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POSITION PAPER

Standardization of clinical outcomes used in allergen immunotherapy in allergic asthma: An EAACI position paper

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Abbreviations: AC, allergen challenge; ACQ, asthma control questionnaire; AEC, allergen exposure chamber; AIT, allergen immunotherapy; AQLQ, Asthma Quality of Life Questionnaire; AR, allergic rhinitis; ATS, American Thoracic Society; DBPC, double blinded placebo-controlled; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; ERS, European Respiratory Society; FOT, forced oscillation technique; GINA, Global Initiative for Asthma; HDM, house dust mite; ICS, inhaled corticosteroid; IOS, impulse oscillometry system; IT IG, immunotherapy interest group; MCID, minimal clinically important difference; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PFT, pulmonary function test; PROMs, patient-reported outcomes measures; QoL, quality of life; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; TF, task force.

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Abstract

Introduction: In allergic asthma patients, one of the more common phenotypes might benefit from allergen immunotherapy (AIT) as add-on intervention to pharmacological treatment. AIT is a treatment with disease-modifying modalities, the evidence for efficacy is based on controlled clinical trials following standardized endpoint measures. However, so far there is a lack of a consensus for asthma endpoints in AIT trials. The aim of a task force (TF) of the European Academy of Allergy and Clinical Immunology (EAACI) is evaluating several outcome measures for AIT in allergic asthma.

Methods: The following domains of outcome measures in asthmatic patients have been evaluated for this position paper (PP): (i) exacerbation rate, (ii) lung function, (iii) ICS withdrawal, (iv) symptoms and rescue medication use, (v) questionnaires (PROMS), (vi) bronchial/nasal provocation, (vii) allergen exposure chambers (AEC) and (viii) biomarkers.

Results: Exacerbation rate can be used as a reliable objective primary outcome; however, there is limited evidence due to different definitions of exacerbation. The time after ICS withdrawal to first exacerbation is considered a primary outcome measure. Besides, the advantages and disadvantages and clinical implications of further domains of asthma endpoints in AIT trials are elaborated in this PP.

Conclusion: This EAACI-PP aims to highlight important aspects of current asthma measures by critically evaluating their applicability for controlled trials of AIT.

KEYWORDS
allergen immunotherapy, allergy, asthma, clinical outcomes, subcutaneous, sublingual

1 | INTRODUCTION

Asthma is a heterogenic disease characterized by chronic inflammation of the lower airways resulting in a reversable airflow limitation. It is affecting approximately 350 million patients globally, with a projected increase to 400 million within the next 30 years.[1–3] The pathogenesis is complex, resulting in different phenotypes,[3–5] with T2-driven inflammatory pathway in the majority of the cases. Allergic asthma is one of the more common phenotypes with allergic rhinitis (AR), atopic dermatitis and/or food allergy as frequent comorbidities.[6–11]

Assessing the role of a relevant allergy in asthma pathophysiology is an important diagnostic step in the disease work-up[12] because patients might benefit from allergen immunotherapy (AIT) as add-on intervention to pharmacological treatment. Remarkably, no diagnostic tools or algorithms have been developed to discriminate between allergic asthma and asthma with allergic sensitization only. The diagnosis of allergic asthma relies on the combination of allergic sensitization together with a detailed clinical history showing typical symptoms of asthma induced by (relevant) allergen exposure. According to the European Academy of Allergy and Clinical Immunology (EAACI) guidelines[13] a diagnosis of house dust mite (HDM)-driven allergic asthma includes (i) evidence of allergic sensitization to HDM and (ii) history confirmation of HDM exposure as the main driver of asthma symptoms and control. In individual cases, sequential assessments of symptoms over a 1-year period might be needed to confirm the diagnosis of allergic asthma.[13] In specialized settings nasal or bronchial allergen provocation is an option for cases with unclear history.[13,14]

Allergen immunotherapy (AIT) is an effective treatment for AR with or without asthma.[15–27] Approved administration routes are administration via a subcutaneous route (SCIT) or sublingually (SLIT) either as drops or tablets.[28,29] AIT has disease modifying properties and confers long-term clinical benefit after cessation of treatment.[20,21,27,30–35] In a meta-analysis published in 2017, AIT was found to improve asthma symptoms and reduced the need for rescue medications.[36] The Global Initiative for Asthma (GINA) update of 2017 included HDM SLIT tablets as a recommendation for patients with HDM-allergic asthma who remain inadequately controlled with pharmacotherapy.[3] This recommendation remained unchanged in the consecutive updates, with GINA 2021 adding SLIT tablets to traditional controller options for adolescents and adults with HDM-driven asthma associated with allergic rhinitis and inadequately controlled on low-medium dose ICS.[3] Also, the EAACI guidelines recommend AIT in patients with HDM-driven allergic asthma.[13,37] In 2022, GINA planned to review the evidence for AIT for asthma in both SCIT and SLIT with subsequent update of recommendations if needed. These changes in international recommendations implicate

a potential upgrading in AIT use for personalized management of allergic asthma including new clinical studies.[3]

As AR is widely considered as a treatable trait in allergic asthma, treatment and reducing symptoms of all traits is advised.[38] In that perspective, AIT can be seen as a treatment optimising a trait in an individual patient. It is still, however unclear how to interpret the outcomes of the AIT treatment, especially in relation to asthma control.

While recommendations for the standardization of clinical outcomes used in AIT trials for AR have been defined,[15] to date, there is no consensus on how to quantify clinical outcomes of AIT on asthma. According to the European Medicines Agency (EMA) 'Guideline on the clinical investigation of medicinal products for the treatment of asthma' published in 2015,[39] AIT is started as add-on therapy which has to be considered in the evaluation of the primary endpoint (e.g. evaluation in the context of a stepwise reduction in controller medication). Lung function, composite scores, number of exacerbations or reduced need for controller medication are considered as primary endpoints. Regardless of the choice of the primary efficacy parameter, the applicant should provide a definition of a clinically meaningful effect in the primary efficacy endpoint and the basis for choosing this value.[39] This is consistent with ICH-E9 guidance (1999) on 'Statistical principles on clinical trials' which emphasizes that primary parameters should 'be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial'.[40]

Asthma control, defined by GINA, as well as by the American Thoracic Society (ATS)/European Respiratory Society (ERS), should be assessed in two domains; current symptom control and future risk of adverse outcomes, exacerbations and loss of lung function.[3,41,42] Current control can be assessed by patient reported outcome measures (PROMs) such as symptom scores and validated questionnaires such as Asthma Control Questionnaire (ACQ)-5. For future risk of adverse outcomes, the risk for exacerbations is of major importance. This is, however, linked to several risk factors including an exacerbation in the previous year, poor adherence, or incorrect inhaler technique.[3,41] Asthma outcome measures quantifying asthma control in AIT trials might have different relevance compared to those reported in real life by patients with allergic asthma.[3,41,43,44]

For proper reviewing of the effectiveness of AIT in patients with allergic asthma, as well as planning future trials for the development of novel products for AIT, a consensus on quantification of clinical outcome of AIT on asthma control is crucial.[45] In clinical practice such a consented position can be used in patient selection, identification of responders and criteria to continue or stop treatment.

The EAACI Immunotherapy Interest Group (IT IG) has set up a task force (TF) on 'Standardisation of clinical outcomes used in allergen immunotherapy in asthma'.

The aim was to (i) define primary and secondary clinical endpoints which can be recommended for future clinical trials of AIT in allergic asthma (ii) identify unmet needs and (iii) advise on their applicability in current daily practice.

BOX 1 Domains of outcome measures

Domain

1. Exacerbation rate
2. Lung function
3. ICS withdrawal
4. Symptoms and rescue medication use
5. Questionnaires (PROMS)
6. Bronchial/nasal provocation
7. Allergen exposure chambers (AEC)
8. Biomarkers

2 | METHODOLOGY

2.1 | Taskforce

After the initial meeting in Lisbon, June 2019, the primary objectives of the TF were confirmed: (i) collect and review clinical outcome data on the effects of AIT for asthma, (ii) consent on clinical outcome measures for clinical research and daily practice, (iii) identify unmet needs for current and future clinical outcome measures.

In total, eight domains of possible outcome measures were identified (Box 1), subgroups of the TF reviewed and drafted the specific domains including advantages and disadvantages of the outcomes, while unmet needs were identified and recommendations have been proposed.

Following a consensus meeting, the TF committee was responsible for drafting the EAACI TF position paper, which was circulated to all TF members for critical review.

2.2 | Review of literature and level of evidence

Literature was retrieved from PubMed using the following MESH terms: immunotherapy, allergic asthma, desensitization, outcomes, allergy. Additional articles were identified by cross checking the references of relevant papers. The following search limits were applied: only studies published in English language, published after 1995 and available on PubMed. Only studies with a placebo or untreated allergic control group were included. No limitation was set on the type of products for AIT.

3 | RESULTS

3.1 | Exacerbation rate

GINA 2022 recommends HDM SLIT as one add-on therapy option to decrease the number of asthma exacerbations in patients with HDM-driven asthma, highlighting a focus on this outcome.[3] GINA also recommends the assessment of asthma control which includes

both symptoms and future risk of adverse outcomes. Hence the number of exacerbations as a primary endpoint is highly relevant. However, although previous clinical trials of AIT in asthma evaluate symptoms/medication use, so far very few have used exacerbations as primary outcome, with variable definitions.[13] The lack of a uniformly used definition of the severity of exacerbations (severe/moderate/mild) limits its applicability as an outcome. For severe and moderate exacerbations, the accepted used definitions refer to the joint ATS/ERS consensus statement, 'severe exacerbations urge for immediate action … to prevent … hospitalization or death'.[41] For moderate exacerbations a temporary intensification of treatment is needed to prevent a severe exacerbation. A definition of a mild exacerbation was considered not justifiable.[41] Overall, definitions include variable items, that is, most commonly the use of short-acting beta-agonists (SABAs) and systemic corticosteroids, unscheduled doctor's visits and hospitalization.[41,46,47]

In a 2015 Cochrane review on SLIT in asthma,[48] the authors noted that there was a lack of data on important clinical outcomes such as exacerbations. More recently, Dhami et al.[36] undertook a comprehensive assessment of AIT in asthma, where six trials[49–54] used an exacerbation endpoint, defined variably. Overall, in these six studies, limited evidence for the reduction in exacerbations was found with the respective SLIT-products, no effect on the reduction in exacerbations was found with the respective SCIT-product.[36] Additionally, as noted in the recent EAACI AIT guidelines,[13] there are other issues when using exacerbations as AIT clinical outcomes, including their infrequent rate in the target population, their different response to specific interventions,[55] and the definition of the endpoint itself for example number of exacerbations versus number of patients with at least one exacerbation versus time to first exacerbation.

3.1.1 | Advantages

- Exacerbation rate is an outcome both used by GINA and by EAACI Guidelines. For the add-on SLIT HDM tablets in HDM-driven asthma this outcome has been confirmed in a clinical trial.[54]
- Exacerbations can be used for a reliable objective primary outcome; especially for severe and, to a lesser extent, moderate exacerbations.
- Exacerbation rate is considered as a clinically relevant outcome.

3.1.2 | Disadvantages

- Limited evidence due to different definitions of exacerbation endpoints.

3.1.3 | Unmet need

- Uniformly use of accepted ATS/ERS definition of an endpoint of exacerbations and severity applicable in clinical studies, for example, the number of exacerbations, time to first exacerbation, patients with at least one exacerbation.

3.1.4 | Clinical applicability

- Number of exacerbations is the most robust outcome to measure future risk.

3.2 | Lung function

Pulmonary function tests (PFT's) are commonly adopted for the diagnosis and treatment monitoring of asthma and other respiratory diseases. For asthma management, GINA 2021 recommends assessing symptoms as well as progressive loss of lung function and/or fixed airflow limitation.

GINA 2023 also highlights the relevance of lung function testing for identifying patients eligible for SLIT administration as an add-on treatment only in inadequately controlled HDM-allergic patients with FEV1 > 70% of predicted.

Spirometry is an objective and reproducible test which can be easily performed during clinical assessment and which can be valuable for monitoring of the response to treatment. A recent meta-analysis by Dhami and coworkers included 25 studies, of variable quality, assessing the efficacy of AIT on several lung function parameters.[36] Collected evidence showed a positive effect on indirect small airways endpoints (i.e. FEF 25%–75%), but no clear improvements in FEV1 or PEF.

Clinical trials so far conducted assessing lung function as primary or secondary outcomes for AIT are substantially heterogeneous and therefore prevent pooling data from different studies and coming to clear conclusions. In most studies adults or adolescents are addressed. In the meta-analysis by Abramson et al.,[56] 20 out of the 88 included studies provided results regarding lung function with overall findings resulting inconclusive when compared to placebo.

Therefore, lung function measures when used as outcomes in AIT studies of asthma should be standardized to enable a conclusive assessment of the impact of this treatment on this parameter. Direct measures of small airways function in a standardized manner like Impulse oscillometry system (IOS) are recommend for that matter.

3.2.1 | Advantages

- PFT's are recommended by GINA 2021 for assessing asthma control and future exacerbation risk.
- Indirect evidence of improvement on small airways function achieved with add-on AIT.

3.2.2 | Disadvantages

- No clear-cut effect of AIT on FEV1, data are substantially heterogeneous, therefore not applicable.

- In asthma patients lung function can vary on a daily basis.
- Available only in a specialized setting (secondary/third care).

3.2.3 | Unmet needs

- Implement direct measures of small airways function in a standardized manner: for example, IOS, forced oscillation technique (FOT), multiple breath washout, etc. as well as effect on (the prevention of) FEV1 (decline over time), in line with other non-bronchodilator controllers.

3.2.4 | Clinical applicability

- Spirometry is often available in clinical practice, especially in specialized settings.

3.3 | ICS decrease and/or withdrawal

The treatment of allergic asthma, both in adults and children, relies on the use of inhaled corticosteroids (ICS) combined with bronchodilators in order to achieve and maintain asthma control. AIT may add to the anti-inflammatory activity of ICS to improve asthma control and decrease the risk of exacerbations. Hence, ICS decrease and/or withdrawal protocols under AIT with asthma exacerbations and/or asthma control assessments as primary endpoints seem a logical approach in evaluating the effect of AIT in allergic asthma in clinical trials.

In a randomized double blinded placebo controlled (DBPC) AIT study, Virchow et al.[54] used the time to the first moderate or severe asthma exacerbation as primary endpoint during a 6-month ICS reduction/withdrawal period. This study showed that the addition of HDM SLIT tablets extended the time period to first moderate or severe asthma exacerbation during ICS reduction of 9%–10% at 6 months. This improvement was primarily based on the AIT effect on moderate exacerbations. A second study with a similar design could not reproduce the results in the primary outcome, the post hoc analysis for salbutamol responders, however, was positive.[57] In another HDM-SLIT tablet trial, the primary endpoint was the lowest ICS dose needed to maintain adequate asthma control.[58] The difference in the decrease of ICS dose between active and placebo at the end of the trial assessment period was in favour of the treatment group. A post hoc analysis showed that subjects with a daily ICS dose of 400–800 μg and partly controlled asthma at randomization experienced a significantly higher treatment benefit for the highest dose in terms of ICS dose reduction and quality of life (QoL) as compared to the rest of the trial population. Another randomized controlled trial (RCT) with HDM-SLIT drops evaluated as the primary efficacy outcome asthma control after a well-defined ICS dose step-down.[59] Although asthma control was achieved by a slightly greater proportion of patients in the AIT treated group compared to the placebo group, the primary efficacy criterion was not met because of a higher-than-expected asthma control rate in the whole study population.[59] In view of the wide range of ICS daily doses used by the patients, a post hoc analysis by asthma severity was performed. Unsurprisingly, this revealed significant clinical benefits in actively treated subjects with moderate, persistent asthma at baseline with better achievement of asthma control and QoL, and a greater mean reduction in ICS use. In an open RCT in children with asthma, SCIT with a mite allergoid added to pharmacotherapy allowed a reduction in the ICS dose needed to maintain disease control compared with pharmacotherapy alone.[60] In a randomized DBPC trial of HDM SCIT the minimal ICS dose for asthma control was evaluated. A statistically significant decrease in ICS dose was only observed in the highest dose SCIT group.[61]

3.3.1 | Advantages

- ICS withdrawal is a useful endpoint evaluating the effect of AIT in allergic asthma in clinical trials.
- ICS decrease under AIT is in alignment with all asthma guidelines recommending to reduce medication (ICS) once asthma control is achieved.
- ICS decrease is an endpoint is of clinical relevance; both decrease of medications, lowering risks for side effects.

3.3.2 | Disadvantages

- The effect on future risk of exacerbations is however unknown.
- Assessing ICS use can be difficult with the intermittent ICS treatment in fixed combination with fast-acting beta-agonist, as currently recommended by GINA for the control of mild asthma.

3.3.3 | Unmet needs

- A guidance for clinical practice to safely reduce ICS should be developed.
- The lowest minimal acceptable dose of ICS achieving the balance between safeguarding asthma control and future risk and the risk of adverse events should be validated prospectively for different age groups and degrees of asthma severity.

3.3.4 | Clinical applicability

- ICS reduction has a good acceptance and should be promoted as a main goal of adding AIT to asthma controller medication in individual patients with allergy-driven asthma.

3.4 | Symptoms and rescue medication use

Because both decreased symptoms and medication use can be used as surrogates for asthma control,[41] standardising an endpoint including these two components is not a straightforward process. SCITs efficacy in reducing asthma symptoms and rescue medication use has been already reported in a 2010 Cochrane review.[56] The meta-analysis by Dhami et al.[36] provided considerable evidence that administration of AIT to patients with allergic asthma can improve medication scores. However, the authors warned that their findings need to be interpreted with caution given that most trials were 'at high or unclear Risk of Bias' in relation to this outcome; although subgroup analysis confirmed the beneficial effect for the respective SCIT-products used in the analyzed studies, it was questionable for the respective SLIT-products in the included studies. The Cochrane meta-analysis from 2010[56] confirmed that SCIT can significantly reduce medication requirements. Unfortunately, there was heterogeneity seen there too which may be partly due to the different scoring systems used.[56] Therefore better-designed studies using validated clinical outcomes[13] are needed, including symptoms and medication use, standardization is obviously required. Abramson[56] observed that medication needs reported as categories showed a significant homogeneity as compared to medication scores, possibly translating into a more clinically useful outcome. Better standardization of outcomes in clinical settings in line with clinical guidelines (e.g. GINA), is not straightforward, because asthma outcomes recommended by health authorities might not be completely comparable to those reported by patients in real life.[13,41] Moreover, for symptoms and medication use as a combined outcome score a clinically relevant threshold expressed as minimal clinically important difference (MCID) has not been determined yet.

3.4.1 | Advantages

- Data on the decrease in rescue medication scores in asthma after AIT are relatively consistent.
- Data are easy to gain (short recall period for patients/caretaker).

3.4.2 | Disadvantage

- Different definitions used in symptoms and rescue medications scores.

3.4.3 | Unmet need

- Standardization and validation of symptoms and medications scores should be correlated with asthma control.

3.4.4 | Clinical applicability

- Pending its standardization, symptoms and medication score can be valuable tools both in clinical trials and for daily practice for monitoring patients with asthma receiving AIT on top of controller medication.

3.5 | Questionnaires (Patient-Reported Outcome Measures [PROMS])

Questionnaires for Health-related Quality of life (QoL) evaluation and questionnaires assessing asthma control form an essential part of the medical evaluation to assess the impact of a given disease on a patient. PROMs can be captured by standardized/validated questionnaires which are easy to use tools to collect data and serve as endpoints in both clinical trials and daily practice.[62] Asthma Control Questionnaire (ACQ)-5, Asthma Control Test (ACT) and Asthma Quality of Life Questionnaire (AQLQ) and Paediatric Asthma Quality of Life Questionnaire (PAQLQ), evaluate disease control and functional status, as well as physical, occupational, emotional and social aspects in patients with asthma.[63,64] The visual analogue scale (VAS) is a psychometric test widely used to measure the perception of symptom severity and disease control in patients with allergic rhinitis.[65] Furthermore, the Control of Allergic Rhinitis and Asthma Test (CARAT) is the first questionnaire to concomitantly assess the degree of control of both asthma and rhinitis, by addressing clinical issues such as upper and lower airway symptoms, sleep interference, physical activity limitation and the need to increase medication dose.[66]

Asthma control and QoL questionnaires have been adopted in several studies testing the safety and efficacy of both SCIT and SLIT in asthmatic patients with allergic asthma. In most published RCTs, questionnaires were only considered secondary outcomes.[36,67]

Questionnaires can be effectively used in AIT studies, due to their simplicity, which translates into reproducibility and high patient acceptance. Additionally, they assess social and psychological factors, including the ability to undertake the normal daily activities, as well as the exposure to psychological stress factors which may have considerable impact on treatment response. They also represent one of the most affordable strategies for gathering quantitative and easy-to-analyse data. Importantly, questionnaires also represent a major instrument among PROMs to take into consideration the patient's preferences and feedback, favouring a participatory and personalized medicine approach. For these questionnaires, the minimal clinical important difference (MCID) has been defined, allowing to assess the clinical relevance of differences between AIT and placebo treatment. Thus, they deserve high consideration for characterising patients' features and interpreting study findings.

However, it should be taken into consideration that questionnaire results might be susceptible to recall bias and personal interpretation. Considering that individual patients may have different understanding of single or multiple questions, results might be skewed by subjective approach. Furthermore, the current lack of a single questionnaire to comprehensively address all relevant aspects of asthma and allergy in relation to AIT administration, requires the adoption and administration of different tests.

3.5.1 | Advantages

- Patient-reported outcomes measures can be used to assess a patient perspective on disease control for the evaluation/monitoring of therapies.
- Patient-reported outcomes measures can assess AR symptoms in allergic asthmatics and may reflect on safe exposure and improvement of symptoms not always directly related to asthma.
- Patient-reported outcomes measures questionnaires are validated and extensively used in both research settings and clinical practice.

3.5.2 | Disadvantages

- In most studies PROMs questionnaires have been considered as secondary outcomes as they are not included as primary endpoint parameters in EMA guidelines. Furthermore, they may be hampered by recall bias and subjective factors that cannot be controlled (personality type, religious and cultural beliefs, etc.).

3.5.3 | Unmet needs

- Validation of questionnaires that addresses asthma control in relation to AIT.
- Real-time data collection via validated health applications (Apps).

3.5.4 | Clinical applicability

- ACQ-5, ACT, AQLQ and PACLQ are well-established questionnaires in asthma management.
- CARAT addresses concomitantly asthma and rhinitis control.

3.6 | Bronchial/nasal allergen provocation

Allergen challenge (AC) is a valuable tool which is capable of inducing airway inflammation by triggering the T2-pathway resulting in the recruitment and activation of effector cells. For many decades, ACs have been used in studies to assess the effectiveness of (targeted) pharmacotherapies as well as AIT in allergic airway disease, including asthma and allergic rhinitis in both adults and children. The most commonly applied airway ACs for this purpose comprise nasal allergen challenge[68–72] and inhaled allergen challenge.[68,73–79] Less frequently used allergen challenges comprise the conjunctival provocation test[80] and repeated low-dose allergen challenge.[14,81,82]

Allergen challenges mimic the acute and in some models also the more chronic features of allergic airway disease in a controlled manner, linking clinical and pathophysiological characteristics to the underlying mechanisms and consequently allowing to study the effect of targeted interventions on these features, as well as their interrelationships.[73,79,82,83] In the context of AIT, ACs also have the advantage of assessing the target of the intervention, that is, allergen-driven inflammatory pathways. Application of an allergen challenge as an efficacy-evaluation tool in AIT studies may help to shorten the overall study duration in contrast to, for example, seasonal exposure which usually extends over at least two seasons.

As with all disease models, the major drawback of ACs is their 'laboratory' nature in which standardized allergen extracts are being administered in compositions and doses under controlled circumstances. Therefore an AC may not fully reflect the everyday reality where other triggers such as air pollution can also be relevant. Furthermore, ACs are complicated by the strict subject inclusion (especially in asthmatic patients) and continuation criteria, the need to avoid potential interference of intercurrent exposure to other allergens in multi-sensitized subjects, the demanding and lengthy nature of the procedure, the extensive safety and monitoring demands as well as the specific requirements. In addition, the reproducibility and validity of several read-outs of the ACs, for example, airway sampling techniques and biomarkers, is also determined by the input/effort of the participating subjects (e.g. sputum induction), variability and dilutions of the biomarkers (e.g. eosinophils in nasal lavage and/or sputum and exhaled biomarkers in exhaled breath condensate), experienced research staff and well-equipped facilities.[71–73,79]

In experienced hands, standardized allergen challenge tests have been shown to yield an excellent intra-subject reproducibility which makes them extremely suitable for cross-over studies with pharmacological interventions allowing to detect a meaningful difference in several key outcome measures in a limited number of subjects.[72,73,79,84] Safety precautions required by the specific challenges need to be taken into account—depending on the allergen challenge protocol and study population.[72,73,79,85] The latter is very relevant for bronchial allergen challenge models which should be performed in specialized centers only.

3.6.1 | Advantages

- Allergen challenge is a validated disease model allowing to study interrelationship between allergen-induced inflammatory responses and clinical and pathophysiological features in allergic airway disease. Good within-subject reproducibility.

- Help to predict clinical response to therapy.
- Enable assessment of symptoms specifically to provoking allergen with a focus on improving asthma and rhinitis on exposure, thus demonstrating that asthmatics can be safely exposed to provoking allergens without necessarily affecting overall control.

3.6.2 | Disadvantages

- Complex and lengthy procedure needing an experienced research staff and well-equipped facilities, not always available in clinical setting. This is particularly important for bronchial challenge tests.
- Limited availability of standardized test allergens for nasal and bronchial provocation test.
- Laboratory models: topical defined allergen administration differs from natural exposure.
- Not yet accepted by the competent authorities as outcome parameters for the primary endpoint of pivotal (Phase III) clinical trials, as hybrid studies are still missing to show correlation between symptom relief under AIT in field exposure versus provocation in chamber exposure (see also domain vii).

3.6.3 | Unmet needs

- Standardization of challenge protocols and clinical validation of challenge models.

3.6.4 | Clinical applicability

- Due to the complexity and demanding nature of the procedure as well as potential safety issues applicability in a clinical setting is limited, especially for bronchial ACs.

3.7 | Allergen exposure chamber (AEC)

Allergen exposure chambers have been developed worldwide aiming to standardize and control surrounding climate parameters such as temperature and humidity and also to challenge allergic patients with a specified amount of allergens to ensure a reproducible methodological setting.[83] However, so far an extrapolation from clinical effects of interventions demonstrated in an AEC to the situation under natural allergen exposure is very limited and further (hybrid) trials are needed for a better technical and clinical validation of the different AEC facilities worldwide.[83,86,87] EAACI has recently reported on the technical details of different AEC facilities worldwide aimed to promote harmonization and comparability across facilities.[88] Multiple clinical endpoints can be measured in AECs, both subjective and objective.[83] The former encompass nasal, conjunctival and bronchial symptoms, whereas the latter include nasal or bronchial functional tests and biosamplings.[83]

Using AEC, asthma symptoms have been used as secondary endpoint in one and in one single-centre RCT on long-term effects of AIT with sublingual HDM in patients with allergic rhinitis with/without allergic asthma.[89,90] Patients with uncontrolled/partly controlled or severe asthma were excluded from the trial. A dose-dependent trend for efficacy on asthma symptoms during standardized exposure has been demonstrated. However, no statistical analyses were performed for asthma symptoms in this trial. Safety during AEC procedures must be guaranteed especially in asthmatic patients. Protocols have defined a threshold of more than 20% decrease in FEV1 or more than 25% decrease in PEF compared to pre-challenge baseline values at baseline and after AIT treatment of 16 and 24 weeks.

3.7.1 | Advantages

- Reproducible procedure (temperature, humidity, allergen exposure) excluding further contamination (allergens, toxins).
- Real-time measurements of symptoms and objective parameters.
- Enable assessment of symptoms specific for provoking allergen with a focus on treatment effects with regard to improving asthma and rhinitis on allergen exposure.

3.7.2 | Disadvantages

- Specialized facilities needed (fixed, but mobile chambers could be an alternative).
- Early phase asthmatic reactions with a risk of late phase asthmatic reactions.
- Extrapolation to natural exposure unknown. Therefore not yet accepted by the competent authorities as outcome parameters for the primary endpoint of pivotal phase III clinical trials.

3.7.3 | Unmet needs

- Clinical validation.
- Standardization of safety criteria especially in asthmatic patients, including stopping-rules.

3.7.4 | Clinical applicability

- Not applicable in clinical practice because of complex and costly procedure.

3.8 | Biomarkers

Identifying biomarkers capable of predicting treatment efficacy in allergic asthma is an area of intense investigation. Biomarkers for AIT efficacy can facilitate the identification of treatment

responders and patients at risk of disease relapse who may require booster treatment to maintain immune tolerance.[91,92] However, no prognostic and predictive biomarker of AIT efficacy in allergic asthma patients with the potential to follow-up the cessation of treatment is available.[91] As long as biomarkers are not validated and not correlated to the clinical outcome, they can only provide supportive information in dose finding studies, but are not feasible for determining a suitable therapeutic dose.[93] Furthermore, objective measurements such as paraclinical parameters (e.g. changes in allergen-specific IgE and IgG levels, cytokines, other inflammatory markers) can give additional information but are no surrogate markers and cannot replace the measurement of clinical symptoms in pivotal studies.[93]

Elevated serum specific IgE (sIgE) levels as part of the allergen sensitization profile are currently one of the inclusion criteria for AIT administration in allergic asthmatic patients.[13] Some studies report an increase in sIgE levels following the first 2 years of AIT followed by a gradual decrease after the third year of treatment, possibly mirroring AIT effects with initial desensitization of effector cells with subsequent induction of immune tolerance.[92,94,95] However, this is contradictory to similar studies, which demonstrated either an increase or no alteration in serum HDM-sIgE levels compared to respective placebo groups.[53,96] There is also a notable heterogeneous readout in total IgE (tIgE) levels and sIgE:tIgE ratios among allergic patients in AIT studies.[97] For example, whereas some studies report that the sensitivity and specificity to predicting clinical response are highest under the curve of the sIgE:tIgE ratio, other studies demonstrate that the sensitivity and specificity under the curve of tIgE are higher.[98,99]

In AR patients, AIT is associated with a 10- to 100-fold increase in the concentration of local and systemic IgG1 and IgG4; this has not been reproduced across all clinical studies in allergic asthmatic patients.[54,95,100] IgG4 antibodies are uniquely dynamic and partake in 'Fab arm exchange', resulting in asymmetric bispecific antibodies with reduced abilities to crosslink allergen and activate downstream effector cell responses.[101–103] Moreover, elevated serum IgG4 functions as a 'protective allergen neutralising antibody' associated with IgE-blocking activities.[100] For instance, allergen-specific IgG4 competes with allergen-specific IgE for allergen-binding, inhibiting IgE-mediated cross-linking of FcεRI receptors on effector cells, reducing their activation and subsequent degranulation.[100] Allergen-specific IgG4 also prevents IgE-allergen complexes binding to FCεRII (CD23) expressed on B cells, investigated through an IgE-facilitated antigen-binding (FAB) flow cytometry-based bioassay.[104] However, although IgE-FAB and immune-solid phase allergy chip (ISAC) can reliably determine the quantities and blocking functionality of IgG antibodies, these are limited to specialized laboratories and are thus not easily applicable in the clinical setting. A conclusive relationship between increased serum sIgE, reduced sIgE/IgG4 ratios and IgG4 protective functions to clinical efficacy scores has yet to be determined. IgG2 antibody are also induced following AIT. Most recently, it was shown that following 1-year sublingual AIT, HDM-specific serum IgG2 responses were elevated in treatment responders compared to low responders.[105]

Type 2 (T2) inflammation in (allergic) asthma is associated with elevated levels of blood eosinophils and fractional exhaled nitric oxide (FeNO)[106]; both biomarkers are used in the diagnostic workup, choice of treatment modality and monitoring of treatment response.[3,107,108] Limited data are available on the response of FeNO and eosinophil levels after AIT. However, some studies have consistently reported a decrease in (seasonal) levels of both blood eosinophils and FeNO after AIT treatment in asthma patients.[109–112] Studies correlating FeNO and blood eosinophils with clinical outcome of AIT in asthma patients are necessary to elaborate on the applicability of these biomarkers.

3.8.1 | Advantages

- Biomarkers have the potential to identify treatment responders and non-responders.
- Measurement of immunological biomarkers alongside clinical outcomes provides insight into AIT mechanisms.

3.8.2 | Disadvantages

- Often, biomarkers fail to demonstrate consistent trends during and following AIT across studies, meaning their physiological importance and correlation to clinical outcomes is difficult to assess. (Therefore not yet accepted by the competent authorities as outcome parameters for the primary endpoint of pivotal (Phase III) clinical trials.)
- Specialized laboratory equipment and skills are required for many of the sophisticated biomarker assays and are therefore not accessible at a clinical setting.

3.8.3 | Unmet needs

- Establish the applicability of FeNO and blood eosinophils as predictive/monitoring biomarkers of AIT in asthma.
- Standardized assays including reference ranges to measure biomarkers, for example, sIgE/IgG4 ratios to allow the comparison of outcomes across studies.
- Studies investigating clinical and immunological parameters to validate the utility of individual biomarkers in AIT.

3.8.4 | Clinical applicability

- FeNO and blood eosinophils are validated point-of-care biomarkers which can predict treatment response to treatments along the T(h)2 pathway and readily available in most asthma clinics.
- Stratification of patients based on validated biomarkers allows a personalized approach in the management of allergic asthma.

4 | OTHER CONSIDERATIONS

4.1 | Real-world evidence

The majority of the evidence is derived from RCTs randomising volunteers fitting with very strict inclusion and exclusion criteria only and being conducted in a highly controlled clinical setting with optimal clinical infrastructure. As a result, the data derived reflect the best case situation of an ideal world scenario, but are usually not representative for clinical practice routine under real-world conditions.[44]

To overcome the gaps arising from these limitations evaluation of treatment effects and safety under real-world conditions is required. As suggested in a recently published EAACI position paper gaining real-world data would provide additional data on treatment effectiveness in asthmatics of all age groups, all comorbidities and demonstrate safety in larger groups. As longer treatment periods are evaluated realistic responder profiles are revealed including possible effects on comorbidities.[113] Prospective observational effectiveness studies as well as database cohort analyses provide valuable new insights often not retrievable by RCTs, provided that quality criteria are carefully predefined and followed.[114] The same methodological standards as for RCTs need to be applied as determined in the consort statement, however without randomization. Reviewed the real-world evidence (RWE) on immunotherapy effectiveness in respiratory allergies from 14 evaluable studies concluded that six studies revealed unique information not retrievable from RCTs in terms of long-term effects up to 20 years after treatment discontinuation, new sensitizations, asthma development and symptom and medication use reduction, respectively.[114,115] None of the studies evaluated, met all of the quality criteria set as a prerequisite for guideline development with 11 out of the 14 showing lacks in results reporting including confounders. In the REACT study, a retrospective cohort analysis, data from a German Health Insurance database from 2007 to 2017 were analyzed to obtain an estimate of AIT treatment effects in patients with AR with and without asthma.[27] It has be shown that AR and asthma medication prescriptions, including both asthma controller and reliever, were reduced as compared to the matching control groups. In the AIT group, a significant reduction of asthma exacerbations next to asthma treatment reduction was demonstrated as well as improvement in associated factors like pneumonia with antibiotic prescriptions, hospitalizations and duration of inpatients stays.[27]

Systematic RWE generation is a new field of research and currently we do not have enough published evidence to conclude on the most reliable parameters.

4.2 | Follow-up on outcome measures

Digital health includes eHealth (electronic health) and areas such as the use of advanced computer sciences. eHealth comprises several components, including electronic health records, telehealth and mHealth (mobile health) that is segmented into mHealth apps, mHealth services and medical devices.[116] Although mHealth is still in development and trials should be carried out, mHealth-based tools are promising for the assessment of AIT efficacy. Moreover, although AIT efficacy is classically measured using daily symptom-medication scores, mHealth allows for newer and disrupting approaches.

Biomarkers that reflect biological processes are essential for monitoring the health of patients, including clinical signs, biological assays, mHealth outcomes, genomic indices and others that can be objectively measured and used as indicators of pathophysiological processes.[117] Combined symptom-medication scores represent the primary outcome for the assessment of rhinitis efficacy in AIT. Using the MASK-air® app,[118,119] a new digitalized combined symptom-medication score (CSMS) has been developed and validated for allergic symptoms in 17,780 patients with rhinitis (conjunctivitis and asthma).[120,121] This CSMS was shown to be more relevant in AIT than the classical VAS global allergy symptoms.[121,122] A similar score has been developed for asthma (Sousa-Pinto, in preparation). These scores have the potential to compare the daily control of the disease with pollen counts and pollution. These data, however, are currently limited available in limited places. In asthma, an attempt to include rhinovirus exposure is in development. Combining eHealth scores with environment may help to reduce the large placebo effect of AIT since only exposed patients may be analyzed.

It is recommended to assess two types of biomarkers in order to asses disease control. In rhinitis, this dual approach is feasible using eHealth. Tests such as the CARAT to assess rhinitis control for 4 weeks and have been digitally validated.[123,124] Second, the daily CSMS, an mHealth biomarker, can be used to asses the daily rhinitis control. In asthma, electronic questionnaires to assess control for a period of 1–4 weeks are also available[125] (e.g. ACQ-5, or CARAT[123,124]). There is a validated daily control test available in several countries based on MASK-air®. Such a tool would allow a rapid analysis of results and could provide alerts to patients and physicians for uncontrolled disease. Although the allergy CSMS has been validated in AIT, the asthma one has not.[121,122] Moreover, providing the dual approach needs to be tested in AIT.

5 | DISCUSSION

Clinical outcome measures in asthma studies consist of establishing current asthma control and future risk of exacerbations. Symptom control and medication use have a central position in international guidelines for the management of asthma.[3,41] Clinical studies often use the number of exacerbation as primary outcomes, with lung function measures (FEV1) and symptoms scores as secondary outcomes. Biomarkers related to T2 inflammation in asthma are important in personalized medicine approach in severe asthma patients used in determining the asthma phenotype as well as in the selection of biological treatment (i.e. patient stratification and prediction).[3,107] Furthermore, clinical application of biomarkers, especially

eosinophils and FeNO in the evaluation of treatment response of asthma seem promising.[126–131]

So far, there is no consensus in clinical guidelines on outcome measures for AIT in allergic asthma, whereas for AR a recommendation on standardization of clinical outcomes to be used in AIT trials exists. As AIT is more frequently used as an add-on disease modifying treatment in allergic asthma, the need for a consensus on clinical outcomes is currently becoming more relevant.

Although GINA and EAACI both recommend SLIT with HDM-extracts to decrease the exacerbation rate in mild/moderate HDM-driven asthma,[3,13,37] the evidence for AIT with other products is still contradictory. It should be noted that studies lack a uniformly accepted definition of exacerbations, varying from number of exacerbations to time to first exacerbation. In clinical practice exacerbation reduction has the potential to be a relevant outcome measure, provided that exacerbations are properly and uniformly registered according to the ATS/ERS consensus statement on exacerbations should be used.[41] However, more data are needed to establish outcome parameters of exacerbations in AIT research. It should be noted that exacerbations, using the current definition, are rare events and therefore can only make sense in large trials, powered accordingly. Attempts have been made to define and use more frequent events increasing sensitivity.[132,133]

Although PFT's (FEV1) are recommended by GINA to use for assessing asthma control and future risk there is no consistent effect of AIT on FEV1. However, a positive effect of AIT on small airways disease was shown, therefore small airway measurements by IOS are a potential outcome measure rather than FEV1.[36]

The minimum but optimal ICS dose in order to achieve asthma control and prevent future risk plays a central role in asthma management.[3] As AIT potentially adds to a reduction of T2 inflammation it is expected that a lower dose of ICS is sufficient, several supporting data are available.[58–61] Therefore, ICS use is a potential outcome measure for AIT in asthma which is also applicable for the clinical setting. If used in the right clinical context it may differentiate responders from non-responders. ICS withdrawal has been used in a randomized DPBC trial in HDM SLIT assessing time to first exacerbation as primary endpoint and can be used in future clinical trials.[54] Evidence on reduction of rescue medication scores is relatively consistent, standardization of these scores is however needed.

Reduction in symptom scores is correlated with the efficacy of SCIT shown in a 2010 Cochrane review,[56] data seem to be consistent. As many studies use different scores, there is again the need for standardization and validation of universal and objective symptom scores. Pending standardization both symptom scores can be a valuable tool in the clinic for regular monitoring the patients with asthma receiving AIT.

Patient-reported outcomes measures such as ACQ and AQLQ questionnaires are widely available and used in both clinical settings as well as secondary outcome measures in clinical trials. They can however be influenced by recall bias and other subjective factors such as personality type, religion or cultural beliefs. So far, no correlations between with AIT has been shown. As questionnaires are easily applicable in clinical and research settings, CARAT, a combined score of the upper and lower airways is advised.

Both nasal/bronchial provocation and AECs are outcome measures that require highly qualified staff and safety measurements. They are therefore valuable tools offering reproducible data, but limited to specialized clinical settings.

Biomarkers and AIT are subject of intense investigation and debate. To date, there are no validated and generally accepted candidate biomarkers that are predictive or indicative of a clinical response to AIT. Although several studies include biomarkers as secondary outcomes, current guidelines do not include biomarkers in the recommendations for clinical AIT trials or clinical response. A 2017 overview suggested allergen-specific sIgG4 as a biomarker for compliance and identified sIgE/tIgE ratio and IgE-FAB as candidate biomarkers for clinical outcome.[91] Asthma related T2-biomarkers, FeNO and eosinophils have the potential to be biomarkers to evaluate the effect of AIT as add-on treatment in allergic-asthma patients.[109–111] Correlation with clinical response still would be necessary for the implementation of FeNO and eosinophil levels as surrogate biomarkers.

Allergen immunotherapy in asthma patients should be assessed as optimising one of the treatable traits in an individual patient resulting in an improved quality of life. In some but not all cases asthma control (exacerbation rate, medication use) will improve as well. Outcome measures, when used in a clinical setting, should therefore be adapted to the individual treatment goal for the patient. Enabling them to be safely exposed (with markedly reduced symptoms) to allergens to which they are sensitized and allergic. It may or may not improve their 'asthma control' exacerbations or reduce their inhaled steroids. This can be the case in perennial allergies. For HDM it is more difficult to demonstrate improved HDM exposure symptoms, whether or not asthma overall will improve depends on how much of the asthma is due to HDM allergy.

Systematic RWE is a relatively new field that can assist in selecting the most reliable representative parameters in a clinical setting; however, currently too little published evidence is available to draw conclusions. eHealth has the potential to be a viable tool for the follow-up of outcome measures and possibly assist in interpreting RWE data.

6 | CONCLUSIONS

Exacerbation rate can be used as a reliable objective primary outcome, although there is limited evidence due to different definitions of exacerbation. Furthermore, the endpoints for allergic asthma and AIT are often more subtle. It is therefore advised that symptom scores and medication use (ICS and reliever medication reduction) are used as clinical outcomes in AIT in asthma patients. All are clinical applicable and easy to use, there is however the urgent need for standardization for use in clinical trials. ACQ5/AQLQ and CARAT are well-established PROMs questionnaires, however, validation addressing asthma control in relation to AIT is an unmet need. After

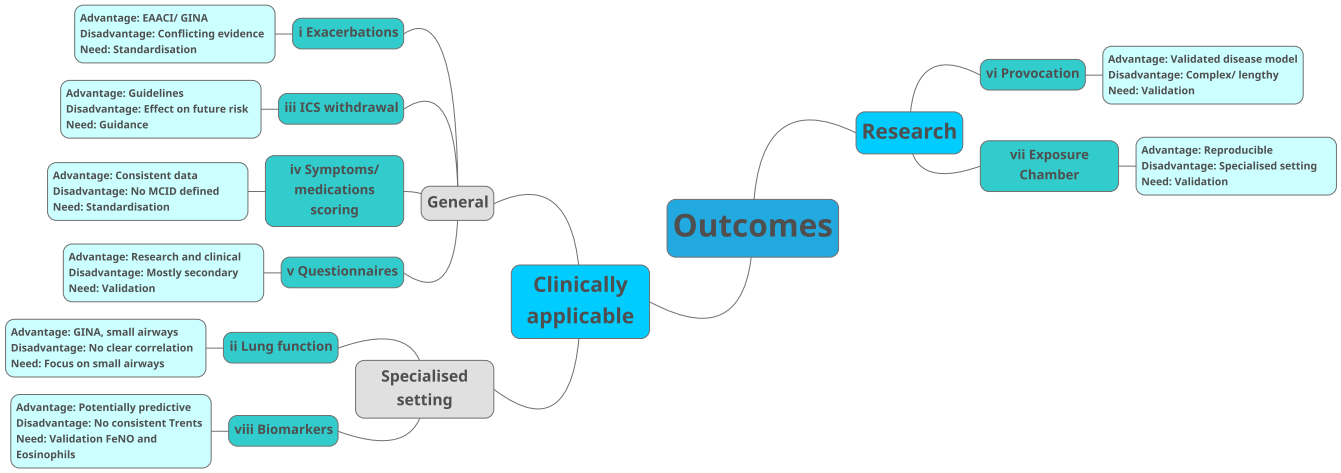

FIGURE 1 Summary of clinical outcomes of AIT in asthma.

ICS withdrawal the time to first exacerbation can be captured as primary outcome measure.

FeNO and eosinophil levels (evaluated in clinical context) have the potential to become surrogate biomarkers of clinical response. Additional studies are needed to confirm and to interpret their association with the clinical response to immunotherapy. A summary of clinical outcomes of AIT in patients with asthma is presented in Figure 1.

Finally, future systemic RWE data are needed to analyze the suggested outcome measures, novel eHealth tools can support these evaluations.

AUTHOR CONTRIBUTIONS

Jasper Kappen, Zuzana Diamant, Roy Gerth van Wijk and Oliver Pfaar produced the manuscript concept and design. All authors were designated to a domain and were involved in the acquisition of data including search, and analysis and interpretation of data. All authors contributed to critical revision of the manuscript for important intellectual content.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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REFERENCES

1. Lai CK, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the international study of asthma and allergies in childhood (ISAAC). *Thorax*. 2009;64(6):476-483.
2. Burney P, Jarvis D, Perez-Padilla R. The global burden of chronic respiratory disease in adults. *Int J Tuberc Lung Dis*. 2015;19(1):10-20.
3. (GINA) Gifa. *Global Strategy for Asthma Management and Prevention*. (GINA) Gifa; 2023.
4. Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J med*. 2017;377(10):965-976.
5. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care med*. 2008;178(3):218-224.
6. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J med*. 2006;355(21):2226-2235.
7. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J*. 2004;24(5):758-764.
8. Sullivan PW, Ghushchyan VH, Slejko JF, Belozeroff V, Globe DR, Lin SL. The burden of adult asthma in the United States: evidence from the medical expenditure panel survey. *J Allergy Clin Immunol*. 2011;127(2):363-369.e1-3.
9. Bernstein JA. Allergic and mixed rhinitis: epidemiology and natural history. *Allergy Asthma Proc*. 2010;31(5):365-369.
10. Martinez FD, Vercelli D. Asthma. *Lancet*. 2013;382(9901):1360-1372.
11. Holgate ST, Wenzel S, Postma DS, Weiss ST, Renz H, Sly PD. Asthma. *Nat Rev Dis Primers*. 2015;1:15025.
12. Del Giacco SR, Bakirtas A, Bel E, et al. Allergy in severe asthma. *Allergy*. 2017;72(2):207-220.
13. Agache I, Lau S, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: house dust mite-driven allergic asthma. *Allergy*. 2019;74(5):855-873.
14. Agache I, Antolin-Amerigo D, de Blay F, et al. EAACI position paper on the clinical use of the bronchial allergen challenge: unmet needs and research priorities. *Allergy*. 2022;77(6):1667-1684.
15. 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(7):854-867.
16. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136:556-568.
17. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108(5 Suppl):S147-S334.
18. 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.
19. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol*. 1998;102(4 Pt 1):558-562.
20. Shamji MH, Ljorring C, Francis JN, et al. Functional rather than immunoreactive levels of IgG4 correlate closely with clinical response to grass pollen immunotherapy. *Allergy*. 2012;67(2):217-226.
21. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J med*. 1999;341(7):468-475.
22. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev*. 2007;2007(1):CD001936.
23. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev*. 2010;2010(12):CD002893.
24. Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy*. 2011;66(6):740-752.
25. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham S. Sublingual immunotherapy for treating allergic conjunctivitis. *Cochrane Database Syst Rev*. 2011;(7):CD007685.
26. Compalati E, Braido F, Canonica GW. An update on allergen immunotherapy and asthma. *Curr Opin Pulm med*. 2014;20(1):109-117.
27. Fritzsching B, Contoli M, Porsbjerg C, et al. Long-term real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma: results from the REACT study, a retrospective cohort study. *Lancet Reg Health Eur*. 2022;13:100275.
28. Bousquet J, Pfaar O, Togias A, et al. 2019 ARIA Care pathways for allergen immunotherapy. *Allergy*. 2019;74(11):2087-2102.
29. Roberts G, Pfaar O, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. *Allergy*. 2018;73(4):765-798.
30. Shamji MH, Durham SR. Mechanisms of immunotherapy to aeroallergens. *Clin Exp Allergy*. 2011;41(9):1235-1246.
31. Matsuoka T, Shamji MH, Durham SR. Allergen immunotherapy and tolerance. *Allergol Int*. 2013;62(4):403-413.
32. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. *World Allergy Organ J*. 2015;8(1):17.
33. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clin Immunol*. 2014;133(3):621-631.
34. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham SR. Sublingual immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis. *Clin Exp Allergy*. 2011;41(9):1263-1272.
35. Lommatzsch M, Brusselle GG, Canonica GW, et al. Disease-modifying anti-asthmatic drugs. *Lancet*. 2022;399(10335):1664-1668.
36. Dhami S, Kakourou A, Asamoah F, et al. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. *Allergy*. 2017;72(12):1825-1848.
37. Muraro R. (ed.)EAACI: Allergen Immunotherapy Guidelines Part 2: Recommendations. 2017. European Academy of Allergy and Clinical Immunology (EAACI) 2017, ISBN Number: 978-3-9524815-1-6.
38. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J*. 2016;47(2):410-419.
39. EMA. *Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Asthma*. EMA; 2015.

40. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International conference on harmonisation E9 expert working group. *Stat med*. 1999;18(15):1905-1942.
41. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care med*. 2009;180(1):59-99.
42. Bourdin A, Bjermer L, Brightling C, et al. ERS/EAACI statement on severe exacerbations in asthma in adults: facts, priorities and key research questions. *Eur Respir J*. 2019;54(3):1900900.
43. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343-373.
44. Price D, Brusselle G, Roche N, Freeman D, Chisholm A. Real-world research and its importance in respiratory medicine. *Breathe (Sheff)*. 2015;11(1):26-38.
45. De Kam PJ, Kramer MF, Shamji MH, et al. Dogmas, challenges, and promises in phase III allergen immunotherapy studies. *World Allergy Organ J*. 2021;14(9):100578.
46. Guibas GV, Makris M, Papadopoulos NG. Acute asthma exacerbations in childhood: risk factors, prevention and treatment. *Expert Rev Respir Med*. 2012;6(6):629-638.
47. Incorvaia C, Ridolo E. In the strategies to prevent asthma exacerbations, allergic asthma needs specific treatment. *Curr med Res Opin*. 2015;31(4):821-823.
48. Normansell R, Kew KM, Bridgman AL. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev*. 2015;2015(8):CD011293.
49. Wang H, Lin X, Hao C, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. *Allergy*. 2006;61(2):191-197.
50. Devillier P, Fadel R, de Beaumont O. House dust mite sublingual immunotherapy is safe in patients with mild-to-moderate, persistent asthma: a clinical trial. *Allergy*. 2016;71(2):249-257.
51. Gomez Vera J, Flores Sandoval G, Orea Solano M, Lopez Tiro J, Jimenez SN. Safety and efficacy of specific sublingual immunotherapy in patients with asthma and allergy to *Dermatophagoides pteronyssinus*. *Rev Alerg Mex*. 2005;52(6):231-236.
52. 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(2):134-140.
53. Pajno GB, Morabito L, Barberio G, Parmiani S. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. *Allergy*. 2000;55(9):842-849.
54. Virchow JC, Backer V, Kuna P, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: a randomized clinical trial. *JAMA*. 2016;315(16):1715-1725.
55. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J med*. 2018;378(20):1865-1876.
56. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2010;(8):CD001186.
57. Tanaka A, Tohda Y, Okamiya K, Azuma R, Terada I, Adachi M. Efficacy and safety of HDM SLIT tablet in Japanese adults with allergic asthma. *J Allergy Clin Immunol Pract*. 2020;8(2):710-720.e14.
58. 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(3):568-75 e7.
59. Wang L, Yin J, Fadel R, Montagut A, de Beaumont O, Devillier P. House dust mite sublingual immunotherapy is safe and appears to be effective in moderate, persistent asthma. *Allergy*. 2014;69(9):1181-1188.
60. Zielen S, Kardos P, Madonini E. Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial. *J Allergy Clin Immunol*. 2010;126(5):942-949.
61. Jutel M, Rudert M, Kreimendahl F, Kuna P. Efficacy and tolerability of a house dust mite allergoid in allergic bronchial asthma: a randomized dose-ranging trial. *Immunotherapy*. 2018;10(13):1149-1161.
62. Kocks JWH, Seys SF, van Duin TS, Diamant Z, Tsiligianni IG. Assessing patient-reported outcomes in asthma and COPD patients: which can be recommended in clinical practice? *Curr Opin Pulm med*. 2018;24(1):18-23.
63. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis*. 1993;147(4):832-838.
64. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the mini asthma quality of life questionnaire. *Eur Respir J*. 1999;14(1):32-38.
65. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. *Clin Exp Allergy*. 2013;43(8):881-888.
66. Azevedo P, Correia de Sousa J, Bousquet J, et al. Control of allergic rhinitis and asthma test (CARAT): dissemination and applications in primary care. *Prim Care Respir J*. 2013;22(1):112-116.
67. Duric-Filipovic I, Caminati M, Kostic G, Filipovic D, Zivkovic Z. Allergen specific sublingual immunotherapy in children with asthma and allergic rhinitis. *World J Pediatr*. 2016;12(3):283-290.
68. Yukselen A, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. 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(3):288-298.
69. Pfaar O, Nell MJ, Boot JD, et al. A randomized, 5-arm dose finding study with a mite allergoid SCIT in allergic rhinoconjunctivitis patients. *Allergy*. 2016;71(7):967-976.
70. Pfaar O, van Twuijver E, Boot JD, et al. A randomized DBPC trial to determine the optimal effective and safe dose of a SLIT-birch pollen extract for the treatment of allergic rhinitis: results of a phase II study. *Allergy*. 2016;71(1):99-107.
71. Diamant Z, Boot JD, Mantzouranis E, Flohr R, Sterk PJ, Gerth van Wijk R. Biomarkers in asthma and allergic rhinitis. *Pulm Pharmacol Ther*. 2010;23(6):468-481.
72. Eguiluz-Gracia I, Testera-Montes A, Gonzalez M, et al. Safety and reproducibility of nasal allergen challenge. *Allergy*. 2019;74(6):1125-1134.
73. Diamant Z, Gauvreau GM, Cockcroft DW, et al. Inhaled allergen bronchoprovocation tests. *J Allergy Clin Immunol*. 2013;132(5):1045-55 e6.
74. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of asthma: a meta-analysis of prospective, randomized, double-blind, placebo-controlled studies. *Clin Ther*. 2000;22(3):329-341.
75. Alvarez MJ, Echechipia S, Garcia B, et al. Liposome-entrapped *D. pteronyssinus* vaccination in mild asthma patients: effect of 1-year double-blind, placebo-controlled trial on inflammation, bronchial hyperresponsiveness and immediate and late bronchial responses to the allergen. *Clin Exp Allergy*. 2002;32(11):1574-1582.
76. Alexander C, Tarzi M, Larche M, Kay AB. The effect of Fel d 1-derived T-cell peptides on upper and lower airway outcome measurements in cat-allergic subjects. *Allergy*. 2005;60(10):1269-1274.
77. Blumberga G, Groes L, Dahl R. SQ-standardized house dust mite immunotherapy as an immunomodulatory treatment in patients with asthma. *Allergy*. 2011;66(2):178-185.

78. Hedlin G, Wille S, Browaldh L, et al. Immunotherapy in children with allergic asthma: effect on bronchial hyperreactivity and pharmacotherapy. *J Allergy Clin Immunol*. 1999;103(4):609-614.
79. Gauvreau GM, Davis BE, Scadding G, et al. Allergen provocation tests in respiratory research: building on 50 years of experience. *Eur Respir J*. 2022;60:2102782.
80. Fauquert JL, Jedrzejczak-Czechowicz M, Rondon C, et al. Conjunctival allergen provocation test: guidelines for daily practice. *Allergy*. 2017;72(1):43-54.
81. Ihre E, Zetterstrom O. Increase in non-specific bronchial responsiveness after repeated inhalation of low doses of allergen. *Clin Exp Allergy*. 1993;23(4):298-305.
82. Dahlen B, Lantz AS, Ihre E, et al. Effect of formoterol with or without budesonide in repeated low-dose allergen challenge. *Eur Respir J*. 2009;33(4):747-753.
83. Pfaar O, Calderon MA, Andrews CP, et al. Allergen exposure chambers: harmonizing current concepts and projecting the needs for the future – an EAACI position paper. *Allergy*. 2017;72(7):1035-1042.
84. Gauvreau GM, Watson RM, Rerecich TJ, Baswick E, Inman MD, O'Byrne PM. Repeatability of allergen-induced airway inflammation. *J Allergy Clin Immunol*. 1999;104(1):66-71.
85. Auge J, Vent J, Agache I, et al. EAACI position paper on the standardization of nasal allergen challenges. *Allergy*. 2018;73(8):1597-1608.
86. Rosner-Friese K, Kaul S, Vieths S, Pfaar O. Environmental exposure chambers in allergen immunotherapy trials: current status and clinical validation needs. *J Allergy Clin Immunol*. 2015;135(3):636-643.
87. Pfaar O, Zieglmayer P. Allergen exposure chambers: implementation in clinical trials in allergen immunotherapy. *Clin Transl Allergy*. 2020;10:33.
88. Pfaar O, Bergmann KC, Bonini S, et al. Technical standards in allergen exposure chambers worldwide – an EAACI task force report. *Allergy*. 2021;76(12):3589-3612.
89. Nolte H, Maloney J, Nelson HS, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. *J Allergy Clin Immunol*. 2015;135(6):1494-501 e6.
90. Zieglmayer P, Nolte H, Nelson HS, et al. Long-term effects of a house dust mite sublingual immunotherapy tablet in an environmental exposure chamber trial. *Ann Allergy Asthma Immunol*. 2016;117(6):690-696.e1.
91. Shamji MH, Kappen JH, Akdis M, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI position paper. *Allergy*. 2017;72(8):1156-1173.
92. Shamji MH, Layhadi JA, Sharif H, Penagos M, Durham SR. Immunological responses and biomarkers for allergen-specific immunotherapy against inhaled allergens. *J Allergy Clin Immunol Pract*. 2021;9(5):1769-1778.
93. CHMP. *EMACfMPfHU. Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases*. CHMP; 2008.
94. 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(6):922-932.
95. Bahceciler NN, Arikan C, Taylor A, et al. Impact of sublingual immunotherapy on specific antibody levels in asthmatic children allergic to house dust mites. *Int Arch Allergy Immunol*. 2005;136(3):287-294.
96. Bousquet J, Scheinmann P, Guinnepain MT, et al. Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. *Allergy*. 1999;54(3):249-260.
97. Weghofer M, Thomas WR, Kronqvist M, et al. Variability of IgE reactivity profiles among European mite allergic patients. *Eur J Clin Invest*. 2008;38(12):959-965.
98. Di Lorenzo G, Mansueto P, Pacor ML, et al. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. *J Allergy Clin Immunol*. 2009;123(5):1103-1110.e4.
99. Li Q, Li M, Yue W, et al. Predictive factors for clinical response to allergy immunotherapy in children with asthma and rhinitis. *Int Arch Allergy Immunol*. 2014;164(3):210-217.
100. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol*. 2017;140(6):1485-1498.
101. Rispens T, Ooijevaar-de Heer P, Bende O, Aalberse RC. Mechanism of immunoglobulin G4 fab-arm exchange. *J Am Chem Soc*. 2011;133(26):10302-10311.
102. Aalberse RC, Schuurman J. IgG4 breaking the rules. *Immunology*. 2002;105(1):9-19.
103. van der Neut Kolfschoten M, Schuurman J, Losen M, et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic fab arm exchange. *Science*. 2007;317(5844):1554-1557.
104. Shamji MH, Francis JN, Wurtzen PA, Lund K, Durham SR, Till SJ. Cell-free detection of allergen-IgE cross-linking with immobilized phase CD23: inhibition by blocking antibody responses after immunotherapy. *J Allergy Clin Immunol*. 2013;132(4):1003-1005.e4.
105. Bordas-Le Floch V, Berjont N, Batard T, et al. Coordinated IgG2 and IgE responses as a marker of allergen immunotherapy efficacy. *Allergy*. 2022;77(4):1263-1273.
106. Diamant Z, Vijverberg S, Alving K, et al. Toward clinically applicable biomarkers for asthma: an EAACI position paper. *Allergy*. 2019;74(10):1835-1851.
107. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J med*. 2022;386(2):157-171.
108. Pavord ID, Afzalnia S, Menzies-Gow A, Heaney LG. The current and future role of biomarkers in type 2 cytokine-mediated asthma management. *Clin Exp Allergy*. 2017;47(2):148-160.
109. Hoshino M, Akitsu K, Kubota K, Ohtawa J. Association between biomarkers and house dust mite sublingual immunotherapy in allergic asthma. *Clin Exp Allergy*. 2020;50(9):1035-1043.
110. Hamada S, Kobayashi Y, Sakamoto D, et al. Long-term sublingual immunotherapy provides better effects for patients with Japanese cedar pollinosis. *Auris Nasus Larynx*. 2021;48(4):646-652.
111. Hoshino M, Akitsu K, Kubota K. Effect of sublingual immunotherapy on airway inflammation and Airway Wall thickness in allergic asthma. *J Allergy Clin Immunol Pract*. 2019;7(8):2804-2811.
112. de Blay F, Gherasim A, Casale TB, Doyen V, Bernstein D. Which patients with asthma are most likely to benefit from allergen immunotherapy? *J Allergy Clin Immunol*. 2022;149(3):833-843.
113. Paoletti G, Di Bona D, Chu DK, et al. Allergen immunotherapy: the growing role of observational and randomized trial "real-world evidence". *Allergy*. 2021;76(9):2663-2672.
114. Di Bona D, Paoletti G, Chu DK, et al. Allergen immunotherapy for respiratory allergy: quality appraisal of observational comparative effectiveness studies using the REal life evidence AssessmeNt tool. An EAACI methodology committee analysis. Clin Transl. *Allergy*. 2021;11(4):e12033.
115. Fritzsching B, Contoli M, Porsbjerg C, Buchs S, Larsen JR, Freemantle N. Real-world evidence: methods for assessing long-term health and effectiveness of allergy immunotherapy. *J Allergy Clin Immunol*. 2022;149(3):881-883.
116. Anto A, Sousa-Pinto B, Bousquet J. Anaphylaxis and digital medicine. *Curr Opin Allergy Clin Immunol*. 2021;21:448-454.
117. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69(3):89-95.

118. Sousa-Pinto B, Sa-Sousa A, Vieira RJ, et al. Behavioural patterns in allergic rhinitis medication in Europe: a study using MASK-air((R)) real-world data. *Allergy*. 2022;77:2699-2711.
119. Bousquet J, Anto JM, Bachert C, et al. ARIA digital anamorphosis: digital transformation of health and care in airway diseases from research to practice. *Allergy*. 2021;76(1):168-190.
120. Bousquet J, Bedbrook A, Czarlewski W, et al. Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma. *Clin Transl Allergy*. 2019;9:16.
121. Sousa-Pinto B, Azevedo LF, Jutel M, et al. Development and validation of combined symptom-medication scores for allergic rhinitis. *Allergy*. 2021;77:2147-2162.
122. Sousa-Pinto B, Azevedo L, Sá-Sousa A, et al. Allergen immunotherapy in MASK-air users in real-life: results of a Bayesian mixed-effects model. *Clin Transl Allergy*. 2022;12:e12128.
123. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. *Allergy*. 2010;65(8):1042-1048.
124. Sousa-Pinto B, Sa-Sousa A, Amaral R, et al. Assessment of the control of allergic rhinitis and asthma test (CARAT) using MASK-air. *J Allergy Clin Immunol Pract*. 2022;10(1):343-5 e2.
125. van Dijk BCP, Svedsater H, Heddini A, Nelsen L, Balradj JS, Alleman C. Relationship between the asthma control test (ACT) and other outcomes: a targeted literature review. *BMC Pulm med*. 2020;20(1):79.
126. Shrimanker R, Keene O, Hynes G, Wenzel S, Yancey S, Pavord ID. Prognostic and predictive value of blood eosinophil count, fractional exhaled nitric oxide, and their combination in severe asthma: a post hoc analysis. *Am J Respir Crit Care med*. 2019;200(10):1308-1312.
127. Kellerer C, Hapfelmeier A, Jorres RA, Schultz K, Brunn B, Schneider A. Evaluation of the diagnostic accuracy of fractional exhaled nitric oxide (FeNO) in patients with suspected asthma: study protocol for a prospective diagnostic study. *BMJ Open*. 2021;11(2):e045420.
128. Busse WW, Wenzel SE, Casale TB, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. *Lancet Respir med*. 2021;9(10):1165-1173.
129. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet*. 2002;360(9347):1715-1721.
130. Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL study group. *Am J Respir Crit Care med*. 1999;159(4 Pt 1):1043-1051.
131. Wang K, Verbakel JY, Oke J, et al. Using fractional exhaled nitric oxide to guide step-down treatment decisions in patients with asthma: a systematic review and individual patient data meta-analysis. *Eur Respir J*. 2020;55(5):1902150.
132. Fuhlbrigge AL, Bengtsson T, Peterson S, et al. A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-hoc analysis of randomised controlled trials. *Lancet Respir med*. 2017;5(7):577-590.
133. Xepapadaki P, Korovessi P, Bachert C, et al. Evolution of airway inflammation in preschoolers with asthma-results of a two-year longitudinal study. *J Clin med*. 2020;9(1):187.

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