

REVIEW ARTICLE

How to design and evaluate randomized controlled trials in immunotherapy for allergic rhinitis: an ARIA-GA²LEN statement

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Abstract

Specific immunotherapy (SIT) is one of the treatments for allergic rhinitis. However, for allergists, nonspecialists, regulators, payers, and patients, there remain gaps in understanding the evaluation of randomized controlled trials (RCTs). Although treating the same diseases, RCTs in SIT and pharmacotherapy should be considered separately for several reasons, as developed in this study. These include the severity and persistence of allergic rhinitis in the patients enrolled in the study, the problem of the placebo, allergen exposure (in particular pollen and mite), the analysis and reporting of the study, the level of symptoms of placebo-treated patients, the clinical relevance of the efficacy of SIT, the need for a validated combined symptom-medication score, the differences between children and adults and pharmacoeconomic analyses. This statement reviews issues raised by the interpretation of RCTs in sublingual immunotherapy. It is not possible to directly extrapolate the rules or parameters used in medication RCTs to SIT. It also provides some suggestions for the research that will be needed. Interestingly, some of the research questions can be approached with the available data obtained from large RCTs.

Specific immunotherapy (SIT) is one of the treatments for allergic rhinitis (1, 2), and an updated Cochrane Collaboration study has confirmed the efficacy of subcutaneous immunotherapy (SCIT) in asthma despite concerns for its safety (3). Recommendations for the performance of randomized controlled trials (RCTs) in subcutaneous and sublingual immunotherapy (SCIT and SLIT) have been made (4, 5). However, for allergists, nonspecialists, regulators, payers, and patients, there remain gaps in understanding the evaluation of RCTs. In particular, in some countries, the reimbursement of SLIT is delayed (6), often because RCTs are compared with those of pharmacotherapy. Although treating the same diseases, SIT and pharmacotherapy should be considered separately for several reasons, as developed later.

Some common criteria should be set for all RCTs, including trial registration before the RCT commences and publication of all studies including those which did not find a significant difference for the primary end point.

According to Allergic Rhinitis and its Impact on Asthma (ARIA) (7), allergen-specific immunotherapy is indicated in patients with moderate–severe intermittent or persistent allergic rhinitis and rhinoconjunctivitis, particularly in those who do not respond sufficiently to current pharmacological treatment (8). Thus, RCTs should study patients with moderate–severe rhinitis defined according to ARIA. However, registration studies need to be carried out on patients without regular medications for the treatment of allergic diseases to assess the magnitude of the treatment effect (9). On the other hand, studies may be needed to define whether SIT is effective in patients who are not controlled by medications administered at recommended doses.

Specific immunotherapy has unique effects on the natural history of allergy and is able to modify the course of the disease (10). The prolonged effects, after the treatment has been stopped, should be considered (11, 12). These considerations may modify the indications for SIT (13).

This statement reviews issues raised by the interpretation of RCTs in SIT. It also provides some suggestions for the research that will be needed. However, some of the questions can be approached with the available recent data obtained from large RCTs [e.g., (14–21)]. This statement will not review long-term modifying studies, which will be considered separately.

Abbreviations

ARIA, Allergic Rhinitis and its Impact on Asthma; CONSORT, Consolidated Standards of Reporting Trials; EMEA, European Medicines Agency; FDA, Food and Drug Agency; ICER, incremental cost-effectiveness ratio; ITT, intent-to-treat analysis; LOCF, last observation carried forward; PP, per protocol; PRQLQ, Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; QOL, quality-of-life; RCT, randomized controlled trial; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; RTSS, Rhinitis total symptom score; SCIT, subcutaneous immunotherapy; SCUAD, severe chronic upper airway disease; SIT, specific immunotherapy; SLIT, sublingual immunotherapy.

Patients enrolled in SIT trials should have moderate–severe rhinitis

The concept of severe chronic upper airway disease (SCUAD) has recently been proposed. Severe chronic upper airway disease defines uncontrolled patients with allergic rhinitis despite adequate (i.e., effective, safe, and acceptable) pharmacologic treatment based on guidelines (8). Many patients with allergic rhinitis are insufficiently controlled by current treatments. In all RCTs with drugs, symptoms are improved, but many patients still remain symptomatic. This was also found in a trial comparing guidelines and free treatment choice (22). Severe chronic upper airway disease has been demonstrated in a large cluster randomized trial of patients with grass pollen rhinitis receiving guideline-based treatment administered by specialists (23). Around 15–20% of these patients, mostly those with moderate/severe persistent allergic rhinitis, present SCUAD. These patients have altered sleep, quality-of-life, and work performance. Moreover, around 15% of them have severe ocular symptoms.

In most large SIT RCTs, enrolled patients have to have had moderate–severe symptoms in previous years. Some studies even request patients who are uncontrolled with pharmacologic treatment (14, 24). It is thought that the best approach would be to start a 1-year placebo trial to select patients sufficiently severe for enrollment. However, because of the large variation of pollen seasons, patients in the placebo group may not present symptoms during the time of the expected season because of low allergen exposure (25), and this approach is not valid (26). Moreover, baseline assessment does not impact randomization as patients are randomly assigned to one group after inclusion. By definition, this has to be independent from symptoms. It does not preclude stratification during the randomization process for known prognostic factors.

Patients' medical allergy history data are used in most RCTs but they may not be reliable or methodologically correct. Patients are likely to recall the most severe symptoms but not the average symptoms from the previous season (27). This is one of the reasons for the low scoring in the placebo group during the evaluation period of pollen immunotherapy studies.

However, many studies have found that the majority of patients consulting in allergy practices have moderate–severe intermittent or persistent rhinitis (28–30). Thus, it is likely that most patients enrolled in SIT RCTs by allergy specialists have moderate–severe symptoms and/or use medications to control their symptoms. However, patients enrolled by CROs or after advertisement in the media may not have such severe disease.

Research needs

As pollen seasons are highly variable between years and areas, it is difficult to propose a run-in period of one season before starting SIT. The study of Bodtger et al. (27) should be repeated to determine whether retrospective scores could be used to enroll patients.

The problem of placebo in SIT RCTs

The studies in SIT should be of the highest methodologic quality, as well as the reporting of the studies in pharmacotherapy. Double-blind, placebo-controlled, SLIT studies have found that up to 65% of subjects on active treatment with allergen versus up to 30% on placebo have had local allergy symptoms during treatment. This imbalance of adverse local/regional reactions makes the blinding of the study difficult (2). However, the choice for a placebo in SLIT remains a problem. Histamine, under the tongue, does not elicit itching, nor are there any other substances that produce similar symptoms to an allergen extract in a person allergic to a given allergen. Therefore, it would be difficult to manufacture a placebo causing local allergy symptoms. In addition, according to certain studies, the adverse local effects of SLIT typically remit within a week or two. Because it is not feasible to devise an active nonallergen placebo, any analysis of efficacy should take into account the incidences of side-effects. However, in two studies, the level of local/regional side reactions was not associated with the level of efficacy (17, 18). In SCIT, a caramelized histamine placebo is often used, but it does not completely mimic the allergen-induced reactions.

Moreover, regarding symptom scores, the placebo arm should be considered differently in SIT and drug RCTs, as placebo-controlled studies of SLIT permit free access to usual antiallergic drugs. This is realistic as these are the circumstances in which SLIT is usually prescribed. The use of the term 'placebo' is legitimate in these circumstances as both the placebo and actively-treated groups have the same access to rescue medication.

Research needs

- There is an urgent need for the characterization of an appropriate placebo in SLIT.
- The following option should be discussed: to include patients with dual allergen sensitivity (e.g., grass and mite allergy) and treat with either grass or mite SIT, each acting as placebo for the other as judged by evaluating symptoms in the relevant season where this is geographically feasible. This 'active allergen placebo' approach might be possible for both SCIT and SLIT by reproducing and therefore blinding local side effects.
- There is need for a placebo-based strategy in RCTs.

Allergen exposure

Pollen

In SIT to pollens, it is requested that symptom scores should be recorded according to the level of pollen exposure (9), and some studies have started to record symptom scores once a certain level of pollen has been reached. Unfortunately, pollen counts are only poorly correlated with symptoms (31). No large-scale study has been published comparing pollen counts and symptoms in individual patients. However, it

could be easy to carry out such studies in the placebo groups of the large SLIT RCTs, in both adults (16–19) and children (20, 21). Correlations should be made in patients living within a short distance from the pollen trap. Many reasons may explain this lack of correlation:

- The level of allergens in ambient air may not correlate with pollen counts because the allergen potency of pollen varies widely (32), and the allergens may be borne by nonpollen particles eventually released outside the pollen season (33). Phenology may be useful for the determination of the pollen season onset.
- Pollen samplers are distributed among centers, but variations between short distances are not taken into account.
- Pollen sampling recovery is heterogeneous, showing differences according to the wind and the distance between the sampling site and the pollen source (34). Furthermore, sensitized subjects are exposed to variable amounts of pollens, whereas pollen traps are only located in a single place. Patients may live at a distance from the sampler and the levels of allergens may differ quite extensively. However, individual allergen exposure can vary in cities because of special climatic conditions and localized vegetation, e.g., mugwort, *Ambrosia*, which may vary largely within a few hundred meters.
- Patients can travel and have an exposure that differs from that of the area.
- Pollen counts do not take into account climatic factors such as rain, which may wash out the allergens from the pollens (35).
- Pollen counts and timing of the season vary largely between years.
- Individual pollen samplers exist but are difficult to use in large studies.
- Simultaneous exposure to allergens and indoor or outdoor air pollutants is common. In some areas and in some patients, pollutants might contribute to symptoms more than pollen. This, in turn, might contribute to the reduced efficacy of SCIT in such circumstances.
- Thus, individual pollen counts are very important for an overall assessment of pollen seasons (36), but cannot appreciate symptoms in individual patients.

Another drawback of pollen counts is that the number of pollen grains needed to elicit symptoms is not well defined. It has been estimated to be 20 or 50/m³ in the large SLIT RCTs (18, 19). It is likely to vary in mono- and polysensitized subjects because of the overlapping of pollen seasons (37) and the possible priming effect on the mucosa (38).

Assessment of allergen content in the air is feasible using antibody-based methods (32) or biomolecular identification of pollen genomes (39), but individual measurements are not possible.

Only large multicentric RCTs can include a sufficient number of patients and overcome all the problems listed earlier. Thus, pollen exposure varies largely, and in some centers, the level of pollens may not be high enough to induce symptoms, even in patients receiving placebo. It has been proposed that centers in which the level of pollen is too low should be *a priori* excluded from the analysis. However, as the thresh-

old level of pollens needed to induce symptoms is unknown, this seems difficult.

Research needs

As pollen exposure using a single sampler for a large population is insufficient for the assessment of symptoms in SIT RCTs, it may be of importance:

- To use individual samplers.
- To evaluate separately the effect of SIT according to individual samplers.
- To study symptoms in the placebo group to characterize both the onset of the pollen season and its severity. It may also be proposed to restrict the analysis to the centers in which the placebo patients have at least a certain level of symptoms.
- To assess whether indoor/outdoor exposure impacts symptoms in patients undergoing SIT or placebo and in non-responders to SIT, e.g., cotinine levels.

House dust mites

It has been recommended to measure house dust mites or their antigens in the house dust of patients undergoing SIT. However, in some studies, unexpectedly, the levels of mite antigens have considerably decreased during the trial (40).

Other confounding factors include polysensitization, in particular to pets, and allergen avoidance. Although mite avoidance measures are not clearly effective in a group of patients (1), they may have an effect on some subjects, and all patients should have the same recommendations during the RCT.

In mite allergy, the level of symptoms depends on many factors such as humidity of the environment, airflow, or other climatic factors, which cannot be standardized.

Research needs

More studies are needed to fully understand the relationship between mite exposure levels and symptoms, in both placebo and treated patients.

Analysis and reporting of the study

The Consolidated Standards of Reporting Trials (CONSORT) statement as well as medical agencies request that studies be analyzed by the intent-to-treat analysis (ITT) principle (41). Intention-to-treat analysis provides information about the potential effects of treatment policy rather than the potential effects of specific treatment. In contrast, per protocol analysis selects the subset of patients who have received the treatment of interest and who have not dropped out. This approach is likely to be flawed, introduces biases to the statistical analysis and inflates the type I error. The ITT principle implies that the primary analysis should include all randomized subjects. An ITT analysis is based on the assumption that, as in real life, all patients do not receive optimal treatment, despite this being the initial intention. Intention-to-treat analyses are carried out to avoid the effects of dropout, which may break the randomization of the treatment groups in an RCT. Empirical

evidence suggests that participants who adhere tend to do better than those who do not adhere, even after adjustment, for all known prognostic factors and irrespective of assignment to active treatment or placebo. Compliance with the ITT principle necessitates a complete follow-up of all randomized subjects for study outcomes (42). This is both appropriate and feasible for studies of pharmacologic agents where, inevitably, the 'ITT', 'safety', and 'efficacy' populations can be synonymous because they may all correspond to the randomized population that receives *at least one* treatment.

On the other hand, the use of strict ITT criteria is more difficult for immunotherapy, where the treatment is administered for several months prior to the collection of seasonal symptom data. In these circumstances, the true 'ITT population' (all those randomized and who have received at least one treatment) is the same as the 'safety population' (all those who have received at least one treatment) but cannot be the same as the 'efficacy' population that includes those few participants who drop out before any pollen exposure (and hence there are no symptoms for evaluation). In these circumstances, it is not a 'fault' of the study, which could still be regarded as 'ITT with missing data' rather than condemned as 'per protocol' as primary analysis and therefore of perceived lower quality. This occurred in a recent review of compliance of reporting of SLIT studies according to CONSORT criteria, in which 44 of 47 recent studies were condemned as 'low-quality' reports. Several of these studies followed ITT guidelines but inevitably included patients who, for legitimate reasons (and not on grounds of failed treatment effect), dropped out before pollen exposure or before symptoms occurred.

It is now argued that the ITT analysis is difficult to be used in SIT as trials usually last for over 6 months, and dropout rates are more important than in shorter-term pharmacologic studies. Some ethical committees are now obliging the centers to pay the patients, as is the case in France. This new attitude may introduce biases including severity of symptoms.

The number of patients to be treated is often not calculated and justified as it should incorporate the dropout rate, which is greater in long-term studies than in short-term pharmacological studies. Although some large RCTs have calculated that at least 150 patients per arm are needed in adults (16–19) and children (20, 21), some have been reported with lower numbers. Consequently, one of these studies appears to be underpowered, and the difference between placebo and allergen is not significant (43).

Research needs

- A clear view of the ITT analysis should be determined by regulators and methodologists.
- A table with the numbers of patients to be treated should be provided in all RCTs. This needs to include the expected dropout rate.
- Papers should be reported following the CONSORT statement (44) and revised according to the latest statement, with the reservation that recommendations regarding the

definition of ITT in relation to immunotherapy studies should be reviewed by an appropriate expert panel.

The mean (median) level of symptoms of placebo-treated patients is low in SIT RCTs

In RCTs in allergic rhinitis, a total symptom score is usually requested as the primary outcome by all regulatory agencies. It is based on the four nasal symptoms (nasal obstruction, nasal pruritus, sneezing, and rhinorrhea) quoted in most but not all trials from 0 to 3 (none to very severe) (2, 9). This leads to a RTSS4 of up to 12. Because SIT also acts on ocular symptoms, RTSS5 or RTSS6 is used (including one or two ocular symptoms), leading to maximal scores of 15–18.

In pharmacotherapy studies, patients are enrolled at the peak of the pollen season, or at least when allergen exposure is sufficient to cause a high level of symptoms. Usually, patients are treated with placebo for a period of 3–7 days to have a RTSS4 of over 6–9 for 2–3 consecutive days, and they often have a mean RTSS4 >7–9 at randomization (45–48). Thus, many patients are excluded for insufficient symptom levels, and only patients who are sufficiently symptomatic are randomized.

It is interesting to note that, in most studies, after 1 day of treatment, RTSS4 decreases by 10–30% in the placebo group from baseline values. After 2–4 weeks, RTSS4 in the placebo-treated patients has usually decreased by 20–50% (45, 46, 49–51). However, even in pharmacotherapy studies, using the most stringent criteria for enrolling moderate–severe patients, the mean RTSS4 is still around 4–7 in the placebo group after a few days of treatment.

In pollen SIT, patients are enrolled 2–6 months before treatment (52), and symptoms are measured when pollen counts are sufficiently high (arbitrary level) to induce symptoms. Symptom–medication scores are then usually followed up by periods varying from 4 to 10 weeks during the pollen season. However, allergen exposure varies widely between centers, the pollen season is not uniform over these 4 weeks (owing to the level of pollens or the patient's activities), and patients under placebo may not have symptoms during many days. For these reasons, studies that include *bona fide* participants with a history of moderate–severe rhinitis and impaired quality of life frequently report a low *mean* Rhinitis total symptom score (RTSS) in placebo-treated patients of 3–5 (18, 20, 22, 27, 28). This is in contrast to studies of pharmacologic agents that recruit participants *in season* according to a predetermined severity of symptom scores. For example, in a recent DB-PC-RCT of an H1-antihistamine in 562 patients with persistent allergic rhinitis, patients under placebo ($N = 261$) had a mean baseline RTSS4 of 9.55 ± 0.21 . Over a period of 1 month, RTSS4 decreased by a mean 2.87 ± 0.21 (46).

Specific immunotherapy patients may have moderate–severe intermittent rhinitis. In this case, they do not suffer from symptoms for the entire month.

Some sensitivity studies have been carried out, stratifying patients according to levels of pollen counts (17, 53) or severity of symptoms (53). Subgroup analyses have been

proposed in the analysis, and centers have been ordered according to pollen counts and placebo RTSS analyzed in tertiles. Specific immunotherapy-treated patients could be stratified according to these placebo tertiles. Days with severe symptoms ('worst days') during the pollen season is a relevant additional efficacy end point, which can be used in immunotherapy trials to support the clinical interpretation of commonly-used efficacy end points (54). This approach might give a better description of efficacy than 'symptom-free days'.

Research needs

- To understand the magnitude of severity of patients under placebo and the clinical relevance of SIT, more studies are needed to investigate the maximum level of symptoms in the placebo group, as well as the number of 'days with severe symptoms'.
- However, for comparability between studies, it is advised to develop a standard RTSS.

Clinical relevance of the efficacy of SIT

One of the criticisms raised against SIT RCTs is the low level of efficacy as compared with medications when mean RTSS is analyzed. Usually, there is a 20–30% mean (and 30–40% median) decrease in RTSS by comparison with placebo, which signifies a 1–1.6 point in a score of 12. This level may be considered by regulators as insufficient to warrant the legislation of SIT in some countries. It appears that the percentage of improvement over placebo is more relevant than the absolute number, which is already low in the placebo group for the above-mentioned reasons.

However, there are many considerations that indicate that SIT RCTs cannot be compared with pharmacotherapy RCTs:

- The exposure to allergens varies during a pollen season, and even in patients with persistent allergic rhinitis owing to indoor allergens, variability exists. Thus, whereas in short-term trials with medications, a greater improvement and patients included at the peak of their symptom scores can be observed, the mean improvement in perennial or persistent allergic rhinitis after a month of treatment is low, and some studies with medications are not even significant (51, 55, 56). This is why the concept of 'worst days' is of interest (54).
- Many patients receive rescue medications, and symptoms are therefore improved.
- The dropout rate is greater in long-term RCTs (SIT) than in shorter-term ones (pharmacotherapy). If dropouts are greater, the mean difference between placebo and active treatment will be smaller in the ITT analysis.
- Quality-of-life is a difficult parameter to be studied in SIT. At inclusion, patients do not have an impaired quality-of-life (QOL). During the pollen season, QOL deteriorates, but less in the active group than in the placebo. Moreover, QOL is measured at defined time points and mean placebo group levels are lower in pollen SIT than for medications

(18, 57) as some patients are not sufficiently exposed on the day of measurement.

- Moreover, the effect of SIT on the natural history of allergy is not considered in the 6- to 12-month studies needed for registration.

These reasons explain why an expert group estimated that an improvement of over 20% of the RTSS was clinically relevant (4). However, the clinical minimal difference has not been determined with sufficient precision.

Research needs

- It is essential to assess and validate the clinical minimal difference of RTSS in SIT RCTs.
- Improvement during 'worst days' should be examined in all large trials.
- A combined symptom–medication score may be the best approach and requires careful evaluation.
- The assessment of the efficacy of SIT over medications should be a priority because most patients use both medications and SIT, which is unable to ablate all symptoms (58). On the other hand, SCUAD patients who cannot be sufficiently controlled by optimal medications (8) represent an important unmet need for SIT. However, there are no data in SCUAD.

Combined symptom–medication scores are needed to mimic real life

In real life, patients receive both SIT and medications to optimally control symptoms. In SIT RCTs, it is unethical not to allow rescue medications because of the possible long duration and intensity of the pollen season, but the intake of medication interferes with RTSS. Thus, CPMP (EMA) has recommended the use of symptom–medication scores but has not specified the recommended instrument (9).

Standardized rescue medications with clear instructions have been used for over 20 years in SCIT (59) and SLIT (60) as well as in the recent large SLIT RCTs. It is therefore possible to calculate a combined score but this has to be defined. Several methods are currently being tested and should be compared by an expert panel.

Research needs

There is an urgent need for defining *a priori* symptom–medication scores, validating them retrospectively in available RCT databases, and comparing them to obtain one or several combined symptom–medication scores for prospective use in further studies.

The efficacy in children may be less than in adults

In the recent meta-analysis on SLIT, the magnitude of the effect appears to be lower in children ranging in age from 5 to 17 years than in adults, whereas in the two large pediatric RCTs, the differences were not so apparent (20, 21, 61). A subanalysis showed that efficacy with grass tablets is simi-

lar in children of 5–11 and 12–18 years of age. EMA and the Food and Drug Agency (FDA) request studies on children of 5–11 years of age but they do not recommend tools specifically adapted for this age group. Moreover, patients' reported outcomes (PROs) have just been proposed in allergy (62, 63), but not for children. The few studies carried out in this age group with intra-nasal corticosteroids (64, 65) or H₁-antihistamines (66, 67) show a similar reduction in efficacy by comparison with studies carried out with the same medications in older patients. The reasons for the possible lower efficacy of SIT in children aged 5–11 years found in some studies may be the following:

- The need for specific instruments assessing the efficacy and safety of antiallergic treatments. The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) has been developed specifically for children (68), but there are few RCTs, and the magnitude of difference by comparison with the Rhinoconjunctivitis Quality of Life Questionnaire for adolescents and adults is not clear. Although sleep problems are captured in the PRQLQ, no score comprehensively identifies the full impact of persistent rhinitis in children with regard to snoring and mouth breathing secondary to nasal congestion, facial tics secondary to itching, behavior problems, and school problems.
- For children, symptoms are recorded by the parents.
- Children appear to have less severe (or briefer) symptoms than adolescents and adults, although no comparisons are available.
- Allergic sensitization and allergic disease are under development and not finally established before adolescence. This may influence the outcome of treatment strategies, especially with regards to symptomatic effect. In this age group, this aspect should be taken into account, and studies assessing long-term development in response to treatment strategies should be performed.
- For rhinitis and conjunctivitis, children may be less responsive to treatment than adults. This has been shown for medications (65), but RCTs may suffer from certain defects. The dose of medication may be insufficient in some RCTs, some may be underpowered, and others may have a flaw in the design. However, for asthma, most children respond quickly and favorably to inhaled corticosteroids, whereas the effect of long-acting β_2 agonists is less clear.

Research needs

- Pediatricians and methodologists should analyze current RCTs in 5- to 11-year-old children to make a comparison between adolescent/adult and children studies (pharmacologic and immunotherapy).
- PROs for children of 5- to 11-years old are needed.

Pharmacoeconomic analyses

The costs of treatment are vital in the therapeutic decision. They should include short-term effects as well as the preventive effect of immunotherapy, which is always difficult to assess and model (69). Some large carryover RCTs

assessing the effect after treatment interruption are available (11, 12).

Sublingual immunotherapy was proposed to be cost-effective for drops (70) and tablets (71, 72) but these analyses suggest a high annual cost and there are some concerns (6). Moreover, there may be certain misconceptions about immunotherapy cost-effectiveness. Many studies are now using the quality-adjusted-life years to make pharmacoeconomic decisions. It is usually accepted that for severe and/or life-threatening diseases, the incremental cost-effectiveness ratio (ICER) threshold should be up to 50 000 € per year. This is the case for omalizumab in severe asthma or many biologicals in cancer or neurodegenerative diseases (73). Thus, some authors have proposed that a similar ICER threshold may be used for immunotherapy (74). However, the majority of patients suffering from allergic diseases have a mild to moderate form of the disease, and cost-effectiveness needs to take into consideration the preventive effect of immunotherapy using models such as Markov (74). A cost-effectiveness model in SCUAD should be developed.

Research needs

- Independent long-term RCTs with *a priori* designed cost-effectiveness analyses should be carried out.
- Before the results of such studies are available, modeling using several scenarios should be carried out by an independent organization with available results.
- Specific immunotherapy may be cost-effective in SCUAD patients.

Conclusions

New methods may need to be developed. They should include new ways of monitoring allergens (e.g., individual samplers) and symptoms (e.g., VAS). Moreover, allergen challenge in chambers may be needed to complement RCTs and to answer certain specific questions such as speed of onset (75) or additive effect of SIT over medications.

It is clear that a joint effort between allergists, methodologists, regulators, patient groups and the allergen manufacturers is needed to obtain answers as rapidly as possible to important research questions, which will benefit the patients. ARIA (7), GA²LEN (76) and the WHO Collaborating Center on Asthma and Rhinitis are proposing to coordinate this effort and to organize a meeting to answer some of the questions raised.

Conflict of interest

C. Bachert has received honoraria for presentations or advice from ALK, Stallergenes, Allergopharma and Biotech comp. J. Bousquet is a member of the Stallergenes board and has received honorarium from ALK-Abello and Stallergenes. A. Briggs has received consultancy payments and honoraria for work relating to asthma products for GSK, Novartis and Amgen. M. Calderon has acted as a consultant for ALK-Abelló, and a speaker for ALK-Abelló, Allergy Therapeutics (UK) Ltd, MSD and GSK. He has appeared on advisory boards for Allergy Therapeutics (UK) Ltd and ActoGeniX, received honoraria from ALK-Abelló, Allergy Therapeutics (UK) Ltd, Schering-Plough, and MSD and research grants from ALK-Abelló and GSK. G.W. Canonica has received research grants as well as lecture fees from Allergy Therapeutics, ALK, Anallergo, Hal, Lofarma, Stallergenes. T. Casale has been a consultant for Stallergenes and Novartis. He has been an investigator on studies for Stallergenes, Novartis, Genentech and Schering. P. Demoly has received lecture fees and honoraria from Stallergenes and ALK. P. Devillier has received fees for speaking, organising education or consulting from Altana Pharma – Nycomed, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Stallergenes, Pfizer, Schering-Plough, Merck Sharp & Dohme and Sanofi-Aventis. S. Durham has received research grants from ALK Abello via Imperial College. Lecture and consultancy fees from ALK Abello, Greer Laboratories and Circassia. R. Gerth van Wijk has received fees for lectures, expert panel participation and consultancy and research support from Allergopharma, Allmiral, Alcon, Crucell, Hal, Merck Sharp & Dome, Novartis, Stallergenes, Artu Biologicals and UCB. D. Larenas has received speakers fees for Astrazeneca and MSD. Advisory board MSD and Boehringer Ingelheim. Speakers fees ALK. Travel grants from ALK, Stallergenes and Allerquim. H.J. Malling has received research support from ALK-Abello, Stallergenes. Actual research cooperations: Stallergenes, France. Advisory board: Stallergenes, France (Development of a Bet v 1 SLIT tablet) and ALK-Abello, Denmark (Anaphylaxis and adrenaline auto-injector). Speakers' bureau: ALK-Abello, Stallergenes, Allergopharma. P. Schmid has received honorarium for being a speaker for Allergopharma, ALK-Abello and Stallergenes. T. Zuberbier: Industry consulting and research grants: Consulting with the following companies: Ansell, Bayer Schering, DST, Fujisawa, HAL, Henkel, Kryolan, Leti, MSD, Novartis, Procter and Gamble, Sanofi-Aventis, Schering Plough, Stallergenes, UCB.

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