



Update on immunotherapy for the treatment of asthma

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Purpose of review

Despite that specific immunotherapy can boast being more than a century old, there is still skepticism about its real effectiveness, and therefore it is still used too little in clinical practice. The purpose of this review was to analyze the most recent articles in the literature to highlight scientific evidence for the proper use of allergen immunotherapy (AIT).

Recent findings

In the near future, the concept of medicine for trials will have to be revised and in certain cases abandoned in favor of a personalized medicine, able to use a drug more targeted for the individual patient and not for the disease.

Summary

For AIT, it will become increasingly important to use products designed properly, standardized and with a well documented effectiveness in clinical studies. We must overcome the disputes of subcutaneous immunotherapy versus sublingual immunotherapy, arrive at the concept of personalized medicine regarding AIT, framing in different phenotypes of asthma patients to use the optimal preparation for each particular patient.

Keywords

allergen immunotherapy, asthma, precision medicine, respiratory allergy, subcutaneous immunotherapy, sublingual immunotherapy

INTRODUCTION

The topic of allergen immunotherapy (AIT) has been recently addressed by our group in this journal [1]. Nonetheless, because of recent data, the relevant decisions of the regulatory authorities and the recent documents published by the Scientific Societies, we believe that updates need to be discussed.

Although AIT has been used for more than a century, nonetheless there is still some skepticism about its clinical effectiveness and safety, and as a consequence, AIT is still underused in asthma [2,3]. The aim of this article is to review the newest data to highlight the scientific evidence for a correct use of AIT in asthma.

One of the major criticisms in the past concerned the 'credibility' of the products used, that is, usually natural extracts without standardization. Currently, it is still true that different manufacturers' products with the potency indicated by means of in-house units that differ among the producers, can contain different amounts of major allergens. Unfortunately this 'old' phenomenon

was insufficiently considered, when the AIT meta-analyses, many in the last decades, were performed.

ALLERGEN IMMUNOTHERAPY AND EVIDENCE-BASED MEDICINE: CRITICISM AND AUTOCRITICISM

The systematic reviews and meta-analyses invariably concluded that AIT is effective and well tolerated in allergic rhinitis, asthma, or both [4–11].

The available meta-analyses grouped all existing studies from the literature (Table 1), but they did not discriminate between different products and,

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KEY POINTS

- According to the latest scientific evidence, we have evaluated the correct approach to the use of AIT in asthmatic patients.
- One of our purposes was to dispel the doubts on the use of AIT in asthmatic patients, using the correct AIT in a specific phenotype of patients.
- Personalized Medicine as a promising therapeutic approach applied to a specific phenotype of patients studied using biomarkers.
- Diatribe SCIT versus SLIT: two different tools in the allergist's therapeutic armamentarium.

initially, even not between different allergens. Although the scientific message was in support of AIT, this message was subsequently also used for products and allergens never tested in clinical trials, since the interpretation was an overall conclusion ('class effect').

A more correct approach was used in meta-analyses considering each single allergen, but again not all products on the market were tested in clinical trials and this situation prompted some of us [14] to start promoting the evaluation of the evidences for each single product whenever efficacy and/or safety was claimed.

We should also finally consider that just recently, some products were formally registered as medications by both the European Medicines Agency and the Food and Drug Administration, whereas others are under evaluation [15]. Some others are under evaluation by the regulatory authorities, and will soon reach the market. This is a historical event, highlighting the officiality of the acceptance of AIT, when correct products and schedules are employed.

In line with this concept, the World Allergy Organization AIT Subcommittee provided a recent document [16[■]]. The most relevant criteria needed for a new AIT product to make claims are listed below:

Criteria for a recommendable product for specific immunotherapy (SIT):

- (1) Minimum expectations for a SIT product to be used in adults:

At least one state-of-the-art double-blind placebo-controlled randomized (DBPCR) trial in adults for the first year of treatment, best preceded by a dose-response study (nasal provocation testing or allergen exposure chambers may be used for the dose finding).

Additional claims can be justified as follows:

Claims on sustained effects of a product should be based on a DBPCR study, based on appropriate sample size calculation, over 3 years of treatment.

Claims on disease modifying effects: such studies have to be followed up at least 2 consecutive years without treatment, while maintaining monitoring symptoms.

Claims for efficacy in asthmatics should be based on an appropriate DBPCR study in the appropriate patient group. For claims on tolerability in asthmatics only, the study can also be performed in allergic rhinitis patients with comorbid asthma.

- (2) Minimum expectations for a SIT product to be used in children:

At least one state-of-the-art DBPCR confirmatory trial in children for the first year of treatment.

- (3) Additional claims can be justified as follows:

Claims on sustained effects of a product should be based on a DBPCR study, based on appropriate sample size calculation, over 3 years of treatment.

Table 1. EBM evidences for allergen immunotherapy in asthma

Efficacy EBM documented on a global basis (all allergens-class effect)

(Abramson *et al.* *Cochrane* 2010 [8] – Erekosima *et al.* *Laryngoscope* 2013 [9] – Calamita *et al.* *Allergy* 2006 [10] – Penagos *et al.* *Chest* 2008 [11])

Efficacy EBM documented for mites

(Compalati *et al.* *Allergy* 2009 [12] – Abramson *et al.* *Cochrane* 2010 [8])

Efficacy EBM documented for pollens

(Abramson *et al.* *Cochrane* 2010 [8])

SLIT efficacy documented by GRADE system

(Lin *et al.* *JAMA* 2013 [13])

EBM, evidence-based medicine; SLIT, sublingual immunotherapy.

Claims on disease modifying effects: such studies have to be followed up at least 2 consecutive years without treatment, while maintaining monitoring symptoms [16[■]].

In line with the suggestions of the regulatory authorities [17], these criteria provide a guideline for proper development of new products for a reliable use of AIT worldwide.

A DIFFERENT AND UPDATED VIEW ON ALLERGEN IMMUNOTHERAPY

Currently, there is ample interest in 'Personalized' or 'Precision Medicine' (these two definitions can be used interchangeably) [18[■]]. For chronic diseases precision medicine is certainly the future approach, and since high-cost treatments are often involved, responders should be identified before starting the treatment.

The major aims of personalized medicine are:

- (1) To improve clinical outcomes and their predictability.
- (2) To reduce side-effects caused by a possibly inappropriate treatment.
- (3) To increase the quality of life.
- (4) To encourage patients' compliance because of a perceived clinical improvement.

To optimize the use of healthcare resources, generic drugs and biosimilars have been developed, aimed to control or at least to reduce the expenses for chronic diseases [19]. This is true for rare diseases and for economically impacting diseases such as severe asthma, where biologics will be the mainstay of its future treatment.

The scientific need to identify different subsets of patients in the general context and the need to control expenses converged on the urgent necessity to define phenotypes, and possibly endotypes, of patients. Also, this approach is essentially intended to define responders to a certain treatment, thus avoiding to treat patients with useless and expensive drugs. The definition of phenotypes was initially a clinical approach, whereas nowadays the research on biomarkers is focusing on molecular instruments [20]. A more sophisticated procedure, using forthcoming biomarkers, for example, through omic sciences, will better define the candidate patient eligible for a specific treatment [21].

Personalized medicine has precise tasks and has also an 'official' definition as reported by Hamburg and Collins [22]. If we translate these same concepts to AIT, as recently proposed [18[■],23[■]], we will have the opportunity to reevaluate AIT in the context of precision medicine. In fact, AIT is fulfilling all the personalized medicine criteria mentioned above, as a therapy applied to a specific phenotype of patients (Fig. 1).

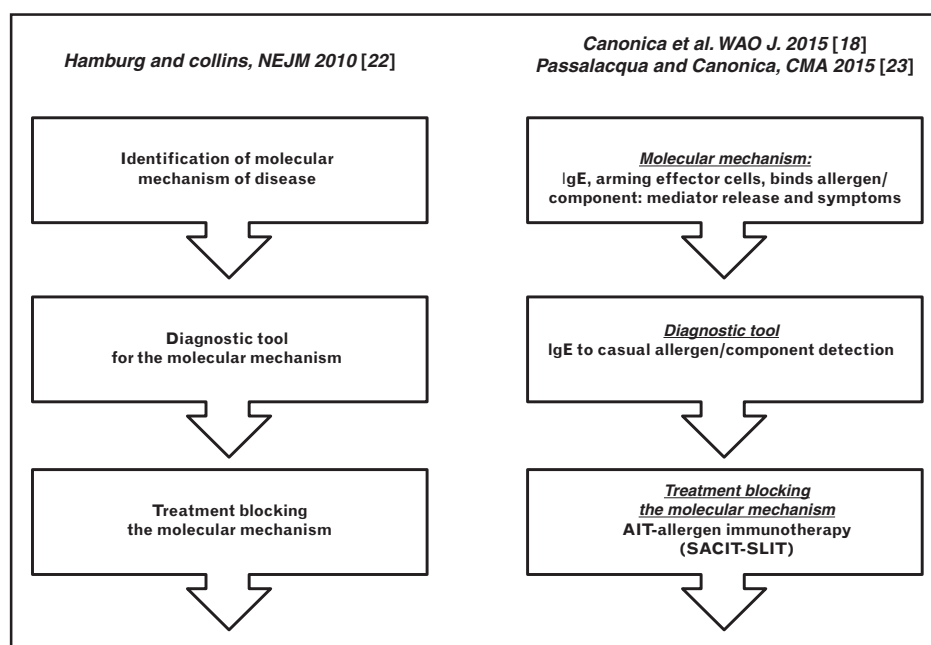


FIGURE 1. Parallelism between the define criteria of personalized medicine and as allergen immunotherapy can fulfill those criteria.

NEW ASPECTS OF ALLERGEN IMMUNOTHERAPY

The role of molecular diagnosis

It has been now established that the IgE response is not generically directed toward an 'allergenic source', but rather to specific proteins (or epitopes) that are contained into the raw material [24[•]]. For instance, the genuine IgE response to 'grasses' is directed to few proteins (Phl p 1, Phl p 5, and Phl p 6), and the IgE response to mite is specific for the proteins Der p1 and Der p2. Such molecules are considered the 'genuine sensitizers'. On the other hand, there are also highly conserved proteins, which are present in different species (e.g., profilins, lipid transfer proteins, and storage proteins). They are called pan-allergens or cross-reacting proteins and are often responsible for multiple positivities in standard diagnostic tests. This has a relevant implication, especially for AIT. In fact, the molecular diagnosis allows to distinguish the genuine sensitizations from cross-reacting proteins, and therefore helps to refine the choice of the allergen to be used for AIT. Several studies have shown that molecular diagnosis significantly modifies the prescription of AIT in polysensitized patients [25]. Currently, many recombinant or purified molecular allergen components are available for skin prick testing and immunoassay, also in multiplexed systems.

Regulatory aspects

Despite the amount of clinical and mechanistic data on AIT and its consolidated use, the regulatory aspects (pharmacological classification of products, marketing authorization, national and supranational approval, and deputy regulatory authorities) remain sometimes vague and largely differ among countries. If in the United States and in the European Community, there are well defined regulatory authorities (namely Food and Drug Administration, European Medicines Agency, and Paul Ehrlich Institute); in other countries, such as Latin America, there is no uniform regulation.

In Europe, numerous official regulatory documents have been released, mainly concerning the good manufacturing practice. Those impose to all members of the European Community-specific standards for the production of allergen extracts. Within the European Community, with few exceptions, allergen extracts are considered named patient products (prepared individually according to the prescription of the physician), but almost all extracts are manufactured by industrial procedures. There is a general effort to abolish the possibility to

have named patient products, with exceptions for rare allergens or special sensitization profiles. In addition, for each new product, a registrative dossier (from phase I to III) is required for the marketing authorization [17,26].

SUBCUTANEOUS IMMUNOTHERAPY VERSUS SUBLINGUAL IMMUNOTHERAPY: AN ANACHRONISTIC AND WRONG APPROACH

This dilemma should nowadays be considered an old fashioned or obsolete topic. Independently of the personal wishes, local culture and experience, and the financial/economical pressure, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) should be considered two different tools in the allergist's therapeutic armamentarium. There are patients eligible to SCIT and some other ones better eligible to SLIT. The choice of one of the two routes of administration should be defined together with the patient, explaining to him/her all the details related to the two different tools [27].

Efficacy

In term of efficacy, there is still a lot of debate, most often not based on data, although recent evidence, supported by a systematic review [28] and a comparative clinical trial [29], does not show a significant difference both on clinical and immunological outcomes between SCIT and SLIT.

A novel experimental clinical strategy is to combine the two forms of AIT, starting with SCIT, while using SLIT as maintenance treatment. The rationale is to take advantage of the best features of both: a possible more rapid effect of SCIT and a safer profile of SLIT [30].

Criteria for properly designing and evaluating AIT clinical trials have been proposed by Scientific Societies [5,31,32] and individual research groups for single allergens [33]. A more harmonized approach will allow a more coherent evaluation of each single trial. In this context, we should consider the recent evidences for a house dust mite (HDM) tablet, specifically investigated in asthma patients by Mosbech and de Blay [34^{••},35]. These two studies are based on a randomized placebo controlled trial with a large number of HDM-sensitized asthma patients, primarily designed to establish the optimally well tolerated and effective dose of allergen to be used. The primary outcome was a reduction in inhaled corticosteroids intake, while maintaining asthma control. The outcome was statistically significant at the end of the study period (12 months), with a satisfactory safety profile.

Surprisingly, the best outcomes, including the quality of life data, were detected in patients with more severe disease and this observation suggests the real perspective to extend AIT asthma treatments to more severe patients, in contrast to those in the very early Global Initiative for Asthma steps, as it was considered before.

Furthermore, in these same patients, AIT was also significantly effective on nasal symptoms [36], supporting once more the importance of the concept of united airways diseases [37,38] and its correct treatment [39].

The more recent data from clinical trials [34²²] clearly showed that HDM sublingual tablet in asthma patients significantly decreased the intake of inhaled corticosteroids, and this is a relevant observation, potentially affecting the global strategy of HDM-induced asthma.

Placebo effect

Placebo effect has been envisaged as a possible confounding factor in evaluating SLIT efficacy in clinical trials [5]. A recent review by Narkus *et al.* [40²³], confirmed the significant placebo effect in AIT clinical trials, especially in SCIT studies, reporting also allergen exposure as well as the route of administration as enhancing factors of it. Depending on the route of administration, they reported a placebo effect in SCIT trials from 24 to 41% in mite, and from 6 to 25% in pollen allergic patients with comparable allergen exposure and up to 51.8% with reduced exposure, which is in contrast to 1.3% or less in SLIT trials. Nonetheless this last data are apparently quite low compared with other SLIT studies; for instance, in a HDM SLIT clinical trial, we obtained a higher placebo response [41].

The differences between the SCIT and SLIT, especially concerning the safety may be explained by the different administration method (i.e., injections vs. oral applications) or by the use of adjunct components, such as alum hydroxide or histamine that are included in the placebo preparations for SCIT, but not for SLIT.

Safety

AIT implies the administration of extracts of allergens to which the individual is sensitized and this can lead to adverse reactions, that can be either local or systemic, this latter, spanning to anaphylaxis and death. The reported occurrence of systemic reactions is largely variable, depending on the allergen, preparation, dose, and induction schedule. The available data (from large populations) come from the surveys regularly performed in the United States

with SCIT, which report about 50 deaths over a 50-year period with a risk of one death every 2 500 000 injections and one near-fatal reaction per million injections. Human errors and uncontrolled asthma were the most frequent causes of SCIT-induced serious adverse events. On the other hand, in the period 2008–2011 no further fatality because of SCIT was reported in the United States and systemic reactions were about 0.1% of injection visits [42]. Evaluating those data, it must be kept in mind that the practice of SCIT profoundly differs between Europe and United States, where allergen mixes and higher concentrations are commonly used [43]. Few systematic data are available in European countries. A recent multicenter observational study [44] suggested that systemic reactions are slightly more frequent in rhinitis with asthma than in rhinitis patients alone. According to the past observations and the few recent data, the scientific community agreed, as a prudential attitude, to consider uncontrolled/severe asthma as a major risk factor for serious adverse events of AIT. Although not based on direct evidence, this attitude has been translated also to SLIT. However, the safety of SLIT is overall superior to that of SCIT [45] at least because no fatality has been reported so far, and only few cases of suspect/ascertained anaphylaxis have been described, none directly attributable to preexisting or worsening of asthma [46].

According to common sense and supported by literature, severe/uncontrolled asthma remains the main risk factor for serious adverse events because of AIT, although for SLIT, severe asthma has been not clearly demonstrated as a specific contraindication. In general, asthma is not an absolute contraindication to AIT, if the patient is well controlled with pharmacotherapy.

As a future perspective, a uniform reporting and grading of side-effects would be desirable and this has recently been addressed by the World Allergy Organization, which proposed a grading system for systemic reactions because of SCIT/SLIT [47,48] and for local reactions because of SLIT.

Adherence

Also adherence has been an argument of debate, but different data have been provided in favor or against, respectively SCIT or SLIT [47].

Cox *et al.* [49] recently reported a very balanced and correct consideration in the light of a revision of the topic in an Editorial on JACI 2014: 'AIT adherence is equally poor regardless of whether or not treatment is administered in a medical supervised setting (SCIT) or at home (SLIT) and comparable with poor adherence with long-term pharmacotherapy'.

Table 2. Some future requirements for allergen immunotherapy as personalized therapy

Component resolved diagnosis

Product based on component resolved diagnosis

System medicine and network medicine will provide a selective stratification of patients eligible for AIT (i.e., patient selection)

AIT, allergen immunotherapy.

Obviously, education is a cornerstone of any strategy to increase adherence, but it cannot be limited to a routine visit to the allergist. The news media and internet can be very helpful in educating and reinforcing this information. Similarly, general practitioners have to be involved and play a key role in any long-term treatment, especially with AIT. If so, also allergists need to update skills and technologies to support patients to adhere [50].

CONCLUSION

In the current review, we highlighted the new data about 'efficacy' and other features of AIT in asthma, corroborating previous evidence and proposing AIT as a strategic tool of clinical therapy. To address such a treatment, proper diagnostic tools (component molecular diagnosis) and 'AIT products' (standardized and documented in clinical trials) should be used nowadays (Table 2).

- (1) New evidence in this context is forthcoming as far as 'HDM asthma' is concerned, possibly leading to a change in the therapeutic strategy of this specific phenotype.
- (2) We argued about the 'controversy SLIT versus SCIT', and vice versa, and we provided several data supporting the nonsense of such a diatribe.
- (3) We wish also to emphasize the vision of 'AIT as model of personalized medicine'.

Possibly, in the past, the concept of AIT as personalized treatment was not properly considered or emphasized, but AIT was and still is upfront in this context.

This approach to treat specifically selected phenotypes of asthma patients will be more realistic for allergic asthmatics, whenever both a correct diagnosis and AIT product are available.

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Conflicts of interest

All the signed authors have equally contributed in the preparation of this review, and have approved its final version and submission. G.W.C. and G.P. have been scientific consultant or speaker for: Alk-Abello'-Allergo-pharma-Allergy Therapeutics-Anallergo-Hal-Lofarma-Stallergenes-Thermo Fisher. The other authors have no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Compalati E, Braido F, Canonica GW. An update on allergen immunotherapy and asthma. *Curr Opin Pulm Med* 2014; 20:109–117.
2. Canonica GW, Baena-Cagnani CE, Compalati E, *et al.* 100 years of immunotherapy: the Monaco charter. Under the high patronage of His Serene Highness Prince Albert II of Monaco. *Int Arch Allergy Immunol* 2013; 160:346–349.
3. Bousquet J, Schünemann HJ, Bousquet PJ, *et al.* How to design and evaluate randomized controlled trials in immunotherapy for allergic rhinitis: an ARIA-GA(2)LEN statement. *Allergy* 2011; 66:765–774.
4. Zuberbier T, Bachert C, Bousquet PJ, *et al.* GA² LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy* 2010; 65:1525–1530.
5. Canonica GW, Cox L, Pawankar R, *et al.* Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J* 2014; 7:6.
6. Passalacqua G, Canonica GW. Specific immunotherapy in asthma: efficacy and safety. *Clin Exp Allergy* 2011; 41:1247–1255.
7. Passalacqua G. Specific immunotherapy in asthma: a synthetic review. *J Asthma* 2014; 51:29–33.
8. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010; 8:CD001186.
9. Ereksima N, Suarez-Cuervo C, Ramanathan M, *et al.* Effectiveness of subcutaneous immunotherapy for allergic rhinoconjunctivitis and asthma: a systematic review. *Laryngoscope* 2013; 124:616–627.
10. Calamita Z, Saconato H, Bronhara Pelá A, Atallah AN. Efficacy of sublingual immunotherapy in asthma. Systematic review of randomized clinical trials. *Allergy* 2006; 61:1162–1172.
11. Penagos M, Passalacqua G, Compalati E, *et al.* Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 2008; 133:599–609.
12. Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. *Allergy* 2009; 64:1570–1579.
13. Lin SY, Ereksima N, Kim JM, *et al.* Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013; 309:1278–1288.
14. Bachert C, Canonica GW, Bufe A. SIT: efficacy depends on product, not on route of application. *Pediatr Allergy Immunol* 2012; 23:401.
15. Thompson CA. Sublingual immunotherapy approved for grass pollen allergies. *Am J Health Syst Pharm* 2014; 71:770.
16. Bachert C, Larché M, Bonini S, *et al.* Allergen immunotherapy on the way to product-based evaluation: a WAO statement. *World Allergy Organ J* 2015; 8:29.
- A document highlighting the importance of considering single documented AIT products.
17. Bonini S. Regulatory aspects of allergen-specific immunotherapy: Europe sets the scene for a global approach. *World Allergy Organ J* 2012; 5:120–123.

18. Canonica GW, Bachert C, Hellings P, *et al*. AIT as prototype of precision medicine. *World Allergy Organ J* 2015 (In press).
- First study addressing AIT as a therapeutic tool of personalized medicine.
19. Braido F, Holgate S, Canonica GW. From 'blockbusters' to 'biosimilars': an opportunity for patients, medical specialists and healthcare providers. *Pulm Pharmacol Ther* 2012; 25:483–486.
20. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012; 18:716–725.
21. Holgate ST. Trials and tribulations in identifying new biologic treatments for asthma. *Trends Immunol* 2012; 33:238–246.
22. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med* 2010; 363:301–304.
23. Passalacqua G, Canonica GW. AIT (allergen immunotherapy): a model for the ■ "precision medicine". *Clin Mol Allergy* 2015; 13:24.
- The study highlights the concept of AIT as personalized treatment.
24. Canonica GW, Ansotegui IJ, Pawankar R, *et al*. A WAO – ARIA – GA²LEN ■ consensus document on molecular-based allergy diagnostics. *World Allergy Organ J* 2013; 6:17.
- An official document on the clinical relevance of molecular-based allergy diagnostics.
25. Passalacqua G, Melioli G, Bonifazi F, *et al*. The additional values of microarray allergen assay in the management of polysensitized patients with respiratory allergy. *Allergy* 2013; 68:1029–1033.
26. Kaul S, May S, Lüttkopf D, Vieths S. Regulatory environment for allergen-specific immunotherapy. *Allergy* 2011; 66:753–764.
27. Calderón MA, Casale TB, Togias A, *et al*. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. *J Allergy Clin Immunol* 2011; 127:30–38.
28. Dretzke J, Meadows A, Novelli N, *et al*. Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. *J Allergy Clin Immunol* 2013; 131:1361–1366.
29. Eifan AO, Akkoc T, Yildiz A, *et al*. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous Immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. *Clin Exp Allergy* 2010; 40:922–932.
30. Keles S, Karakoc-Aydiner E, Ozen A, *et al*. A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes. *J Allergy Clin Immunol* 2011; 128:808–815.
31. Pfaar O, Demoly P, Gerth van Wijk R, *et al*. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy* 2014; 69:854–867.
32. Canonica GW, Baena-Cagnani CE, Bousquet J, *et al*. Recommendations for standardization of clinical trials with allergen-specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007; 62:317–324.
33. Pfaar O, Gerth van Wijk R. Mite-allergic rhinitis: how to evaluate clinical efficacy in allergen-specific immunotherapy trials? *Curr Treat Options Allergy* 2015; 2:1–9.
34. Mosbech H, Deckelmann R, de Blay F, *et al*. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014; 134:568–575.
- First study of mite SLIT tablet to be effective in asthma.
35. de Blay F, Kuna P, Prieto L, *et al*. SQ HDM SLIT-tablet (ALK) in treatment of asthma: post hoc results from a randomised trial. *Respir Med* 2014; 108:1430–1437.
36. Mosbech H, Canonica GW, Backer V, *et al*. SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms. *Ann Allergy Asthma Immunol* 2015; 114:134–140.
37. Passalacqua G, Ciprandi G, Canonica GW. United airways disease: therapeutic aspects. *Thorax* 2000; 2:S26–S27.
38. Compalati E, Ridolo E, Passalacqua G, *et al*. The link between allergic rhinitis and asthma: the united airways disease. *Expert Rev Clin Immunol* 2010; 6:413–423.
39. Bousquet J, Khaltaev N, Cruz AA, *et al*. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; 63 (Suppl 86):8–160.
40. Narkus A, Lehnigk U, Haefner D, *et al*. The placebo effect in allergen-specific ■ immunotherapy trials. *Clin Transl Allergy* 2013; 3:42.
- The study summarizes the evidences about placebo effect in AIT trials.
41. Passalacqua G, Pasquali M, Ariano R, *et al*. Randomized double-blind controlled study with sublingual carbamylated allergoid immunotherapy in mild rhinitis due to mites. *Allergy* 2006; 61:849–854.
42. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, Year 3: what practices modify the risk of systemic reactions? *Ann Allergy Asthma Immunol* 2013; 110:274–353.
43. Cox L, Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol* 2009; 103:451–459.
44. Schiappoli M, Ridolo E, Senna G, *et al*. A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. *Clin Exp Allergy* 2009; 39:1569–1574.
45. Cox LS, Linnemann DL, Nolte H, *et al*. Sublingual immunotherapy: a comprehensive review. *J Allergy Clin Immunol* 2006; 117:1021–1035.
46. Calderón MA, Simons FE, Malling HJ, *et al*. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. *Allergy* 2012; 67:302–311.
47. Cox L, Larenas Linneman D, Lockey RF, Passalacqua G. Speaking a common language in immunotherapy. WAO grading of systemic reactions. *J Allergy Clin Immunol* 2010; 125:569–574.
48. Passalacqua G, Baena Cagnani C, Bousquet J, *et al*. Grading local side-effects of sublingual immunotherapy for respiratory allergy: speaking the same language. *J Allergy Clin Immunol* 2013; 132:93–98.
49. Cox LS, Hankin C, Lockey R. Allergy immunotherapy adherence and delivery route: location does not matter. *J Allergy Clin Immunol Pract* 2014; 2:156–160.
50. Passalacqua G, Baiardini I, Senna G, Canonica GW. Adherence to pharmacological treatment and specific immunotherapy in allergic rhinitis. *Clin Exp Allergy* 2013; 43:22–28.