

Accepted Manuscript

Guideline recommendations on the use of allergen immunotherapy in house dust mite allergy: time for a change?

Moisés A. Calderón, MD, PhD, Jean Bousquet, MD, G. Walter Canonica, MD, Lars-Olaf Cardell, MD, PhD, Dolores Hernandez Fernandez de Rojas, MD, PhD, Jörg Kleine-Tebbe, MD, Pascal Demoly, MD, PhD

PII: S0091-6749(17)30761-3

DOI: [10.1016/j.jaci.2017.01.049](https://doi.org/10.1016/j.jaci.2017.01.049)

Reference: YMAI 12808

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 26 July 2016

Revised Date: 15 December 2016

Accepted Date: 27 January 2017

Please cite this article as: Calderón MA, Bousquet J, Canonica GW, Cardell L-O, Fernandez de Rojas DH, Kleine-Tebbe J, Demoly P, Guideline recommendations on the use of allergen immunotherapy in house dust mite allergy: time for a change?, *Journal of Allergy and Clinical Immunology* (2017), doi: 10.1016/j.jaci.2017.01.049.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Guideline recommendations on the use of allergen immunotherapy in house dust mite allergy: time for a change?

Moisés A. Calderón^a MD, PhD, Jean Bousquet^b MD, G. Walter Canonica^c MD, Lars-Olaf Cardell^d MD, PhD, Dolores Hernandez Fernandez de Rojas^e MD, PhD Jörg Kleine-Tebbe^f MD, Pascal Demoly^g MD, PhD

Affiliations:

^a Section of Allergy and Clinical Immunology, Imperial College London - NHLI, Royal Brompton Hospital, London, UK. m.calderon@imperial.ac.uk

^b Dept of Respiratory Diseases, University Hospital, Hôpital Arnaud de Villeneuve, Montpellier, France Inserm, CESP Centre for Research in Epidemiology and Population Health, U1018, Respiratory and Environmental Epidemiology Team, Villejuif, France. jean.bousquet@orange.fr

^c Personalized Medicine Clinic Asthma & Allergy, Humanitas Clinical and Research Center, Dept. of Biomedical Science, Humanitas University-Rozzano, Milano, Italy; and DIMI-Medical School, University of Genoa, Genoa, Italy. canonica@unige.it

^d Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden. Lars-olaf.cardell@ki.se

^e Department of Allergy, IIS Hospital La Fe, Av. Fernando Abril Martorell 106, 46026 Valencia, Spain. hernandez_dol@gva.es

^f Allergy and Asthma Center Westend, Outpatient Clinic Hanf, Ackermann & Kleine-Tebbe, Berlin, Germany. kleine-tebbe@allergie-experten.de

^g Département de Pneumologie et Addictologie, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, France; and Sorbonne Universités, UPMC Paris 06. pascal.demoly@inserm.fr

Correspondence to:

Prof. Pascal Demoly
Département de Pneumologie et Addictologie,
Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, France
Tel: +33 467 336 107
Fax: +33 467 042 708
Email: pascal.demoly@inserm.fr

Keywords: house dust mite; allergy; allergic asthma; allergic rhinitis; treatment guidelines

Word Count: 2,889

List of abbreviations

AA	Allergic asthma
AIT	Allergen immunotherapy
AR	Allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BTS	British Thoracic Society
EMA	European Medicines Agency
FAS	Full analysis set
FAS	Full analysis set
GINA	Global Initiative for Asthma
HDM	House dust mite
ICS	Inhaled corticosteroid
MCID	Minimal clinically important difference
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
TCRS	Total combined rhinitis score
WAO	World Allergy Organization

Abstract:

Guidelines on the treatment of asthma, allergic rhinitis (AR) and allergen immunotherapy (AIT) lack recommendations for house dust mite (HDM) allergy. An expert panel reviewed current guidelines in the light of new data, to assess whether guidelines could be improved. Most guidelines and key position papers did not provide specific recommendations on treatment of allergic asthma (AA) caused by HDM allergy, although some included AIT as a treatment option for AA in general. Around half of the guidelines stated that AIT with HDM extract was an effective treatment for AR, with several indicating sublingual immunotherapy (SLIT) as an option. This heterogeneity is caused by quality issues affecting studies of AIT with perennial allergens in AA and AR, including use of different diagnosis and severity criteria, lack of consistent scoring or grading systems for primary and safety outcomes, and lack of consensus on treatment parameters. There is a need for well-designed clinical trials to serve as a basis for guideline recommendations. Although results from recent studies strengthen the evidence base for the efficacy and safety of SLIT in HDM AA and AR, their impact on

64 subsequent guideline updates will depend on the methodology and evidence
65 model used by each guideline.

ACCEPTED MANUSCRIPT

INTRODUCTION

Despite house dust mite (HDM) allergy being a major cause of respiratory allergic disease most often implicated as a trigger for asthma and perennial allergic rhinitis (AR), specific treatment guidance for AR and allergic asthma (AA) caused by HDM are to date not well defined. The choice of allergen-specific treatment for patients suffering from HDM allergy is not facilitated by recommendations of current national and international allergen immunotherapy (AIT) guidelines. Most guidelines focus on treatment of AR or AA, regardless of the type and number of sensitising allergens, rather than on the cause, assuming that all respiratory allergies are the same. As approximately 50% of patients with HDM AR also have AA, support to clinicians is needed for integrated management. Although guidelines written by allergists widely support the use of AIT in AR, its use in patients with AA or AR with AA is contentious, as demonstrated in the current review. Some guidelines consider that level of efficacy, adverse effects and resource expenditure associated with AIT completely offset the clinical benefit, while others perceive it as cumbersome and costly and recommend its use only as last-line treatment¹⁻³. In addition, the choice of sublingual *versus* subcutaneous administration is ultimately determined by patient and doctor preferences.

An expert panel was convened to review the recommendations of the current treatment guidelines on the use of AIT and sublingual immunotherapy (SLIT) in AA and AR caused by HDM allergens, identified by searching the literature. Based on this, and on the panel's clinical expertise, the authors propose how the guidelines could be improved for general use and ask if it is time to re-evaluate the available evidence, in the light of recent new data in both HDM-induced AA and AR reporting favorable safety and efficacy profiles for SLIT tablets in adults^{4,5}.

GUIDELINE RECOMMENDATIONS ON THE USE OF ALLERGEN IMMUNOTHERAPY IN HOUSE DUST MITE ALLERGY

Specific guideline recommendations for allergic rhinitis

All reviewed guidelines on treatment of AR included AIT as a possible treatment for selected patients with AR (**Table 1**). Some specified that AIT with HDM extracts was effective in both adults and children⁶⁻⁸. Several guidelines included SLIT as an option for treatment of AR in adults⁶ or adults and children⁹⁻¹¹, and some specified that SLIT with HDM allergens was effective and safe in AR^{3,7,12}. The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines gave a conditional recommendation for both SCIT and SLIT in AR caused by HDM allergy, owing to the moderate quality of the available evidence in adults and the low quality evidence in children⁶.

Specific guideline recommendations for allergic asthma

Several asthma guidelines and key position papers include AIT as a treatment option for AA (**Table 2**). Some advise that subcutaneous immunotherapy (SCIT)¹³⁻¹⁵ with HDM extract is an effective treatment for AA caused by HDM allergy, and one specified that SLIT has an effect on inflammation and bronchial hyper-reactivity in asthmatic children sensitized to HDM¹⁵; however, most did not provide specific information on treatment of HDM AA.

We did not find a consensus among the current guidelines on treatment of AA by AIT. Of the guidelines reviewed, most included AIT as a treatment option for persistent asthma in selected adults^{7,10,13,16} and children^{7,10,13-17}, and in patients with AR and AA⁶ in addition to pharmacotherapy. In some cases, allergen avoidance measures and asthma education are recommended when there is clear evidence of a relationship between symptoms and exposure to an allergen. The use of AIT for AA was more widely supported in children than in adults, which appears to be based on data showing that the role of allergy in asthma is greater in children¹⁴ and not on the number of AIT trials in this population group.

The most recent asthma guidelines from the British Thoracic Society (BTS) state that SCIT or SLIT are not recommended for the treatment of asthma in children or adults², and the Global Initiative for Asthma (GINA) 2016 guideline states that the efficacy of AIT in asthma is limited¹.

Evidence base for guideline recommendations

Most of the guidelines reviewed were evidence-based. Some made recommendations based largely on published systematic reviews and meta-analyses², whereas others, such as ARIA, performed meta-analyses where possible and evaluated the quality of the underlying evidence. Some guidelines, but not all, used evidence models such as GRADE^{6,18}, SIGN^{2,9,19}, Shekelle^{7,9} or The American Academy of Pediatrics classification scheme²⁰.

The quality of evidence for a clinically beneficial effect of AIT in AR was higher than for AA. Factors that lowered the quality of the body of evidence supporting the use of AIT in AA included difficulty quantifying the effect of AIT due to heterogeneity in study design and reporting of outcomes^{2,3}, small clinical benefits^{1,17}, small benefits at the expense of significant adverse effects², and the cost of prolonged treatment¹.

Guidelines on AR cited findings of meta-analyses on both SCIT and SLIT and well-conducted, randomized controlled trials showing reduced symptom and medication scores, and possible modification of the disease course. The ARIA guideline suggestion for the use of SLIT in adults, but not children, with HDM AR was based on moderate quality evidence and placed a relatively high value on avoiding adverse effects of SLIT in children and reducing resource expenditure, and a relatively low value on a possible small reduction in nasal symptoms⁶.

The most comprehensive analysis of the efficacy of SLIT for HDM AR and AA, to date, is the GA2LEN meta-analysis²¹. Although the authors found beneficial effects of SLIT with HDM extract in AR and AA, they noted a significant clinical and methodological heterogeneity between the studies. Only the 2014 BTS asthma guideline² cited this most recent meta-analysis.

Specific quality issues affecting allergen immunotherapy trials with perennial allergens in allergic asthma and allergic rhinitis

Although the AA endotype has been well defined^{22,23}, this definition encompasses a wide range of disease aetiology, severity and treatment responses. Approximately half of adult asthmatics are allergic to common and relevant airborne allergens²⁴. Depending on the study inclusion criteria, this leads to significant heterogeneity in study populations. Moreover, there are differences

among allergens concerning important factors such as the degree and type of exposure (e.g., seasonal, perennial, occupational), enzymatic content, etc.

Importantly, there are no universally accepted endpoints for studies of AIT in AA. The recent revision of the European Medicines Agency (EMA) Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Asthma, includes considerations for AIT development in asthma, suggesting lung function, composite scores, number of exacerbations or reduced need for controller medication as primary endpoints²⁵. Clinical relevance in the primary efficacy should be specified. Likewise, there is currently no validation of the proposed standardization of clinical outcomes used in AIT trials in AR^{26,27}, and few include follow-up assessments of long-term efficacy. In addition, there is variability in the potency and composition of the allergen extracts used in different studies, which stems from differences in source material and standardization between manufacturers.

The onset and duration of exposure to perennial allergens may vary significantly over the annual period²⁶. HDM AIT studies start at different times of the year and have differing durations²⁷, therefore allergen exposure during a study is unknown, as few measure levels of HDM allergens or employ provocation tests^{26,27}. Even when provocation testing is used, there is no standardization between studies²⁶. Moreover, for a large phase III trial, provocation tests are likely to be impossible to implement.

A recent evidence-based analysis of SLIT for HDM AR and AA highlighted the lack of consensus on basic treatment parameters (e.g., dose and duration) between studies²⁸. A comprehensive review of AIT for the treatment of AR and/or asthma by the US Agency for Healthcare Research and Quality found moderate clinical effects of SLIT in children with mild to moderate persistent AA due to HDM allergy, but not with AR, and also noted a great deal of heterogeneity in the literature reviewed²⁹, including:

- Varying criteria for diagnosing asthma and assessing asthma severity and control
- The lack of consistent scoring or grading systems for reporting primary outcomes

- Deficiencies in statistical reporting
- The lack of a consistent reporting and grading system for the adverse outcomes, which made it impossible to pool safety data across studies
- Lack of information due to publication bias

Moreover, as the quality of reporting of most AIT trials does not consistently meet Consolidated Standards of Reporting Trials (CONSORT) criteria for the reporting of randomized trials³⁰, it is often difficult to assess how closely available guidance was followed (see **Table 3** for EMA guidance for trials in perennial AR and or AA). However, these trials were performed and published before these guidelines were launched; recent and future trials should no longer suffer these drawbacks.

The 2014 update of the World Allergy Organization (WAO) position paper on SLIT also found that the conclusions of the available meta-analyses on SLIT are limited by heterogeneity of allergen doses, duration of treatment, and patient selection between studies, and noted that the quality of systematic reviews and meta-analyses of SLIT could be improved by considering heterogeneity and increasing transparency¹². A recent evaluation of meta-analyses of SLIT for AA and AR cast doubts on the robustness of previous meta-analyses, due to inconsistencies in study design and the variable quality of studies³¹. Meta-analyses pool data from heterogeneous studies, for example SLIT studies with different allergens, which may lead to the conclusion that all related AIT products are effective. The result is that many untested products for AIT are available on the market as named patient products. Guidelines, however, are more likely to value conventional product development through phases I–III, rather than class development. Until now, there has been a lack of robust data on the efficacy and safety of products for AIT for AR and AA caused by HDM allergy through conventional product development.

These concerns about the quality of the evidence base have led many to call for better designed rigorous, long-term, placebo-controlled randomized clinical trials^{21,27-29,32} using standardized products. Moreover, the WAO recently called for a move towards product-based evaluation, indicating that the heterogeneous quality of evidence for individual AIT products makes overall conclusions on routes of delivery or ‘class effects’ unjustified³³.

EVIDENCE NEEDED TO SUPPORT AIT TREATMENT RECOMMENDATIONS FOR HDM ALLERGY IS EMERGING

The recently published outcomes of large, randomized, double-blind, placebo-controlled AIT field studies in HDM AA (MITRA: MT-04, ALK, EudraCT 2010-018621-19⁵) and HDM AR in Europe (MERIT: MT-06, ALK EudraCT 2011-002277-38⁴ and VO57.07, Stallergenes, EudraCT 2011-002277-38³⁴) the US (MK-8237-001, Merck³⁵) and Japan (Torii Pharmaceuticals³⁶) show that three different HDM SLIT-tablet formulations are effective and safe for the treatment of HDM respiratory allergy.

In a large trial by Bergmann et al., 300IR and 500IR HDM sublingual tablets significantly reduced mean Average Adjusted Symptom Scores in adults with AR by -17.9% ($p=0.0150$) and -20.2% ($p=0.0066$), respectively compared with placebo, with efficacy maintained during a treatment-free follow-up year³⁴. Treatment was well tolerated with no difference in the safety profile between active treatment groups. The most commonly reported SLIT emergent AEs were oral pruritus, throat irritation, and mouth oedema, which were generally mild to moderate in intensity.

In the study by Virchow et al., up to 18 months of treatment with two doses (6 SQ-HDM and 12 SQ-HDM) of the SQ[®] HDM SLIT-tablet in patients with HDM AA significantly reduced the risk of moderate or severe asthma exacerbation compared to placebo during an inhaled corticosteroid (ICS) reduction period (risk reduction 31% and 34%, hazard ratio [HR] (full analysis set, FAS) 0.69 and 0.66, $p=0.03$ and 0.02 respectively). Treatment was well tolerated, and there were no safety findings of clinical concern even in a group of patients being uncontrolled according to GINA classification at randomization (while still fulfilling the inclusion criteria on lung function of $FEV_1 \geq 70\%$ and no severe exacerbations within 3 months)⁵. Thus, among adults with HDM allergy-related asthma not well controlled by ICS, HDM SLIT-tablet significantly prolonged the time to the first asthma exacerbation during ICS reduction. This is to our knowledge the first study specifically showing an effect with AIT on asthma exacerbations in this subset of patients.

Demoly et al. reported that in adults with moderate to severe persistent HDM AR, 6 SQ-HDM and 12 SQ-HDM significantly reduced the total combined rhinitis score (TCRS) at all time points from 14 weeks to approximately 1 year of treatment (absolute reduction in TCRS *versus* placebo [pre-specified minimal clinically important difference (MCID)] 1.18 [p=0.002] and 1.22 [p=0.001] for 6 SQ-HDM and 12 SQ-HDM, respectively). In relative terms based on adjusted mean and median reduction in TCRS for the 12 SQ-HDM dose this corresponds to 18-22%⁴. The safety profile of both doses was appropriate for home administration after the first dose was taken under medical supervision; the most frequently reported adverse events (AEs) were oral pruritus, throat irritation and mouth oedema that abated within minutes to hours⁴.

Key questions that can be raised for any clinical trial touch on the clinical relevance of the outcomes, and on whether enrolled subjects reflect those encountered in everyday clinical practice. This depends on the choice of primary and secondary endpoints, and on study limitations (e.g. patient inclusion criteria, severity of asthma, degree of asthma control). In the study summarised above by Virchow *et al.*⁵, the choice of a primary endpoint based on exacerbations during ICS reduction is a novel approach in AIT trials. As mentioned above, there are no universally accepted endpoints for AIT trials in AA. A MCID has been proposed for some AR clinical endpoints³⁷, but were calculated based on studies that were not AIT studies of patients with HDM-associated AR, and that did not use Average Adjusted Symptom Scores. As such, there are to date no data defining a MCID for the average adjusted symptom score in these patients, therefore this needs to be specified and argued for by each drug developer.

COULD DATA FROM NEW WELL-DESIGNED, HIGH QUALITY STUDIES PROVIDE SUFFICIENT EVIDENCE FOR A RECOMMENDATION IN GUIDELINES?

Well-designed and -conducted trials are a key step in obtaining regulatory approval for new treatments; however, trial populations do not always closely represent the type of patients encountered in routine care³⁸. Over half of asthma patients do not achieve control with their current pharmacotherapy, and even

well-controlled asthmatics experience on average 6 worsenings per year (defined as occasions when asthma symptoms were bothersome or hindering)³⁹; similarly, not all patients with AR are fully controlled by pharmacotherapy (up to 13% are uncontrolled in one study⁴⁰). In the MT-04 study by Virchow et al., patients with AA were not well-controlled based on Asthma Control Questionnaire scores of 1–1.5 at randomization, and 28% of subjects were uncontrolled according to GINA criteria as mentioned above⁴¹. In MT-06 by Demoly et al., patients' AR at inclusion was not well controlled, as they had a high level of symptoms and impact on their quality-of-life despite use of pharmacotherapy. The choice of study population for these studies is therefore in line with the high unmet need in patients who do not have well-controlled disease.

The design of these recent studies complies with EMA guidance on the clinical development of products for AIT⁴² (**Table 3**) and the design and primary endpoint of MT-04 are in line with the latest EMA guidance on AIT products intended to modify the immunological mechanism underlying AA²⁵. The efficacy and safety data meet the demands for robust evidence from well-conducted, randomized clinical trials called for in guidelines, reviews and meta-analyses. The ARIA guideline noted that new data from rigorously designed and executed randomized trials of SLIT in children would likely have an important impact on recommendations for the use of SLIT in children with AR without AA and for patients with AR and AA⁶.

The impact of these new results on guideline recommendations remains to be seen, and will depend on the methodology and evidence model used by the different guidelines. However, adoption may take several years; publication of 3 studies on tiotropium in 2010, 2011, 2012 led to addition to GINA only in 2015, and 2 studies of mepolizumab published in 2009 and 2012 led to its appearance in GINA in 2016¹. Nevertheless, these new outcomes discussed above strengthen the evidence base for the efficacy and safety of HDM SLIT-tablet in AA and/or AR, and are an important step towards the possible inclusion of this treatment option in future guideline updates.

CONCLUSIONS

Even though AIT was first described over a century ago, and up to 50% of patients with HDM AR also have AA, specific treatment recommendations for AIT in AA and/or AR caused by HDM allergy remain unclear. This has largely been due to the relatively low quality of the body of evidence supporting the use of AIT in this context, which has complicated quantification of AIT's effect. Reasons include heterogeneity in study design and reporting of outcomes, a lack of universally accepted endpoints and MCID estimates, and differences in the efficacy of allergen preparations in different trials.

Recent data in HDM-induced AA with the SQ-HDM SLIT tablet and in HDM AR with two different HDM SLIT products reporting favorable safety and efficacy profiles in adults, come from studies that conform to the current guidance, and mark a step towards a product-based evaluation. These data, together with the outcomes of further well-designed trials powered to show clinically relevant superiority in comparison to conventional pharmacotherapy with topical corticosteroids and antihistamines, will serve as a basis for future guideline recommendations.

Conflict of interest

Moisés A. Calderón has received honoraria for lecturing from ALK, Allergopharma, Hal Allergy, Merck, and Stallergenes, and for participating in advisory boards with ALK, Hal Allergy, and Stallergenes. Jean Bousquet has received honoraria for serving on the Scientific and advisory boards of Almirall, Meda, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach; given lectures during meetings for Almirall, AstraZeneca, Chiesi, GSK, Meda, Menarini, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach; and served on the board of directors of Stallergènes. G. Walter Canonica has received research grants as well as lecture or advisory board fees from: ALK, Allergy Therapeutics, Anallergo, Circassia, Hal Allergy, Lofarma, and Stallergenes. Lars-Olaf Cardell is a consultant for ALK-Abello and MEDA. Dolores Hernández Fernandez de Rojas acted as a consultant and/or speaker for ALK-Abello, Allergopharma, Allergy Therapeutics, Astra, Bial, Chiesi, Hal Allergy, Leti, Novartis, Shire, Stallergenes and ThermoFisherScientific in 2010-2015. Jörg

Kleine-Tebbe is a consultant for ALK-Abelló, Bencard, Circassia, LETI, Novartis, MERCK USA and a speaker for Allergopharma, AstraZeneca, Boehringer Ingelheim, HAL Allergy, Lofarma, Roxall, Stallergenes, ThermoFisherScientific, and received industry-sponsored grants from Allergopharma, ALK-Abelló, Circassia, HAL Allergy. Pascal Demoly is a consultant and a speaker for ALK-Abello, Chiesi, Circassia, DBV, Stallergenes, ThermoFisherScientific and a speaker for AstraZeneca, Allergopharma, GlaxoSmithKline, Menarini and Merck in 2010-2015.

Financial support: Financial support for the development of this paper was provided by ALK-Abelló.

Acknowledgements

We would like to thank all participants for their contributions to the discussion, and Prof. Eric Bateman for his valuable comments on the manuscript. We also thank Dr. Ron Hogg of Copentown UK for assistance in preparing the manuscript.

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2016. Available from: <http://www.ginasthma.org>.
2. SIGN 141. British guideline on the management of asthma. A national clinical guideline. British Thoracic Society. October 2014. Available from: <https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014/>.
3. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases. Allergo Journal International 2014;23:282-319.
4. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol 2016;137:444–51.
5. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial. JAMA 2016;315:1715-25.
6. Brożek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126:466-76.
7. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127:S1-55.

8. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;122:S1-84.
9. Scadding G, Durham S, Mirakian R, Jones N, Leech S, Farooque S, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy* 2008;38:19-42.
10. Zuberbier T, Bachert C, Bousquet P, Passalacqua G, Canonica G, Merk H, et al. GA2LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy* 2010;65:1525-30.
11. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg* 2015;152:S1-S43.
12. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J* 2014;7:6.
13. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol* 2007;120:S94.
14. Papadopoulos N, Arakawa H, Carlsen KH, Custovic A, Gern J, Lemanske R, et al. International consensus on (ICON) pediatric asthma. *Allergy* 2012;67:976-97.
15. Motala C, Green RJ, Manjra A, Potter P, Zar HJ. Guideline for the management of chronic asthma in children-2009 update. *SAMJ: South African Medical Journal* 2009;99:898-912.
16. Joint Task Force on Practice Parameters AAoAA, Immunology, American College of Allergy A, Immunology, Joint Council of Allergy A, Immunology. Attaining optimal asthma control: a practice parameter. *J Allergy Clin Immunol* 2005;116:S3-11.
17. Bacharier L, Boner A, Carlsen KH, Eigenmann P, Frischer T, Götz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008;63:5-34.
18. Sveum R, Bergstrom J, Brottman G, Hanson M, Heiman M, Johns K, et al. Institute for Clinical Systems Improvement. Diagnosis and Management of Asthma. Updated July 2012. Available from: https://www.icsi.org/_asset/rsjvnd/Asthma.pdf.
19. Nicholson P, Cullinan P, Taylor AN, Burge P, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med* 2005;62:290-9.
20. American Academy of Pediatrics. Classifying recommendations for clinical practice guidelines. *Pediatrics* 2004;114:874-7.
21. 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;64:1570-9.
22. Corren J. Asthma phenotypes and endotypes: an evolving paradigm for classification. *Discov Med* 2013;15:243-9.
23. Lötvall J, Akdis CA, Bacharier LB, Björner L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355-60.
24. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999;54:268-72.
25. Committee for Medicinal Products for Human Use (CHMP). Draft note for guidance on clinical investigation of medicinal products for treatment of asthma. CHMP/EWP/2922/01Rev.1 01 May 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/12/WC500198877.pdf.
26. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, et al. Recommendations for the standardization of clinical outcomes used in allergen

- immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. *Allergy* 2014;69:854-67.
27. Nelson HS. Update on house dust mite immunotherapy: are more studies needed? *Curr Opin Allergy Clin Immunol* 2014.
 28. Calderon MA, Casale TB, Nelson HS, Demoly P. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. *J Allergy Clin Immunol* 2013;132:1322-36.
 29. Lin SY, Erekosima N, Suarez-Cuervo C, Ramanathan M, Kim JM, Ward D, et al. Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review. Comparative Effectiveness Review No. 111. AHRQ Publication No. 13-EHC061-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2013.
<http://www.effectivehealthcare.ahrq.gov/reports/final.cfm>.
 30. Bousquet PJ, Calderon MA, Demoly P, Larenas D, Passalacqua G, Bachert C, et al. The Consolidated Standards of Reporting Trials (CONSORT) Statement applied to allergen-specific immunotherapy with inhalant allergens: a Global Allergy and Asthma European Network (GA(2)LEN) article. *J Allergy Clin Immunol* 2011;127:49-56.
 31. Nieto A, Mazon A, Pamies R, Bruno L, Navarro M, Montanes A. Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. *J Allergy Clin Immunol* 2009;124:157-61.
 32. Eifan AO, Calderon MA, Durham SR. Allergen immunotherapy for house dust mite: clinical efficacy and immunological mechanisms in allergic rhinitis and asthma. *Expert Opin Biol Ther* 2013;13:1543-56.
 33. Bachert C, Larche M, Bonini S, Canonica GW, Kündig T, Larenas-Linnemann D, et al. Allergen immunotherapy on the way to product-based evaluation - a WAO statement. *World Allergy Organ J* 2015;8:29.
 34. Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol* 2014;133:1608-14 e6.
 35. Nolte H, Bernstein DI, Nelson HS, Kleine-Tebbe J, Sussman GL, Seitzberg D, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2016;138:1631-8.
 36. Okubo K, Masuyama K, Imai T, Okamiya K, Stage BS, Seitzberg D, et al. Efficacy and Safety of the SQ House Dust Mite SLIT-tablet in Japanese Adults and Adolescents with House Dust Mite-induced Allergic Rhinitis. *J Allergy Clin Immunol* 2016.
 37. Barnes ML, Vaidyanathan S, Williamson PA, Lipworth BJ. The minimal clinically important difference in allergic rhinitis. *Clin Exp Allergy* 2010;40:242-50.
 38. Costa DJ, Amouyal M, Lambert P, Ryan D, Schünemann HJ, Daures JP, et al. How representative are clinical study patients with allergic rhinitis in primary care? *J Allergy Clin Immunol* 2011;127:920-6.e1.
 39. Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med* 2006;6:13.
 40. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007;62 Suppl 85:17-25.
 41. Backer V, Virchow JC, Villesen HH, Fejerskov PA, Riis B, de Blay F. HDM sublingual AIT tablet is well-tolerated and effective in partly and uncontrolled allergic asthma. Presented at the Annual Congress of the European Respiratory Society, 6th-10th September, 2014, in Munich, Germany.
 42. Committee for Medicinal Products for Human Use (CHMP) and Efficacy Working Party (EWP): Guideline on the clinical development of products for specific

- 500 immunotherapy for the treatment of allergic diseases;
501 EMEA/CHMP/EWP/18504/2006.
502 43. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing
503 guidelines. *BMJ* 1999;318:593-6.
504 44. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International
505 consensus on allergy immunotherapy. *J Allergy Clin Immunol* 2015;136:556-68.
506 45. Jadad AR, Moher M, Browman GP, Booker L, Sigouin C, Fuentes M, et al.
507 Systematic reviews and meta-analyses on treatment of asthma: critical evaluation.
508 *BMJ* 2000;320:537-40.
509

Table 1. Summary of guideline recommendations on the use of AIT in allergic rhinitis

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
Evidence-based				
ARIA 2010 revision	“Should subcutaneous specific immunotherapy be used for treatment of AR in adults without concomitant asthma?” Recommendation. We suggest subcutaneous allergen specific immunotherapy in adults with seasonal (conditional recommendation / moderate-quality evidence) and persistent AR caused by house dust mites (conditional recommendation / low-quality evidence). Underlying values and preferences. This recommendation places a relatively high value on relieving the symptoms of AR and a relatively low value on avoiding adverse effects and on resource expenditure. Should sublingual specific immunotherapy be used for treatment of AR in adults without	“Should subcutaneous specific immunotherapy be used for treatment of AR in children without concomitant asthma?” Recommendation. In children with AR, we suggest subcutaneous specific immunotherapy (conditional recommendation / low-quality evidence). Underlying values and preferences. This recommendation places a relatively high value on probable reduction in symptoms of AR and the potential prevention of the development of asthma and a relatively low value on avoiding adverse effects in children and resource expenditure. Should subcutaneous allergen-specific immunotherapy be used in patients with AR and asthma? Recommendation. In patients with AR and asthma, we suggest subcutaneous specific immunotherapy for treatment of asthma (conditional recommendation / moderate-quality evidence).	Guideline (GRADE)	6

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
	concomitant asthma? Recommendation. We suggest sublingual allergen specific immunotherapy in adults with rhinitis caused by pollen (conditional recommendation / moderate-quality evidence) or house dust mites (conditional recommendation / low-quality evidence). Underlying values and preferences. This recommendation places a relatively high value on alleviating the symptoms of rhinitis and a relatively low value on avoiding adverse effects and resource expenditure. Remarks. Local adverse effects are relatively frequent (35%). An alternative choice may be equally reasonable if patients' values or preferences differ from those described. Should sublingual specific immunotherapy be used for treatment of AR in children without concomitant asthma?	Underlying values and preferences. This recommendation places a relatively high value on reducing the symptoms of asthma and a relatively low value on avoiding adverse effects and limiting the cost of subcutaneous specific immunotherapy. In patients who are more averse to the side effects of subcutaneous specific immunotherapy, an alternative choice may be equally reasonable. Remarks. Subcutaneous specific immunotherapy may also be used in patients with asthma and concomitant AR for treatment of rhinitis. Resource limitations will have stronger implications for the implementation of this recommendation. Should sublingual allergen-specific immunotherapy be used in patients with AR and asthma? Recommendation. In patients with AR and asthma, we suggest sublingual specific immunotherapy for treatment of asthma (conditional recommendation / low-quality evidence). Underlying values and preferences. This recommendation places a relatively high value on possible reduction of asthma symptoms and		

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
	Recommendation. In children with AR caused by house dust mites, we suggest that clinicians do not administer sublingual immunotherapy outside rigorously designed clinical trials (conditional recommendation / very low-quality evidence)."	a relatively low value on avoiding adverse effects and limiting the cost of sublingual specific immunotherapy. SLIT may also be used in patients with asthma and concomitant AR for treatment of rhinitis. Resource limitations will have stronger implications for the implementation of this recommendation."		
BSACI guidelines for the management of allergic and non-allergic rhinitis Scadding et al. 2008	-	"Immunotherapy is highly effective in selected cases. Subcutaneous AIT, sublingual/nasal AIT, seasonal allergic rhinitis, perennial allergic rhinitis. All recommended GRADE A."	Guideline (Shekelle ⁴³ , SIGN)	9
Allergen immunotherapy: A practice parameter	"Immunotherapy is effective for pollen, animal allergens, dust mite, mold/fungi, and Hymenoptera hypersensitivity. Therefore immunotherapy should be considered as part of the management	"Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or asthma Allergen immunotherapy should be considered for patients who have demonstrable evidence	Practice parameter (Shekelle ⁴³)	7

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
third update Cox et al. 2010	program in patients who have symptoms related to exposure to these allergens, as supported by the presence of specific IgE antibodies (Strength A recommendation)."	of specific IgE antibodies to clinically relevant allergens. Immunotherapy is effective for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity. Therefore immunotherapy merits consideration in patients with these disorders as a possible treatment option (Strength A recommendation). Allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens (Strength D recommendation). Immunotherapy should not be given to patients with negative test results for specific IgE antibodies or those with positive test results for specific IgE antibodies that do not correlate with suspected triggers, clinical symptoms, or exposure. This means that the presence of specific IgE antibodies alone does not necessarily indicate clinical sensitivity."		
Clinical Practice Guideline: Allergic	-	"Clinicians should offer, or refer to a clinician who can offer, immunotherapy (sublingual or subcutaneous) for patients with AR who have inadequate response to symptoms with	Guideline (American Academy of	11

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
Rhinitis Seidman et al. 2015		pharmacologic therapy with or without environmental controls. Recommendation based on RCTs and systematic reviews, with a preponderance of benefit over harm.”	Pediatrics classification scheme ²⁰⁾	
The diagnosis and management of rhinitis: An updated practice parameter Wallace et al. 2008	-	“Allergen immunotherapy is effective for the treatment of allergic rhinitis (Strength A recommendation). Allergen immunotherapy should be considered for patients with allergic rhinitis who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens, and its use depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications (Strength A recommendation). Allergen immunotherapy may prevent the development of new allergen sensitizations and reduce the risk for the future development of asthma in patients with allergic rhinitis (Strength B recommendation). Effective management of allergic rhinitis may require combinations of medications,	Practice parameter (proprietary evidence model?)	8

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
		aggressive avoidance measures, management of coexisting conditions, and/or allergen immunotherapy."		
Non-evidence-based				
GA2LEN/EA ACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma 2010	-	"AIT can be of benefit in all patients with proven IgE sensitization to inhalant allergens with clinical significance. Consider AIT in patients with moderate/severe intermittent or persistent allergic rhinitis, in particular in those who do not respond sufficiently to current pharmacological treatment. Independent studies show that both forms of immunotherapy (SLIT, SCIT) are effective in allergic rhinitis, if optimally used."	Guideline (no evidence model used)	10
Sublingual immunotherapy: World Allergy Organization position paper 2013	"House dust mite SLIT is effective in children with asthma and allergic rhinitis. Grass or house dust mite SLIT can be used for allergic rhinitis in children with asthma.	"SLIT may be considered as initial treatment. Failure of pharmacological treatment is not an essential prerequisite for the use of SLIT. SLIT may be proposed as an early treatment in the therapeutic strategy for respiratory allergy. SLIT may be particularly indicated in the	Position paper (no evidence model used)	12

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
update Canonica et al. 2014	SLIT must not be suggested as monotherapy for treating asthma.”	following patients: •Patients whose allergy is uncontrolled with optimal pharmacotherapy (that is, those with severe chronic upper airway disease). •Patients in whom pharmacotherapy induces undesirable side effects. •Patients who refuse injections. •Patients who do not want to be on constant or long-term pharmacotherapy.”		
Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases Pfaar et al. 2014	“In case of a confirmed house dust mite allergy, AIT is an option if measures for mite avoidance (mite allergen-proof mattress encasings, washable blankets and further measures to reduce house dust mite allergens) are insufficient and no improvement in symptoms is observed after 3 months of mite avoidance. SCIT or SLIT with pollen or mite allergens can be performed in patients with allergic rhinoconjunctivitis using allergen extracts that have been proven to be effective in at least one	-	Guideline (no evidence model used)	3

Guideline	<i>Specific recommendations for HDM allergy</i>	<i>General recommendations for allergen immunotherapy</i>	<i>Type of publication (evidence model)</i>	<i>Reference</i>
	DBPC study.”			
ICON allergy immunotherapy Jutel et al. 2015	-	“AIT achieves substantial clinical results in patients with AR by improving nasal and ocular symptoms and reducing medication need, improving quality of life, preventing progression of AR to asthma, and reducing new sensitizations.”	Consensus document (no evidence model used)	44

Table 2. Summary of guideline recommendations on the use of AIT in allergic asthma

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
Evidence-based				
GINA 2016	-	“The efficacy of allergen immunotherapy in asthma is limited (Evidence level A: evidence from endpoints of well-designed RCTs or meta-analyses that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants).” “Allergen-specific immunotherapy may be an option if allergy plays a prominent role, e.g. asthma with allergic rhinoconjunctivitis. There are currently two approaches: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Overall, most studies have been in mild asthma, and few studies have compared immunotherapy with pharmacological therapy, or used standardized outcomes such as exacerbations.” “Compared to pharmacological and avoidance options, potential benefits of allergen immunotherapy (SCIT or SLIT) must be	Strategy document (GINA method)	1

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
		weighed against the risk of adverse effects and the inconvenience and cost of the prolonged course of therapy, including for SCIT the minimum half-hour wait required after each injection (Evidence level D: panel consensus - category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above listed criteria)."		
BTS 2014	-	"The use of SCIT is not recommended for the treatment of asthma in adults or children. SLIT is not licensed for use in the treatment of asthma. SLIT cannot currently be recommended for the treatment of asthma in routine practice in children or adults."	Guideline (SIGN)	2
NAEPP 2007	"Immunotherapy for steps 2–4 in the stepwise approach for managing asthma in youths ≥ 12 years of age and	"Consider SCIT for patients who have persistent asthma when there is clear evidence of a relationship between symptoms and	Guideline (Jadad et	13

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
	adults is based on Evidence B for HDM, animal danders, and pollens.”	exposure to an allergen to which the patient is sensitive.”	al. ⁴⁵⁾	
Allergen immunotherapy: A practice parameter third update Cox et al. 2010	“Immunotherapy is effective for pollen, animal allergens, dust mite, mold/fungi, and hymenoptera hypersensitivity. Therefore immunotherapy should be considered as part of the management program in patients who have symptoms related to exposure to these allergens, as supported by the presence of specific IgE antibodies (Strength A recommendation).”	“Indications for allergen immunotherapy in patients with allergic rhinitis, allergic conjunctivitis, or asthma • Allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. • Immunotherapy is effective for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity. Therefore immunotherapy merits consideration in patients with these disorders as a possible treatment option (Strength A recommendation). • Allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens (Strength D recommendation). • Immunotherapy should not be given to patients with negative test results for specific	Practice parameter (Shekelle ⁴³⁾	7

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
		IgE antibodies or those with positive test results for specific IgE antibodies that do not correlate with suspected triggers, clinical symptoms, or exposure. This means that the presence of specific IgE antibodies alone does not necessarily indicate clinical sensitivity."		
Attaining optimal asthma control: A practice parameter 2005	-	"The physician should be attentive to the possibility of overtreating and undertreating asthma and to the cost and adverse effects of medication. This should include consideration of allergen immunotherapy that has been shown to be effective and safe in properly selected patients with asthma."	Practice parameter (proprietary evidence model?)	16
Non-evidence-based				
Guideline for the management of chronic asthma in children – 2009 update	"Immunotherapy is also effective for children when used sublingually (Evidence B). Sublingual immunotherapy is___effective in paediatric patients with allergic rhinitis (Evidence A) and has an effect on inflammatory parameters and bronchial hyper-reactivity in asthmatic children	"The Expert Panel of the USA's Department of Health and Human Services recommends that allergen immunotherapy be considered for patients who have persistent asthma if there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive (Evidence B). A meta-analysis of 75 randomised placebo-	Guideline ("methodology utilized in current guideline documents")	15

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
Motala et al.	sensitised to house dust mites (Evidence B). Although both subcutaneous and sublingual immunotherapy are effective in asthmatic children (monosensitive to HDM or pollen), the latter is safer (confirmed in post-marketing studies (Evidence B). Based on the above evidence, sublingual immunotherapy could be used as adjunctive treatment to pharmacotherapy in children >5 years old with rhinitis and mild to moderate asthma (FEV₁ >80%), to enhance asthma control and, in some cases, effect a cure.”	controlled studies has confirmed the effectiveness of subcutaneous immunotherapy in asthma with a significant reduction in asthma symptoms and medication and with improvement in bronchial reactivity (Evidence A).”		
Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report 2008	-	“Based on a meta-analysis of 75 studies, immunotherapy can be recommended for individuals with asthma who have proven sensitization to allergens. Efficacy of immunotherapy will depend on the quality of the extracts used.”	Consensus report (no evidence model used “report employed a consensus	17

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
			approach based on available published literature (until June 2007) and on best current clinical practice")	
ICON paediatric asthma 2013	"SCIT is effective in allergic asthma, when standardised allergen extracts of HDM, animal dander, grass, weed, or tree pollen are administered."	"AIT should be considered for children whose symptoms are clearly linked to a relevant allergen. SLIT is painless, child-friendly and has an excellent safety profile. Most guidelines recommend additional evidence of efficacy before recommending it; however efficacy has been confirmed in recent meta-analyses."	Guideline (no evidence model used)	14
GA2LEN/EA ACI pocket guide for allergen-specific	-	"AIT can be of benefit in all patients with proven IgE sensitization to inhalant allergens with clinical significance. AIT can be used in mild allergic asthma proven	Pocket guide (no evidence	10

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
immunotherapy for allergic rhinitis and asthma 2010		to be caused by a well-defined allergen, if asthma is under control and FEV ₁ is above 70%."	model used)	
Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases Pfaar et al. 2014	"In case of a confirmed house dust mite allergy, AIT is an option if measures for mite avoidance (mite allergen-proof mattress encasings, washable blankets and further measures to reduce house dust mite allergens) are insufficient and no improvement in symptoms is observed after 3 months of mite avoidance. Compared with allergic rhinoconjunctivitis, there are only a limited number of studies on the efficacy of SLIT in patients with allergic bronchial asthma. At present, clinical trials are underway for the indication in asthma due to house dust mite allergy, some of the results of which have already been published, whilst others are still awaited."	-	Guideline (no evidence model used)	3

Guideline	Specific recommendations for HDM allergy	General recommendations for allergen immunotherapy	Type of publication (evidence model)	Reference
ICON allergy immunotherapy Jutel et al. 2015	-	“AIT cannot be presently recommended as single therapy when asthma is the sole manifestation of respiratory allergy. SLIT and SCIT can be used in patients with mild and moderate asthma associated with allergic rhinoconjunctivitis provided that asthma is controlled by pharmacotherapy. A measurable clinical benefit on asthma symptoms and a steroid-sparing effect is expected.”	Consensus document (no evidence model used)	44

Table 3. EMA guidelines on ‘The Clinical Development of Products For Specific Immunotherapy for the Treatment of Allergic Diseases’⁴²

- History of AR/rhinoconjunctivitis or AA should cover at least 1 year for perennial allergy, and diagnosis should follow current international guidelines, such as GINA and ARIA.
- To avoid bias of results of clinical studies, trials with perennial allergens should not include patients with other clinically relevant perennial allergies. For patients with clinically relevant seasonal allergies the control periods for collection of efficacy data of perennial allergens must not overlap with the season for the seasonal allergens.
- It is important to minimize variations in the levels of perennial indoor allergens. If sanitation measures are planned they should be finished before the start of a clinical trial; baseline symptoms should be measured after sanitation. No further sanitation measures should be performed during the trial. It is recommended to document the exposure level for the individual patient especially for the evaluation periods to evaluate the variation of indoor allergens.
- For perennial allergies, significant results on efficacy of specific immunotherapy in AR/rhinoconjunctivitis may be obtained after the evaluation of one or two control periods.
- In studies of AR, the use of rescue medication has an impact on symptom severity. Therefore, the primary endpoint has to reflect both, symptom severity and used rescue medication.
- Endpoints should be evaluated several times during the treatment for perennial allergies and at least at the end of follow-up.