

Immunotherapy: clinical trials – optimal trial and clinical outcomes

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Purpose of review

The methodology of randomized clinical trials is essential to assess and register treatment interventions. Although specific immunotherapy was introduced a century ago, very few trials meet the criteria for pivotal studies. The paper reviews the methods which should be used to investigate specific immunotherapy.

Recent findings

Large pivotal trials on specific immunotherapy were published within the last year and made sublingual immunotherapy an accepted treatment in Europe. Moreover, a study proposed the guidelines for conducting trials on immunotherapy. Phase I studies were also published on sublingual immunotherapy. A large trial on subcutaneous immunotherapy confirmed its efficacy, but showed that this form of treatment is associated with side effects.

Summary

The clinical efficacy of subcutaneous and sublingual immunotherapy with pollen and mites is well established for both rhinitis and asthma, but the methodology of many specific immunotherapy trials was found to be insufficient until recent large pivotal studies. The present paper reviews the requirements for conducting trials in allergen-specific immunotherapy including allergen standardization, patient inclusion and exclusion criteria, phase I trials to assess safety, dose-ranging studies, and pivotal trials. These need to be randomized, parallel group, placebo-controlled designs. The number of patients should be sufficient. Primary and secondary outcome measures are listed. Trials for asthma need specific requirements. In all trials, safety should be carefully monitored. Studies in children are required.

Keywords

asthma, rhinitis, specific immunotherapy, clinical trials

Abbreviations

SCIT	subcutaneous immunotherapy
SIT	specific immunotherapy
SLIT	sublingual immunotherapy

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Introduction

Allergen specific immunotherapy (SIT) is the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with the subsequent exposure to the causative allergen. There is high-quality evidence that immunotherapy using inhalant allergens is clinically effective to treat allergic rhinitis and asthma [1,2[•],3,4[•],5[•]]. A recent paper under the auspices of the World Allergy Organization [6[•]] has been used as a basis for the present paper. Moreover, the Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases is pending and a draft is available [7].

Until recent large pivotal studies, the methodology of many SIT trials had been found to be insufficient [8].

Diseases and allergens to be investigated

The clinical efficacy of subcutaneous immunotherapy (SCIT) is well established for both rhinitis and asthma. Meta-analyses relating to its efficacy on asthma [9,10] and rhinitis [11] are available. Sublingual immunotherapy (SLIT) has also been validated [12,13,14[•],15].

For other allergic diseases such as atopic dermatitis [16] and food allergy [17,18], SIT is not yet recommended, but trials need to be carried out to critically assess its efficacy and safety. In any trial with foods, safety is a key issue [19]. Immunotherapy with latex should also be considered investigational [20,21]. Immunotherapy using venoms will not be considered in this paper [22].

Quality and standardization of allergen vaccines

The quality of the allergen vaccine is critical for both diagnosis and treatment. Whenever possible, standardized vaccines of known potency and shelf-life should be used [23]. The most common vaccines used in clinical allergy practice are now available as standardized products [23] or are pending standardization. It is likely

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that in the near future recombinant allergens will provide standards for allergen analysis, and, as a consequence, new diagnostic and therapeutic products will be developed [2^{••},4^{••}].

Allergen vaccines are labeled in units of biological potency based on skin tests. Methods differ throughout Europe [24] and the US [25]. Each manufacturer defines specific units and concentrations, and a whole range of unrelated names for specific units currently appear on the labels of marketed products.

The measurement of major allergens for standardization is now a realistic and desirable goal which should be encouraged [1,26]. It is recommended in the future that allergen manufacturers should state the content of representative major allergens in their products in mass units (micrograms per milliliter). Comparison between different manufacturers labeling, however, may not be possible due to differences in assays and methodologies for measurement of the major allergens [2^{••},4^{••}]. In the future, new types of vaccines may improve standardization [27].

Patient characteristics

Patients characteristics should be considered as described in the following sections.

Selection of patients

The only patients who should be treated with SIT are those with a very accurate diagnosis of allergy, and in whom the allergen sensitization and exposure is correlated with the time of symptoms. The diagnosis of allergy should be based on skin prick tests and the measurement of allergen-specific IgE in serum. It appears that studies carried out in patients who are not perfectly selected may not show any benefit from SIT [28].

Allergic diseases should be classified in terms of duration and severity (or control) according to the most recent guidelines: Allergic Rhinitis and its Impact on Asthma for allergic rhinitis [29] and Global Initiative for Asthma for asthma [30]. Patients enrolled in SIT studies should have a minimal level of symptoms (historical for pollen trials or at baseline).

Since most allergic patients are polysensitized, it is important to characterize the different inhalant allergens to which the patients are sensitized, and to differentiate mono- and polysensitized subjects.

Patients should not have had any form of immunotherapy within the past 5 years.

Comorbidities

Most patients sensitized to pollens present with conjunctivitis. Some patients may also have asthma. Most of

these patients only present bronchial symptoms, however, and lung function (forced expiratory volume in 1 s) or peak expiratory flow are not altered during the exposure to allergens [31].

In patients sensitized to indoor allergens, asthma and rhinitis are common. On the other hand, ocular symptoms are less common and usually mild.

Comedication

In most patients, the indication of SIT with inhalant allergens is not to replace pharmacologic treatment, but to improve the control of patients who are insufficiently controlled using drugs [1]. Concomitant medication is therefore needed in most patients. In most SIT trials, rescue medications are proposed and should be administered in a standard way in order to calculate a medication score [32]. In another study, patients were instructed to use medications in order to control symptoms as best as possible and the primary endpoint was the medication score [33].

Design of clinical trials

Clinical trials are designed as follows.

Phase I studies

Phase I studies have been carried out recently in the development of SIT. Although the first randomized trials were performed half a century ago, safety phase I studies were done only recently and mostly with SLIT [34,35]; however, more data are needed to fully confirm the efficacy of SLIT in asthma and in children. It is important that phase I studies should be undertaken for all new vaccines or new forms of SIT.

Phase II studies

Phase II studies are designed as follows.

Outcomes to be measured

Many different outcomes may be examined in phase II studies in order to suggest the efficacy of SIT. They are detailed in the World Allergy Organization paper (Table 1) [6^{••}].

Dose-finding studies

One important issue concerning both SCIT and SLIT is the optimal dose of allergen that should be used to obtain the maximal efficacy without side effects [36]. Dose-finding studies are therefore required. It has been suggested that challenge studies may be used, but it appears that randomized clinical trials are more appropriate.

Phase III studies

Phase III studies are designed as follows.

Table 1 Surrogate or paraclinical parameters

Target organ: allergen-specific reactivity	Immunological parameters
Skin: endpoint skin test, late cutaneous response	Total and allergen specific IgE and IgG subclasses
Nose, eye and bronchi: allergen-specific provocation test	Mucosal IgA
Nonspecific organ reactivity	Lymphocyte subsets and cytokines (e.g. interferon- γ , and interleukin-5, -10 and -12).
Bronchial challenge with methacholine, carbachol, histamine, adenosine monophosphate	Local and systemic inflammatory markers (e.g. adhesion molecules, urinary leukotrienes, serum eosinophil cationic protein, tryptase)

From [6**].

Baseline assessment

In pollen allergy, the inclusion of a baseline period of observation, e.g. one pollen season before randomization, would be optimal. Owing to the unpredictability and variability of allergenic exposure to pollen allergens, however, the use of a baseline period is unadvisable [37].

In house dust mite allergy, a baseline may be used [38] and the fluctuations in the levels of indoor allergens may be observed throughout the studies [39]. In the case of corticosteroid-withdrawal studies, a baseline observation period is needed to stabilize asthma and to assess the baseline level of inhaled corticosteroids.

Randomized clinical trial in rhinoconjunctivitis

Clinical efficacy of allergen SIT is still debated, despite documentation based on double-blind, placebo-controlled trials and meta-analyses. Indeed, many SIT studies have methodological flaws such as the inclusion of a small number of participants, a high frequency of withdrawals and conclusions based on studies of unmatched groups with respect to disease severity. Another problem with SIT trials is that symptom and medication scores are assessed independently, whereas successful treatment reduces both. By contrast, most clinical trials of anti-allergic drugs only assess symptoms.

One of the problems with SIT is that most clinical trials have been carried out using small numbers of patients and that meta-analyses have been required in order to have an insight on the efficacy [12]. New studies have, however, confirmed the effect of SCIT and SLIT for some allergens [4**,40]. More studies are therefore needed using a very precise methodology.

SCIT raises contrasting efficacy and safety issues [41]. It is therefore of importance to carefully assess side effects during clinical trials. Although SLIT appears to be safer, safety should also be carefully assessed.

A randomized, parallel group, placebo-controlled and double-blind design remains the gold standard to determine efficacy of allergen products because of the variability in individual clinical responses, unpredictability and variability of allergenic exposure, and the subjective

nature of symptoms assessment [6**]. These trials should be registered.

Number of patients needed to be treated. In most SIT trials, the number of patients treated is very low and the interpretation of the results difficult. It is clear that future phase III trials for registration will need a large number of subjects. From the recent phase III trials in SLIT, it seems that 150–200 patients per group is adequate [13,14*,15]; however, an appropriate power calculation is necessary depending on the primary outcome chosen.

Primary outcome parameters. The primary endpoint should, if possible, be a single endpoint globally assessing the patient and the comorbidities. In the case of allergic rhinitis induced by pollens, it is advisable to use the total symptom score including all nasal symptoms (nasal obstruction, rhinorrhea, sneezing and pruritus) with one or more ocular symptoms. In some studies, other nonnasal symptoms are used, but this is less classical. It is advisable to use electronic devices to assess the daily symptom score. There is no universally accepted system to measure symptoms: ordinal scales, days free of symptoms, days free of medications, symptom scores corrected for medications, among others. The most frequently used approach in SIT clinical trials is a four-point rating scale (from 0 = absent to 3 = severe) applied to each symptom.

The use of rescue medication has an impact on symptom severity. Therefore, a primary endpoint may have to reflect both symptom severity and intake of rescue medications. Different approaches to combine the two scoring system have been proposed, but there is no standardized method.

Use a global symptom score including all nasal, ocular and bronchial symptoms would be of interest, but this has only been used for medications.

Secondary outcome parameters. Several secondary outcome parameters can be used. Rescue medications may be needed in all studies. Individual symptoms can be recorded [42]. Studies evaluating the symptom response to perennial allergens over a long period may employ a visual analogue scale which is sufficiently sensitive to detect changes in severity. Quality of life

is another important parameter to be studied [43]. Symptom-free days, and physician- and patient-rated clinical global improvement are other secondary outcomes.

Other outcomes such as nasal or conjunctival challenges may complement the studies, but are usually restricted to small studies.

Exploratory outcome parameters. Exploratory outcomes include the evolution of skin tests to allergens and immunologic parameters [44].

Safety. Adverse drug reactions should be codified using the Medical Dictionary for Regulatory Activities [45,46]. The Medical Dictionary for Regulatory Activities is a clinically validated international medical terminology used by regulatory authorities in many countries including the European Union, Japan and the US, as well as by the regulated biopharmaceutical industry throughout the entire regulatory process, from premarketing to postmarketing activities, and for data entry, retrieval, evaluation and presentation. In addition, it is the adverse event classification dictionary endorsed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [45].

Moreover, the adverse drug reactions should eventually be classified as anaphylaxis by a group of experts according to the Second Symposium on the Definitions of Anaphylaxis [47].

Finally, the severity of the reaction needs to be reported using the proposals of the European Academy of Allergy and Clinical Immunology [2^{••}].

Study duration. For pollen allergy, the pollen count is important and the clinical effects of SIT should be recorded during the entire pollen season. The primary outcome analysis can, however, be made for the peak of the pollen season, represented for instance by the weeks including 50% of the total pollen load. House dust mites and animal dander can induce both intermittent and persistent symptoms, and thus patients with persistent rhinitis and/or asthma should be carefully selected.

Another parameter which needs to be better understood is the duration of the treatment before it is effective [48–50].

Concomitant medications and allergen avoidance. SIT improves the control of allergic diseases, but does not alleviate all symptoms, especially when the allergen load is heavy (e.g. peak pollen season). It is therefore mandatory from an ethical point of view that all patients are provided with a rescue medication. The rescue

medication to be used ‘as needed’ must be the same for all subjects and its use recorded on the diary card. The recommended rescue medications to be used are:

- (1) An oral second-generation H₁-antihistamine (once daily)
- (2) An inhaled short-acting β_2 bronchodilator
- (3) An ocular H₁-antihistamine
- (4) An intranasal antihistamine
- (5) An oral corticosteroid (for short periods in the case of unresponsive/intolerable symptoms)

Since the clinical effects of drugs are of different magnitude and duration, a correction factor should be applied. For instance, one point be attributed to each dose of nasal, ocular, oral antihistamines and bronchodilator. For inhaled or nasal corticosteroids at the usual dose a score of 2 should be used. Daily use of an oral corticosteroid is scored 3.

Randomized clinical trials in asthma

For a claim of efficacy in asthma, specific trials should be performed.

Bronchial symptoms (wheezing, shortness of breath, cough) can be used as a primary outcome, but it is usual to associate a co-primary end point, forced expiratory volume in 1 s, or peak flow which can be measured serially using electronic diaries. As secondary outcomes, the control of the disease and quality of life appear to be the most important parameters. Other outcomes such as nonspecific bronchial hyperresponsiveness may complement the study.

Most guidelines propose avoiding SIT in moderate to severe asthmatics because of the increased rate of severe asthmatic reactions; however, a recent study suggested that patients with moderate asthma may be safely treated by SCIT [15]. If new studies are carried out, it will be of great importance to carefully scrutinize their safety.

In asthma, many studies have attempted to find a sparing effect of treatments on asthma control or symptoms. Many of these studies were, however, inconclusive with medications because the placebo effect is significant. In SIT, two studies have been carried out in asthma and the results were not conclusive.

Studies in children

The European Medicinal Agency (Directive 2001/20/EC) and US Food and Drug Administration state clearly that children are not small adults and that specific trials should be conducted. Special ethics should be considered since children cannot usually give their informed consent.

Moreover, the efficacy of SIT in children is less well defined than in adults. Two recent meta-analyses in children showed that sublingual delivery of allergen vaccination constitutes a safe and effective alternative to the injectable route to reduce allergy respiratory symptoms and drug intake [51,52]. New studies have been published, however, and not all have shown efficacy [28,53–55].

Cost-effectiveness studies

New studies will need to incorporate cost-effectiveness parameters [56–59].

Conclusion

The present paper critically describes how to conduct clinical trials in immunotherapy. Unfortunately, only a few studies meet the criteria proposed.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 595).

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