


REVIEW

One hundred and ten years of Allergen Immunotherapy: A journey from empiric observation to evidence

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Abstract

One hundred and ten years after Noon's first clinical report of the subcutaneous application of allergen extracts, allergen immunotherapy (AIT) has evolved as the most important pillar of the treatment of allergic patients. It is the only disease-modifying treatment option available and the evidence for its clinical efficacy and safety is broad and undisputed. Throughout recent decades, more insights into the underlying mechanisms, in particular the modulation of innate and adaptive immune responses, have been described. AIT is acknowledged by worldwide regulatory authorities, and following the regulatory guidelines for product development, AIT products are subject to a rigorous evaluation before obtaining market authorization. Knowledge and practice

Abbreviations: AGREE, APPRAISAL OF GUIDELINES RESEARCH & EVALUATION; AIT, allergen immunotherapy; APC, antigen-presenting cells; ARIA, Allergic Rhinitis and its Impact on Asthma; Breg, regulatory B cell; CCL, chemokine ligand; CONSORT, Consolidated Standards of Reporting Trials; COVID-19, coronavirus disease 2019; DBPC, double-blind, placebo-controlled; DC, dendritic cells; DCreg, regulatory dendritic cells; EAACI, European Academy of Allergy and Clinical Immunology; EBM, Evidence-Based Medicine; EMA, European medicines agency; EU, European Union; FAB, fragment antigen-binding; GINA, Global Initiative for Asthma; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HDM, house dust mite; ICER, Incremental cost-effectiveness ratio; IFN- γ , Interferon-Gamma; Ig, Immunoglobulin; IL, interleukin; ILC, innate lymphoid cells; iTreg, induced regulatory T cells; MPL, monophosphoryl lipid; NAEPP, National Asthma Education and Prevention Program; NPP, named patient products; nTreg, natural regulatory T cells; PDG2, prostaglandin D2; PLGA, poly(lactic-co-glycolic acid); QALYs, Quality-adjusted life years; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCIT, subcutaneous AIT; SLIT, sublingual AIT; T2, Type 2; Tfr, FOXP3⁺-T follicular regulatory cells; TGF- β , Transforming growth factor-beta; Th, T-helper; TLR, Toll-like receptor; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin; VAS, visual analogue scale; VIT, venom immunotherapy; VLP, virus-like particles; WAO, World Allergy Organization; WHO, World Health Organization.

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are anchored in international guidelines, such as the recently published series of the European Academy of Allergy and Clinical Immunology (EAACI). Innovative approaches continue to be further developed with the focus on clinical improvement by, for example, the usage of adjuvants, peptides, recombinants, modification of allergens, new routes of administration, and the concomitant use of biologicals. In addition, real-life data provide complementary and valuable information on the effectiveness and tolerability of this treatment option in the clinical routine. New mobile health technologies and big-data approaches will improve daily treatment convenience, adherence, and efficacy of AIT. However, the current coronavirus disease 2019 (COVID-19) pandemic has also had some implications for the feasibility and practicability of AIT. Taken together, AIT as the only disease-modifying therapy in allergic diseases has been broadly investigated over the past 110 years laying the path for innovations and further improvement.

KEYWORDS

allergen immunotherapy, allergic rhinitis, evidence, innovations, mechanisms

1 | INTRODUCTION

Noon's publication in 1911,¹ in which he described the beneficial effect of subcutaneous injections with grass pollen extract on himself, can be considered as a starting point of a clinical and scientific journey that led to the position currently held by allergen immunotherapy (AIT, Figure 1.²). AIT has evolved into a treatment underpinned by high-quality placebo-controlled studies, systematic reviews, and health technology assessment.^{3,4} The emphasis on the methodological aspects of AIT trials⁵⁻⁷ has led to more solid studies further strengthening the evidence.

Our knowledge of the immune modulatory mechanisms behind AIT has increased significantly, which may help us finding ways to improve the efficacy and practicalities of AIT. The scientific journey went from the measurement of IgG antibodies⁸ and the discovery of IL-10 producing regulatory T cells⁹ to the new insights which is available now about the role of the innate and adaptive immune system¹⁰ in AIT.

Importantly, AIT has found its way to regulatory, clinical guidelines, and care pathways. AIT has been acknowledged by national and supra-national regulatory bodies as an effective treatment for allergic rhinoconjunctivitis. In addition, in recent years EAACI has embedded AIT in a series of guidelines.¹¹⁻¹⁵ Finding ways to modify and improve AIT and to obtain better implementation of AIT in real life are the challenges for the next decades.

2 | MECHANISMS IN AIT

Characteristic features of allergic inflammation include IgE-dependent activation of mast cells and local recruitment and activation of eosinophils and basophils under the influence of Th2 type T lymphocytes that secrete interleukin (IL)-4, IL-5, IL-9, and IL-13.¹⁰ Recent knowledge has highlighted the role of innate immune cells in Type 2 immunity. These include innate lymphoid cells (ILC-2s)¹⁶ and

basophils as potent alternative sources of type 2 (T2) cytokines.¹⁷ Dendritic cells (DC2s),¹⁸ under the regulation of the respiratory epithelium-derived cytokines thymic stromal lymphopoietin (TSLP) and IL-33, have been shown to augment preferential induction of Th2 T cells and ILC-2s.¹⁹

Within 2–4 weeks of commencing allergen immunotherapy, and at low allergen doses, there is an increase in regulatory T cells that produce cytokines including IL-10^{9,20} and TGF- β ^{21,22} that suppress antigen-driven Th2 cells and induce B cells to undergo immunoglobulin heavy chain switching toward, respectively, allergen-specific IgG2²³ or IgG4²⁴ and IgA production,²⁵ detectable in serum and local nasal secretions²⁶ (Figure 2). Competition with IgE for allergen prevents IgE-allergen complex formation resulting in inhibition of Fc ϵ R1-dependent mast cell and basophil activation^{27,28} and a decrease in Fc ϵ R2 (CD23)-dependent IgE-facilitated activation of memory T cells.^{29,30} Within 12 months, high dose allergen exposure during continued allergen immunotherapy results in immune deviation in favor of allergen-specific Th1 responses^{31,32} under the influence of IL-12³³ and IL-27³⁴ with an increase in interferon-gamma that suppresses IL-4-induced B-cell IgE switching in favor of allergen-specific IgG antibodies.

Recent novel findings include distinct subsets of T cells that include antigen-specific CD27⁺-Th2A cells³⁵⁻³⁷ and IL-21-producing T follicular helper cells³⁸ that contribute to Th2 cytokine synthesis and IgE-switching. These events are inhibited within months during immunotherapy, likely under the influence of regulatory cells that include a distinct subset of regulatory T cells that produce IL-35 (IL-35-Tregs),³⁹ in addition to regulatory B cells^{40,41} and FOXP3⁺-T follicular regulatory (Tfr) cells,⁴² both of which represent alternative sources of IL-10. Innate lymphoid cells (including ILC-2s) do not possess T-cell receptors and are therefore unable to respond directly to antigen triggering but likely augment/amplify Th2-driven inflammation under the influence of epithelial cytokines.¹⁹ Seasonal increases in ILC-2s are inhibited by pollen immunotherapy.⁴³ Recently, a distinct

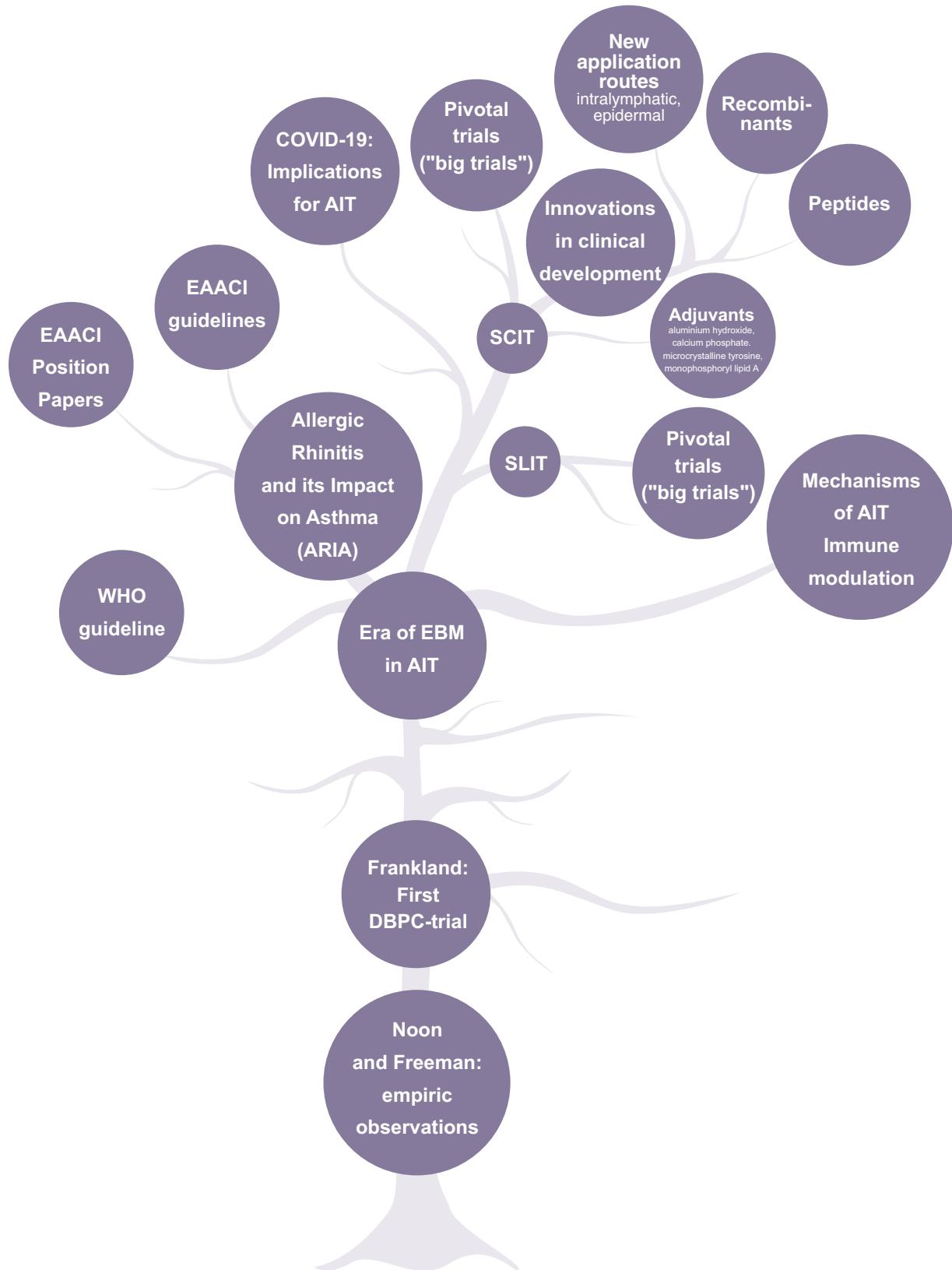


FIGURE 1 Allergen immunotherapy: 110 years of evidence-based evolution and innovations. Abbreviations: AIT, allergen immunotherapy; ARIA, Allergic Rhinitis and its Impact on Asthma; COVID-19, coronavirus disease 2019; DBPC, double-blind, placebo-controlled; EAACI, European Academy of Allergy and Clinical Immunology; EBM, Evidence-Based Medicine; WHO, World Health Organization; SCIT, subcutaneous AIT; SLIT, sublingual AIT.

subset of ILC-2s that produce IL-10 and have regulatory properties has been identified⁴⁴ that increases after immunotherapy and may contribute to an overall suppression of Th2 immunity during immunotherapy.

Grass pollen allergen immunotherapy, when given for a minimum of 3 years, results in persistence of clinical benefit for several years beyond cessation of treatment,⁴⁵⁻⁴⁷ accompanied by persistent IgE-blocking activity. It is not known whether the prolonged memory responses necessary for this long-term antigen-specific tolerance reside within T-cell or B-cell compartments, or both, a key issue that requires resolution. Although detectable in controlled clinical trials, whether these novel findings will translate into biomarkers to predict

or monitor responses to immunotherapy in individual patients remains to be tested.^{48,49} Using large cohorts of individual data from DBPC AIT studies may allow stratification of high/medium/low responders aimed at better identification of candidate biomarkers.⁴⁶

3 | REGULATORY PREREQUISITES, UNMET NEEDS, AND FUTURE DEMANDS

Allergen products for in vivo diagnostics and therapeutic applications are considered medicinal products and, thus, subject to regulation by competent authorities.⁵⁰ Based on an evolving framework

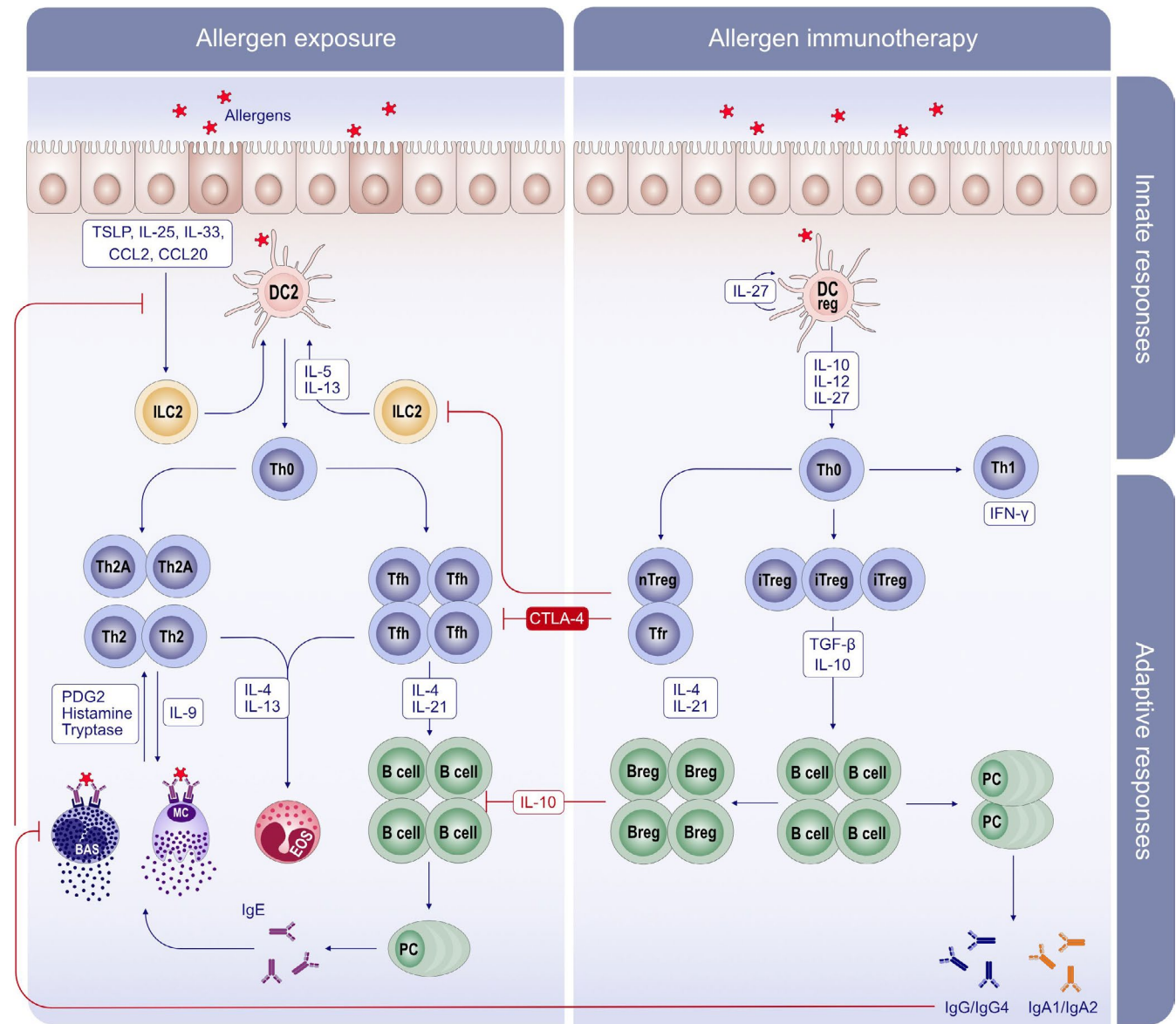


FIGURE 2 Mechanisms of allergen immunotherapy. Reproduced with permission from.¹⁰ Abbreviations: Breg, regulatory B cell; CCL, chemokine ligand; DC, dendritic cells; DCreg, regulatory dendritic cells; Ig, immunoglobulin; IL, interleukin; IFN- γ , interferon-gamma; iTreg, induced regulatory T cells; nTreg, natural regulatory T cells; PC, Plasma cell; PDG2, prostaglandin D2; Tfr, FOXP3⁺-T follicular regulatory cells; TGF- β , transforming growth factor-beta; Th, T-helper; TLR, Toll-like receptor; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin.

Conclusion:

The disease-modifying effects of allergen immunotherapy are associated with immune modulation of the innate and adaptive immune responses. The recent advances in understanding the mechanisms underpinning AIT will enable us to identify immune monitoring biomarkers as well as biomarkers of efficacy and tolerance. Furthermore, this knowledge will pave the way for novel therapeutic targets that can be used in conjunction with immunotherapy to shorten treatment duration and improve patient compliance and efficacy.

Conclusion:

Current regulations of allergen products by competent authorities have successfully integrated scientific progress in modern allergology and clinical development. Definitions of homologous allergen groups based on biological and molecular relationship, manufacturing, and quality aspects have been combined with a framework for the clinical development of allergen products. Finally, a list of in vivo diagnostic and AIT products has to be market authorized, if based on important European allergen sources, including pollen, dust mites, pets, and venoms.

for European Union (EU) member states, new guidelines⁵¹ have been developed within the European Medicines Agency (EMA), recently reviewed by experts of the Paul Ehrlich Institute, German Federal Institute for Vaccines and Biomedicines.⁵² In brief, this document⁵¹ provides principles and guidance for future regulation of medicinal allergen products facilitating further harmonization within the EU built on already existing EMA guidelines focusing on a) quality aspects and b) clinical development of allergen products. The EMA guideline on quality aspects⁵³ introduced the concept of homologous allergen groups not only based on taxonomic relationship of the allergen sources but also on structural homology of their major allergens.^{54,55}

Another EMA document⁵⁶ provides a framework for the stepwise development with the goal of market approval after dose-finding studies for safety and efficacy and at least one large, multi-center, randomized, controlled field study demonstrating clinically relevant efficacy and safety of AIT compared to placebo treatment.

The guidelines acknowledge that efficacy of AIT is product-specific. Differences in qualitative and quantitative composition, formulation of the product, route of administration, number and intervals of application occur in products from the same source material. Therefore, each allergen product is separately evaluated by competent authorities for quality, efficacy, and safety. This does not apply for rare allergen sources being provided as named patient products (NPP) for individual use. The new guidelines do not allow the use of NPPs for preparations containing allergens from common sources listed in Table 1, whether alone or in combination.⁵² A question remains as to whether properly powered clinical studies will be possible for Mediterranean allergen sources from the *Oleaceae*, *Cupressaceae*, and *Parietaria* groups in the future. If this is not the case, these allergen sources may continue to be marketed as NPP and as such will allow more flexibility regarding mixing with, that is, related allergens and/or dose adaptation resembling a "personalized" approach in AIT.

In addition, several aspects of AIT beyond market authorization need to be addressed in future studies, including rigorous "real-world" and additional studies that further explore the efficacy and safety of AIT during routine clinical use, in patients with asthma and children as well as their long-term efficacy (Table 2).

4 | CLINICAL EFFICACY OF AIT

Since Noon's publication in 1911,¹ AIT has gained a permanent place in the therapeutic arsenal for the patient with allergy. While evidence in the first decades of the 20th century was mainly supported by practical experience, case reports, and patient series, in later years solid clinical studies provided increasingly better evidence for the effectiveness of immunotherapy. The first placebo-controlled grass pollen study was published by Frankland in 1954.⁵⁷ In 1986, Scadding reported the first placebo-controlled study on the effectiveness of sublingual immunotherapy using very low doses.⁵⁸

In the 1960s-1970s, pioneering research from Norman and Lichtenstein provided tools to design and perform clinical studies of immunotherapy.⁵⁹ They defined measurable immunological and clinical parameters. Moreover, they underpinned the use of well characterized allergenic extracts, defining an optimal immunizing dose with minimal risk of anaphylaxis. Studies on subcutaneous AIT (SCIT) were initially limited by low numbers of participants. The largest grass pollen study with 410 patients was published by Frew et al.⁶⁰ Large appropriately randomized placebo-controlled sublingual AIT (SLIT) tablet studies for grass pollen in adults^{61,62} and children,⁶³⁻⁶⁵ for house dust mites in adults and adolescents,⁶⁶⁻⁶⁸ ragweed pollen,⁶⁹ and birch pollen in adults⁷⁰ have confirmed the efficacy and safety of SLIT with tablets. Efficacy and safety have also been established with ragweed⁷¹ and birch pollen drops.^{72,73} There was a persistence of the effect after cessation of SLIT ("carry-over"-effect).^{74,75} The demand for harmonization of study design and outcome measures led to the requirements for studies to meet the Consolidated Standards of Reporting Trials (CONSORT) criteria,⁶ the recommendations by the World Allergy Organization (WAO)⁵ and the guidance in the EAACI position paper on outcome measures.⁷

The strength of immunotherapy lies in its potential to alter the natural course of allergic disease. Disease modification may imply that the effect of immunotherapy persists after discontinuation of treatment. In 1999, a small study showed that the effect of SCIT with grass pollen lasts 3–4 years after discontinuation.⁴⁵ Three years of sublingual immunotherapy with grass pollen induced persistent efficacy of 2 years.⁴⁶ Another aspect of disease modification is the

TABLE 1 Common allergen sources^a for AIT or in vivo allergen diagnosis in Europe.

Common allergen sources^a for AIT or in vivo allergen diagnosis in Europe

Pollen from the group of sweet grasses of the *Poaceae* (*Gramineae*) family
 Pollen from the birch group
 Pollen from the *Oleaceae* group
 Pollen from the *Cupressaceae* group
 Pollen from *Ambrosia artemisiifolia* and *Ambrosia trifida*
 Pollen from *Parietaria judaica* and *Parietaria officinalis*
 The group of house dust mites of the *Dermatophagoides* genus
 Bee and wasp venom
Felis domesticus (Cat)
Arachis hypogaea (Peanut)
Prunus persica (Peach)

Abbreviations: AIT, allergen immunotherapy.

^aFull documentation and market authorization considered mandatory (from Annex I of Recommendations on common regulatory approaches for allergen products⁵¹).

TABLE 2 Important aspects of AIT post-market authorization.

- Long-lasting AIT effects, covering not only 2, but 5 or even 10 years of follow-up
- Efficacy and safety of AIT in patients with asthma
- Efficacy and safety in pediatric populations (also outlined in the pediatric investigation plan¹⁵²) including preventive effects regarding disease progression, that is, asthma development and new sensitizations

Abbreviations: AIT, allergen immunotherapy.

prevention of asthma development in children. Two landmark papers have been published. The open-controlled PAT study⁷⁶ showed less asthma in children treated with SCIT in the 7-year follow-up period. The placebo-controlled GAP study reported less asthma symptoms and medication use in the group treated with sublingual grass pollen tablets.⁷⁷ However, the primary outcome—the time to the diagnosis of asthma—was not different between both groups. In addition, the GAP study also showed a long-term effect on rhinitis symptoms, 2 years after discontinuation of treatment.

AIT found its origin in treating hay fever patients, but gradually other areas were explored. In an early prospectively controlled 14-year study among asthmatic children. Johnstone and Crump demonstrated that 72% in the treated group lost their asthma symptoms compared to 22% in the placebo group.⁷⁸ Warner showed that those children who benefit most from AIT with *D. pteronyssinus* lost the late-phase reaction after bronchial provocation.⁷⁹ While SCIT is hampered by potential risks for asthma patients,⁸⁰ a successful study with sublingual dust mite tablets offers new perspectives for adult allergic asthma patients.⁸¹ Sublingual AIT was shown to have a beneficial effect on asthma exacerbations⁸¹ which led to market authorization of this sublingual tablet by EMA and to a recommendation in the current Global Initiative for Asthma (GINA)⁸² as step 3 or 4 medication. However, this treatment was not regarded as effective by the National Asthma Education and Prevention Program (NAEPP) in the US and further

clinical confirmation of efficacy based on a study investigating exacerbations in the field is needed.

In 1962, Mary Loveless demonstrated in a classical study that wasp allergic patients were protected by pure venom injection.⁸³ Only in 1978, this could be confirmed in a placebo-controlled double-blind study.⁸⁴

The first placebo-controlled study with injections of peanut extract was effective but had to be terminated due to a fatal anaphylactic reaction in a placebo patient who accidentally received active treatment.⁸⁵ However, the way was paved for many high-quality oral,⁸⁶⁻⁹¹ sublingual,⁹²⁻⁹⁴ and epicutaneous^{95,96} immunotherapy trials with food.

Conclusion:

During a history of 110 years, AIT has evolved to become one of the pillars of the therapeutic approach for allergic patients. Both effectiveness and disease-modifying properties have been proved in numerous studies. Moreover, having originated as a treatment for hay fever patients, nowadays AIT is also indicated in patients with asthma and insect venom allergy and is being developed for the use in food allergy.

5 | GUIDELINES IN ALLERGEN IMMUNOTHERAPY

5.1 | Need for guidelines

Every year more data on different approaches to allergen immunotherapy is published. Some publications should lead to a change in practice while others should not. So there is a need for a quality assessment of published studies and a synthesis of the results focusing on what they mean for clinical practice. This is the realm of evidence-based clinical practice guidelines. The first guidelines were the US Practice Parameters⁹⁷ and the 1998 World Health Organization (WHO) Position Paper on AIT.⁹⁸ It was followed by *Allergic Rhinitis and its Impact on Asthma* initiative (ARIA)⁹⁹ and other guidelines.

5.2 | Approach to developing guidelines

Clinical guideline development has improved over recent decades. An EAACI review of AIT guidelines published from 1980 to 2016 found 31 guidelines. Unfortunately, most of them scored very poorly on the *APPRAISAL OF GUIDELINES RESEARCH & EVALUATION* (AGREE II) assessment tool, particularly in terms of applicability, rigor, and stakeholder involvement.¹⁰⁰ The recent EAACI AIT Guidelines Project followed the AGREE II approach.¹⁰¹ Each guideline task force consisted of members from all the stakeholder groups, including patient representatives. They defined the scope of each guideline

and the key clinical questions. This led to a systematic review and meta-analysis of the relevant literature. This underpinned the resulting guideline. Recommendations were developed by the guideline task force weighing up the risks and benefits of each potential intervention according to the available evidence. The AIT guidelines have now been published, and work is ongoing to disseminate and implement them.¹⁰¹

5.3 | EAACI AIT Guidelines

Five guideline papers with numerous supporting systematic reviews and position papers have been published.^{11,12,13,15,101} The key recommendations are summarized in Table 3. For a detailed description of the underpinning evidence including safety data and the strength of each recommendation, the individual guideline should be reviewed. The earlier guidelines used a modified Oxford Centre for Evidence-Based Medicine approach to rate the evidence at a study/paper level and help to determine the strength of the recommendation. For the final guideline focused on asthma, the *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE) approach was followed.¹⁰² This approach rates evidence at the level of each outcome (e.g., asthma exacerbations, asthma control) and includes all the studies/papers that include this endpoint. GRADE is a more complicated methodology but provides a more robust summary of the quality and strength of the evidence—it is becoming the leading approach to developing clinical guidelines within the AGREE II framework. However, current guidelines in AIT emphasize the important unmet need to fill existing gaps in evidence, such as better clinical documentation of AIT in allergic asthma, treatment efficacy in children and adolescents or polysensitized patients. Besides, further evolution of possible biomarker candidates and data on long-term outcomes after cessation of AIT will help to even increase the impact of guidelines for the application of AIT as the only disease-modifying treatment option available.

Conclusions:

To date, international high-quality, evidence-based, clinical practice guidelines for AIT are available. However, there is room for improvement in addressing different aspects in the clinical documentation of AIT and underlying evidence. An increasing number of trials fulfilling modern methodological requirements will help to improve the guidelines' quality and applicability.

6 | COST-EFFECTIVENESS

Cost-effectiveness for AIT is still a matter of debate. Almost every EU country has a different health system and reimbursement strategy (national or regional), so it is impossible to harmonize data.

Costs may be quantified using *Quality-adjusted life years* (QALYS) or *Incremental cost-effectiveness ratio* (ICER). In 2011, a systematic review and economic evaluation of SCIT and SLIT was carried out in AR. Economic modeling suggested that, when compared with symptomatic treatment, both SCIT and SLIT may become cost-effective at a threshold of £20,000–30,000 per QALY from around 6 years, or 5 years for SCIT compared with SLIT (United Kingdom National Health Service and patient perspective)¹⁰³ This is the level that is acceptable for a biologic in asthma. In a more recent systematic review,¹⁰⁴ 19 studies investigated the cost-effectiveness of AIT in AR, of which 7 were based on data from RCTs with economic evaluations conducted from a health system perspective. The quality of the studies was generally low with issues with handling missing data. Using a Markov model, ICER for AIT was around 15,000 to 17,000 €. The outcomes of cost-effectiveness analyses based on RCTs and on modeling depend on unexplored assumptions. An example is the suggestion that a treatment effect persists for 6 or 9 years after discontinuation of AIT.¹⁰⁴ Another assumption is that AIT prevents the development of asthma. This has been documented for children but not for adults. A lack of a preventive effect will increase the ICER.¹⁰⁵ Cost-effectiveness studies do not take patient compliance in real life into account. A recent Markov-based study comparing grass pollen SLIT and SCIT calculated an ICER for SCIT of €11,418 and € 15,212 for SLIT. ICERs greater than € 120,999 for both SCIT and SLIT were demonstrated in a scenario assuming low treatment persistence rates.¹⁰⁵ This study underwrites the importance of real-life cost-effectiveness studies aimed to assess adherence and indirect costs. The estimated yearly cost of AR in Europe owing to presenteeism ranges from €25 to 50 billion.¹⁰⁶ A novel model of reimbursement of medications should be developed with, for example, enterprises paying for a potential new treatment with a precise cost-effectiveness analysis showing potential benefits. Mobile health can have a role in the cost-effectiveness analysis.¹⁰⁷⁻¹¹²

Conclusions:

It has been shown that both SCIT and SLIT are cost-effective. However, the quality of studies is low. High-quality cost-effectiveness studies are needed to meet the requirements of national health care systems. Furthermore, real-life cost-effectiveness studies are needed to estimate the effects of compliance and social costs.

7 | FUTURE DIRECTIONS OF AIT

7.1 | Innovative approaches

The clinical efficacy of AIT has been established beyond question. However, allergic adverse events substantially limit uptake, reduce compliance, and result in cessation of therapy. The severity, but not prevalence, of adverse events is reduced by SLIT.¹¹³ The goals

of novel forms of AIT are (i) to increase safety while maintaining, or even increasing, efficacy, (ii) improvement (shortening) of AIT schedules, (iii) obtaining fast onset relief and, (iv) prolonging the effect after AIT cessation. Perspectives in AIT are well established,^{2, 113} and many new products are in development.¹¹⁴⁻¹¹⁷ However, the majority of attempts to date have failed to achieve one or more of these goals. Future directions are based on modification of allergens, the use of adjuvants,¹¹⁸ nanotechnology,¹¹⁹ biologics,¹²⁰ or probiotics.¹²¹ Several attempts have been made to improve tolerance and efficacy using molecular allergy vaccines acting specifically on B or T cells but none have produced convincing results to date.¹²²

In addition to their innate immune stimulatory function, adjuvants have the capacity to enhance safety by creating allergen depots that restrict systemic distribution of allergen, while in certain cases generating allergen-adjuvant nanoparticles which are more readily taken up by antigen-presenting cells (APC). Several adjuvants have been licensed for use in infectious disease vaccines and are safe and effective in inducing protective immune responses. In addition to four adjuvants licensed for allergen immunotherapy in Europe (aluminum hydroxide, calcium phosphate, microcrystalline tyrosine, monophosphoryl lipid (MPL) A; all of which act to some degree through activation of the inflammasome¹¹⁸), novel adjuvant approaches under development include microparticles containing polymers (e.g., polylactic-co-glycolic acid; PLGA), liposomes, metals, carbohydrates, bacterial TLR agonists (e.g., MPL-TLR4; CpG DNA-TLR9), and vitamin D3.¹²³ Various novel routes of administration are being pursued including intra-lymphatic, mucosal, and skin delivery. Allergen proteins have also been used to decorate the surface of virus-like particles (VLP), which can elicit "anti-viral" Th1 responses, in addition to carrying additional adjuvant payloads (e.g., CpG DNA). Combining adjuvants also has the potential to be an effective strategy in infectious diseases/cancer therapy, and thus may prove beneficial in AIT.^{114,117-119,124,125}

A variety of approaches have been adopted to reduce the allergenicity of AIT preparations. Building on the established practice of chemical modification of proteins to generate allergoids, several novel strategies including genetic mutation to alter structure (e.g., to remove disulfide bridges), recombinant fusion of proteins to enhance allergen uptake and processing (e.g., fusion of HIV trans-activator of transcription; TAT peptide, and an invariant chain fragment to allergen), production of large recombinant fragments, synthetic peptides (ranging from 71 amino acids to as few as 13), hydrolyzed allergens (generating fragments of 1–10 kDa), major allergen trimers, selection of natural hypoallergenic mutants, and hybrid molecules containing B-cell epitopes fused to non-allergen carrier proteins. Several of these approaches have shown promise in phase 2 clinical trials, but few have been evaluated in phase 3 field studies, and with mixed results.^{114,117,125}

The coronavirus disease 2019 (COVID-19) pandemic has highlighted the promise of nucleic acid approaches (DNA/RNA) for the delivery of immunogenic proteins to the immune system. Success in murine models of plasmid-based delivery of allergen proteins for AIT, recently prompted clinical evaluation of a plasmid vaccine encoding Cry j 2 a major Japanese cedar allergen. The first into human

study reported reductions in skin prick test reactivity, but with no associated change in levels of allergen-specific IgG or IgE.¹²⁶ A subsequent study with intradermal delivery (ClinicalTrials.gov Identifier: NCT03101267) failed to meet its primary and secondary endpoints. A related study in peanut allergy is currently underway (ClinicalTrials.gov Identifier: NCT03755713).

The application of biologics to AIT is an emerging area of interest. At present, most experience has been with omalizumab which has been successfully used to reduce allergic symptoms during allergen up-dosing (particularly effective for food AIT/OIT), and also to improve efficacy outcomes in aeroallergen AIT¹²⁷ and food AIT. Most recently, anti-TSLP has been evaluated in combination with cat allergen AIT. At the time of writing, results were only available on clinicaltrials.gov (Identifier: NCT02237196) and showed that the addition of anti-TSLP to cat allergen AIT was not superior to cat allergen AIT alone. Passive immunotherapy through administration of monoclonal IgG4 preparations targeting allergens has recently shown impressive efficacy in a study of cat allergic individuals.^{128,129,130}

Conclusion:

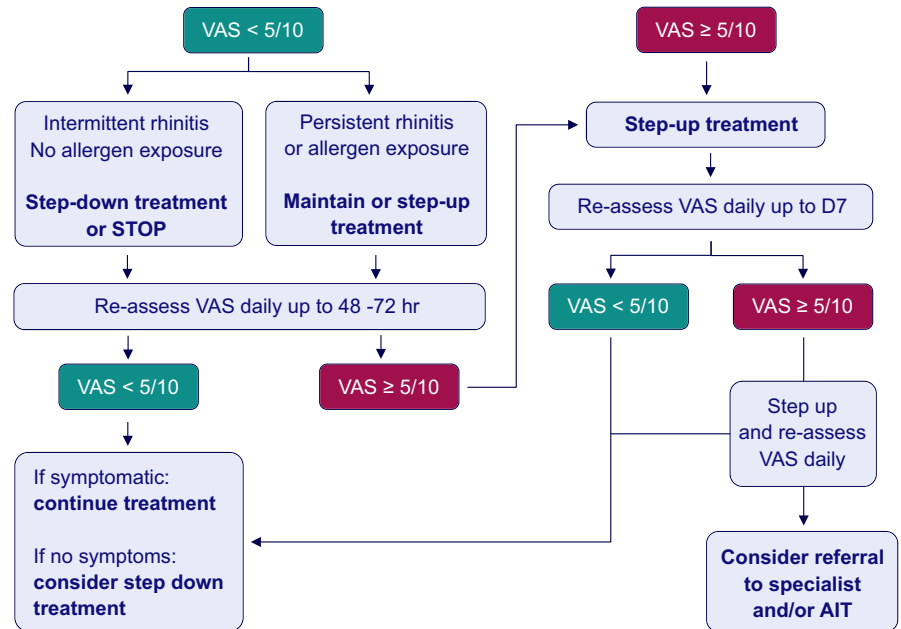
Route of delivery of AIT can improve the safety profile, and multiple routes are currently under evaluation. Adjuvants have proven effective in enhancing immunogenicity, while in some cases improving safety. Novel adjuvant approaches continue to be developed. Structural modification of allergens to reduce allergenicity may improve safety, but the majority of approaches have not reached phase 3 trials; of the few that have, results have been mixed. Some biologics are effective as adjuncts to AIT and can markedly improve safety in food AIT. Passive immunotherapy with monoclonal blocking IgG4 antibodies has shown clinical efficacy in a phase 2 study in cat allergy and will likely expand to more allergens. Nucleic acid-based AIT has begun to be evaluated in clinical trials but has not been effective to date.

8 | AIT IN REAL-LIFE CARE

Few data exist on-real-world data (RWD) for AIT with consequently, a lack of information on how AIT effectively works in real life.¹³¹ The EAACI Methodology Committee recently initiated a systematic review of observational studies of AIT, which will use the RELEVANT tool and the Grading of Recommendations Assessment, Development and Evaluation approach (GRADE) to rate the quality of the evidence base. Data are not available yet.

Retrospective analyses of longitudinal prescription databases have been carried out. AR patients treated with grass pollen SLIT tablets were compared with a control group not having received AIT. Sophisticated statistical analyses were performed and suggested that treatment of AR patients with grass pollen SLIT tablets was associated with slower AR progression, less frequent asthma onset,

FIGURE 3 Step-wise algorithm for the optimal care of untreated patients as proposed by ARIA. Reproduced with permission from¹³⁸ and¹⁵³ Abbreviations: AIT, allergen immunotherapy; ARIA, Allergic Rhinitis and its Impact on Asthma; VAS, visual analogue scale.



and slower asthma progression.¹³² Similar data were found for birch AIT¹³³ and for mite allergoids.¹³⁴ These studies are of importance but are only hypothesis-generating.

Using the MASK-air (Mobile Airways Sentinel Network) approach,^{135,136} it was recently found that AIT was improving allergic symptoms and work productivity.¹³⁷

Patient stratification is needed to identify patients unresponsive to optimal pharmacologic treatment that will benefit from AIT and to predict the benefit before AIT is started.¹³⁸ This leads to precision medicine with real-world data using IT tools that will inform the physicians for patient's adherence and resistance to pharmacologic treatment (Figure 3). Treatment of AR can also be improved by the use of shared decision-making. In AR, data from mobile technology has revealed that patients are not adherent to treatment and self-medicate using as many medications possible to control their disease. Accordingly, there is an urgent need to propose shared decision-making using mobile health tools to optimize allergic rhinitis treatment and to propose AIT.¹³⁹

Conclusion:

The delivery of cost-effective modern health care is challenging for the allergic diseases. Innovative solutions—based on mobile health devices—are required to support authorities and they should foster transformation of health and care toward integrated care with organizational health literacy.

AIT. Several guidelines and position papers have been published by learned societies aimed to optimize treatment of allergic patients in daily routine.¹⁴¹⁻¹⁴⁶ One early ad-hoc statement of the EAACI and the ARIA-initiative provided practical recommendations on AIT¹⁴⁷ and recommended temporal interruption of AIT in suspected or confirmed COVID-19 in accordance with recommendations with infectious diseases in general.¹⁴⁸⁻¹⁵⁰ However, in case of a patient without any signs of a COVID-19 infection or *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) infection both SCIT and SLIT should be continued. However, these recommendations have not been formulated on evidence, but reflected the authors' consensus on this important topic. To address this further, the EAACI initiated a retrospective survey including 27 questions on practicability and safety of AIT in worldwide clinical routine.¹⁵¹ 417 physicians responded to the online survey. The analysis raised no concern regarding the safety of AIT under the current pandemic in general. However, as in other areas of medical care, this first international survey revealed a high portion of under-treatment of AIT which may result in a long-lasting negative impact on allergic patients.

Conclusion:

A recent retrospective “real-world” analysis has confirmed the safety of AIT during the current COVID-19 pandemic in general. However, a high degree of unjustified under-treatment of AIT has also been revealed.

9 | AIT AND THE COVID PANDEMIC

The pandemic of COVID-19¹⁴⁰ has led to an increased uncertainty regarding the applicability of immuno-modulating therapies such as

10 | CONCLUSION

Allergen Immunotherapy started from empirical evidence published 110 years ago and has evolved to the most relevant therapeutic modality in the treatment of allergic diseases not only targeting allergic

TABLE 3 Key recommendations from EAACI AIT guidelines.¹⁰¹

Indication	Key recommendations	References
Allergic rhinoconjunctivitis	<ul style="list-style-type: none"> • AIT should be considered with symptoms strongly suggestive of allergic rhinitis, +/- conjunctivitis; evidence of IgE sensitization to clinically relevant allergen(s); and moderate-to-severe symptoms despite regular treatment and/or avoidance strategies. • Standardized AIT products with evidence of efficacy in the clinical documentation should be used when they are available. • Key contraindications are severe or uncontrolled asthma; active, systemic autoimmune disorders; active malignant neoplasia. • An individual product-based evaluation of the evidence for efficacy is recommended before treatment with a specific product is initiated—more details in the guideline. • Polysensitized patients who are poly-allergic for taxonomically related homologous allergens can be recommended to receive either a single allergen or a mixture of homologous allergens from that biological family that covers all the major allergens. • Patients who are poly-allergic for non-homologous allergens may be recommended to start AIT with either the allergen responsible for most of their allergic rhinoconjunctivitis symptoms or separate treatment with the 2 clinically most important allergens 	11
House dust mite (HDM)-related Allergic Asthma	<ul style="list-style-type: none"> • HDM SCIT is recommended for children and adults with controlled HDM-driven allergic asthma as an add-on treatment to regular therapy • HDM SLIT-tablets are recommended for adults with controlled and partially controlled HDM-driven allergic asthma as an add-on treatment to regular therapy 	12
Venom allergy	<ul style="list-style-type: none"> • Venom immunotherapy (VIT) is recommended in children and adults with detectable sensitization and systemic sting reactions exceeding generalized skin symptoms • VIT is not recommended in individuals with incidentally detected sensitization and no systemic symptoms 	13
Prevention properties	<ul style="list-style-type: none"> • A 3-year course of AIT (SCIT or SLIT) may be considered in children with moderate-to-severe allergic rhinoconjunctivitis and grass/birch pollen allergy, not sufficiently controlled with optimal pharmacotherapy to prevent the onset of asthma in addition to the control of allergic rhinoconjunctivitis. 	15
General Recommendations	<ul style="list-style-type: none"> • Premedication with an antihistamine is recommended as it reduces the frequency and severity of local and systemic cutaneous reactions. • It is recommended that patients should wait in the clinic for at least 30 minutes after a SCIT injection or initial SLIT dosage. • It is recommended that SCIT should be administered by trained staff with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis. • To achieve long-term efficacy, it is recommended that a minimum of 3 years of therapy is used. 	13 11

Abbreviations: AIT, allergen immunotherapy; EAACI, European Academy of Allergy and Clinical Immunology; HDM, house dust mite; SCIT, subcutaneous AIT; SLIT, sublingual AIT.

rhinoconjunctivitis, but also allergic asthma, and venom hypersensitivity. Additionally, progress has recently been made with AIT for food allergy. It remains as the only disease-modifying treatment option to be offered to allergic patients.

Mechanistic studies have revealed that these effects are associated with immune modulation of the innate and adaptive immune response. Current studies may lead to identification of biomarkers to monitor patients, with the aim of optimizing efficacy and tolerance.

The broad evidence is reflected in multiple regulatory guidelines ensuring market authorization of AIT products based on high quality and the full picture of modern clinical documentation. Evidence-based recommendations in international guidelines aim to assist the clinician in ensuring best care for allergic patients.

Future developments are focused on, for example, new application routes in AIT, use of adjuvants, modification of allergens, the use of monoclonal antibodies (biologicals) to boost tolerance induction. Besides obtaining real-life data, the use of mobile health tools

and shared decision-making pave the way to better implementation and monitoring of AIT while improving treatment convenience and adherence. During the current COVID-19 pandemic, AIT should not be interrupted in patients without any signs of a COVID-19 infection or a SARS-Cov-2 infection and a recent survey confirmed the safety of AIT under real-life observations.

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Dr. Roberts, Dr. Shamji, and Dr. Gerth van Wijk have nothing to disclose.

AUTHOR CONTRIBUTION

OP and RGW provided the first conceptualization of this article and divided the manuscript into different chapters to be elaborated by coauthoring international key experts in AIT. After compilation of all parts, the draft of the manuscript has been critically reviewed and amended where applicable by all co-authors who all have given final approval for submission.

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