REVIEW ARTICLE

Perspectives on allergen-specific immunotherapy in childhood: An EAACI position statement

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Abstract

This article is the result of consensus reached by a working group of clinical experts in paediatric allergology as well as representatives from an ethical committee and the European Medicine Agency (EMA). The manuscript covers clinical, scientific, regulatory and ethical perspectives on allergen-specific immunotherapy in childhood. Unmet needs are identified. To fill the gaps and to bridge the different points of view, recommendations are made to researchers, to scientific and patient organizations and to regulators and ethical committees. Working together for the benefit of the community is essential. The European Academy of Allergy and Clinical Immunology (EAACI) serves as the platform of such cooperation.

Nowadays, allergen-specific immunotherapy is considered as an important treatment modality for the allergic patient. Immunotherapy has been positioned as the only treatment that may alter the natural course of allergic disease. However, it has to be acknowledged that the scientific evidence that should support such claims is far from optimal. Moreover, for many products, the current evidence does not meet the conditions set by regulatory agencies to obtain a marketing organization. Long-term trials are needed to support such claims. Although scientifically sound, such trials form a major challenge for the field of paediatric allergy. The issue of long-term placebo-controlled randomized trials in children has frequently been addressed by ethical committees all over the world. Particularly, the application of placebo via the classical subcutaneous injections has led to controversies (1). Also, concerns have been raised about the feasibility of such trials. Therefore, a working group of clinical experts in paediatric allergology as well as representatives from an ethical committee and the European Medicine Agency (EMA) met for a 2-day workshop in Berlin in September 2011 to discuss the chances for the implementation of the new frame conditions to remove possible barriers and look for a consensus

regarding long-term paediatric randomized controlled trials. The aim was to bridge the need for solid scientific evidence and the requirements from EMA on the one hand and the necessity of practical and ethically accepted trials on the other hand. The working group identified gaps in our knowledge and made further recommendations to develop and implement allergen-specific immunotherapy in an effective way.

Background

During the last decade, the requirements to obtain certain claims of allergen manufactures providing extracts for allergen-specific allergen immunotherapy have been specified by the EMA (2). At the same time, pharmaceutical companies including allergen manufactures entering the markets are supposed to provide a paediatric investigation plan (PIP), which is meant to provide evidence for both short- and long-term efficacy and safety of an immunotherapeutic intervention in children, thereby guaranteeing that in future, treatment will be purely based on best evidence (3). For the evidence of long-term efficacy, 3-yr randomized double-blinded placebo-controlled (DBPC) clinical trials with 2-yr blinded follow-up are warranted (3).

Most children in Europe are treated with allergen products that have not obtained a marketing authorization (MA) according to the Directive 2001/83/EC as amended. This directive mandates that all medicinal products manufactured by an industrial process require an MA based on results of clinical trials, demonstrating the quality, efficacy and safety of the medicinal product (4). To date, only a few allergen products obtained an MA according to this Directive. In many, though not all, European countries, it is still common practice to manufacture so-called named patient allergen products for an individual patient on the basis of an individual prescription. Without an MA, the quality, efficacy and safety of named patient products have not been independently evaluated according to Directive 2001/83/EC.

As the current PIP refers to respiratory disorders (3), this position paper mainly focuses on respiratory allergies. However, the PIP may affect other areas such as insect venom allergy and food allergy. In particular, in the field of food allergy, research to the induction of oral tolerance with oral, sublingual or epicutaneous allergen immunotherapy has gained much attention (5) and is discussed briefly. It can be foreseen that advances in this field may lead to new products for registration in the near future.

EMA standards for paediatric studies

The International Congress of Harmonization (ICH) guideline on clinical investigation of medicinal products in the paediatric population requires that paediatric patients should be given medicines that are adequately evaluated for their use (6). The European Regulation (EC) No 1901/2006 on medicines for paediatric use (the Paediatric Regulation) entered into force in 2007 to promote high-quality research into the development of medicines for children and to increase the availability of medicines for children (7). With this law, companies are obliged to conduct studies in children under the age of 18 in accordance with an agreed PIP unless a formal waiver has been agreed. A Paediatric Committee (PDCO), including patient representatives, was established at the EMA with the task to evaluate PIPs proposed by industry.

The PDCO at the EMA prepared a standard PIP for allergen products for allergen-specific immunotherapy (SIT) following the conclusions of an experts meeting held at the EMA (8). This standard PIP provides a detailed study design based on the requirements of the EMA guideline on the conduct of clinical trials with allergen products for allergen-specific immunotherapy (2), emphasizing the need to demonstrate long-term efficacy. Modification of the response to allergens at an early stage and, thereby, of the natural history of a respiratory allergic disease by preventing disease progression would constitute the key benefit of SIT in children. Specific immunotherapy is associated with discomfort and/or pain for the children and the risk of local adverse events and of serious adverse events including anaphylactic shock. To compensate for the discomfort and the risks and to support a positive benefit–risk balance, the PDCO concluded that SIT should provide long-term benefit to children. At present, evidence for such long-term benefit and disease-modifying effect in children is still very limited from a few controlled, but unfortunately open, studies (9, 10). Yet, authorization of products for allergen immunotherapy must be based on scientifically sound evidence and not simply on data from year-long use following named patient prescription, which has not the necessary scientific robustness.

Available evidence does not allow a conclusion as to whether or not long-term efficacy and the disease-modifying effect of allergen immunotherapy in children might be extrapolated from adult data. While the basic pathophysiological mechanism of IgE-mediated reactions, albeit not fully understood, is assumed to be identical in adult and paediatric populations and while SIT is expected to act in the same way in children and adults, the magnitude of the effect and the safety profile could differ. Because of the plastic nature of the paediatric immune system (11), the long-term benefit in children might be expected to be even better than in adults. Therefore, long-term studies in the paediatric population are needed until such evidence is available. This requirement in the standard PIP will be revised with the evolution of knowledge and increased availability of long-term data.

Because of the variability in individual clinical responses, the unpredictability and variability of allergen exposure and the subjective nature of symptom assessment, double-blinded comparison with placebo is the best design able to validate efficacy for allergen products (12). At present, no allergen product with demonstrated long-term efficacy is authorized for children, precluding the use of an active comparator instead of placebo for clinical studies in children.

In conclusion, the standard PIP for allergen products for allergen-specific immunotherapy aims at filling the gap in knowledge concerning the benefits of SIT for children and at obtaining the data needed to support evidence-based

authorization of allergen products for SIT for the paediatric population. Close cooperation between academia, regulators, industry and parent/patient organizations is needed to facilitate the conduct of large long-term studies in children, which eventually will allow both patient and physicians to make evidence-based treatment decisions.

Allergen-specific immunotherapy in paediatric respiratory allergy

In the majority of cases, allergic rhinoconjunctivitis develops from early childhood through adolescence causing symptoms, which may persist for years or decades (13). The allergic immune response in the pre-clinical and very early clinical phase in childhood is weaker and probably more susceptible to be influenced by immunological treatment (14). By contrast, the immune response is highly complex and molecularly heterogeneous in more advanced disease stages (15). Thus, early childhood offers a window of opportunity for early intervention with a higher chance to affect the natural history of disease. On the other hand, birth cohort studies also indicate that intermittent as well as persistent allergic rhinitis, even in early years, may lead to an impaired quality of life (16). At present, allergen-specific immunotherapy is the only treatment that has the potential to modify the disease's expression and consequently might prevent the progression from allergic rhinitis to asthma (17).

Allergic rhinitis

The scientific evidence of efficacy of subcutaneous allergen immunotherapy (SCIT) for the treatment for allergic rhinoconjunctivitis has been demonstrated mainly in adults (18–23). Therefore, the levels of evidence of SCIT efficacy in children are low (24). Considering the ethical problems to carry out DBPC trials in children, papers with a lower level of evidence may not be discarded in children. In the last two decades, evidence that supported the efficacy and safety of sublingual allergen immunotherapy (SLIT) as an alternative treatment for seasonal allergic rhinoconjunctivitis in the paediatric population has been published (20, 25–29).

Allergic asthma

The efficacy of SCIT for allergic asthma in adults and children has been shown in a recent Cochrane meta-analysis (30); however, no conclusive evidence data type 1A (e.g. from meta-analyses of RCTs) can be obtained for the paediatric population (30). It is important to highlight that in this Cochrane review, no children's sub-analysis was performed, heterogeneity was high, and there was a discrepancy in respiratory outcomes used. Nevertheless, individual paediatric studies have shown moderate efficacy of SCIT in seasonal (31) and perennial (32) asthma and significant reduction in corticosteroid doses in mite-induced asthma (33). SCIT is still not indicated in severe asthma until an adequate control is achieved (34). At present, there is no clear consensus regarding the use of SLIT in allergic children with asthma symptoms. A systematic review and meta-analysis of nine DBPC RCT in asthmatic children following SLIT treatment (35) was hampered by a relevant heterogeneity owing to widely differing scoring systems and because of a potential publication bias (36). Interestingly, in a recent large trial on SLIT grass tablet used for rhinoconjunctivitis in children aged 5–16 yr, their asthma symptoms (coughing, wheezing, shortness of breath and exercise-induced symptoms) were significantly reduced, whereas the use of rescue medication for asthma was reduced, but not significantly (26). Comparative studies addressing the relative efficacy between SCIT and SLIT are still lacking.

Safety

The safety profile of both SCIT and SLIT in the paediatric population has been thoroughly evaluated in most of the clinical studies. It has been shown that SCIT is safe in children with allergic rhinitis and mild–moderate asthma However, SCIT should be administered by experienced and trained physicians (specialists or general practitioners) in settings with all facilities to attend any severe adverse event. Fatal and near-fatal reactions owing to SCIT are very rare in children (34, 37). On the other hand, SLIT, which has been proposed as an alternative to SCIT for its easy use at home and better safety profile, has shown an important safety profile concerning severe systemic reactions in children (38). Most of the reactions are localized to the oral mucosa, and very few systemic serious reactions are reported (39). Only few cases of anaphylaxis in children have been reported after the use of SLIT (39). Despite these reported cases of anaphylaxis, SLIT is generally considered to have a better safety profile than SCIT (20, 40). No fatalities have been reported owing to SLIT (20, 40).

Long-term effects and prevention

Follow-up studies after discontinuation of SCIT in children (9, 41–46) have demonstrated a carry-over effect, which lasts up to 12 yr after the cessation of SCIT, although most of these studies are neither randomized nor do they include a control group. New data indicate a role of SCIT not only as a therapeutic agent but also as a preventive strategy to reduce progression from rhinitis to asthma (10, 47) and onset of new sensitization to non-related allergens (48, 49). Because of the possible preventive and disease-modifying effects of SCIT (evidence I IIb; e.g. individual RCT with narrow confidence interval), children are believed to derive potentially greater benefit from allergen immunotherapy to inhalant allergens. Therefore, SCIT should be started early in the disease process even in children with well-controlled allergic symptoms. Regarding SLIT, some randomized controlled open trials have suggested its preventive effect on asthma and new sensitizations (50, 51). A long-term efficacy effect has been reported in a study in adults over a 2-yr follow-up of a 3-yr therapy with SLIT (52), Whether these results might be extrapolated to children (32) is still a matter of debate.

Extrapolation of efficacy, safety and long-term follow-up data from adult studies to children is not acceptable according to the PIP (3). The long-term effect of SLIT using the timothy grass tablet in terms of asthma prevention in children with hay fever is now under investigation in the GAP study (53).

Unmet needs of allergen-specific immunotherapy in children

- Optimal dose and dosing frequency of administration
- Frequency of side effects and safety
- Efficacy and safety in patients unresponsive to pharmacotherapy
- For SLIT: Drops vs. tablets
- Duration of treatment
- Long-term efficacy and safety
- Preventive capacity (asthma, new sensitizations)
- Identification of immunological biomarkers
- Definition of duration of disease before starting treatment (minimal age)
- Development of generally accepted primary outcome measures (i.e. symptom medication scores)
- Studies targeting children with moderate asthma
- Evaluating the effectiveness of allergen-specific immunotherapy in real life in allergic rhinitics with concomitant asthma, especially in terms of a steroid-sparing effect.
- Cost-effectiveness studies and pharmaco-economic aspects
- Developing strategies to enhance adherence

Apart from these clinically oriented needs, basic research is required focusing on the generation, lifespan and different roles of T-regulatory cells in immunotherapy. Biomarkers that may predict the outcome of treatment are needed. Immune tolerance and local tissue events elicited by the different forms of immunotherapy should be studied in detail. In particular, the mechanisms behind long-term maintenance of allergen tolerance are important to understand.

Allergen-specific immunotherapy in paediatric primary food allergy

Primary food allergy is a common disease. In the majority of cases, it develops in infancy or early childhood (54). Hen's egg, cow's milk, peanut, tree nuts, wheat, soy and fish are the most common food allergens. In the majority of cases, hen's egg, cow's milk, wheat and soy allergy are outgrown until school age, whereas peanut and tree nut allergy tends to persist until adulthood. Food-allergic reactions are the most common cause of anaphylaxis in children (55). Up to date, the only available therapy is the avoidance of the allergenic foods (56). The risk of accidental ingestion and reaction often lead to an impaired quality of life. Allergen-specific immunotherapy has the potential to modify the disease's expression and might induce oral tolerance (57). Allergen-specific immunotherapy for primary food allergy has been mainly studied in the paediatric population, owing to its greater prevalence in this age group. Different ways of application such as subcutaneous, sublingual, oral have already been tested in humans, using native or modified allergens, whereas the epicutaneous or intralymphatic route has been investigated primarily in animal models and more recently in humans (58).

The Scientific evidence of efficacy of subcutaneous allergen immunotherapy for the treatment for peanut allergy with unmodified peanut extract has demonstrated significant side effects. Currently, oral and sublingual allergen immunotherapy (OIT and SLIT) for the treatment for food allergy seems to be the most promising approach (59). The first controlled studies have been performed in paediatric patients (60–62). It appears that the efficacy is better with OIT than with SLIT, but the safety is better under SLIT (63). Unfortunately, the long-term effect is still unknown.

Unmet needs of allergen-specific immunotherapy in food allergy

- Definition of the severity of disease before starting treatment.
- Optimal protocols (dose and dosing frequency)
- Definition of criteria for OIT or SLIT
- Safety issues
- Optimal time point (minimal age)
- Duration of treatment
- Long-term efficacy and safety
- Preventive capacity (anaphylaxis or the atopic march?)
- Development of generally accepted primary outcome measures
- Identification of immunological biomarkers
- Cost-effectiveness studies
- Economic studies on the preventive effect of SCIT and SLIT
- Influence on the natural course of disease.

Concluding remarks

During the last decades, considerable progress has been made in obtaining clinical evidence for allergen-specific immunotherapy in paediatric respiratory allergy. However, although some studies evaluated the long-term and preventive effects of allergen immunotherapy in childhood, a solid scientific base for such actions is lacking. The current PIP aims to strengthen the available evidence by requiring 5-yr studies in children. Although scientifically sound, this approach raised profound concerns about the ethical aspects and the feasibility of such a strategy. It is feared that instead of strengthening the field and expanding the therapeutic arsenal, treatment options will be limited and innovative research is being restricted. At this stage, a series of questions remain unanswered. Is there room for shortening the study period? To what extent can evidence obtained in adults be transferred to children? Would it be ethical to deprive children of the potential benefits of SIT because the highest level of evidence is not available for this age group? All stakeholders are called to ensure that children have access to and are treated with allergen products with established efficacy.

Paediatric trials on pharmacotherapy as well as allergen immunotherapy need specific benefit–risk assessments, because children are not supposed to give an informed consent to be included and randomized in clinical studies. Usually, the informed consent of both caregivers/parents has to be obtained. In this specific group of patients, long-term randomized controlled trials are particularly delicate, because they may involve placebo medication or placebo injection for several years at an age, when active allergen immunotherapy might be most effective, both clinically and in terms of preventing disease progression.

Recommendations

To fill the gaps and to bridge the different points of view, working together for the benefit of the community is essential. European Academy of Allergy and Clinical Immunology launched a series of initiatives resulting in 'A European Declaration on Immunotherapy' (http://www.eaaci.net/component/content/article/2-3articles/1616-a-european-declaration-on-immunotherapy)and a recent review on immunotherapy produced during an EAACI summit on immunotherapy (64). European Academy of Allergy and Clinical Immunology serves as the platform for cooperation between relevant stakeholders. Several recommendations can be made for the different stakeholders.

For academia-research

Many of the unmet needs should be addressed by academics and pharmaceutical industries. In this area, academicians are forming networks of research to perform multicentre studies. These efforts should be intensified to strengthen the position of SIT as an important early treatment modality in children. Although academicians may focus on short- and long-term efficacy and optimization of treatment, issues such as effectiveness and implementation need to be addressed also. Lack of compliance with a form of treatment that needs to be administered for several years may be the major threat for SIT. Studies about the real-life effectiveness of allergen-specific immunotherapy are also necessary. Academicians and pharmaceutical companies should therefore identify potential barriers for compliance. Early molecular markers and predictors to decide whether to start or stop therapy and how to measure or predict therapeutic success should be identified. Communication with patients and patient organizations might be helpful in this process.

For regulatory authorities

For EMA, the PIP is the current starting point. Accepting this, ways should be identified to find the balance between searching for scientific evidence and feasibility of studies. Both regulatory authorities and academicians should search for possibilities to extrapolate results obtained in adults to children. In this dialogue, EAACI should be actively involved.

Ethics

Local ethical committees may handle the complexity of long-term studies in children differently. To avoid disparities between regions and countries, investigators need a more general guidance beyond the advices of local committees regarding the ethics of the long-term studies being planned in children. Such studies designed according to the requirement of the PIP may be more acceptable than long-term paediatric studies with SCIT.

To patient organizations

Patient organizations should have a more pronounced role in the positioning of SIT. Together with scientific organizations such as the EAACI, they may advocate for a better awareness and accessibility to this form of treatment. As stated above, patients might be helpful in identifying and understanding the barriers for implementation and adherence.

To industry

Both researchers and industry may profit from standard outcome measures. They should support initiatives to harmonize outcome measures beyond the borders of their own trials. Research on biomarkers should be strongly supported by the industry.

To help implementation

There is a role for EAACI together with patient organizations in creating awareness for SIT. Outreach to the different countries in Europe might be facilitated by developing and translating pocket guidelines. For example, this has already successfully been done in the ARIA guidelines. More recently, the European Federation of Allergy (EFA) and Airways Diseases Patient Organizations has launched recently a 4-yr project EFA Respiratory Allergy Awareness Project (65). With this project, EFA, together with EAACI, ERS, Ga2len, ARIA, WHO-GARD and IPCRG, is advocating for the better recognition of respiratory allergies, early diagnosis and early specific treatment to relieve the burden of these diseases for the patients, caregivers and the society at large.

Disclaimer

The views presented in this Correspondence should not be understood or quoted as being made on behalf of the European Medicines Agency or its scientific Committees.

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