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REVIEW



Advances in allergen immunotherapy as a treatment of asthma

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ABSTRACT

Introduction: Specific immunotherapy is the only treatment acting on causes and not only on symptoms of respiratory allergy. It was first introduced as subcutaneous immunotherapy (SCIT) with the aim to induce immunological tolerance to the administered allergen(s). In the 1980s, sublingual immunotherapy (SLIT) was developed, mainly to improve the safety, which was a critical issue at that time.

Areas covered: This article reviews the available literature, including a large number of randomized controlled trials, meta-analyses, and real-life studies as well, on the outcomes of SCIT and SLIT concerning the treatment critical issues of the two routes, that are efficacy, safety, cost-effectiveness, and compliance to treatment.

Expert opinion: SCIT and SLIT are similarly effective in treating patients with respiratory allergy, providing, based on the induction of typical changes in the immunologic response, an early control of symptoms that steadily increases during the treatment and, once reached the recommended duration of 3 years, continues to work after stopping. This outcome is the major factor influencing the economic advantage of SCIT and SLIT over drug treatment.

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1. Introduction

The birth of allergen immunotherapy (AIT) dates back to the age of empiricism, when the knowledge on the mechanisms of allergy was poor. The first paper describing the efficacy of desensitization to grass pollen by administering to patients with 'hay fever' increasing amounts of a Phleum pratense pollen extract dates back to 1911. The author theorized that the symptoms were caused by a soluble toxin in the grass pollen to which only some individuals were sensitive, and that inoculations of the Phleum pollen extract would induce the production of antitoxins [1]. Six years later, in the first study on patients with asthma, Walker hypothesized a role for proteins in patients' desensitization, although he suggested that the sources of these proteins were bacteria, food and animal hair [2]. The discovery of IgE in 1966 [3] helped in the comprehension of the pathophysiology of allergic diseases and, therefore, the effectiveness of this treatment. In particular, the position paper on AIT endorsed by the World Health Organization in 1998 highlighted two major outcomes, that are the ability to induce tolerance toward the administered allergen and to change the natural history of the allergic disease [4]. SCIT represents the first-choice treatment for Hymenoptera venom allergy, while oral and sublingual desensitization for food allergy, which is supported by a large literature, is likely to achieve approval [5], at least for foods causing anaphylactic reactions associated with mortality [6]. However, AIT is born and has a large evidence of efficacy in the field of respiratory allergy, regarding both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). The role of AIT in the treatment of respiratory allergy, both allergic rhinitis and

asthma, is empowered by guidelines, also using technological tools for communication [7].

While the role of immunotherapy in allergic rhinitis is well established [8], in asthma the situation is more complex. Here we will discuss the current state of AIT for the treatment of allergic asthma.

2. The advances in efficacy and safety of AIT for asthma

The first randomized placebo-controlled trial (RPCT) on AIT, then named hyposensitization, was performed by Aas in 1971 using SCIT on children suffering from dust mite-induced asthma [9]. In subsequent years, a number of trials investigated the efficacy and safety of SCIT with the major sources of respiratory allergy, including pollens, molds, and animal epithelia. In 1986, SLIT was introduced by a RPCT, involving patients with dust mite allergy, though limited to subjects with rhinitis [10], while the first RPCT on patients with mite-induced asthma was performed in 1990 [11], followed by several trials.

2.1. Evidence and achievements of SCIT in asthma

From the 1970s to the early 1990s RPCTs on SCIT included a fairly low number of patients (commonly between 20 and 50), roughly half randomized to active treatment and the others to placebo. Such small groups were an important limit to the consistency of scientific observations, due to the probability that the results obtained were stochastic. A powerful tool to overcome this limit is the meta-analysis, which collects all the trials on a given

Article highlights

- Asthma is a serious health problem with increasing prevalence, affecting patients of all age and causing a significant burden of disease.
- Allergen immunotherapy is the only treatment acting on the causes of allergic asthma and not simply on symptoms.
- Allergen immunotherapy was first introduced as subcutaneous immunotherapy (SCIT), while sublingual immunotherapy (SLIT) was developed in the 1980s, mainly to reduce the risk of adverse reactions.
- Both routes of administration result in a clinical effectiveness on asthma which persists also after treatment withdrawal, provided the recommended duration of at least 3 years is reached.
- The overall data from meta-analyses suggest a higher efficacy for SCIT and a higher safety for SLIT, but the quality of allergen extracts is the crucial issue for effectiveness.
- The results from controlled trials with high quality dust mite SLIT tablets were acknowledged in the GINA guideline as add-on therapy in mite allergic adult patients who have asthma exacerbations despite inhaled corticosteroid treatment.

medical therapy, obtaining numbers of patients as high as to warrant statistical reliability [12]. Meta-analysis may be performed by commercially available software, but the highest level of trustworthiness is provided by the Cochrane Collaboration. Cochrane Collaboration requires adherence to standards, such as identification of relevant studies from a number of different sources, selection of studies for inclusion and evaluation of their strengths and limitations on the basis of predefined criteria, systematic collection and appropriate synthesis of data [13]. The result of a meta-analysis is expressed by the standardized mean difference (SMD), which summarize the statistic when the studies all assess the same outcome but measure it in a variety of ways and therefore requires to standardize the results of the studies to a uniform scale before they can be combined. The SMDs express the size of the intervention effect in each study relative to the variability observed in that study [14]. Abramson et al. performed, from 2000 to 2010, three Cochrane meta-analyses on SCIT for asthma [15–17]. Table 1 shows the main features of these meta-analyses. The first meta-analysis concluded that ‘Immunotherapy may reduce asthma symptoms and use of asthma medications, but the size of the benefit compared to other therapies is not known’ [15], while in the second meta-analysis found more promising results for SCIT in asthma, concluding that ‘Immunotherapy reduces asthma

symptoms and use of asthma medications and improves bronchial hyper-reactivity’ [16]. Given the importance of bronchial hyper-reactivity in the pathophysiology of asthma, the effect AIT on this characteristic of the disease was of particular interest [18]. In 2010 the conclusion was alike, and no further meta-analysis was carried out by these authors. In all meta-analyses, the readers were invited to consider the possibility of local or systemic adverse effects, including anaphylaxis [17]. Out of the 88 RPCTs included in the latest meta-analysis, 42 regarded dust mites, 27 various pollens, 10 animal dander, 2 molds, 2 latex, and 6 multiple allergens. The prevalence of dust mite trials, corresponding to almost half of the total number, reflects the great clinical importance of mites as a cause of asthma [19]. The efficacy of SCIT in mite-induced asthma was confirmed in 2015 in a meta-analysis. The trial selection was performed by search in electronic databases, including the Cochrane Library, MEDLINE, Embase, and PubMed and limited to the period from January 1990 to February 2013. A total of 19 trials including 796 patients were analyzed. The data obtained showed that SCIT significantly reduced the asthma symptom scores (SMD of -0.94) and the asthma medication scores (SMD of -1.06) when compared to the control group. Nonetheless, no significant difference was observed between SCIT treated patents and the control group in lung function, as measured by the forced expiratory value in 1 second (FEV1) the forced vital capacity (FVC) and the peak expiratory flow (PEF). In the trials reporting safety data, the incidence of systemic reactions was 9.1%, with no severe adverse events [20]. The evidence provided by the meta-analyses resulted in a growing favorable opinion on the role of SCIT in asthma [21,22]. However, when it comes to clinical practice, to expect efficacy in asthmatic patients crucial issues must be implemented, such as the presence and quantification in the immunotherapy products of all clinically relevant allergens [23,24] and the administration of adequate allergen dosages [25]. Real-life studies (also named real-world) are now used to assess the outcome of SCIT, especially in ordinary patients seen in daily practice, who are unlikely to meet the strict criteria for admission to trials and whose response to AIT is unpredictable. In addition, the number of patients included in real-life studies is hugely larger than in trials [26]. For instance, in a cohort analysis of a German longitudinal prescription database, 9001 patients treated with AIT for birch pollen allergy received ≥ 2 successive seasonal treatment cycles, while 45,005 matched non-AIT control patients had ≥ 3 drugs prescriptions in three seasons, with up to 6

Table 1. Main features of Cochrane meta-analyses on subcutaneous immunotherapy for asthma.

Reference	Authors, year	Number of trials	Outcome indexes	Results
[15]	Abramson et al, 2000	54	Asthma symptom scores Need of medications Specific and non specific bronchial hyper reactivity (BHR)	Patients receiving immunotherapy were less likely to require medication and showed a reduced specific BHR.
[16]	Abramson et al, 2003	75	Comparison of asthma symptom score in actively and placebo treated patients by the standardized mean difference (SMD) Number needed to treat (NNT) Specific and non specific BHR	SMD -0.72 , 95% confidence interval -0.99 to -0.33 Need to treat 5 (95%CI 4 to 6) patients with immunotherapy to avoid one requiring increased medication Significant reduction of specific BHR
[17]	Abramson et al, 2010	88	Comparison of asthma symptom score in actively and placebo treated patients by the SMD Number needed to treat (NNT) Specific and non specific BHR	SMD -0.59 , 95% confidence interval -0.83 to -0.35 Need to treat 4 patients (95% CI 3 to 6) with immunotherapy to avoid one requiring increased medication. Significant reduction of specific BHR

years of follow-up. Multiple regression analysis showed that significantly more AIT compared with non-AIT patients were asthma medication-free or reduced existing asthma medication use ($P < 0.001$) [27].

2.2. Evidence and achievements of SLIT in asthma

The first meta-analysis on efficacy of SLIT in asthma used the Cochrane Collaboration method to evaluate 25 studies with 1706 patients, in terms of asthmatic symptoms, use of asthma medications, lung function, and bronchial provocation. SLIT was found to significantly reduce asthma severity when parameter compositions were analyzed by categorical outcomes, while the reduction in asthma symptoms was non-significant when analyzed using SMD. The authors concluded that SLIT is beneficial for asthma treatment although the extent of the effect is not very large [28]. Instead, the meta-analysis by Cochrane Collaboration method restricted to pediatric patients gave better results. Seventy-three articles were reviewed, 9 of them (on a total of 441 patients) were included in the analysis; 232 patients received SLIT and 209 patients received placebo. The results showed a relevant heterogeneity due to broadly differing scoring systems; nevertheless, a significant reduction in both symptoms (SMD -1.14 ; $P = 0.02$) and medication use (SMD, -1.63 ; $P = 0.007$) in SLIT treated children was detected [29]. A more recent meta-analysis addressed only trials on adult patients, including 20 trials on an overall number of 2,288 patients treated with SLIT as add-on therapy and 1,268 patients treated only with classic drugs. The results showed that SLIT add-on therapy gave significant improvements in lower and upper airway scores, a higher FEV1, and bronchial reactivity, also significantly reducing drug consumptions compared with standard therapy [30]. As for SCIT, a meta-analysis limited to trials on efficacy of dust mite extracts is available. Liao et al. investigated the efficacy and safety of dust mite SLIT in children with asthma, with the mean change in asthma symptom score as primary outcome and medication score and changes in mite-specific IgE and IgG4 levels as secondary outcomes. SLIT significantly decreased ($P = 0.007$) asthma symptom score and increased sIgG4 levels ($P = 0.011$) compared with control children not treated with SLIT, while no significant difference was detected between SLIT and control groups according to medication score and specific IgE levels [31]. In the official Cochrane systematic review, Normansell et al. identified trials from the Cochrane Airways Group Specialized Register, ClinicalTrials.gov, and the World Health Organization (WHO) trials portal. Randomized controlled trials, irrespective of blinding or duration, evaluating SLIT versus placebo or as an add-on to standard asthma treatment, and including both adults and children with asthma of any severity and with any kind of allergen-sensitization were selected. Trials on patients with rhinitis were also included, with at least 80% of participants affected by asthma. A global number of 52 trials met the inclusion criteria, randomly assigning to treatments 5077 participants; 18 studies recruited only adults and 25 only children. Insufficient descriptions of allocation procedures were found, and approximately a quarter of the studies were at high risk of bias for performance or detection. Within secondary

outcomes, broad and various reporting of largely unvalidated asthma symptom and medication scores impeded meaningful meta-analysis. A general trend proposed SLIT advantage over placebo, but dissimilarity in scales made the results difficult to interpret. Lack of data precluded most of the planned subgroup and sensitivity analyses [32]. A further meta-analysis including RPCTs with both SCIT (54 trials) and SLIT (34 trials) found a SMD -1.64 for SCIT and -0.35 for SLIT, but the heterogeneity of trials leads the authors to claim for more data [33].

A decisive advance to overcome the obstacle of heterogeneity was prompted by the need to develop SLIT products able to satisfy the requirements of regulatory agencies such as European Medicine Agency (EMA) and Food and Drug Administration (FDA) to obtain their registration as pharmaceutical therapies. Actually, this entails to include in the RPCTs very large populations of patients, comparable to those included in meta-analyses but free from the problem of heterogeneity, because all patients undergo the same methods and assessment measures [34]. The standardized SLIT tablets of grass pollen extract were the first to be registered, including the 1-grass tablets [35] and the 5-grass tablets [36] and recruiting in the trial 855 and 628 patients, respectively. However, these studies addressed the effectiveness in seasonal rhinitis, while in 2014 the first trial on the efficacy of dust mite SLIT tablets in 604 patients with asthma was published. The primary endpoint was the use of inhaled corticosteroid (ICS), which was adjusted at baseline and the end of 1 year of treatment to the lowest dose giving asthma control. The mite tablets reduced the daily ICS dose by a mean difference of 81 μg compared with placebo ($P = 0.004$) [37]. Despite the modest result, these findings were very interesting for the possible role of AIT in asthma. The same mite tablets were evaluated in a RPCT performed in US recruiting 1492 patients (741 actively and 741 placebo treated). Although designed primarily to evaluate allergic rhinitis, this study included 460 patients with asthma (228 actively and 232 placebo treated). Only patients with well-controlled asthma were admitted. The endpoint for asthma outcome was the average daily symptom score DSS, i.e. the sum of cough, wheezing and chest tightness/dyspnea on a scale from 0 to 3. In the full analysis set, the mean asthma DSS decrease was significantly higher ($P = 0.002$) in patients treated with mite tablets compared placebo-treated patients [38]. Virchow et al. evaluated the efficacy of house dust mite sublingual allergen immunotherapy tablet in adults with house dust mite-related asthma, not controlled with ICS. Two dosages were used: 6 SQ-HDM and 12 SQ-HDM. The trial demonstrated an improvement in asthma exacerbations with the addition of HDM SLIT to maintenance medications. Both the 6 SQ-HDM and 12 SQ-HDM tablets significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo [39]. The SQ HDM SLIT-tablet was the first allergy immunotherapy to be tested prospectively in patients with asthma. The effect was found favorable modifying end points such as needed inhaled corticosteroid (ICS) or the time to first asthma exacerbation upon ICS reduction. On behalf of these data, experts suggest that SQ HDM SLIT-tablet treatment may contribute to improving overall asthma control [40]. This achievement in the field

of AIT for house dust mites resulted in the acknowledgment as add-on therapy in mite-allergic adult patients who have asthma exacerbations despite ICS treatment, provided a FEV1 value of at least 70% of predicted is measured, in the 2017 update of the Global Initiative on Asthma (GINA) guidelines [41].

2.3. Safety of SCIT and SLIT in asthma

Severe adverse reactions to SCIT have been a critical issue in the past. In fact, in the 1980s a number of fatal reactions to SCIT were reported in the United Kingdom (UK) and the United States (US). In particular, there were 26 fatalities in the UK [42] and 46 fatalities (also including some case of anaphylaxis to skin tests) in the US [43]. The reported rare fatal cases casted a shadow on SCIT use [44] producing concerns about this practice as well as the search of alternative routes of administration. Various studies identified the threshold of SCIT allergen doses, above which the risk of systemic reactions increased, defining as safe doses (in mcg of major allergens) equivalent to 7 mcg for Der p 1 from dust mites and to 13 mcg for Fel d 1 from cat. The dose dependency with respect to both efficacy and safety made crucial to accurately consider the risk/benefit ratio in each patient eligible for SCIT [45]. Indeed, the identification of concomitant uncontrolled asthma at the time of the allergen extract injection as the major risk factor for fatalities was a key advance in prevention of severe adverse reaction, as shown by the great rarity of fatal reactions when such risk was circumvented [46]. However, in the most recent survey of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma, and Immunology, in the period from 2015 to 2017, there was a slight increase in SCIT-related fatalities with no identification of precise risk factors [47]. Data from trials, with minimum risk of errors in allergen extracts administration, ensured by strictly controlled conditions and analyzed in systemic reviews, were promising. In fact, out of 466 RPCT included in the analysis, 13 anaphylactic reactions were described in four RPCTs and no fatalities [48]. In the European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI), which evaluated both SCIT and SLIT, in a total of 4316 patients, 109 systemic reactions were reported, 97 of them (89%) concerning SCIT, the most frequent being urticaria, rhinitis, dyspnea, and cough. Adrenaline was administered in 17 systemic reactions; however, only 65% of such reactions were successively classified as anaphylaxis. Independent risk factors for systemic reactions to SCIT the use of natural extracts, the absence of symptomatic allergy medications, an asthma diagnosis, sensitization to animal dander or pollens, and cluster regimens. The authors suggested that a personalized analysis of risk factors could be used to minimize systemic reactions to SCIT [49]. As to SLIT safety, all consensus documents underline the fact that, in more than 20 years of use, no fatal reactions were reported [1,5,32,33]. Indeed, the search for routes of administration safer than the injection was a strong impulse for development and confirmation of SLIT. The first studies were based on quite low allergen doses. After the statement from the Allergic Rhinitis and its Impact on Asthma (ARIA) document that doses at least 50 times higher than SCIT were needed to expect clinical efficacy [50] increasingly high dosages were administered with SLIT. In 2005 an analysis of all the available studies on

SLIT safety was performed. Of interest, no difference in the risk of adverse reactions, mostly consisting of oral itching or burning, lip or tongue swelling, throat irritation, nausea, stomachache (all due to the contact with the allergen in the mouth and gastrointestinal system) was found comparing studies using low and high allergen doses [51]. Still, very high doses may result in anaphylactic reactions. For example, there has been a report about a patient who, after discontinuing SLIT for several months, took the previously unused doses all at once, developing an anaphylactic reaction but surviving [52]. Based on the high allergen dosage of the latest generation SLIT tablets, studies on safety of these products are extremely interesting. Concerning the 1-grass (*Phleum pratense*) tablet, which are designed to be used starting with the maintenance dose, with no buildup, two cases of anaphylaxis after the first dose were reported [53]. However, the two patients underwent SLIT because of the indication to shift to SLIT subjects with severe reaction to SCIT, which is no more valid. Anyhow, when schedules with no buildup are used, it is recommended in recent guidelines that the first dose is administered under medical control in hospital [54].

Nolte et al. analyzed the use of epinephrine in 2408 patients recruited in trials on SLIT tablets with grass pollen (13 trials), ragweed (5 trials) and dust mites (11 trials). Totally, there were 32 epinephrine administrations (10 for grass pollen, 9 for ragweed pollen, and 13 for dust mite tablets). The reactions treated with epinephrine were not life-threatening. The authors concluded that epinephrine use in SLIT tablets is uncommon and typically occurs in the initial phase of treatment [55]. Another known approach to increase the safety of SCIT and SLIT is based on the use of allergoids, which are aimed at decreasing allergenicity while maintaining immunogenicity. This goal is obtained through different chemical modifications and polymerization of natural allergens by means of formaldehyde and Al(OH)₃, glutaraldehyde and tyrosine, glutaraldehyde, tyrosine, and monophosphoryl lipid A, and glutaraldehyde and Al(OH). However, the low allergenicity observed for some allergoids was intrinsically linked to a significantly lower immunogenic response [56]. When the balance of allergenicity and immunogenicity is suitable, good results of both efficacy and safety of allergoid-based SCIT were reported [57–59]. Since the 2000s, a carbamylated monomeric allergoid to be used with SLIT is available, which was found to be efficacious and safe in patients allergic to dust mites [60,61], and grass pollen [62]. Of interest, a study from the Institute of Medical Statistics, Informatics and Epidemiology of the University of Cologne, Germany investigated the possible role of carbamylated monomeric allergoid in cat allergy, which is a challenging model of immunotherapy [63]. Actually, a limited high-quality evidence on the effectiveness and safety of cat immunotherapy, as resulting from studies based on a limited array of immunological, physiological and patient-reported outcome measures in both SCIT and SLIT, is available. Moreover, cat immunotherapy is concerned by systemic reactions, that are particularly worrying in patients with asthma [64]. Even if interesting, this result is deeply affected by the fact that the study was uncontrolled and that, in consideration of the placebo effect in immunotherapy (30–50%) the interpretation of the results is difficult to assess. In the German study, 70 patients with cat allergy were treated with carbamylated monomeric allergoid tablets. Twenty-nine percent of patients with rhinitis were symptom free within the first year of treatment and 53% were

symptom free in the second year of treatment. As to asthma, 35% and 58% of patients were symptom free in the first and second year, respectively. No serious adverse reaction was reported. The authors concluded that SLIT with the monomeric allergoid results in excellent safety and good efficacy and may be proposed in patients with cat allergy [65]. Clearly, such outcome needs to be confirmed by controlled trials.

3. Expert opinion

Allergic asthma has a high prevalence worldwide and may be treated with very effective drugs, but their therapeutic action cannot continue beyond treatment withdrawal. By contrast, AIT has its most remarkable outcome in the persistence of clinical effect also following treatment end. This exclusive effect is due to the mechanism of action of immunotherapy, which induces (similarly in SCIT and SLIT) tolerance to the administered allergy by modifying the immunological response, particularly the pattern of T cell response from the Th2 dominance (typical of the allergic pattern) to the Th1 dominance with the related cytokine production, and by inducing the generation of T regulatory cells as well [66]. Moreover, a study on pediatric population has shown that AIT has a prolonged efficacy, even after the treatment discontinuation, in reducing the ICS dose needed to control asthma [67]. Clinically, the effectiveness of SCIT was clearly showed by Abramson et al. in three Cochrane meta-analysis from 2000 to 2010 [15–17]. The latest analyzed 88 RPCTs and concluded as to efficacy that 'Immunotherapy reduces asthma symptoms and use of asthma medications and improves bronchial hyper-reactivity', and as to safety that 'The possibility of local or systemic adverse effects (such as anaphylaxis) must be considered' [17]. Concerning SLIT, there is evidence for a better safety, while for efficacy the results of meta-analyses are less solid, mainly because of a significant heterogeneity of the used methods, doses, and assessment parameters [32].

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Declaration of interest

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