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Allergen immunotherapy in asthma: current evidence and future requirements

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Key words

Allergen - specific immunotherapy, asthma, efficacy, outcomes

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Summary

The role of allergen-specific immunotherapy in asthma (AIT) is still a matter of debate. Actually, many controlled clinical trials have proved efficacy and safety of AIT in asthma, and some published meta-analyses, despite some methodological weaknesses, have confirmed these findings, the most recent and convincing being a meta-analysis on injection AIT studies. For sublingual AIT evidences do exist, but SLIT meta-analyses are mostly questioned due to some biases and inconsistencies. Most of these arise from methodological problems in single studies, usually small, underpowered and carried out with mixed populations. The main need, therefore, is to perform AIT clinical studies only in patients with asthma and following standardized protocols, as recommended by international Guidelines. Studies of AIT in asthma should also focus more on the long term and preventive effects of the treatment, rather than considering only the immediate efficacy on allergic symptoms. Furthermore, specific asthma features, such as lung function, bronchial reactivity, asthma control and exacerbations, should be included among the study outcomes.

Introduction

In 2007, during a session at the EAACI annual Congress in Goteborg, professor Peter Barnes stated that "there is no need to perform allergy tests in asthma, since asthma treatment is the same, whether is an allergic asthma or not". This quite provocative statement was a consequence of a long debate about the real efficacy of allergen specific immunotherapy (AIT) in allergic asthma.(1-3). This debate is somewhat paradoxical, since it is well known that allergens play an important role in the pathogenesis of asthma (4, 5).

Maintaining different positions and outcomes for allergic asthma and allergic rhinitis can also be considered a paradox, since it is common knowledge that the two conditions very frequently coexist in allergic patients (6), and AIT is effective and specific for all the aspects of respiratory allergies. As Passalacqua and Canonica correctly point out, there is curiously no such difference in symptom evaluation regarding venom immunotherapy (7).

Clinical evidence

In the past years, many single trials, even if small, not adequately powered and not specifically designed for asthma, investigated the effects of AIT on asthma symptoms: overall, many of these trials reported an improvement of asthma symptoms and medication use, and in some cases also a decrease in bronchial reactivity (8, 9).

Table 1 - Published meta-analyses of AIT in asthma

Study	Patients	Ait	Symptom scores SMD (95% CI)	Medication scores SMD (95% CI)	Comment
Abramson et al, 2010 (11)	3459 children and adults	SCIT Seasonal or perennial	-0.59 (-0.83, -0.35) I2 5 90%	-0.53 (-0.80, -0.27) I2 5 67%	Open trials included No detailed evaluation of safety Considerable heterogeneity
Calamita et al, 2006 (12)	1706 adults and children	SLIT Seasonal and perennial	-0.38 (-0.79, 0.03) I2 5 64%	-0.91 (-1.94, 0.12) I2 5 92%	Considerable heterogeneity Weak methodology Open trials included
Penagos et al, 2008 (13)	441 children	SLIT Seasonal and perennial	-1.14 (-2.10, -0.18) I2 5 94%	-1.63 (-2.83, -0.44) I2 5 95%	Considerable heterogeneity
Olaguibel and Alvarez Puebla, 2005 (14)	193 children	SLIT Seasonal and perennial	-1.42 (-2.51, -0.34) I2 5 not reported	Not reported	Small numbers Heterogeneity not reported
Compalati et al, 2009 (15)	476 adults and children	SLIT House dust mite	-0.95 (-1.74 -0.15) I2 5 93%	-1.48 (-2.70, -0.26) I2 5 96%	Considerable heterogeneity despite focus on a single allergen

With the diffusion of Evidence Base Medicine concepts, meta-analyses have become a very popular way of evaluating the efficacy and safety of medical interventions. By combining information from all relevant clinical trials meta-analyses can increase the precision of the summary estimates that is typically obtained through small studies thus allowing a more objective appraisal of the evidence. (10). Table 1, taken from (10) summarizes the published meta-analyses about AIT in asthma.

The first meta-analysis about the efficacy and safety of allergen injection immunotherapy in allergic asthma was published in 1995 (16). This revision included 20 DBPC studies, and the Authors concluded that "allergen immunotherapy is a treatment option in highly selected patients with extrinsic ("allergic") asthma". The same Authors, members of the Airway Study Group of the Cochrane Collaboration, published several subsequent updates of this revision (17, 18), up to a final version , published in 2010 (11). This last draft included:

- 88 randomised controlled studies;
- 3792 patients;
- 42 studies on efficacy of subcutaneous SIT (SCIT) with house dust mites extracts;
- 27 studies on efficacy of SCIT with pollen extracts (grasses, birch, olive, ragweed);
- 10 studies on efficacy of SCIT with animal dander;
- Several trials on rare allergens (six with multiple allergens).

Table 2 shows the results for symptom score and medication score according to extract composition.

Table 2 - Symptom score and medication score according to extract composition in Abramson meta-analysis (11)

Outcome	N. of studies	N. of participants Active	N. of participants Placebo	Standardized mean difference (95%-CI)
Symptom score (mites)	12	247	161	-0,48 [-0,96; 0,00]; n.s.
Medication score (mites)	12	242	182	-0,61 [-1,04; -0,18]
Symptom score (pollens)	18	374	289	-0,61 [-0,87; -0,35]
Medication score (pollens)	8	182	142	-0,52 [-0,91; -0,13]
Symptom score (other)	5	106	107	-0,83 [-1,92; 0,26]; n.s.
Medication score (other)	1	61	60	-0,26 [-0,62; 0,10]; n.s.

Results can be summarized as follows:

- Overall, there was a significant reduction in asthma symptoms and medication, and improvement in bronchial hyper-reactivity following immunotherapy.
- There was a significant improvement in asthma symptom scores (standardized mean difference -0.59, 95%confidence interval -0.83 to -0.35) and it would have been necessary to treat three patients (95% CI 3 to 5) with immunotherapy to avoid one deterioration in asthma symptoms.
- Overall it would have been necessary to treat four patients (95% CI 3 to 6) with immunotherapy to avoid one requiring increased medication.
- Allergen immunotherapy significantly reduced allergen specific bronchial hyper-reactivity, with some reduction in non-specific bronchial hyper-reactivity as well. There was no consistent effect on lung function.
- If 16 patients were treated with immunotherapy, one would be expected to develop a local adverse reaction. If nine patients were treated with immunotherapy, one would be expected to develop a systemic reaction (of any severity).

According to these results, the Authors concluded that "Immunotherapy reduces asthma symptoms and use of asthma medications and improves bronchial hyper-reactivity. One trial found that the size of the benefit is possibly comparable to inhaled steroids. The possibility of local or systemic adverse effects (such as anaphylaxis) must be considered" (11).

These conclusions were in agreement with a previous meta-analysis, who found that injection AIT in asthma was effective in 17 out of 24 studies (71%) ineffective in 4 and equivocal in 3 (19).

All these results refer to subcutaneous immunotherapy: but which are the evidences for sublingual AIT (SLIT) in asthma?

Up to recent large studies, the published articles of SLIT (and SCIT) involved small patient populations, and were consequently underpowered to show positive effects. This prompted the currently large use of meta-analyses to combine the results of individual studies and increase the power of the analysis. Some meta-analyses about efficacy and safety of SLIT in asthma have now been published, three addressing SLIT with different allergens (12-14), and one focusing only on house dust mite treatments (15). Two of these meta-analysis were performed with paediatric studies (13, 14).

Only two meta-analyses were specifically designed to address the efficacy and safety of sublingual AIT in allergic asthma (12, 13). The most important review used the Cochrane Collaboration Method and found that using the standardized mean difference (SMD) the efficacy on asthma symptoms was not significant, while the difference compared with Placebo group was significant when all allergic symptoms were grouped together (rhinitis, conjunctivitis, asthma). The Authors concluded that SLIT in asthma was effective, albeit the effect was clinically modest. The second meta-analysis in asthma dealt with paediatric population (441 patients < 18 years) and found a significant efficacy both on symptoms (P=0.02) and medication score (P=0.007) (13). Studies included in this meta-analysis were characterized by a high degree of heterogeneity (7, 13).

"Never say meta-analyses?"

The use and methodology of meta-analyses in AIT studies has many pitfalls and has been vastly criticized (10, 20, 21). SLIT meta-analyses reports and conclusions have been more frequently examined. A revision of the meta-analysis by Calamita (12), found many discrepancies, the most important being that not all the patients included in the studies had asthma, and an analysis on the subgroup of asthma patients was not provided (20). The problem of patient population was also evident in the meta-analysis of AIT in grass rhinitis by Di Bona et al (22), where the presence of patients with asthma ranged from 10 to 100% in the 18 included studies. The well known publication by Nieto et al. (21) made an extensive and thorough evaluation of SLIT meta-analyses, reporting discrepancies, inconsistencies, and lack of robustness, and concluding that "the meta-analyses on sublingual immunotherapy do not provide enough evidence to support its current routine management in patients with allergic asthma or rhinoconjunctivitis".

As confirmed in the World Allergy Organization SLIT Position Paper (23). SLIT meta-analyses "involve very heterogeneous trials, often without a proper sample size calculation: publication biases and discrepancies in data collection are additional concerns. Thus, meta-analyses provide only suggestive evidence". The same conclusion can probably be applied to present SCIT meta-analyses, and underscore the need for a standardization of AIT trials design and reporting.

Safety

Safety of AIT, especially of SCIT, has been a focus of a long debate, and it is well known that uncontrolled asth-

ma is the major risk factor for systemic reactions (9, 24), even if not all the reviews found this association (25). The recent update of the Practice Parameter for Allergen Immunotherapy (24) recommends that "assessment of asthma control should be considered at each injection visit". Accordingly, some studies have demonstrated that, when asthma is adequately controlled, SCIT is safe and well tolerated even in asthmatic children (26, 27).
By contrast, SLIT is generally considered a safe treatment, and so far there are no evidences that asthma is a risk factor for adverse events to SLIT. Nevertheless, data are limited, and it has been suggested to avoid even SLIT administration in uncontrolled asthma (7). Of course, being SLIT a self-administered treatment, this is not easy to be accomplished. According to the recent SLIT Position Paper, assessing the safety of SLIT in moderate to severe asthmatics is still un unmet need (23).

Further points of interest

Efficacy and safety of AIT in allergic asthma has already been reported by many publications [for a more detailed description of these studies and relative meta-analyses see some very recent revisions (7, 28-32)]. Here we would like to raise some other points of interest that still need to be addressed.

Clinical trials

First of all, it is required that clinical studies with AIT be designed and reported in a standardized way, in order to eliminate all the bias referring to studies heterogeneity: many publications now express recommendations for performing and reporting AIT clinical trials (33-37). Standardized studies will allow to compare different results and to build more appropriate meta-analyses, with more reliable conclusions about AIT efficacy and safety in asthma (38).
The most important issue, in our opinion, comes from the "EMA Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases", stating that "for a claim of efficacy in asthma separate trials should be conducted and specific guidance for asthma therapy should be followed", even if the same document states that, for safety data only, patients with asthma co-morbidity can be included in rhinitis studies (34). Another recommendation is that "the efficacy of products for specific immunotherapy has to be evaluated in special trials in the paediatric population and not in combined trials with paediatric population and adults" (34). Accordingly, specific trials in asthmatic patients must be performed, with design and outcomes adjusted to the specific features and history of allergic asthma, and the same must be recommended for specific studies in paediatric populations. Specific plans and requirements for AIT investigations in children have also been published.(33)

Levels of efficacy

The same document states that in AIT studies different claims for efficacy are possible:
1. Treatment of allergic symptoms: Short term clinical trials conducted to show efficacy in the first pollen season after start of specific immunotherapy or to show efficacy in perennial allergies after some months of treatment.
2. Sustained clinical effect: Maintenance of significant and clinically relevant efficacy during two to three treatment years.
3. Long-term efficacy and disease modifying effect: Sustained significant and clinically relevant efficacy in post treatment years.
4. Curing allergy: Sustained absence of allergic symptoms in post treatment years (34).

The vast majority of specific asthma studies, either with SCIT or SLIT, have focused on the immediate improvement of allergic symptoms, with only few publications investigating the "sustained clinical effect" in SCIT (27, 39-43) and SLIT (41, 44-48). But long term efficacy and the disease modifying effect are by far the most important outcomes of AIT, and what makes the real difference from pharmacologic treatment (9, 24, 49). So far, the best evidence about the preventive effect of AIT comes from the classic Preventive Asthma Treatment study (50) in which children with allergic rhinitis, treated with SCIT for 3 years, developed significantly less asthma compared with a control group on pharmacologic treatment. The follow-up of this study also demonstrated the long term efficacy of this treatment, since children previously treated with SCIT were still significantly more likely to be free from asthma after 10 years, compared with the control group (49).
Prevention of asthma development has been demonstrated with SLIT only in two open studies (51, 52), while no long term efficacy in asthma has so far been investigated.

Specific outcomes

Given that specific asthma trials are recommended (34). specific asthma features should be included among the study outcomes. Recent asthma guidelines point out that the goal of asthma treatment is "the control of the disease", defined as a set of different outcomes, either clinical and functional, that have all to be met in order to reach the control the disease (4, 53). Unfortunately, the vast majority of AIT asthma studies have focused on partial features of the disease, usually the symptom and the medication scores, with few studies investigating also functional parameters, such as lung function or specific and non-specific bronchial reactivity (BHR). Abramson et al. (11) analyzed within their meta-analysis the studies reporting functional features and concluded that there were modest improvements in indices of nonspecific BHR, while allergen immunotherapy significantly reduced allergen specific BHR. No conclusion could be drawn about lung function, due to the high heterogeneity of the few studies reporting this outcome.

Probably the most important outcome in asthma treatment and control is the prevention of asthma exacerbations, since the major morbidity, mortality and health care costs associated with asthma are related to exacerbations. (53, 54). We have found few scattered reports about incidence of asthma exacerbations during treatment with AIT in asthmatic patients. Adkinson et al. (27) reported with SCIT the number of days on which oral corticosteroids were used, which can be considered a surrogate marker for asthma exacerbations, while in a study by Rodriguez-Santos (55) the attendance to emergency services by children submitted to SLIT was lower in the study group than in the control group, with a relative risk of 0.39 with a 95% confidence interval of 0.19-0.8. Again Chen et al. concluded that "one year of dermatophagoides pteronyssinus SIT can significantly reduce the frequencies of emergency visiting for asthma attack" (56).

Add-on therapy

Another quite neglected key point is the value of AIT as add-on therapy in asthma, and the steroid-sparing effect of AIT in patient with mild to moderate persistent asthma (5). Few studies, either with SCIT and SLIT, have addressed the question, with conflicting results (Table 3).

The well known study by Adkinson et al. (27) failed to find a significant additional benefit of SCIT in asthmatic children under optimal pharmacologic therapy. This paper received was much criticized both for study design (the use of mixtures of allergenic extracts, up to seven different allergens, and patients selection) and conclusions. (59-62) Another study with SCIT performed by Maestrelli et al. included 72 dust-mite allergic subjects with mild-to moderate asthma randomized to receive dust-mite SCIT or placebo after an observational year of pharmacologic treatment. The Authors found that the addition of SCIT was associated with a significant decrease in the number of subjects requiring rescue bronchodilators, an increase in morning and evening peak expiratory flow, and a reduced skin test sensitivity to dust mites, but no significant effect was observed on the cumulative dose of inhaled corticosteroids, asthma symptoms, lung function, or non- specific BHR (58). A positive randomized, placebo-controlled SCIT study was made by Blumberga et al. (39) in adults with house dust mite allergy and inhaled steroid requirements of at least 500 mg/d. After 3 years, the median reduction of inhaled steroids in the SIT group was 82% compared with 42% in the placebo-treated group. Two more studies, carried out with SLIT, also yielded conflicting results, probably due to different study designs and treatment duration (45, 57).

This question was addressed in a recent controlled study by Zielen et al. (26). Sixty-five asthmatic children (GINA treatment levels II and III; 6 to 17 years old), after reaching asthma control with inhaled steroids during a five-month baseline period, were randomized for subcutaneous mite allergoid immunotherapy plus fluticasone pro-

Table 3 - Symptom score and medication score according to extract composition in Abramson meta-analysis (11)

AUTHOR	Journal , YR	AIT	Patients	Outcome	Result
Zielen (26)	JACI, 2010	SCIT	Children	Steroid reduction	Positive
Ozdemir (45)	Pediatr Allergy Immunol, 2007	SLIT	Children	Steroid reduction	Positive
Pham-Thi (57)	Pediatr Allergy Immunol, 2007	SLIT	Children	Steroid reduction	Negative
Blumberga (39)	Allergy, 2006	SCIT	Adults	Steroid reduction	Positive
Maestrelli (58)	JACI, 2004	SCIT	Adults & children	Steroid reduction	Negative
Adkinson (27)	NEJM, 1997	SCIT	Children	Steroid reduction	Negative

pionate (FP) or FP therapy alone for two years. During two subsequent five-month winter periods, steroid therapy was adjusted according to predefined dose steps, determining and comparing the changes in FP dosages and the lowest FP dose still sufficient to maintain asthma control. Immunological and functional investigations were also carried out. Children treated with house dust mite SCIT plus FP were able to significantly reduce the FP dose by more steps ($p < 0.05$), compared with the control group on FP alone. In this 2-year study, two exacerbations, defined as the use of oral steroids, were observed in the AIT plus FP group, and one in the FP alone group. In his Editorial accompanying the publication (63). Adkinson states that "The European study on the steroid-sparing effects of specific immunotherapy (SIT) in children with asthma published in this issue of the Journal adds substantial credibility to this controversial claim in the list of potential benefits from aeroallergen immunotherapy".

Future directions and conclusions

Despite all the discussed unmet needs, and the methodological weaknesses of some studies and meta-analyses, there are many clinical data pointing to the efficacy and safety of AIT in allergic asthma, provided that patients are correctly selected and adequate extracts, in term of standardization and doses, are used. Due to these evidences, the major asthma guidelines, in Europe and United States, now include AIT among the treatment options for allergic asthma (4, 53). Nevertheless, future directions and needs include:

- Performing specific, adequately powered, trials in asthma and in paediatric age with standardized protocols, outcomes, and reporting. This will also allow to generate consistent meta-analyses, with more convincing conclusions (21).
- Focusing more clinical studies, which are now lacking, on long-term efficacy and disease modifying effect, either as a long term clinical results on asthma symptoms or prevention of asthma development.
- Addressing asthma outcomes with a more updated vision, focusing on modern concepts of asthma control, including exacerbations, add-on therapy and steroid-sparing effect. As Franklin Adkinson concludes in his mentioned Editorial, "to take full clinical advantage of any steroid-sparing benefits attributable to SIT, future studies will need to explore these and other factors capable of modifying the clinical outcomes from aeroallergen SIT" (63).

Waiting for the innovative forms of allergen immunotherapy that are being developed (64, 65), and beside the usual key points of discussion about AIT (mechanisms, optimal dosage, schedules, duration, cost-effectiveness…), addressing these needs will lead to a better understanding of the efficacy, safety and position of current vaccines in allergic asthma and to a larger and more beneficial use of AIT in asthmatic patients.

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