, there is more evidence of a long-term preventive effect with SCIT compared with SLIT.
- Long-term efficacy data for SCIT and SLIT are only available in adults.
- Demonstration of long-term efficacy is required for the mandatory paediatric investigation plan (PIP) that must accompany applications for marketing authorization submitted to the EMA.
- For environmental allergens, the most urgent task is to focus on the prevention of asthma. There is an opportunity for studies of secondary prevention in high-risk populations that have expressed clinical symptoms or patterns of sensitization. These patients should be given high priority, as there are currently no drugs that are effective in prevention.
- The priority given to the development of studies on primary prevention using allergen immunotherapy should be reconsidered.

Conclusion

It has taken allergen immunotherapy some time before reaching its current level of robustness. Several appropriately designed clinical trials have nevertheless proved its effectiveness in allergic rhinitis, asthma and venom allergy (61). As illustrated here, although some questions remain unanswered, allergen immunotherapy should now be regarded as a new therapeutic class.

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Author contributions

MC, VC and PD had the original idea, chose the subject matter, organized the meeting and co-ordinated the writing of the manuscript. MC, VC, PD, GP, JK-T, EV, SRD, RD, H-JM, AF, MF-R, RV, UW and AB participated in discussions, wrote the text and reviewed successive drafts of the manuscript.

Conflicts of interest

MAC has received consulting fees, honoraria for lectures and/or research funding from ALK-Abelló, Stallergenes, Allergopharma and Allergy Therapeutics. VC has received honoraria as a speaker or advisor for ALK-Abelló, LETI and Stallergenes. PD is a consultant and a speaker for Stallergenes, ALK and Therabel and was a speaker for Schering-Plough, MSD, AstraZeneca and GlaxoSmithKline in 2009–2011. GP has received speaking fees from Anallergo, ALK-Abelló, Almirall, AstraZeneca, GSK, MSD, Menarini, Lofarma, Stallergenes, and Schering-Plough. JK-T has received lecture fees from Allergopharma, ALK-Abelló, AstraZeneca, Bencard, Boehringer Ingelheim, Essex, HAL Allergy, Leti, Lofarma, Novartis, Thermo Fisher Phadia, Roxall and Stallergenes; research grants from Allergopharma, ALK-Abelló
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