



Allergen immunotherapy for pediatric asthma: current evidence and knowledge gaps

Giovanni Passalacqua^a, Massimo Landi^{b,c}, and Diego G. Peroni^d

Purpose of review

The introduction of high-quality and standardized extracts for immunotherapy has renewed the interest in the treatment of pediatric allergic asthma that represents a high-prevalence disease.

Recent findings

In addition to clinical trials, several systematic reviews and metaanalyses were published, confirming overall the clinical efficacy of allergen immunotherapy in pediatric asthma. In addition, new data on the preventive effect of the treatment on asthma onset were published. Despite this, many intriguing questions emerged, in parallel to the development of knowledge.

Summary

Allergen immunotherapy is overall effective for the treatment of asthma in children, but a class-effect should not be claimed, rather the efficacy of each single product. According to the recent findings, the challenge for the future research will be to clarify: when to start immunotherapy in children, which are (if they exist) the predictive biomarkers for efficacy in the single individual, the magnitude of the preventive effect and the optimal duration of the treatment.

Keywords

allergen-specific immunotherapy, allergic asthma, children, efficacy, preventive effects

INTRODUCTION

Asthma, especially in its allergic form is a high-prevalence disease, in particular in the pediatric age, where age-specific issues with diagnosis and management emerge. It is acknowledged that asthma is a heterogeneous disease [1], but in the pediatric age allergic asthma is the most common presentation [2^a,3,4]. This is a typical type-2 high asthma phenotype characterized by early onset, atopic background and family history of atopy, IgE sensitization to aeroallergens, and a Th2-driven inflammation [5].

Allergen-specific immunotherapy (AIT), introduced more than one century ago on an empirical basis, is a 'biological response modifier,' capable to interfere with and to modulate the specific Th2 response to allergens. This results in a wide array of mechanisms including: induction of regulatory T cells; secretion of allergen-specific IgG4 which can compete with the IgE-mediated antigen presentation; reduction in IgE-mediated mast-cell activation (for review, see [6]). Recently, also B cells and innate lymphoid cells 2 appeared to be involved in the mechanisms of action of AIT [7^a].

It is believed that as earlier is the application of AIT as greater are the benefits obtained. Thus, the

pediatric age would seem to be the optimal time frame to use this therapeutic approach. Indeed, there are numerous experimental evidences showing that AIT is effective (reduction in symptoms and rescue medication use) for respiratory allergy in children, but the majority of the clinical trials were conducted with rhinitis as the main outcome. In the pediatric studies of AIT, asthma has ever been evaluated as a secondary outcome (subgroups of rhinitis children who had also concomitant asthma). Metaanalyses about the efficacy of AIT in asthmatic children are also available, but they are distorted by the great heterogeneity of the included studies.

^aDepartment of Internal Medicine, Allergy and Respiratory Diseases, IRCCS Policlinico San Martino, University of Genoa, Genoa, ^bPediatric National Healthcare System, Turin, ^cInstitute of Biomedical Research and Innovation, Palermo and ^dPediatrics, Department of Experimental Medicine, University of Pisa, Pisa, Italy

Correspondence to Giovanni Passalacqua, MD, Department of Internal Medicine, Allergy and Respiratory Diseases, IRCCS Policlinico San Martino, University of Genoa, L.go R. Benzi 10, 16132 Genoa, Italy. E-mail: passalacqua@unige.it

Curr Opin Allergy Clin Immunol 2020, 20:000–000

DOI:10.1097/ACI.0000000000000618

KEY POINTS

- Allergen immunotherapy is overall effective for the treatment of asthma in children, despite the large variability of the clinical trials.
- Numerous metaanalyses confirmed the efficacy, but a class-effect should not be claimed, rather the efficacy of each single product.
- The data concerning the reduction of the risk of developing asthma are encouraging, but further studies are required.
- Several 'knowledge gaps' remain: when to start immunotherapy, optimal duration of the treatment, biomarkers predictive of efficacy.

Another interesting aspect in children is the possibility to prevent the evolution of the allergic respiratory disease, from rhinitis to asthma. Indeed, there is experimental evidence suggesting the preventive effect of AIT. Although there is evidence that AIT can modulate and improve asthma in children, there are many unsolved questions in this context that still need to be elucidated [8]. We will review herein the main experimental evidence about the use of AIT in pediatric asthma and will also review the main knowledge gaps in this context.

CURRENT EVIDENCE FOR ALLERGEN-SPECIFIC IMMUNOTHERAPY IN ASTHMATIC CHILDREN

There are numerous reviews and metaanalyses, and certainly many trials concerning the efficacy of AIT in pediatric asthma. From the historical viewpoint, Penagos *et al.* [9] first conducted a metaanalysis of AIT in the pediatric age, extracting the data from the studies available at that time, and reported a significant effect versus placebo. Indeed, in the last 20 years, there were some clinical trials specifically investigating AIT in pediatric asthma [10–19] that confirmed its efficacy by assessing various parameters (e.g., symptom score, medication intake, quality of life, exacerbations, pulmonary function) (Table 1).

Evidence for SCIT in pediatric asthma

There are few studies specifically designed to assess the effects of SubCutaneous ImmunoTherapy (SCIT) in pediatric asthma [10,11]. One of them included more than 200 patients [10] and showed a reduction in symptom score, but not in medication intake. Another study with 197 children was conducted with various extracts (trees, mite, grass) and showed

a reduction in combined symptom and medication scores [11].

Evidence for SLIT in pediatric asthma

SLIT was studied more extensively [12–18], probably because the sublingual administration is considered more comfortable for children than injections. Two studies, with more than 100 patients provided negative results for dust-mite SLIT [16,17]. Indeed, in one of those trials [16], the patients were almost totally symptom-free at enrolment, thus measurable clinical changes could not be expected. In the other negative trial [17], the recruitment setting (primary care) could have affected the outcome. The remaining trials provided positive results in term of symptoms, medication intake and respiratory function.

SLIT versus SCIT

One double-blind, double-dummy trial with a mite extract compared SLIT, SCIT, and placebo [19]. It failed to detect a difference between the two routes in term of efficacy and safety, and both routes were significantly more effective than placebo. This study has a robust experimental design, but the number of patients enrolled (10 per group) is small. Of note, in an open randomized controlled study, involving 48 children with single dust-mite sensitization, SLIT and SCIT showed a similar efficacy in reducing rhinitis score, asthma score, medication score, and specific nasal reactivity and were more effective than pharmacotherapy alone [20]. Finally, Keles *et al.* [21] explored the possibility to use SCIT as induction mode followed by SLIT as maintenance. In this open study, 60 children with dust-mite allergy were randomized to receive SCIT, SLIT, SCIT and SLIT or pharmacotherapy for 18 months. Briefly, SCIT and SCIT and SLIT were superior to SLIT alone in reducing inhaled corticosteroids, asthma exacerbations, and asthma scores, with a more pronounced effect on specific IgG4 for SCIT and SCIT and SLIT.

A quite up-to-date summary of the studies, including the older ones, can be found in [22²³,23–25]. Certainly, the majority of clinical trials were conducted with the sublingual administration (SLIT) that for its convenience and safety is generally preferred in the pediatric ages. Of note, as per Table 1, there is a great heterogeneity in the studies, and a large variability in the number of patients enrolled.

The available data confirm, in fact the good safety profile of SLIT in children, independent of the presence of asthma, and asthma in children receiving SLIT seems not to be a risk factor for severe

Table 1. Randomized, double-blind placebo-controlled studies with SLIT in pediatric asthma

Author, year (Ref.)	Participants (n)	Age range (years)	Allergen	AIT type	Duration	Dose	Main efficacy results	Main safety results
Roberts, 2006 [10]	39	3–16	Grass	SCIT	2 years	20 µg Phl p 5 per injection	↓ Symptoms + medications 2nd pollen season; no change in inhaled steroids and rescue bronchodilators	Local AEs: active = placebo 30 SAEs (21 active/9 placebo) Mo withdrawal due to AEs
Alzakar, 2010 [11]	197 ^a	7–12	Various	SCIT	1 year	Not specified	↓ Asthma symptom score and medication score ↓ Specific IgE	No SAE; no withdrawal
Bufe, 2009 [12]	253	6–18	Grass	SLIT	6 months	15 mg Phl p 5/day; tablet	↓ Asthma symptoms and days with asthma in peak and entire season. No change in medications	32% with local AEs in active and 2% in placebo; no SAE; 4 withdrawal in active
Bahceciler, 2001 [13]	15	7–15	Mite	SLIT	6 months	72 µg Der p 1/month; Cumulative: 0.56 mg	↓ Asthma symptom score, exacerbations, bronchodilators; ↑ PEF. No change inhaled steroids	No SAE reported
Niu, 2006 [14]	110	6–12	Mite	SLIT	6 months	320 µg Der p 1/month Cumulative: 1.7 mg	↓ Nighttime, daytime, total asthma score ↑ FEV1 versus baseline but not between groups	No difference in AEs between groups
Lue, 2006 [15]	20	6–12	Mite	SLIT	8 months	Cumulative: 1.7 mg Der p 1	↓ Night symptom score, medication use. No change FEV1 and PEF	No AE/SAE reported
Pham Thi, 2007 [16]	111	5–11	Mite	SLIT	18 months	810 µg Der p 1/month Cumulative 6.9 mg	No change in asthma symptoms, medications, QoL, and pulmonary function	All AE: active = placebo 1 withdrawal each group
De Boi, 2012 [17]	251	6–18	Mite	SLIT	2 years	700 BU twice week µg not stated	No change in asthma symptom and medication score	All AE: active = placebo AE: 6 active 3 placebo
Stelmach, 2009 [18]	50	6–18	Grass	SLIT	6 months 2 years	Cumulative: 3.65 mg Phl p 5	↓ Asthma symptom and medication score and FeNO	AE: 35% active 33% placebo mainly local; no drop out
Yukselen, 2012 [19]	30	6–12	Mite	SCIT/SLIT	1 year	Cumulative/year Der p 1 11 885 TU SCIT and 86 866 TU SLIT	↓ Asthma symptoms and VAS both treatments; ↓ asthma medications only SCIT; ↑ IgG4 and ↓ bronchial specific reactivity only SCIT; ↓ nasal specific reactivity both treatments	No SAE in both groups Local AEs SLIT > SCIT 1 withdrawal SLIT

AE, adverse event; AIT, allergen-specific immunotherapy; FeNO, exhaled nitric oxide; FEV1, forced expiratory volume 1 s; PEF, peak expiratory flow; QoL, quality of life; SAE, systemic adverse event.

^aSingle blinded.

adverse events. The most frequently occurring adverse events with SLIT remain the local ones (oral itching, swelling, lip edema, stomach ache, which usually subside in few days [26²²,27]. This is well confirmed also in the pediatric population, as derived by the available literature [28–30].

THE PREVENTIVE EFFECTS

More than 50 years ago, in an observational non-randomized controlled study, Johnstone observed that among children with allergic rhinitis, those treated with AIT developed significantly less asthma than those receiving pharmacotherapy only [31]. This observation remained substantially ignored for years. At the beginning of the 21st century, this aspect was reconsidered. There were three open randomized controlled trials, one with SCIT (grass pollen) and two with SLIT (one with grass pollen and one with dust mite, grass, weeds, or trees) [32–34] which confirmed that in children with allergic rhinitis only, the use of AIT could significantly reduce the risk of subsequently developing overt asthma. Notably, the preventive effect obtained with SCIT resulted still present at a 10-year follow-up [35]. These three trials provided consistent results in term of magnitude of the effect, but they were criticized for the absence of blinding and of a placebo group, in fact the control groups received openly the standard drug therapy. More recently, the GAP trial [36²²] involved more than 800 children with allergic rhinitis who were randomized to receive either grass-SLIT or placebo for three years in a double-blind fashion. They were then followed-up for further two years to evaluate several parameters: use of inhaled steroids, use of bronchodilators, pulmonary function, asthma symptoms, and so on. Despite the too ambitious primary outcome (asthma defined as documented wheezing with or without prolonged phase of forced exhalation and a change in FEV1 > 12% after b2-agonist administration) was not reached, the result incontrovertibly showed that there was a significant preventive effect on experiencing asthma symptoms or using asthma medication. This effect was also confirmed in a large retrospective study, involving more than 2800 grass-SLIT children and more than 71 000 controls [37].

In the last decades, some studies suggested also that AIT can prevent the development of new sensitizations, but the recent reviews on this aspect showed that the available data are of low methodological quality and overall inconsistent [38,39]. Thus, based on the current evidence, there is no robust enough evidence to recommend the use of AIT for the prevention of the development of new sensitizations [40,41].

Finally, despite the hypothesis of AIT as primary prevention of allergy is attractive, there are so far few and not conclusive data in humans [42,43].

KNOWLEDGE GAPS

As summarized above, we have now available an amount of clinical trials and metaanalyses showing that, overall, AIT is effective in reducing asthma symptoms and medication intake in children. The majority of trials were conducted with SLIT and with grass or dust-mite extracts, whereas for less common allergens the evidence is insufficient as a general consideration, when the allergic nature of asthma is ascertained, the offending allergen is clearly identified and a high-quality standardized product is used, AIT is effective for the treatment of asthma in children. Nonetheless, the majority of the trials were designed with allergic rhinitis as primary outcome, and patients with asthma represented only subgroups [44]. Thus, clinical trials designed specifically for asthma are needed to assess the real efficacy, using appropriate outcome [45]. Moreover, diagnosing allergic asthma in very young children may be difficult, as occasional wheezing and viral-induced wheezing have to be taken into account. Also, the metaanalyses, although positive are affected by the large variability and heterogeneity of the methodology. In fact, metaanalyses put together different allergens, products, outcomes, patients' selection criteria, doses, and regimens of administration [46]. Thus, it is now recognized that the efficacy of AIT should be not considered as a 'class effect,' but the efficacy and safety must be defined for each single product [47]. So far, there is no reliable tool to be used to compare each other the single clinical trials. In children, the most relevant cause of allergic asthma is house dust mite. In such case, the exposure is largely variable and difficult to assess (differently from pollen exposure that can be easily quantified) and, therefore, long periods of observation are needed. The evaluation of the efficacy of AIT in asthma in children also implies the choice of a reliable outcome. This probably can be achieved, in addition to symptom score, with the evaluation of the rate of exacerbations, the use of bronchodilators and the dose of inhaled corticosteroids [48].

Other relevant knowledge gaps are the optimal age when to start AIT in children; the optimal duration of the treatment [49,50]; the optimal selection of patients to start an AIT course. Concerning the later aspect, there is so far no uniform direction, and recommendations differ among countries [51,52²²,53]. It is true that the molecular diagnostic approach would allow to refine the prescription of

AIT by defining better the sensitization profile [54], and this approach has been formally shown to change the prescription patterns [54–57]. The molecular or component resolved diagnosis is certainly one of the most promising fields for AIT in children (for review see 58[58]). Another important aspect, not fully defined, is the standardization of extracts and the use of named-patient products which are currently discouraged by regulatory authorities, but still largely used. In fact, only few products are accepted and marketed as formal drugs [59]. With the intent to abolish Named Patient Products, the European Parliament has recently recognized allergens as medicinal products, which need to be manufactured according to the procedures established for all drugs and to follow a registration dossier through all phases of clinical trials to get a marketing authorization [60,61].

Finally, the most important knowledge gap is the lack of biomarkers (either single or in panel) which can predict the response to AIT in each single individual. This will be the most relevant challenge for the future research in this field [8,62].

CONCLUSION

AIT rapidly evolved during the last 10 years. The use of more and better characterized and standardized extracts and the large trials produced important information. In particular, the efficacy of some AIT products in adult asthma was demonstrated. This renewed the interest in pediatric asthma, where less data are available. Trials and metaanalyses confirmed the overall safety and efficacy of AIT in asthmatic children, in particular for SLIT, although both trials and metaanalyses are largely heterogeneous. An important aspect is the recent confirmation of the preventive effect (reduction of the risk of asthma development) in a large study in grass-allergic children, which needs to be confirmed also for other allergens.

The interest in AIT ad pediatric asthma revealed and evidences some major knowledge gaps including the lack of well-designed large trials having asthma parameters as primary outcome; the optimal age when to start AIT; the optimal duration of the treatment; the refined identification of whose children to treat (also in the case of an expected preventive effect). The probably most important and urgent undefined aspect is the lack of biomarkers that could be predictive of the efficacy of AIT in each single individual. Thus, although a relevant amount of experimental work has been done with AIT in pediatric asthma, there is still room for improvement of the knowledge on the argument.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are 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. Global Initiative for the Management of Asthma, 2018. www.ginasthma.org (last accessed February 2019).
2. Oksel C, Custovic A. Development of allergic sensitization and its relevance to paediatric asthma. *Curr Opin Allergy Clin Immunol* 2018; 18:109–116.
- An interesting and up-to-date overview on the relationship between sensitization and its change over time and asthma.
3. Comberiati P, Di Cicco ME, D'Elios S, Peroni DG. How much asthma is atopic in children? *Front Pediatr* 2017; 5:122.
4. Schoos AM, Jelding-Dannemand E, Stokholm J, *et al.* Single and multiple time-point allergic sensitization during childhood and risk of asthma by age 13. *Pediatr Allergy Immunol* 2019; 30:716–723.
5. De Ferrari L, Chiappori A, Bagnasco D, *et al.* Molecular phenotyping and biomarker development: are we on our way towards targeted therapy for severe asthma? *Expert Rev Respir Med* 2016; 10:29–38.
6. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol* 2017; 140:1485–1498.
7. Satitsuksanoa P, van de Veen W, Akdis M. B-cell responses in allergen immunotherapy. *Curr Opin Allergy Clin Immunol* 2019; 19:632–639.
- The most up-to-date review on the role and functions of B cells in allergy and allergen immunotherapy.
8. Comberiati P, Marseglia GL, Barberi S, *et al.* Allergen-specific immunotherapy for respiratory allergy in children: unmet needs and future goals. *J Allergy Clin Immunol Pract* 2017; 5:946–950.
9. 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.
10. Roberts G, Hurley C, Turcanu V, Lack G. Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma. *J Allergy Clin Immunol* 2006; 117:263–268.
11. Alzakar RH, Alsamarai AM. Efficacy of immunotherapy for treatment of allergic asthma in children. *Allergy Asthma Proc* 2010; 31:324–330.
12. Bufe A, Eberle P, Franke-Beckmann E, *et al.* Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009; 123:167–173.
13. Bahçeciler NN, Işık U, Barlan IB, Başaran MM. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. *Pediatr Pulmonol* 2001; 32:49–55.
14. Niu CK, Chen WY, Huang JL, *et al.* Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multicenter, double-blind, randomized, and placebo-controlled study in Taiwan. *Respir Med* 2006; 100:1374–1383.
15. Lue KH, Lin YH, Sun HL, *et al.* Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. *Pediatr Allergy Immunol* 2006; 17:408–415.
16. Pham-Thi N, Scheinmann P, Fadel R, *et al.* Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. *Pediatr Allergy Immunol* 2007; 18:47–57.
17. de Bot CM, Moed H, Berger MY. Et Sublingual immunotherapy not effective in house dust mite-allergic children in primary care. *Pediatr Allergy Immunol* 2012; 23:150–158.
18. Stelmach I, Kaczmarek-Woźniak J, Majak P, *et al.* Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen. *Clin Exp Allergy* 2009; 39:401–408.
19. Yukselen A, Kendirli SG, Yilmaz M, *et al.* Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. *Int Arch Allergy Immunol* 2012; 157:288–298.

20. 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.
 21. 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; 128:808–811.
 22. Rice JL, Diette GB, Suarez-Cuervo C, *et al.* Allergen-specific immunotherapy in the treatment of pediatric asthma: a systematic review. *Pediatrics* 2018; 141. doi: 10.1542/peds.2017-3833.
- An extensive and up-to-date review of the clinical studies in pediatric asthma, with critical discussions.
23. Dhami S, Kakourou A, Asamoah F, *et al.* Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. *Allergy* 2017; 72:1825–1848.
 24. Liao W, Hu Q, Shen LL, *et al.* Sublingual immunotherapy for asthmatic children sensitized to house dust mite: a metaanalysis. *Medicine* 2015; 94:1–14.
 25. Richards JL, Stumpf JR. House dust mite sublingual immunotherapy for pediatric patients with allergic asthma. *Ann Pharmacother* 2018; 52:1019–1030.
 26. Rodriguez Del Rio P, Vidal C, Vidal C, *et al.* The European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a paediatric assessment. *Pediatr Allergy Immunol* 2017; 28:60–70.
- Probably the first European systematic survey on the safety of AIT in the pediatric age.
27. Passalacqua G, Nowak-Węgrzyn A, Canonica GW. Local side effects of sublingual and oral immunotherapy. *J Allergy Clin Immunol Pract* 2017; 5:13–21.
 28. Agostinis F, Tellarini L, Canonica GW, *et al.* Safety of sublingual immunotherapy with a monomeric allergoid in very young children. *Allergy* 2005; 60:133.
 29. Fiocchi A, Pajno G, La Grutta S, *et al.* Safety of sublingual-swallow immunotherapy in children aged 3 to 7 years. *Ann Allergy Asthma Immunol* 2005; 95:254–258.
 30. Arasi S, Passalacqua G, Caminiti L, *et al.* Efficacy and safety of sublingual immunotherapy in children. *Expert Rev Clin Immunol* 2016; 12:49–56.
 31. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children: a 14-year study. *Pediatrics* 1968; 42:793–802.
 32. Moller C, Dreborg S, Ferdousi HA, *et al.* Immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT study). *J Allergy Clin Immunol* 2002; 109:251–256.
 33. Novembre E, Galli E, Landi F, *et al.* Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004; 114:851–857.
 34. Marogna M, Tomassetti D, Bernasconi A, *et al.* Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008; 101:206–211.
 35. Jacobsen L, Niggemann B, Dreborg S, *et al.* Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; 62:943–948.
 36. Valovirta E, Petersen TH, Piotrowska T, *et al.* Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol* 2018; 141:529–538.
- A methodologically robust prospective clinical trial, formally demonstrating in more than 800 children the reduction of the risk of asthma development by grass allergen immunotherapy.
37. Zielen S, Devillier P, Heinrich J, *et al.* Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy* 2018; 73:165–177.
 38. Kristiansen M, Dhami S, Netuveli G, *et al.* Allergen immunotherapy for the prevention of allergy: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2017; 28:18–29.
 39. Di Bona D, Plaia A, Leto-Barone MS, *et al.* Efficacy of allergen immunotherapy in reducing the likelihood of developing new allergen sensitizations: a systematic review. *Allergy* 2017; 72:691–704.
 40. Halken S, Larenas-Linnemann D, Roberts G, *et al.* EAACI guidelines on allergen immunotherapy: prevention of allergy. *Pediatr Allergy Immunol* 2017; 28:728–745.
 41. Wahn U. Preventing new sensitization and asthma onset by allergen immunotherapy: the current evidence. *Curr Opin Allergy Clin Immunol* 2017; 17:443–446.
 42. Holt PG, Sly PD, Sampson HA, *et al.* Prophylactic use of sublingual allergen immunotherapy in high-risk children: a pilot study. *J Allergy Clin Immunol* 2013; 132:991–993.
 43. Zolkipli Z, Roberts G, Cornelius V, *et al.* Randomized controlled trial of primary prevention of atopy using house dust mite allergen oral immunotherapy in early childhood. *J Allergy Clin Immunol* 2015; 136:1541–1547.
 44. Asamoah F, Kakourou A, Dhami S, *et al.* Allergen immunotherapy for allergic asthma: a systematic overview of systematic reviews. *Clin Transl Allergy* 2017; 7:25.
 45. Dinakar C, Chipps BE. Clinical tools to assess asthma control in children. *Pediatrics* 2017; 139:e20163438.
 46. Larenas-Linnemann D, Luna-Pech JA. What you should not miss from the systematic reviews and meta-analyses on allergen-specific immunotherapy in 2017. *Curr Opin Allergy Clin Immunol* 2018; 18:168–176.
 47. 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; 8:2.
 48. Agache I, Lau S, Akdis CA, *et al.* EAACI guidelines on allergen immunotherapy: house dust mite-driven allergic asthma. *Allergy* 2019; 74:855–873.
 49. Scadding GW, Eifan AO, Lao-Araya M, *et al.* Effect of grass pollen immunotherapy on clinical and local immune response to nasal allergen challenge. *Allergy* 2015; 70:689–696.
 50. Arroabarren E, Tabar AI, Echechipia S, *et al.* Optimal duration of allergen immunotherapy in children with dust mite respiratory allergy. *Pediatr Allergy Immunol* 2015; 26:34–41.
 51. Pajno GB, Bernardini R, Peroni D, *et al.* Clinical practice recommendations for allergen-specific immunotherapy in children: the Italian consensus report. *Ital J Pediatr* 2017; 43:13.
 52. Tosca MA, Licari A, Olcese R, *et al.* Immunotherapy and asthma in children. *Front Pediatr* 2018; 6:231.
- Another updated, explicative and easy to read review on the argument of AIT in asthmatic children
53. Tortajada-Girbés M, Mesa Del Castillo M, Larramona H, *et al.* Decision-making for pediatric allergy immunotherapy for aeroallergens: a narrative review. *Eur J Pediatr* 2019; 178:1801–1812.
 54. 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.
 55. Melioli G, Savi E, Crivellaro MA, Passalacqua G. Potential of molecular based diagnostics and its impact on allergen immunotherapy. *Asthma Res Pract* 2016; 2:9.
 56. Martínez-Cañavate Burgos A, Torres-Borrego J, Molina Terán AB, *et al.* Molecular sensitization patterns and influence of molecular diagnosis in immunotherapy prescription in children sensitized to both grass and olive pollen. *Pediatr Allergy Immunol* 2018; 29:369–374.
 57. Stringari G, Tripodi S, Caffarelli C, *et al.* The effect of component-resolved diagnosis on specific immunotherapy prescription in children with hay fever. *J Allergy Clin Immunol* 2014; 134:75–81.
 58. Matricardi PM, Dramburg S, Potapova E, *et al.* Molecular diagnosis for allergen immunotherapy. *J Allergy Clin Immunol* 2019; 143:831–843.
- A comprehensive review, with critical appraisal on the role of molecular diagnosis in the prescription and choice of allergen immunotherapy.
59. Li JT, Bernstein DI, Calderon MA, *et al.* Sublingual grass and ragweed immunotherapy: clinical considerations: a PRACTALL consensus report. *J Allergy Clin Immunol* 2016; 137:369–376.
 60. European Medicines Agency. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. CHMP/EWP/18504/2006, European Medicines Agency. <http://emea.europa.eu> (last accessed November 20, 2008).
 61. Rose K, Kopp MV. Pediatric investigation plans for specific immunotherapy: questionable contributions to childhood health. *Pediatr Allergy Immunol* 2015; 26:695–701.
 62. Sindher SB, Long A, Acharya S, *et al.* The use of biomarkers to predict aeroallergen and food immunotherapy responses. *Clin Rev Allergy Immunol* 2018; 55:190–204.