



An update on allergen immunotherapy and asthma

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Purpose of review

The aim is to review recent literature up to July 2013 concerning the effect of allergen-specific immunotherapy (AIT) on asthma. AIT, effective in combined allergic rhinitis and asthma, was previously described as a convenient approach able to improve clinical outcomes and reduce bronchial hyperresponsiveness. In addition, long-term and preventive effects on the onset of new sensitizations and progression from allergic rhinitis to asthma have been shown.

Recent findings

Recent investigations, mainly based on observational or small open trials, confirmed previous findings, showing improvement in asthma control, symptoms and medication usage and steroid-sparing effects, sometimes inconsistent with changes in lung function. Some meta-analyses support the clinical benefit on adult and paediatric asthma. Only few trials, however, were specifically designed to explore asthma endpoints.

Summary

Clinical studies primarily have focused on AIT, and research on asthma endpoints is scarce; however, the evidence of beneficial effect of AIT for the treatment of adults and children affected by allergic rhinitis with or without asthma suggests that this treatment can favourably affect asthma. In children, sublingual AIT has been more extensively investigated than injective. Confirmatory, adequately powered trials are needed to reinforce the evidence of efficacy for individual AIT products. The main drawback in using injective AIT for asthma is the risk of serious adverse reactions and uncontrolled asthma. The sublingual route is better tolerated and does not appear inferior. As standard controller pharmacotherapy seems unable to affect the natural course of asthma, the potentially disease-modifying effect of AIT represents an appealing perspective that requires further investigation.

Keywords

allergen-specific immunotherapy, asthma, efficacy, evidence

INTRODUCTION

Allergen-specific immunotherapy (AIT) is the practice of administering allergen extracts to patients with allergic disorders, in order to modify or abolish the clinical manifestations caused by natural exposure to the allergens. A precise diagnosis and identification of the provocative allergen is a prerequisite for AIT [1]. Although the fine mechanisms involved remain partially uncertain, a significant body of clinical evidence is available to support the use of AIT. AIT results in profound immunological changes in the response to allergens, characterized by a down-modulation of the T-helper 2 (Th2) responses and an induction of regulatory T cells, producing interleukin-10 (IL-10) and transforming growth factor- β (TGF- β).

AIT was introduced at the beginning of the previous century by Noon and Freeman, on an empirical basis. It was initially characterized by unjustified and often incorrect prescriptions, clinical empiricism

and absence of specific guidelines, leading to concerns about its clinical efficacy and safety [1,2]. During the last 25 years, there has been an impressive development of basic and clinical research in the field of AIT, and recently clinical trials following the principles of the modern methodology of research have confirmed its effectiveness when properly indicated and conducted. Since the official statements of the WHO in 1998, AIT has been validated as a causal treatment for respiratory allergy (rhinitis and

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Curr Opin Pulm Med 2014, 20:109–117

DOI:10.1097/MCP.000000000000016

KEY POINTS

- Clinical efficacy found in individuals suffering from allergic rhinitis with or without bronchial symptoms suggests that AIT can favourably affect asthma.
- Grass pollen and HDM AIT has been largely investigated, nonetheless well designed large studies exploring subjective and objective outcomes in asthma are needed.
- Both adults and children are good candidates for AIT, but more supporting data are needed to assess if the length of asthma diagnosis and polysensitization may affect the treatment outcome.
- Superiority of SCIT or SLIT is currently not defined.
- The disease-modifying and preventive effects represent the main advantage of AIT, while current pharmacotherapy seems unable to change the natural course of allergic disease.

asthma) and venom allergy [3]. Allergen desensitization is very effective in those diseases with predominant immunoglobulin E (IgE)-mediated reaction, such as venom allergy, whereas in respiratory allergy, in particular asthma, many different underlying pathophysiological mechanisms are involved, which may justify the heterogeneous responses to AIT in this population [4].

Subcutaneous immunotherapy (SCIT) remained for several decades the only available administration route. Although SCIT is effective and generally well tolerated, a remote risk of severe side-effects exists, mainly when improperly prescribed or administered [5]. The concerns about safety have resulted in limited use of SCIT for asthma treatment in some countries and have stimulated the search for safer administration routes [6]. Among them, sublingual immunotherapy (SLIT) has gained progressive credibility and was introduced in official documents as a viable alternative to the classic allergy injections [3,7]. SLIT is currently commercially available and largely employed in European countries as tablets or drops, marketed in standardized extracts either biologically or immunologically based on an in-house reference. No US Food and Drug Administration-approved formulation for SLIT is still available in the United States, but some registration clinical trials were recently published or are currently ongoing.

ALLERGEN IMMUNOTHERAPY AND ASTHMA

Asthma is a chronic inflammatory disease of the airways associated with hyperresponsiveness, that

leads to recurrent episodes of wheezing, dyspnoea, chest tightness and cough, as well as variable airflow obstruction that with time may become permanent due to airway remodelling [8].

Allergic asthma is frequently characterized by an abnormally polarized Th2-type immune response against specific allergens, leading to inflammatory responses. The consequent activation of the epithelial mesenchymal trophic unit has been hypothesized to be responsible for the observed persistent changes of airway remodelling [9].

Currently, the pharmacological treatment of asthma is aimed at controlling the clinical manifestations of the disease, by suppressing airways inflammation and relieving the bronchospasm. So far, none of the available drugs has been demonstrated to be capable of modifying the progression of the disease, which invariably relapses on ceasing the treatment [10]. AIT may represent a curative approach for allergic asthma due to its immunomodulatory properties that yield sustained disease-modifying effects [11,12]. SCIT has been shown to provide a protective or less harmful Th1 response and the induction of regulatory T cells causing anergy or tolerance of allergen-specific T lymphocytes [13]. The induction of a population of IL-10/TGF- β -producing CD4⁺ CD25⁺ regulatory cells is usually associated with an increase in serum allergen-specific immunoglobulin G (IgG) and IgG4 levels, exhibiting some functional inhibition of mast cell degranulation [13,14].

AIT has long been regarded as a controversial treatment for asthma and although beneficial effects on clinically relevant outcomes have been observed in randomized controlled trials, the recommendations of several professional bodies have ranged from cautious acceptance to complete refusal, likely because of the potential risk of severe, and sometimes fatal anaphylaxis. For instance, despite recognizing the clinical efficacy and the long lasting and preventive effects of AIT, GINA (Global Initiative for Asthma) guidelines state that the role of AIT in adult asthma is limited (and considered only after environmental measures and failure of pharmacological treatment), owing to the modest benefit compared with other treatment options, weighed against the risk of adverse events and the inconvenience of a prolonged course of injections for SCIT [8]. On the other hand, almost all the large surveys conducted in the United States indicated that severe or uncontrolled asthma is the most important and independent risk factor for both nonfatal and fatal adverse reactions to SCIT [15–17]. The comprehensive Cochrane systematic review by Abramson *et al.* [18], including 88 randomized controlled trials, concluded that the possibility of local or systemic

adverse effects due to SCIT (such as anaphylaxis and very rarely fatal reactions) must be considered. If 16 patients are treated with SCIT, one would be expected to develop a local adverse reaction (wheal and itching at the injection site), and if nine patients are treated, one would be expected to develop a systemic reaction of any severity (rash, wheezing and breathlessness). The implication is that patients must be observed long enough to deal with any major systemic reactions (typically within 30–45 min) and adequate resuscitation equipment and medications must be promptly available [19]. Importantly, this Cochrane review reported an overall clinical efficacy, that is reductions in asthma symptom scores, medication usage and allergen-specific bronchial hyper-reactivity (BHR), with some reduction in nonspecific BHR as well. The number of patients needed to treat in order to avoid asthma symptoms deterioration or increase in medications were estimated as three and five, respectively. The effects on lung function were not consistent among trials. In addition to the small size of most trials and some methodological limitations, a significant inter-study heterogeneity was present, thus downgrading the overall quality of the evidence. Unfortunately, this meta-analysis provided limited information concerning the extent of benefit provided by SCIT in comparison to other standard therapies.

No paediatric meta-analyses are available for SCIT, and in children with perennial asthma a benefit has been less easy to demonstrate, while small studies have demonstrated some benefit in pollen and animal dander allergy [20–22].

SLIT has been shown to work differently from SCIT, the extract being captured by dendritic cells in the oral mucosa (expressing high levels of FcεRI receptors, major histocompatibility complex class I and II and costimulatory molecules compared with their skin counterparts) and migrating to draining lymph nodes, wherein regulatory or suppressive T cells secreting interferon-γ (IFN-γ) and/or IL-10 are stimulated and blocking IgG1 and IgG4 antibodies are generated [23].

Recent meta-analyses suggested the clinical efficacy of SLIT in allergic rhinitis and asthma, both in adults and in children [24–27]. One of them, including 25 open or blind controlled trials in more than 1000 patients, showed a significant benefit of SLIT on the explored outcomes (i.e. symptoms and medications and lung function) while symptoms alone failed to reach statistical significance [24]. A more recent meta-analysis restricted to the paediatric population reported a moderate effectiveness on asthma symptoms and medication intake [27]. However, some reasonable concerns were raised about shortcomings in the robustness of these

systematic reviews, mainly explained by the substantial inter-study heterogeneity and by the fact that older randomized controlled trials had limitations in adequate sample size and methodology [28,29].

It is important to establish if SLIT can exacerbate asthma as a side-effect and if asthma itself represents a risk factor for adverse events with SLIT. Concerning the first point, SLIT has been shown to be safer than SCIT and so far no fatalities have been reported. The side-effects of SLIT, occurring with an incidence of 30–70% in clinical trials and in less than 10% in postmarketing surveys, are mainly local (oral itching/swelling, throat irritation, nausea and stomach ache) and self-resolving, with a general agreement that asthma worsening is exceptional [30]. Concerning the second point, there is no formal demonstration that asthmatic patients more frequently experience adverse reactions, including asthma exacerbations, than patients with only allergic rhinitis [31–33]. In none of the total of 11 cases with anaphylaxis reported in the literature following SLIT was asthma identified as a possible risk factor; however, as a prudential choice, SLIT is not recommended to be administered in uncontrolled disease [30,34[■]].

Up to June 2009, The World Allergy Organization position paper on SLIT pointed out that only eight out of more than 60 randomized double-blind placebo-controlled trials were specifically designed to evaluate its efficacy on asthma [30,31,35–41]. In the same year, one large pivotal trial has assessed the effect of grass pollen tablets in asthmatic children, demonstrating a significant reduction of symptoms and a positive trend for less intake of rescue medication [42]. In 2011, a proof of concept trial including 602 individuals to determine if treatment of asthmatic patients allergic to house dust mite (HDM) with sublingual tablet can reduce the need of inhaled corticosteroids (ICSs) revealed very promising preliminary results: a positive therapeutic effect on asthma control was demonstrated by a reduction in the dose of inhaled budesonide (mean: >80 μg/day) for the active group compared with the placebo after 1 year of daily treatment. Overall, SLIT treatment was well tolerated, and only mild-to-moderate local reactions were reported [43]. An ongoing study will be able to establish whether HDM SLIT can reduce the frequency and the time to first exacerbation after ICSs reduction [44].

A matter of debate is related to the fact that isolated allergic asthma without allergic rhinitis is rare, whereas asthma is present in more than 30% of rhinitics [45]. This is the reason why the majority of the clinical trials have been conducted in allergic rhinitis with or without asthma, and very few trials

were specifically designed to address the effect of AIT in asthma. As a consequence, none of the trials evaluating asthma symptoms have been adequately powered on this primary outcome or specifically designed to avoid biases [46,47]. Moreover, no consensus exists on the optimal endpoints to be used, that is, asthma symptoms, the use of medications, the number of asthma exacerbations, asthma-free days and/or lung function. As a consequence, objective measurements were only rarely recorded. Hence, it is not possible to provide fully evidence-based answers on the role of AIT in asthma alone.

Beyond these considerations, AIT remains a valid approach for treating patients with allergic rhinitis and asthma. Its potentially complementary value to pharmacological treatment consists of the sustained disease-modifying effects and preventive effects on the natural progression of the allergic disease, that is, from allergic rhinitis to the development of full-blown asthma [48]. In randomized open trials, both pollen SCIT and SLIT were associated with a reduction in the risk of developing BHR or asthma in children and adults with allergic rhinitis [49–51]. Head-to-head open randomized trials versus ICSs in mild asthmatic patients showed in the long-term an overall superiority of AIT, suggesting

that this option may be more cost-effective, providing a benefit after discontinuation and a steroid-sparing effect [11,52]. A summary of the potential expected effect of AIT in asthma is proposed in Fig. 1.

RECENT ADVANCES IN ALLERGEN IMMUNOTHERAPY TREATMENT OF ASTHMA

In the following paragraphs, we summarize the relevant publications since January 2012, including primary and secondary research, investigating the effect of AIT on asthma endpoints.

Subcutaneous immunotherapy

Reviewing the literature of the past 18 months shows confirmatory findings on the effectiveness of SCIT in asthma, however without any novel or outstanding scientific advances (Table 1) [53[■], 54–60]. As the optimal duration for an AIT course is still a matter of debate, the study by Stelmach *et al.* [53[■]], investigating possible differences in the long-term effectiveness between 3 and 5 years treatment courses in 90 asthmatic children monosensitized to

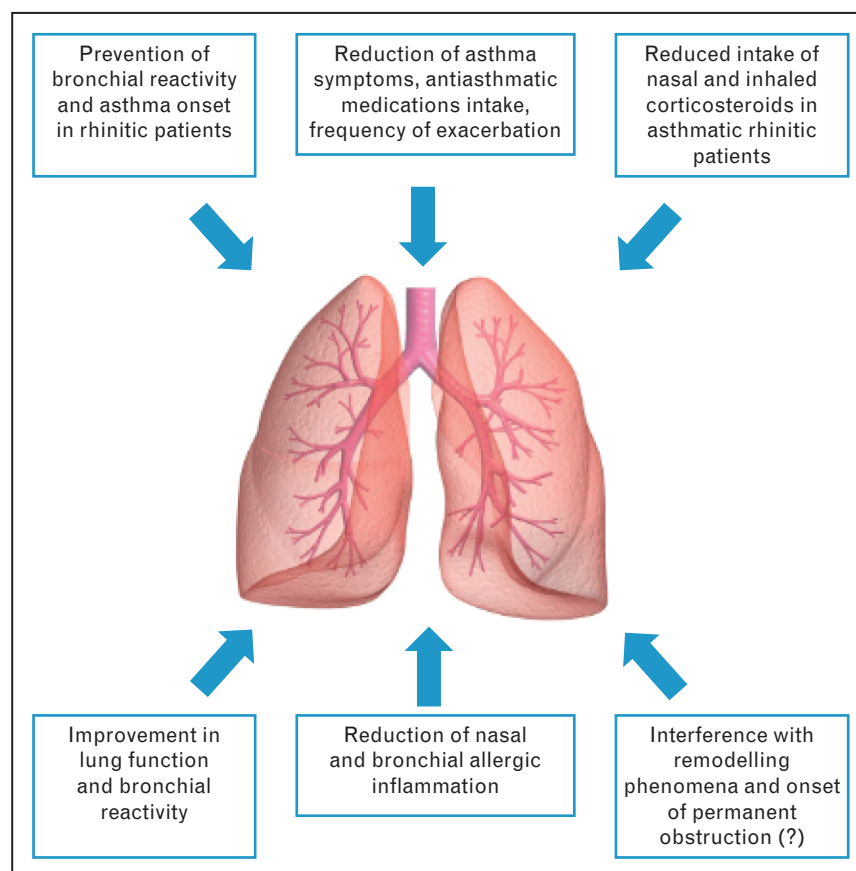


FIGURE 1. Potential effects of allergen immunotherapy on asthma.

Table 1. Studies on the clinical efficacy of allergen immunotherapy in asthma published after January 2012 till July 2013

References	Population age and disease	Immunotherapy (sample size)	Allergen	Comparison (sample size)	Follow-up	Outcomes	Study design
Stelmach 2012 [53 [■]]	8–18 A	SCIT 3 years (n = 30); SCIT 5 years (n = 30)	HDM	Controls (30)	3 years	Asthma remission in SCIT 3: 50%, in SCIT 5: 54%, controls: 3%; at discontinuation ICS dose reduction in SCIT 3: 50%, in SCIT 5: 75%; after 3 years ICS dose reduction in SCIT 3: 94%, in SCIT 5: 100%	Retrospective
Yukselen 2012 [54]	Mean 10 (SD 3); A (AR)	SCIT (n = 10)	HDM drops	SLIT (11); placebo (11)	1 year +; 1 year observation	SCIT > SLIT in ↓ symptoms; SCIT > placebo in ↓ symptoms and medication scores; SCIT and SLIT improved all outcomes from baseline	DBPCR double-dummy
Stelmach 2012 [55]	6–18; AR (A)	SLIT (n = 20 continuous; n = 20 pre-seasonal)	Grass drops	Placebo (20)	2 years	↓ asthma symptom, medication scores, and exhaled nitric oxide; no changes in lung function and BHR.	DBPCR
Wahn 2012 [56]	4–12; AR (A)	SLIT (n = 158)	Grass drops	Placebo (49)	8 months	↓ asthma symptoms and medication scores, severity and frequency of exacerbation and skin reactivity	DBPCR
Trebuchon 2012 [57]	5–18; AR (A)	SLIT (n = 735)	HDM drops	-	>2 years	↓ asthma medications (26% stopped taking ICSs)	Retrospective and observational
Zheng 2012 [58]	4–14; A (cough variant asthma only)	SLIT (n = 53)	HDM drops	Conventional treatment (53)	-	↓ symptoms and serum EOS level increase in PEF	RCT
Marogna 2013 [59]	18–65 A (AR)	SLIT (n = 21)	Birch tablet	3 Pharmacotherapy options	3 years	↑ asthma control and lung function; ↓ symptoms and medications, bronchodilators, BHR, nasal eosinophils and nasal steroids	RCT
De Castro 2013 [60]	6–14; A (AR)	SLIT (n = 70)	Multiple	Control (70)	3 years	↓ asthma symptoms and medication	Case-control

A, asthma; AR, allergic rhinitis; BHR, bronchial hyperreactivity; DBPCR, double-blind placebo-controlled randomized; EOS, eosinophils level; HDM, house dust mite; PEF, inspiratory peak flow; RCT, open randomized controlled; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

HDMs, yielded interesting data. Both SCIT regimens produced excellent results with significantly higher asthma remissions obtained in both groups (50% after 3 years and 54% after 5 years, respectively) versus untreated controls (3.3%). The minimal controlling ICS dose reduction in the 5-year group (median, 75%) was significantly higher compared with the 3-year group (median, 50%) after immunotherapy discontinuation. After 3 years without SCIT, no differences were seen between the two groups (median, 100 and 94%, respectively), whereas the minimal ICS dose controlling the symptoms did not change in the control group and was significantly higher. The study concluded that 3 years of SCIT is an adequate duration for the treatment of HDM-dependent childhood asthma.

In children, few comparative placebo-controlled studies between SCIT and SLIT are available. In a study comparing both AIT regimes (HDM) in 32 asthmatic patients during 1 year in a double-dummy placebo-controlled randomized design, all disease-related parameters were equally improved, although the study was not powered to show differences between both active groups, so no conclusion can be drawn in this respect. SCIT significantly diminished symptom and medication scores for both asthma and allergic rhinitis. Similarly, SLIT reduced these outcomes, except asthma medications, but this reduction was not significantly different from placebo. Although both treatment options were found immunologically active, bronchial provocative doses and sputum eosinophil increments after bronchial challenge were reduced only with SCIT [54].

In a recent retrospective evaluation in asthmatic children, 5–16 years of age, some factors predicting the response to AIT were identified, that is: the age of onset of wheezing and BHR [61]. In addition, bronchial allergen provocation was found to be a useful and objective tool to assess the effectiveness of SCIT. This parameter exhibited significant improvements after 1 year of SCIT against HDM in 60.7% of the patients and was also able to identify the non-responders to treatment [62].

Sublingual immunotherapy

Concerning paediatric studies of the past 18 months, most data on effectiveness of pollen SLIT on asthma outcomes came from studies in which seasonal allergic rhinitis was the leading disease, thus they were not adequately designed or powered to detect changes in asthma symptoms or medication (Table 1). The largest double-blind randomized placebo-controlled study involved 207 children aged 4–12 years with grass pollen rhinitis with or without

intermittent or mild-persistent asthma according to GINA severity criteria [8]. As compared to placebo, grass pollen SLIT drops given for 8 months in a pre-seasonal regimen produced a significant reduction in the mean area under the curve of the overall allergy symptoms and medication scores from the baseline of the previous run-in season. The number of well days (defined as the number of days with symptoms score ≤ 4 and medication score = 0) and the percentage of responders were greater in the active group, with changes in allergen-specific IgE and IgG levels indicating a significant immunologic effect, but unfortunately no explicit information on asthma outcomes were reported [56].

The comparative effect of pre-seasonal and continuous grass pollen SLIT in children has been investigated by Stelmach *et al.* [55], who included 20 asthmatic patients among 60 monosensitized patients aged 6–18 years with allergic rhinitis in a 2-year prospective, randomized, double-blind, placebo-controlled trial. Both pre-seasonal and continuous regimens were similarly associated with a substantial reduction in the combined symptoms/medication score, including the asthma score, when compared with placebo. However, no significant changes were observed between treatments throughout the study in the morning peak inspiratory flow (PEF), forced expiratory volume in 1 s and nonspecific BHR. As compared with placebo, a similar significant decrease in exhaled nitric oxide (FeNO) level was found in both active groups.

In recent years, the primary goal of asthma treatment has been aimed at reaching disease 'control', a composite outcome including all the primary clinical and functional aspects, while different strategies have been developed to avoid the long-term downsides of ICSs [8]. A number of studies have compared different asthma medication modalities, nevertheless studies directly comparing therapeutic approaches including AIT reached controversial conclusions [31,63–68]. A recent study investigated whether SLIT (birch pollen) can provide any advantage in disease control in a real-life setting in patients with mild-persistent asthma related to birch pollen compared with increasing doses of ICS or low dose ICS and antileukotrienes [59]. After 3 years of treatment, it was found that adult patients inadequately responding to a fixed low-dose of inhaled budesonide may be better and safely controlled by adding SLIT for 12 weeks from February to April using a hypoallergenic allergoid. This finding suggests a potential steroid-sparing effect of SLIT, of particular relevance in patients with allergic rhinitis and coexisting asthma frequently forced to administer both nasal and bronchial corticosteroids.

SLIT with HDM drops appeared an effective and highly safe option for the cough variant asthma of 106 children included in a randomized study, wherein SLIT was superior and faster compared with conventional treatment in decreasing symptom scores and serum eosinophils level and improving PEF [58].

The results of a large, retrospective, observational study confirmed the efficacy and tolerability of HDM SLIT in routine French practice in a real-world setting. In this study, Trebuchon *et al.* [57] randomly selected 139 allergy specialists to include and monitor for at least 2 years 1289 patients (57% under the age of 18) with a respiratory allergy and proven sensitization to HDM treated with SLIT. Among them 50% also suffered from asthma, and their symptoms improved in 63% of the patients, with a concomitant reduction in symptomatic medication intake.

A 3-year case-control study evaluated 140 children (6–14 years) with allergic asthma and allergic rhinitis, treated with multiallergen SLIT or symptomatic drugs. SLIT exhibited a significant improvement from baseline in asthma symptoms scores, and the benefit was independent of age and monosensitization or polysensitization status [60].

Finally, confirmatory findings on the effectiveness of AIT on outcome measures of asthma come from three very recent systematic reviews that graded the evidences of effect of SCIT and SLIT (off-label use of subcutaneous aqueous allergens for sublingual desensitization) by adapting an evidence grading scheme recommended by the Grading of Recommendations Assessment, Development and Evaluation Working Group [69–71,72]. The most updated review, through to December 2012, concluded that strong evidence supports that SLIT improves asthma symptoms, with eight of 13 studies reporting greater than 40% improvement versus the comparator (placebo, pharmacotherapy or other SLIT regimens) [69]. Overall, moderate evidence came from 16 out of 41 studies that SLIT could reduce asthma medication use by more than 40%. The second systematic review, including only paediatric studies through May 2012, analysed 13 trials with 920 children receiving SCIT or standard care, and 18 studies with 1583 children receiving SLIT or usual care. The authors concluded that the strength of evidence was moderate and low that SCIT improves asthma symptoms and medication scores, respectively, while high evidence was provided that SLIT can improve asthma symptoms. Overall, there was low evidence supporting SCIT over SLIT for improving asthma or rhinitis symptoms or medication usage [70]. Similar conclusions were reached by the third comprehensive

review, updated to May 2012, including 74 references on SCIT, 60 on SLIT and eight comparative (SCIT versus SLIT) studies. Despite some variation across outcomes and studies, overall, moderate-to-high (somewhat weaker in children) evidence was found for the efficacy and safety of both SCIT and SLIT for the treatment of allergic rhinitis and asthma, with unknown superiority of either route over the other [71].

CONCLUSION

Despite the official consensus statements and the relatively wide clinical use of AIT, some aspects need urgently to be clarified to provide clear and evidence-based recommendations for the clinical use of AIT in asthma. Recent findings on the clinical effectiveness of AIT in asthma, although confirming previous data, come mainly from open controlled or observational small studies. The variability of route of administration, patient selection, treatment durations and regimens among the studies is another major issue that affects the overall interpretation of results. More robust and adequately sized studies, specifically addressing asthma endpoints, were recently carried out with interesting positive findings for HDM tablets; however, future research should be extended to all other relevant allergens (grass, birch, ragweed, HDMs, cat and alternaria) in order to detect eventual allergen-dependent differences in the expected clinical benefit. Evaluation of exacerbation rates in combination with objective outcomes such as pulmonary function, BHR and immunological changes is anticipated to be a key prerequisite in future research, as current data are inconsistent.

The need for univocal criteria to identify the best candidates for AIT is expected to be answered by new advances providing a better characterization of patients' sensitization profile and more sensitive biomarkers. Whether polysensitized patients are less responsive to AIT than monosensitized is still an open question, as the evidence of efficacy of single-allergen AIT in polysensitized patients mainly derives from posthoc analyses of few large trials including monosensitized or polysensitized patients with symptoms referred to one single allergen, whereas multiallergen AIT in polysensitized patients requires more supporting data to validate its efficacy. In view of the chronic inflammation and remodelling phenomena, future studies on AIT should assess if and how much the disease duration and length of an asthma diagnosis could affect a positive treatment outcome.

The perspective of vaccines with reduced allergenicity could overcome the limitations due to safety issues in uncontrolled or severe asthma. Long-term

and pharmaco-economic studies are required to verify the clear cost-effectiveness of AIT over time.

Acknowledgements

This work was partially supported by ARMIA (Associazione Ricerca Malattie Immunologiche e Allergiche, Genoa, Italy).

Conflicts of interest

Financial disclosure/Acknowledgements: Dr Compalati received a consultancy grant from Lofarma S.p.A (immunotherapy manufacturer). Prof Canonica have financial involvement (consultancies, research grants, honoraria for lectures) with different immunotherapy stakeholders. Prof Braido has not conflicts of interest to declare concerning this article.

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