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REVIEW

Hot topics in allergen immunotherapy, 2023: Current status and future perspective

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Abstract

The importance of allergen immunotherapy (AIT) is multifaceted, encompassing both clinical and quality-of-life improvements and cost-effectiveness in the long term. Key mechanisms of allergen tolerance induced by AIT include changes in memory type allergen-specific T- and B-cell responses towards a regulatory phenotype with decreased Type 2 responses, suppression of allergen-specific IgE and increased IgG_1 and IgG_4, decreased mast cell and eosinophil numbers in allergic tissues and increased activation thresholds. The potential of novel patient enrolment strategies for AIT is taking into account recent advances in biomarkers discoveries, molecular allergy diagnostics and mobile health applications contributing to a personalized approach enhancement that can increase AIT efficacy and compliance. Artificial intelligence can help manage and interpret complex and heterogeneous data, including big data from omics and non-omics research, potentially predict disease subtypes, identify biomarkers and monitor patient responses to AIT. Novel AIT preparations, such as synthetic compounds, innovative carrier systems and adjuvants, are also of great promise. Advances in clinical trial models, including adaptive, complex and hybrid designs as

well as real-world evidence, allow more flexibility and cost reduction. The analyses of AIT cost-effectiveness show a clear long-term advantage compared to pharmacotherapy. Important research questions, such as defining clinical endpoints, biomarkers of patient selection and efficacy, mechanisms and the modulation of the placebo effect and alternatives to conventional field trials, including allergen exposure chamber studies are still to be elucidated. This review demonstrates that AIT is still in its growth phase and shows immense development prospects.

KEYWORDS
allergen immunotherapy (AIT), biomarkers, efficacy endpoint, novel vaccines, trial design

1 | INTRODUCTION

Allergen immunotherapy (AIT) was initially reported at the beginning of the 20th century and performed in clinical routine for more than 110 years.[1] A high level of evidence for its efficacy and safety has been elaborated throughout the recent decades for various forms of application, sublingual (SLIT) and subcutaneous (SCIT), as well as oral immunotherapy (OIT), the latter being used in managing food allergies, especially peanut, cow's milk and hen's egg allergy (Table 1).[2–7] Also, new administration routes, like patches applied on back—epicutaneous immunotherapy (EPIT) or direct injection into lymph nodes (intralymphatic immunotherapy [ILIT])—are clinically effective.[8–11] The major aim of AIT is achieving immune tolerance to allergens, which can be defined as a long-term clinical tolerance towards natural exposure or in vivo challenges, including allergen exposure chambers (AEC).[2]

The core strength of AIT lies in its ability to provide sustained relief from symptoms and prevent the progression from allergic rhinitis to asthma—particularly crucial in paediatric populations.[12,13] This enduring impact can be attributed to AIT's unique ability to trigger a cascade of desensitization mechanisms, which can be achieved by modulating both innate and adaptive immunity.[14] The effectiveness assessment evokes the concept of theratypes, which delineate therapy responders and non-responders based on a comprehensive understanding of pathophysiological mechanisms dictating disease manifestation and response to therapy in various patient groups.[15]

AIT is a well-established treatment for specific allergic conditions in Europe. The European Academy of Allergy and Clinical Immunology (EAACI) provided guidelines for AIT with respect to allergic disease and sensitization to specific allergens including insect venom.[16] Also, the peanut OIT has been approved by The European Commission in paediatric patients.[17] There are ongoing trials in food allergy aiming at widening indications for this treatment modality.

This review presents an in-depth insight into the latest developments in AIT while envisioning the key trajectories for its future progress and growth. Along with delving into the novel developments in AIT preparations, we underscore the critical role of clinical and biomarker endpoints' definition and assessment, including the extension to real-world data (RWD) and evidence (RWE), big data management and application of artificial intelligence (AI), the new methodology of clinical trials, disease endotypes and application of biologicals, personalized approaches as well as pharmacoeconomics.

2 | MECHANISMS OF TOLERANCE IN AIT

Allergen-specific immune response studies have demonstrated changes in memory type allergen-specific T- and B-cell responses, regulation of allergen-specific IgE and IgG, as well as mast cell and basophil activation thresholds that do not cause symptoms anymore, and have been demonstrated as putative mechanisms of allergen tolerance (Figure 1A,B).[18–21] Prevention of new allergen sensitizations and avoidance of progression to more severe diseases, such as the development of asthma after allergic rhinitis,[22] is the main clinical implications of immune tolerance.[23,24] Studies during the last three decades have demonstrated evidence that allergen tolerance utilizes similar mechanisms as shown in other diseases, such as autoimmunity, tumour tolerance and organ transplantation.[25,26]

2.1 | T_{REG} cells and allergen tolerance

Clinical allergen tolerance linked to immune tolerance was investigated in allergic tissue biopsies and skin late-phase responses. A decrease in allergen-specific cells, in particular, Type 2 T-helper (T_H2) cells and eosinophils during AIT and a parallel increase in T regulatory (T_{REG}) cells and their cytokines in allergic tissues were reported in asthma and allergic rhinitis.[27] In murine models, the essential role of T_{REG} cells in inducing and maintaining immune tolerance has been demonstrated, where their adoptive transfer was shown to prevent or cure several T-cell-mediated disease models, including asthmatic lung inflammation, autoimmune diseases and allograft rejection.[28] Both subcutaneous and sublingual AIT are shown to induce peripheral T-cell tolerance, characterized by the generation of allergen-specific Treg cells and a decrease in Th2 and Th1 cells.[29–32] Interleukin (IL)-10, IL-35, tumour necrosis factor-beta (TGF-β), cytotoxic T-cell antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) with programmed death-ligand 1 (PD-L1)-interactions were proposed as main molecular players.[33,34] Increased numbers of forkhead box P3 $(Foxp3)^+$ cluster of differentiation $(CD)3^+$ $CD25^+$ cells after AIT of allergic rhinitis, their association with clinical efficacy and suppression of seasonal allergic inflammation strengthen the concept of T_{REG} cell-mediated allergen tolerance in humans.[35] In addition, $CD4^+CD25^+$ T_{REG} cells from atopic donors have a reduced capability to suppress the proliferation of $CD4^+CD25^-$ T cells.[36] A marked loss of IL-4-producing T cells and

TABLE 1 AIT routes of exposure.

Route of exposure	Description	Duration	Uses	Safety
SCIT	Injecting small and gradually increasing doses of the allergen under the skin, usually in the upper arm	Typically, patients first go through a 'build-up' phase, which may last several months, followed by a 'maintenance' phase where the allergen dose remains consistent	Effective for various allergic conditions, including allergic rhinitis, allergic asthma and stinging insect allergies	Risk of systemic reactions, which can occasionally be severe (anaphylaxis)
SLIT	Placing a tablet or drop containing the allergen under the tongue	Daily administration is common, but the duration can vary based on the specific product	Approved for certain seasonal and perennial allergens (e.g. grass pollen, house dust mites)	Good safety profile with local side effects (e.g. mouth itching or swelling), the risk of severe systemic reactions is lower than with SCIT
OIT	Consuming the allergen in gradually increasing amounts, often mixed with food	The 'build-up phase' usually lasts for several months, and the maintenance dose may last for several years	Aims to increase the threshold of exposure to the allergen required to trigger a reaction	Side effects can range from mild (mouth itching) to severe (anaphylaxis)
EPIT	Delivers allergen through the skin using a patch	Clinical trials for 12 months, then up to 60 months of open-label treatment	Mainly being investigated for food allergies (not approved)	Most reactions are skin-related (e.g. local redness or itching)
ILIT	Injecting allergen directly into lymph nodes	Typically, three injections over several months	Initial studies have targeted allergic rhinitis and pollen allergies	Side effects can range from mild (lymph node enlargement) to severe (anaphylaxis)

Abbreviations: AIT, allergen immunotherapy; EPIT, epicutaneous AIT; ILIT, intralymphatic AIT; OIT, oral AIT; SCIT, subcutaneous AIT; SLIT, sublingual AIT.

the acquisition of IL-10-producing and FoxP3$^+$ antigen-specific CD4$^+$ T-cells.[37,38] The role of T_{REG} cells in allergen tolerance has also been shown in T-cell epitope peptide AIT.[32]

2.2 | B_{REG} cells and allergen tolerance

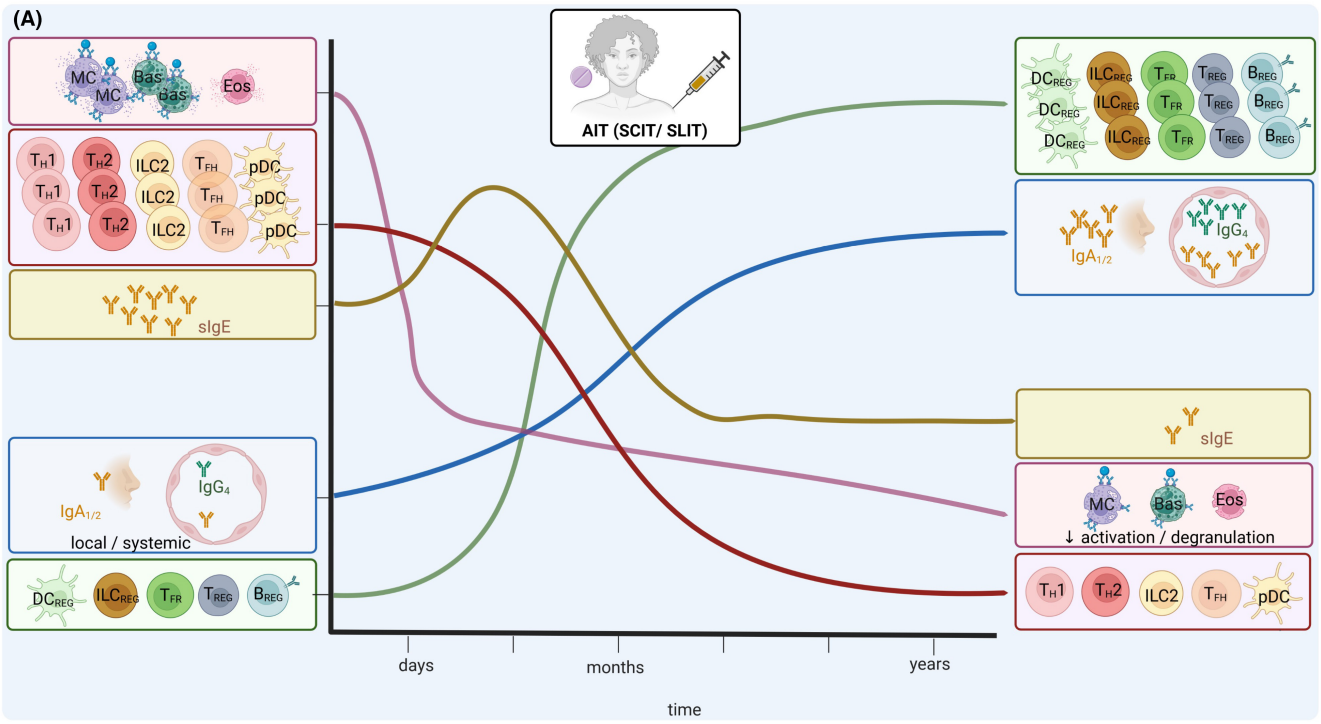
IL-10-producing regulatory B (B_{REG}) cells suppress immune responses, and the lack of these cells exacerbates symptoms in mouse models of chronic inflammation, transplantation and chronic infection.[39] Inducible IL-10-secreting B regulatory 1 ($B_{REG}1$) cells express high surface CD25 and CD71 and low CD73 levels, produce high levels of IL-10 and potently suppress antigen-specific CD4$^+$ T-cell proliferation. Furthermore, the frequency of IL-10$^+$ phospholipid antigen-specific (PLA)-B cells increased in allergic patients receiving AIT. The suppressive B cells and immunoglobulin class G (IgG)4-expressing B cells are both confined to IL-10$^+$ BR1 cells in human subjects.[39] IL-10-overexpressing B cells demonstrate a prominent immunoregulatory profile comprising upregulation of suppressor of cytokine signalling 3 (SOCS3), glycoprotein A repetitions predominant (GARP), the IL-2 receptor alpha chain (CD25) and PD-L1. Furthermore, IL-10-overexpressing B cells secrete less IgE and potently suppress proinflammatory cytokines in peripheral blood mononuclear cells (PBMC), maturation of monocyte-derived dendritic cells (rendering their profile to regulatory phenotype) and antigen-specific proliferation.[40]

2.3 | Regulation of mast cells, basophils and eosinophils by AIT

Although there are individual differences and risks for developing systemic anaphylaxis during the course of AIT, the suppression of mast cells and basophils continues to be affected by changes in other immune parameters, such as the generation of allergen-specific T_{REG} cells and decreased specific IgE. Significantly enhanced tryptophan degradation and elevated human Ig receptors inhibitory transcript (ILT4) expression in monocytes were found within a few hours after the first injection on Day 1, representing markers of very early changes.[41] In addition, early reduction in basophil sensitivity predicts symptom relief with grass pollen AIT.[42] Furthermore, the basophil expression of diamine oxidase significantly increases after AIT and is suggested as a novel biomarker.[43]

2.4 | Innate lymphoid cells and AIT

Type 2 innate lymphoid cells (ILC2) play a key role in asthma and upper respiratory inflammation.[44] Type 2 immunity (T2) consists of GATA-3$^+$ ILC2s, Type 2 T cytotoxic (T_C2) cells and T_H2 cells producing IL-4, IL-5 and IL-13, which induce mast cell, basophil and eosinophil activation, as well as IgE antibody production, thus protecting against helminths and venoms.[45] Seasonal increases in peripheral ILC2s are inhibited by grass pollen SCIT.[46] Recently discovered IL-10



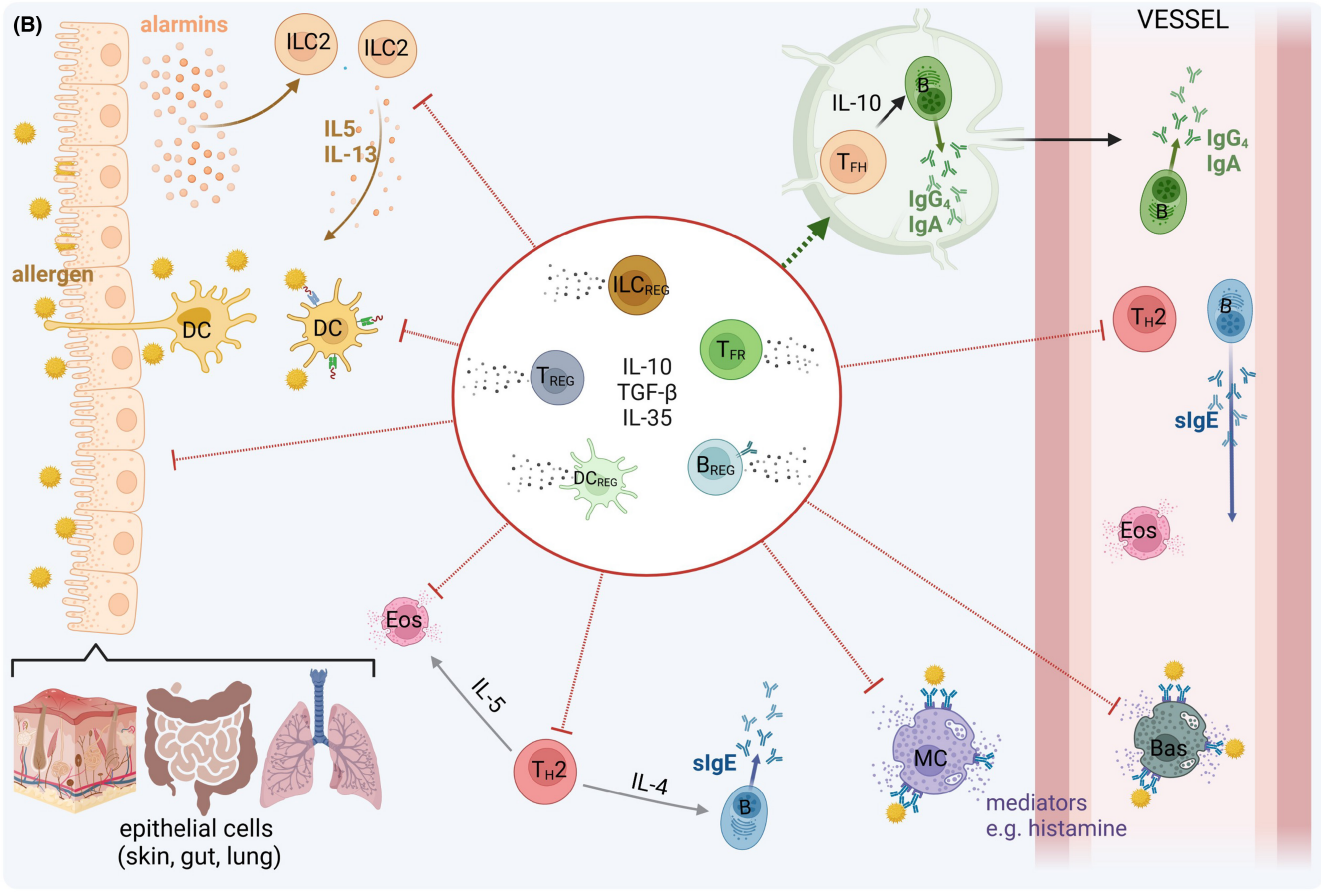


FIGURE 1 (A) Immunologic changes during the course of AIT. Starting with the first injection/tablet, decreases in mast cell and basophil activity, degranulation and tendency for systemic anaphylaxis degranulation occur within the first hours. This is followed by the generation of allergen-specific T_{REG}, B_{REG} and ILC_{REG} cells and the suppression of allergen-specific T_H1 and T_H2 cells and innate ILC2. Specific IgE shows an early increase and decreases relatively late. These events are in parallel to increases in IgG_4 that continuously increase as long as the treatment continues. Also, an increase in local and systemic $IgA_{1/2}$ is noticed. After several months, the allergen-specific IgE/IgG_4 ratio decreases. T_{FR} cells restrict T_{FH} cell-mediate IgE antibody production. After a few months, decreases in tissue mast cells and eosinophils lead to reductions in released mediators and skin late-phase response occurs. DC_{REG} cells can help differentiate naive T cells into T_{REG} cells and shift T_H2 to T_H1 responses. A significant decrease in Type I skin test reactivity is also observed relatively late in the course. It has to be noted that there is significant variation between donors and protocols sometimes leading to variability in results. (B) Role of regulatory cells in the suppression of allergic inflammation. The balance between T2 cells and regulatory cells is critical for the development or suppression of allergic inflammation. Regulatory cells and their cytokines suppress T2 immune responses and contribute to controlling allergic diseases in several major ways. Red arrows indicate the regulatory and suppressive effects of T_{REG}, B_{REG}, DC_{REG}, ILC_{REG} and T_{FR} cells, which exert their regulatory functions directly or indirectly on B cells by inducing IgG_4 and IgA and suppressing IgE; on vascular endothelium by suppressing T_H2 cell homing to tissues; on mast cells, basophils and eosinophils via direct and indirect suppressive effects; and on, direct and indirect, suppression of epithelial cell activation and proinflammatory properties. In addition, B_{REG} cells also suppress effector T cells and contribute to IgG_4 synthesis. AIT, allergen immunotherapy; B, lymphocytes B cell; Bas, basophil; B_{REG}, B regulatory cells; DC_{REG}, tolerogenic Dendritic cells; Eos, eosinophil; IL, interleukin; ILC, innate lymphoid cells; ILC_{REG}, regulatory innate lymphoid cells; MC, mast cell; pDC, plasmacytoid dendritic cells; SCIT, subcutaneous AIT, (s)IgE/$A_{1/2}$/G_4, (specific) immunoglobulin class E/$A_{1/2}$/G_4; SLIT, sublingual; T_{FH}, follicular T helper cells; T_{FR}, T follicular regulatory cell; $T_H1/2$, T lymphocyte type 1/2; T, lymphocytes T; T_{REG}, T regulatory cells.

expression suppressive ILCs,[47] namely the regulatory ILCs (ILC_{TEG}) increase during AIT.[45]

2.5 | Modulation of allergen-specific IgE and IgG responses during AIT

Early increase in specific IgG Abs, particularly IgG_4 and late decrease in specific IgE are classically observed in AITs.[48,49] It is highly possible that the decrease in IgE/IgG_4 ratio during AIT is a feature of skew from allergen-specific T_H2 to T_{REG} cell predominance. IL-10 is a potent suppressor of both total and allergen-specific IgE, while it simultaneously increases IgG_4 production.[29,50] In house dust mite (HDM)-AIT, IgG_2 induction and correlation with IgG_4 and IgE have been proposed to indicate high therapy response.[51] There are several features of IgG_4, which may play a role in its non-inflammatory role. The two arms of IgG_4 have the ability to separate and repair by antigen-binding fragment (Fab) arm exchange that leads to bi-specific antibodies that are functionally monomeric.[52,53] Furthermore, IgG_4 does not fix complement and can inhibit immune-complex formation by other isotypes, giving this isotype anti-inflammatory characteristics. The nasal and systemic $IgA_{1/2}$ antibody levels during SLIT are increased.[54]

In addition to T_H2 cells, follicular helper T (T_{FH}) cells are crucial in controlling IgE production. In contrast, follicular regulatory T (T_{FR}) cells, a specialized subset of T_{REG} cells resident in B-cell follicles, restrict T_{FH} cell-mediated help in extrafollicular antibody production, germinal centre formation, immunoglobulin affinity maturation and long-lived, high-affinity plasma and memory B-cell differentiation.[38] Upregulation of T_{FH} cell activities, including a skewing toward Type 2 T_{FH} ($T_{FH}2$) and IL-13 producing T_{FH} ($T_{FH}13$) phenotypes, and defects in T_{FR} cells have been identified in patients with allergic diseases. AIT reinstates the balance between T_{FH} and T_{FR} cells in patients with allergic diseases, resulting in clinical benefits.[55]

3 | NOVEL PATIENT ENROLMENT STRATEGIES

The precision medicine approach is essential to successful AIT. The key elements include precise definitions of disease phenotype and endotype.[56] It is essential to discern who is most likely to benefit from AIT. Novel diagnostic tools and biomarker validation enable the better selection of patients for treatment in this respect distinguishing between responder and non-responder patients. In a larger sense, the tailored approach should incorporate adjustments to each patient's personal and human (personomics, humanomics) background. This ensures optimal treatment efficacy (Figure 2).

3.1 | Novel biomarkers and clustering

Biomarkers, whether determined in vivo or in vitro, have emerged as a critical tool in the field of precision medicine for predicting clinical outcomes. The ideal biomarker samples should be collected at the point of care using quick and noninvasive methods, and the assessment should be cost-efficient.[56] Data from one disease can be meta-analyzed across diseases using breakthrough AI algorithms, expediting the development of new biomarkers for responsiveness or non-responsiveness to medication or novel targets for therapeutic intervention based on molecular pathway similarity.[57] Although there are currently no validated biomarkers to indicate a good response to AIT, research has revealed distinctions between responder and non-responder patients.[26] Potential AIT biomarkers are shown in Table 2.

Cluster analysis, a part of unsupervised learning, can uncover hidden patterns in complex data sets and provide novel insights into allergy and asthma sub-phenotypes and the underlying mechanisms of these conditions.[58] It allows us to find natural groupings

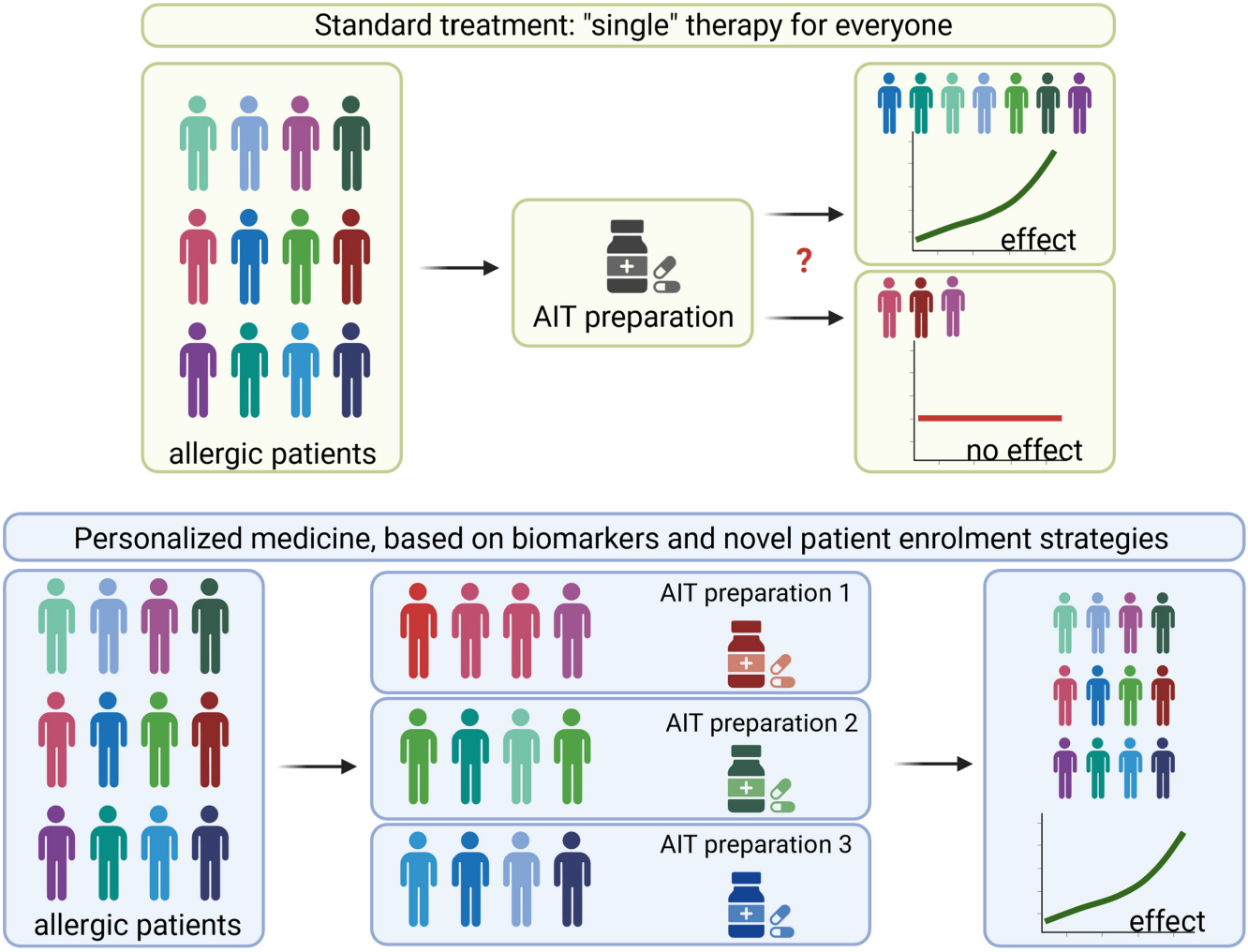


FIGURE 2 Novel approaches for successful AIT. Personalized medicine allows the selection of treatment that is most likely to benefit patients based on understanding their disease phenotype and endotype. Current AIT approaches aim to identify specific biomarkers, including patient sensitization at the molecular level aiming at cluster analysis. Cluster analysis is a statistical tool that groups patients into clusters based on their similarities. In the context of allergies, patients might be grouped based on shared symptoms, biomarkers or responses to different treatments. AIT, allergen immunotherapy.

that are difficult to identify manually, especially in high-dimensional data. The strength of these findings lies in their potential to enable personalized diagnosis, treatment and prevention strategies.

Clustering algorithms can effectively identify ex vivo predictive biomarkers in peanut allergy. A high-resolution view of immune cell populations and their changes during diagnostic oral food challenges reflects the dynamic of inflammation processes. It potentially provides a safer, more efficient method for monitoring therapeutic interventions like OIT.[59]

3.2 | Applications of mobile Health (mHealth)

Digital Health will greatly impact different aspects of AIT,[72] including a better selection of patients to be treated, a more precise selection of allergens and improved monitoring of adherence to treatment, side effects and clinical efficacy. Baseline monitoring of pollen exposure and disease severity is facilitated by dedicated electronic (e)Diaries, such as MASK-Air,[73] AllergyMonitor,[74] Hustenblume[75] and others. They allow patients to daily record their symptoms, quality of life, and drug intake so that trajectories of internationally validated severity scores, such as daily symptom score (dSS), combined symptom medication score (CSMS), visual analogue scale (VAS), are made available to the doctor through comprehensive reports.[76,74] Through this, doctors can get prospective information on disease severity and symptom control achieved via preventive measures and therapeutic intervention.[77,78] On the other hand, by matching trajectories of disease severity against those of pollen counts, doctors get more precise insights into a potential causal-effect relationship between one specific pollen and the patient's symptoms.[79] Some eDiaries also allow daily registration of AIT side effects, which can be particularly useful for prompt clinical evaluation and, if necessary,

TABLE 2 Potential biomarkers for the AIT efficacy, stratification and efficacy prediction.

Biomarker	AIT efficacy	Ref.
Basophil response to allergens	A valuable tool for monitoring the effects of AIT. A decrease in basophil sensitivity after 3 weeks of SCIT predicted long-term improvement in seasonal SMS	60
IL-10$^+$CTLA-4$^+$ ILCs	This subset of ILCs showed an increase after 24 months of AIT in patients with AR triggered by HDM. The increase is correlated with the SMS	61,62
CD29$^+$ (beta 1 integrin ITGB1) B memory cells	CD29 is upregulated on two unique subsets of allergen-specific B memory cells after 4 months of SLIT for grass pollen allergy. It can be used as an early biomarker for treatment effects	63
Surface IgG$_4$ and CD23$^+$ (FCER2) B memory cells	An increase in the proportion of allergen-specific B memory cells expressing surface IgG4 and CD23 was seen after SLIT. It is indicative of changes due to the treatment	
CD38$^+$ B cells	Their presence is associated with poor therapeutic effects of AIT in AR patients. CD38$^+$ B cells convert T_{REG} cells into T_H17 cells. CD38$^+$ B-cell frequency was negatively correlated with T_{REG} and T_{FR} cells frequencies	64
IgA$_1$ in nasal fluid	This correlates with the suppression of nasal symptoms during SLIT	65
Serum IgA, IgE, IgG$_4$	These, added to other parameters, enhance the ability to identify non-responsive patients in the second year of AIT	
Mast cell functional assay	A new method using passive sensitization of transgenic mast cells with patient serum. This might assess AIT treatment effectiveness and longevity of response	66
Metabolic biomarkers (eicosanoids, 12(S)-HETE, 15(S)-HETE)	Monitors AIT response in allergic asthma or AR. Their levels increased in the first year of SCIT treatment and then decreased from Years 1 to 3	67,68
Biomarker	**AIT stratification/efficacy prediction**	**Ref.**
CD4$^+$ CD25$^+$ FoxP3$^+$ CD127$^-$ cells	The increase in the frequency of CD4$^+$ CD25$^+$ FoxP3$^+$ CD127$^-$ cells after the AIT, and the low level of cells at the onset of AIT correlate with better treatment efficacy	69
T2 cells (IL-4$^+$-IL-13$^+$-CD4$^+$ cells)	Predictive of peanut and baked egg tolerance before AIT. High egg-specific T2 cells frequency is most predictive of oral AIT failure	70
Chemokine receptor protein 6 (CCR6$^+$) cells	These were not predictive of peanut and baked egg tolerance at baseline	
Bronchial allergen challenge	Biomarker for AIT in asthma, specifically the response to the early (EAR) and late asthmatic reaction (LAR). Reduction in response was reported, and those who develop a dual response (EAR and LAR) with high eosinophilic inflammation are more likely to respond to AIT	13
Serum periostin levels	High levels are associated with an effective response to SLIT. The improvement of the rhinoconjunctivitis quality of life questionnaire (RQLQ) directly correlated with the serum periostin level	71

Abbreviations: +, presence; −, absence; AIT, allergen immunotherapy; AR, allergic rhinitis; B, B lymphocyte cell; CD, cluster of differentiation; HDM, house dust mite; HETE, hydroxyeicosatetraenoic acid; IgA/E/G, immunoglobulin class A/E/G; IL-10, interleukin 10; ILC, innate lymphoid cell; SCIT, subcutaneous AIT; SLIT, sublingual AIT; SMS, symptom-medication score; T2, Type 2 immune response; T_{FR}, T follicular regulatory cell; T_{REG}, T lymphocyte regulatory cells.

intervention or AIT dosage modulation. Moreover, the possibility to record daily medication intake provides real-time information on adherence, for example, to SLIT.[80,81] This gives the allergist a chance to support a reluctant patient by him/her with convincing information on the importance of adherence to AIT. Last but not least, disease severity trajectories during the baseline pollen season compared to those of seasons during or following AIT treatment, may give information on the level of treatment efficacy.

3.3 | Molecular allergy diagnostics

The most known benefit of the molecular allergy IgE tests (also designated 'component resolved diagnostics'—CRD) in the diagnostic work-up of allergic patients is their potential to differentiate genuine primary sensitizations from cross-reactivity due to the presence of IgE towards panallergens.[82] This is primarily useful for patients with many positive extract-based test results or those with an inconclusive clinical history. As a targeted prescription of AIT is often difficult, if not impossible, for those patients, additional information on the molecular IgE profile can reduce the number of primary elicitors and facilitate the choice of suitable therapeutic preparations.[83,84] Further, allergens of low abundance in the source material may be underrepresented or even missing in extract-based test solutions (Figure 3). As this may also be the case for batches of therapeutic preparations, knowledge of the width of a patient's molecular IgE profile may provide valuable information to estimate the chances of treatment success.[85,86] In addition, the presence of IgE to certain molecules may serve as a clinical risk marker (e.g. sIgE to Der p 23—house dust mite (HDM)[87] or Phl p 7—timothy grass[88] as risk markers for asthma), facilitating the decision on AIT prescription, also in a potential setting of

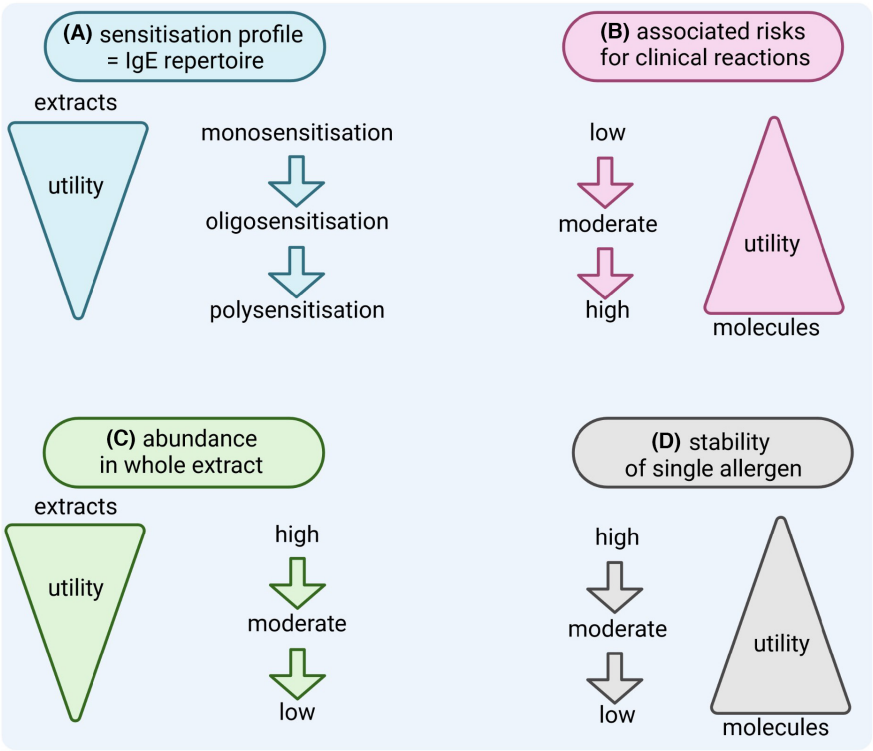


FIGURE 3 Utility of allergen extracts and allergenic molecules for the diagnostic work-up. Extract-based diagnostics are more suitable for: (A) mono/limited oligo sensitizations (B) and/or minor clinical risks (C) as well as a high abundance of molecules in the suspected allergen source (D) and/or allergens of high stability. The use of allergenic molecules should be considered in cases of polysensitizations and/or allergen triggers associated with high clinical risks and low abundant and/or labile allergenic molecules in the extract. Reprinted with permission.[90] IgE, immunoglobulin E.

tertiary prevention.[89] While our knowledge of new (pan)allergens and their clinical relevance is constantly growing, structured information is important for clinicians and researchers alike. For example, an updated summary of allergen molecules and their use in allergy diagnosis and AIT prescription is now available in the 2nd edition of the EAACI Molecular Allergology User's Guide.[90]

4 | NEW METHODOLOGY FOR CLINICAL RESEARCH

The classical type of experimental design is randomized controlled trials (RCTs), where participants are randomly assigned to one of two or more groups: (1) an experimental group, which receives the intervention or treatment under investigation; or (2) a control group, which receives a placebo treatment (participants are blinded to their allocations), in addition to standard care or no intervention. The random assignment helps to ensure that any differences between groups are due to the intervention itself and no other variables, thus reducing potential bias and confounding factors. However, enrolled participants differ from one another in known and unknown ways that can influence study outcomes, and cannot be directly controlled.[91]

Lately, there has been interest in novel trial designs, for more flexibility, efficiency, and cost-effectiveness. One of them is adaptive trial design, a type of clinical trial that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial. These changes can be made based on observations from the data collected during the trial.[92] Adaptations can involve one or more aspects of the trial, such as sample size re-estimation, number of treatment arms (adding or stopping early), randomization ratio, modification in inclusion/exclusion criteria or modification in statistical hypothesis.[93] Another group of trials are complex clinical trials, which allow the evaluation of more than one or two therapies in more than one patient type or disease within the same overall trial structure. This design includes multiple targeted therapies in the context of a single disease (umbrella study), single targeted therapies in the context of multiple diseases (basket study), or multiple targeted therapies in the context of a single disease that allows different therapies to enter or leave the platform (platform studies); all based on the master protocol overreaching to answer multiple study questions.[94] However, these designs may be a sources of bias, that can influence participants as well as investigator behaviour, and statistical estimates, also the study integrity may be damaged.[95]

There are also hybrid approaches that incorporate elements from multiple types of trial designs. It could involve a study design that has elements from both RCTs and adaptive trials.

There are not a lot of adaptive or complex studies in AIT. A three-stage design for AIT trials was developed to avoid maintaining the control arm on placebo for the course of the study, which can result in numerous dropouts, while still allowing for a stage-wise statistical evaluation to test for benefit at the end of each stage. The placebo group in Stage 1 becomes the active treatment group in Stage 2. In Stage 3, AIT is stopped to see if benefits are maintained after therapy.[96]

Another type of clinical data is real-world data (RWD) which refers to information that is collected outside the confines of RCTs.[97] RWD can come from various sources, such as electronic health records, insurance claim databases, patient registries, health surveys,

wearable devices and even social media posts.[98] When RWD is systematically analyzed, it generates real-world evidence (RWE), which can provide insights into a treatment's effectiveness, safety and cost-effectiveness in everyday clinical practice.[99]

RCTs and RWE complement each other in several ways. RCTs are considered the gold standard for determining a treatment's efficacy because they control for confounding variables through randomization and maintain strict protocols for treatment administration.[97,100] However, the patient populations in RCTs are often carefully selected and may not fully represent the diversity of patients seen in real-world clinical practice. RWE studies provide evidence from larger, more diverse and unselected patient populations, and the treatment is given under routine clinical conditions. This means RWE can capture a broader range of patient experiences, from different demographics to those with comorbidities, thus providing insights into how a treatment performs in 'real-life' conditions.

The application of RWE shows some limitations. The quality and completeness of RWD can vary greatly, depending on the data source and collection methods. There might be errors or gaps in data, and missing data can introduce bias. Because RWD is observational, it may not be possible to establish a clear cause-effect relationship as in RCTs. Variability in clinical practice can introduce confounding factors that are hard to control for in the analysis.[101]

Several AIT registries have been developed to provide consistent, high-quality RWD, such as the British Society for Allergy and Clinical Immunology—BSACI Registry for ImmunoTherapy (BRIT)[102] and the OmaBASE registry,[103] or Danish National Health Service Prescription Database and Statistics Denmark Database.[104] These registries are helping to further our understanding of the safety and efficacy of AIT and biologicals for allergies and urticaria in real-world settings.

RCTs have shown that AIT is effective in reducing allergy symptoms, and RWD-based studies have provided evidence that these benefits can extend to the long term and in diverse patient groups.[105–108] Additionally, in patients with concurrent asthma, AIT was associated with a reduced likelihood of asthma exacerbations and pneumonia.[109] RWD of persistence and adherence rates showed for SCIT and SLIT significant variability depending on the study methodology and duration of follow-up.[110,111] Furthermore, RWD can capture the effectiveness of AIT in reducing healthcare costs and the rates of adherence to therapy, areas often not covered in RCTs.[112–114]

5 | METHODS IN AIT DEVELOPMENT PROGRAMS: CURRENT STANDARDS AND FUTURE NEEDS

In Europe, the regulatory background for the clinical development programs in AIT refer to methodological guidelines by the European Medicines Agency (EMA).[115,116] These guidelines emphasize a scientific need for further investigations on 'ideal' clinical endpoints (by, e.g. reflecting the clinical relevance of treatment effect sizes reported), placebo effects and alternatives to conventional field trials.[117–119]

The EAACI has published a consented position paper on 'standardisation of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis' aimed to extract characteristics of different endpoints broadly used in AIT development programs.[120] The EAACI-Task Force has elaborated a standard definition for a homogeneous CSMS for the primary endpoint in future trials to harmonize this important parameter for the clinical readout of trials.[121] Although frequently used in recent pivotal trials, a formal (clinical) validation of this definition is still needed. Recently published first analyses have used RWD from apps to generate and validate several CSMS definitions. Based on this data, mobile health tools can play an important role in future stratification and follow-up of patients in controlled trials and RWE.[122] Another study has correlated several patient-reported outcome measures (PROMs) with a validated questionnaire-based tool on data from a pivotal randomized, placebo-controlled trial on SLIT in birch pollen allergic patients.[123]

The methodological problem in AIT clinical trial programs is a huge placebo effect demonstrated for both SCIT and SLIT application routes in many studies.[124,125] High response in the placebo arm within controlled trials minimizes the treatment effect size for the investigated AIT product, found in several trials on promising candidates in AIT development.[126] However, methodological recommendations from learned societies such as the EAACI provide solutions in conducting clinical trials in AIT aimed to minimize the treatment effect of inactive comparators revealing the real potential of future candidates in AIT.[125]

Several confounders impact clinical trials in AIT development programs, such as false reporting of PROMs, imputation of missing data or the role of natural (non-standardized) allergen exposure impacting the outcome of a (field-) trial.[116] Allergen provocation under standardized conditions in so-called allergen exposure chambers (AECs) may overcome methodological flaws.[127] Still, to date, this technology is not clinically validated to replace 'classical' field trials under natural exposure, as emphasized by EMA in the aforementioned guideline.[128] However, an EAACI task force comprising worldwide clinicians, AEC providers and delegates from regulatory authorities has provided overviews of the similarities and differences of current AEC facilities with the aim of further harmonization.[129] An important step in this direction has been the compilation of technical validation data reported by international AEC providers, opening the path for the next step of AEC development, the clinical validation, for example, through a hybrid approach.[130,131]

6 | ADVANCED DATA MANAGEMENT: BIG DATA AND ARTIFICIAL INTELLIGENCE (AI)

Biomedical big data can be broadly classified into two categories: omics and non-omics data. Non-omics data are highly variable and includes epidemiological information, clinical data, lab tests, imaging parameters, environmental monitoring and electronic health records

registered by healthcare professionals.[132] Collecting data might face difficulties due to data protection regulations. Omics data (such as genomics, epigenomics, transcriptomics, proteomics and metabolomics), generated using high-throughput biological platforms, offers many features at different biological levels, such as DNA, RNA, proteins and metabolites.[133,134] Challenges arise from the inherent heterogeneity of non-omics data and its subjective nature, which can lead to dataset biases.[135] While omics data are generally bias-free, its complexity, heterogeneity, dynamics, uncertainty and high dimensionality can pose difficulties in data integration.[134,136]

The analysis of big data using AI encompasses a variety of processes and techniques, including the investigation of patient data, genetic information, environmental factors and medical records, to uncover potential triggers and risk factors.[137] This can facilitate early interventions and prevention strategies, improving patient outcomes.[138] For example, AI can mine clinical trial data, and patient records, published literature, identifying new insights into the mechanisms of allergic reactions and potential therapeutic targets, or can be leveraged for disease subtyping, deriving mechanistic insights or biomarker prediction.[139] A subset of AI, machine learning (ML), is particularly adept at processing large volumes of intricate data, making unbiased meaning and insights extraction possible.[140] However, building causal genotype–phenotype associations and understanding environmental impact remain computationally challenging.[141]

AI and ML are currently employed in allergy for various tasks such as monitoring airborne pollen counts and predicting the risks associated with air pollution,[142] a significant contributor to the exacerbation of respiratory diseases.[143] Also supporting the diagnosis of adverse reactions to drugs or vaccines, improving patient engagement, diagnostic accuracy and personalized treatment plans.[144,145] AI's capabilities also extend to predicting disease sub-phenotypes in food-allergic patients, aiding in patient stratification into distinct disease or exposure subgroups, risk stratification, cluster analysis and biomarker identification.[146–148]

A limited number of studies have investigated AIT outcomes. ML-assisted fourier-transform infrared (FTIR) spectroscopy allowed for the discrimination of sera obtained from healthy, allergic and AIT-treated humans, thereby demonstrating its potential for rapid diagnosis of allergy and monitoring of patients. AI can predict the probability of sustained unresponsiveness after milk oral AIT.[149] ML also can enable unbiased phenotyping and identification of cell subsets that are involved in AIT treatment.[150]

Despite the immense potential, RWE, passively collected through hospital systems or public health data-capturing procedures, often presents challenges. The issues of data structuring, quality and missing fields can obstruct traditional analysis. However, AI is demonstrating its value by addressing these problems and unlocking the potential within these large and less structured datasets. In the context of allergy and allergen immunotherapy, the use of AI in managing and interpreting such RWD can lead to the development of more personalized and effective therapeutic strategies, paving the way for the next generation of allergy care.[140,151]

7 | PHARMACO-ECONOMY OF AIT/COST-EFFECTIVENESS

According to Directive 2001/83/EC, test and therapy allergens are medicinal products in all European Union (EU) member states and are subject to marketing authorizations.[152,153] Allergic diseases, including allergic rhinoconjunctivitis, asthma and atopic dermatitis, have a significant impact on the health of the individual patient, but also on healthcare costs (direct, indirect and intangible) and the economy as a whole.[154–160] The role of AIT in the treatment of allergic diseases has been proven on the basis of clinical trials and long-term observations in real practice (RWE), but according to the EMA guidelines, the assessment of the AIT effects should take into account product-by-product treatment of allergy maintenance of efficacy during 2–3 treatment years, long-term efficacy and disease-modifying effect in post-treatment years.[161,162] Health technology assessment is based on the evaluation of incremental benefits (in terms of clinical efficacy and safety) related to the introduction of technology to clinical practice (comparative effectiveness assessment clinical, relative effectiveness assessment, in relation to the related incremental costs).[163–166] These analyses allow for the comparison of different therapy methods and single products, facilitate the evaluation of the advantages and disadvantages from an economic point of view, as well as play an important role in decision-making, for example, to support reimbursement decisions.

All forms of pharmacoeconomic studies are available in the current international literature on AIT. Unfortunately, factors such as differences in the methodology, differences in quality of health economic models, lack of studies on various allergens and guidelines of the four-stage approach to assessing the effectiveness of AIT required by EMA make economic assessments incomparable. In addition, AIT effectiveness is strongly dependent on treatment compliance.[112,167–174]

In Portugal, the cost-effectiveness of SCIT and SLIT in paediatric patients with HDM-triggered allergic asthma was investigated. Both therapies were cost-effective, particularly SCIT, which reduced drug use and exacerbations that required emergency room visits. SLIT had a bigger overall influence on the quality of life.[175] Another study found that SCIT, in combination with inhaled corticosteroids (ICS) was more cost-effective than ICS alone in HDM-induced asthma.[176] Interestingly, switching from SCIT to ILIT for bee venom allergy can result in significant cost savings, potentially halving the treatment costs over 5 years.[177]

In 2021, it was suggested that AIT may be cost-effective for people with allergic rhinitis with or without asthma and in high-risk subgroups for venom allergy. No conclusions on the cost-effectiveness of AIT for food allergy were shown in this study.[164] Moreover, in some publications, it is indicated that parameters such as quality-adjusted life year (QALY) and incremental cost-effectiveness ratio (ICER) may not be suitable for the economic assessment of chronic diseases.[112,166]

These complicated issues could be a challenge both for physicians prescribing allergens and for the payer/regulator in each

country. The Professional Society for health economics and outcomes research (ISPOR) guidelines indicate that cost-effectiveness analysis provides a standardized approach to value assessment. Still, this definition is interpreted differently by each stakeholder—patients, payers, providers or society at large.[178]

8 | ADVANCES IN AIT COMPOUND TECHNOLOGY

8.1 | Novel preparations

The extensive research concerning novel preparations in AIT, like recombinant allergens, synthetic peptides (T- and B-cell epitopes), IgG antibodies against allergens, carrier systems or adjuvants, are crucial to improve treatment efficacy, safety and patient compliance.

There are a few types of allergen derivatives that can reduce allergens' allergenicity while retaining their immunogenicity, unlike extracts that are obtained from natural sources that may contain a mix of allergenic and non-allergenic substances.[179] Wild-type recombinant allergens resemble all of the properties of adequate natural allergens, especially IgE-binding. Synthetic and recombinant hypoallergens can exhibit strongly reduced IgE-binding capacity and allergenic activity but contain allergen-specific T-cell epitopes (long synthetic peptides, recombinant hypoallergenic allergen derivatives) or carrier compounds providing T-cell help (peptide carrier-based B-cell epitopes).[180] Allergoids are chemically modified natural allergens, usually by polymerization or treatment with formaldehyde or glutaraldehyde, which show strongly reduced IgE-binding capacity.[181,182]

Recombinant birch (Bet v 1) allergens have been tested in clinical trials, showing an improvement in clinical symptoms.[183,184] Hypoallergenic B-cell epitopes based on grass pollen (Phl p 1) are safe and effective in AIT.[185–187] Also synthetic T-cell epitope peptides from the major cat allergen Fel d 1,[188] and birch, Bet v 1, can induce symptom reduction.[189] Monoclonal IgG antibodies against the dominant cat allergen Fel d 1 can prevent IgE binding and simultaneously prevent clinical symptoms,[190] and cocktail of antibodies against Bet v 1 can reduce symptoms after nasal challenge.[191]

Allergoid-mannan conjugates can interact with monocyte differentiation and reprogram them into stable tolerogenic dendritic cells (DC), which in turn could reduce allergic responses. This process involves metabolic and epigenetic changes and promoting T_{REG} cell production.[192]

A very promising approach is provided by modern adjuvant approaches. Adjuvant is a substance or compound that is co-administered with the allergen extract and has the ability to increase allergen immunogenicity and/or modulate the immune response. Adjuvants can be used to reduce the unwanted side effects associated with AIT by slowing allergen diffusion, lowering the risk of anaphylaxis and reducing allergen doses, which decreases the number of required injections, hence enhancing the safety profile. However, adjuvants can cause inflammation at the administration site.[193] Innovative adjuvants include microbial products such as TLR4-ligand monophosphoryl lipid A (MPLA) that is safe and effective in treating asthma in patients sensitized to olive pollen,[194] flaggelin, that enhances immunogenicity and reduces allergenicity for birch AIT,[195] or CpG which has in some studies been shown to be effective in the treatment of allergic rhinitis.[196] Other potential candidates include virus-like particles (VLPs), enhancing immunomodulation during AIT.[197] Notably, HDM-SCIT packaged into VLP with CpG was deemed safe.[198] Nanoparticles, both biocompatible and biodegradable, can act as adjuvants and might carry allergens in their complexes, and shield allergens from enzymatic digestion.[199,200]

TABLE 3 Biologicals used to support AIT.

Biological	AIT type	Outcomes	Ref.
Dupilumab (anti-IL-4 and IL-13 signalling)	SCIT in AR triggered by grass pollen	Improve SCIT tolerability but did not reduce post-allergen challenge nasal symptoms	202
	HDM-SLIT in asthmatic patients with AR	Benefits in controlling asthma	203
Omalizumab (anti-IgE)	Multifood OIT	Help patients consume multiple foods and allow for dose escalation, decreasing the time required to reach maintenance dosing and adverse effects	204–206
	Aeroallergens AIT in asthmatic patients	Fewer systemic allergic reactions to AIT enabled to achievement the target maintenance dose	207,208
	VIT	Overcoming severe adverse reactions to VIT	209
	Peanut OIT	Adjunctive omalizumab facilitated quicker peanut desensitization, but nearly 50% of patients stopped OIT within 72 months due to adverse reactions	210
Tezepelumab (anti-TSLP)	SCIT in AR triggered by cat allergy	Enhance the efficacy of SCIT and promote tolerance after a 1-year course of treatment	211

Abbreviations: AIT, allergen immunotherapy; AR, allergic rhinitis; HDM, house dust mite; IgE, immunoglobulin E; IL-4Rα, interleukin-4 receptor alpha subunit; OIT, oral immunotherapy; SCIT, subcutaneous AIT; SLIT, sublingual AIT; TSLP, thymic stromal lymphopoietin; VIT, venom immunotherapy.

8.2 | Combination of AIT and biologicals

The combination of AIT with biological increases the efficacy and safety of the treatment (Table 3). The synergistic influence of AIT and (T2 directed) biologicals shifts the balance toward type 1 immune response (T1). In addition, AIT induces the regulatory mechanisms (regulatory cells), while biologicals influence the effector compartment of T2 inflammation (desensitization of effector cells), so combining both can show an additive effect.[201]

9 | AIT FOR ALLERGIC ASTHMA

The precise pathways supporting the beneficial AIT effects for allergic asthma still remain unclear.[160,212–214] Thus, it exerts an overall anti-inflammatory effect reflected in the reduction of exacerbations and the dose of inhaled glucocorticosteroids (ICS) needed to control symptoms. There is also a small reduction in non-specific airway hyperresponsiveness (AHR) and a more significant impact on allergen-specific AHR.[215,216] AIT impacts both the late-phase response, involving the recruitment, activation and persistence of eosinophils and T cells at sites of allergen exposure and the immediate response to allergen provocation which is mast cell mediated.[217] The impact on lung function is less clear, probably because the small airways compartment was not properly evaluated in clinical trials, which mainly focused on large airways via measurement of forced expiratory volume in the first second (FEV_1) and peak expiratory flow (PEF).[218] Allergic inflammation can impair interferon (IFN) production via alarmins such as IL-33, T2 cytokines such as IL-4 and IL-13 and allergen/IgE interactions. It is interesting if inhibition of allergic pathways via AIT in allergic asthma can boost the anti-viral IFN production and protect against viral infections.[219,220]

The results of the RCTs show asthma symptom control, decrease in exacerbations and medication use are currently confirmed by RWEs.[105,221–223] It has been shown, that HDM-SLIT enhances bronchial epithelial antiviral tolerance against viral infection. These findings could explain why HDM-SLIT is effective at reducing allergic asthma exacerbations.[224] In both seasonal and perennial allergic asthma, AIT effectively reduced the risk of exacerbations and lower respiratory tract infections.[225] Clinical benefits have also been confirmed with pollen allergen extracts (both SCIT and SLIT).[12] Similar results were reported by REACT (real-world effectiveness in AIT) study, where in addition to the decrease in asthma treatment and severe asthma exacerbations in the AIT group, reductions in pneumonia with antibiotic prescriptions, hospitalizations and duration of inpatients stays were all in favour of AIT.[109] Studies of prescription databases in Europe indicate that AIT is effective in the treatment and management of asthma, outperforming groups that received only anti-asthmatic medication. Furthermore, birch pollen AIT has proven its long-term effectiveness, reducing AR and asthma medication intake up to 6 years post-treatment.[221] Asthma patients in the AIT group also had higher rates of complete drug reduction.[222] Additionally, the cost-effectiveness of AIT for allergic asthma, particularly SCIT, has been demonstrated, which may influence future policy decisions and prescribing habits. Even when accounting for allergic rhinitis as a comorbidity, SCIT remained cost-effective. As such, the studies support the wider use of AIT, and particularly SCIT, in the management of allergic asthma.[169]

Identifying the right patient for AIT is crucial.[226] Research suggests that polysensitized patients with allergic rhinitis and class 2–4 asthma, according to the Global Initiative for Asthma (GINA) guidelines, as well as those with a high eosinophilic response, are likely good responders to AIT.[13] After successful trials with HDM-SLIT tablets, current guidelines recommend AIT for patients with controlled or partially controlled HDM allergic asthma.[227] Using a biologic can improve asthma control and may allow more patients to be eligible for AIT.

10 | CHALLENGES, GAPS AND FUTURE DIRECTIONS

The primary advantage of AIT is its long-term disease-modifying effect. Among numerous challenges and gaps, the need for a more personalized and precision-driven approach to patient stratification and AIT management is crucial. It is necessary to refine phenotyping and endotyping using mHealth, molecular allergy diagnosis and comprehensive immune biomarker assessments. These tools can contribute significantly to both prospective and retrospective patient stratification, offering greater precision and optimizing therapeutics (theratypes). Additionally, it is crucial to focus on the development of innovative AIT preparations that are not only more effective but also safer and more convenient for patients. Combining AIT with biological therapeutics has shown great promise, and broadening its application may help improve patient compliance by reducing therapy-associated risks, duration and costs. The limited resources in the healthcare system present a challenge, especially concerning costs. Nonetheless, increased awareness among patients and payers about AIT's preventive effect on limiting allergic disease and asthma development or exacerbation should help address this challenge.

The progress is inherently connected to the methodology we utilize for clinical research. As these studies are resource-demanding, methodological enhancements are crucial to preserving resources and simultaneously producing high-quality evidence that meets regulatory requirements. This evidence is often gathered from RCTs and RWE. Dealing with the vast amount and complexity of data involved in these processes requires an advanced management approach. Here, AI can play an indispensable role by assisting with the processing of large datasets and generating meaningful insights from them.

In order to address the challenges and gaps in the field, we must focus on utilizing and advancing novel patient enrolment strategies, improving the methodologies for clinical research and further developing our approach to advanced data management. By harnessing the potential of mobile health, biomarkers, molecular diagnosis, big data, and artificial intelligence, we can make significant strides in personalizing and improving AIT for allergic patients. Future efforts should also

aim to maximize the pharmacoeconomic benefit, thereby making it a more cost-effective solution for allergy sufferers worldwide.

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