Check for updates

Accepted Article

PROF. OLIVER PFAAR (Orcid ID : 0000-0003-4374-9639)
PROF. JEAN BOUSQUET (Orcid ID : 0000-0002-4061-4766)
PROF. STEPHEN R. DURHAM (Orcid ID : 0000-0001-5264-6207)
DR. JÖRG KLEINE-TEBBE (Orcid ID : 0000-0002-2862-7353)
PROF. MARK LARCHE (Orcid ID : 0000-0002-1439-7593)
PROF. GRAHAM C ROBERTS (Orcid ID : 0000-0003-2252-1248)
DR. MOHAMED H SHAMJI (Orcid ID : 0000-0003-3425-3463)
DR. ROY GERTH VAN WIJK (Orcid ID : 0000-0002-9608-8742)

Article type : Review

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

Manuscript Acceptance Date: 24-Jul-2021

Pfaar O[1], Bousquet J[2 3], Durham SR[4], Kleine-Tebbe J[5], Larché M [6 7], Roberts G[8 9 10], Shamji, MH[4] , Gerth van Wijk, R[11]

[1] Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy, University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany.

[2] Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Berlin, Germany.

[3] University Hospital Montpellier, France.

[4] National Heart and Lung Institute, Allergy and Clinical Immunology, Imperial College NIHR Biomedical Research Centre, Asthma UK Centre in Allergic Mechanisms of Asthma, London, United Kingdom.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ALL.15023

This article is protected by copyright. All rights reserved

[5] Allergy & Asthma Center Westend, Outpatient and Clinical Research Center, Berlin, Germany.

[6] Department of Medicine, McMaster University, Hamilton, ON, Canada.

[7] Firestone Institute for Respiratory Health, St. Joseph's Healthcare, Hamilton, ON, Canada.

[8] Faculty of Medicine, University of Southampton, Southampton, UK.

[9] The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK.

[10] NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK.

[11] Section of Allergology and Clinical Immunology, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands.

Corresponding author:

Oliver Pfaar

Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy, University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany

Baldingerstraße,

D-35043 Marburg, Germany.

e-mail: oliver@pfaar.org

Short title: *110 years of AIT*

Journal: Allergy, invited

Word count: Abstract =247; body-manuscript~4200

This article is protected by copyright. All rights reserved

Accepted Article

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

This article is protected by copyright. All rights reserved

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

Ig, Immunoglobulin

IL, interleukin

ILC, innate lymphoid cells

IFN-γ, Interferon-Gamma

iTreg, induced regulatory T-cells

MPL, monophosphoryl lipid

NAEPP, National Asthma Education and Prevention Program

This article is protected by copyright. All rights reserved

NPP, named patient products

nTreg, natural regulatory T-cells

PDG2, prostaglandin D2

PLGA, polylactic-co-glycolic acid

QALYS, Quality-adjusted life years

SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2

T2, Type 2

Tfr, $FOXP3^{+}$-T follicular regulatory cells

TGF-ß, Transforming growth factor-beta

Th, T-helper

TLR, toll-like-receptor

Treg, regulatory T-cell

TSLP, thymic stromal lymphopoietin

SARS-Cov-2, severe acute respiratory syndrome coronavirus type 2

SCIT, subcutaneous AIT

SLIT, sublingual AIT

VAS, visual analogue scale

VIT, Venom immunotherapy

This article is protected by copyright. All rights reserved

VLP, virus-like particles

WAO, World Allergy Organization

WHO, World Health Organization

Key-words: allergen immunotherapy, allergic rhinitis, evidence, mechanisms, innovations

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 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 e.g., 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

This article is protected by copyright. All rights reserved

Accepted Article

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.

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 trials(5-7) 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 antibodies(8) and the discovery of IL-10 producing regulatory T cells(9) to the new insights which is available now about the role of the innate and adaptive immune system(10) 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.

Mechanisms in AIT

Accepted Article

This article is protected by copyright. All rights reserved

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-b(21, 22) that suppress antigen-driven Th2 cells and induce B cells to undergo immunoglobulin heavy chain switching towards, respectively, allergen-specific IgG2 (23) or IgG4(24) and IgA production(25), detectable in serum and local nasal secretions ((26), Figure 2). Competition with IgE for allergen prevents IgE-allergen complex formation resulting in inhibition of FceR1-dependent mast cell and basophil activation(27, 28) and a decrease in FceR2(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 favour of allergen-specific Th1 responses(31, 32) under the influence of IL-12(33) and IL-27(34) with an increase in interferon-gamma that suppresses IL-4-induced B cell IgE switching in favour of allergen-specific IgG antibodies.

Recent novel findings include distinct subsets of T cells that include antigen-specific $CD27^{-}$-Th2A cells(35-37) and IL-21-producing T follicular helper cells(38) 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

This article is protected by copyright. All rights reserved

subset of ILC-2s that produce IL-10 and have regulatory properties has been identified(44) 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 biomarker (46).

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.

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 for European Union (EU) member states, new guidelines(51) have been developed within the European medicines agency (EMA), recently reviewed by experts of the Paul-Ehrlich-Institut, German Federal Institute for Vaccines and Biomedicines(52). In brief, this document(51)

This article is protected by copyright. All rights reserved

Accepted Article

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) and clinical development of allergen products. The EMA guideline on quality aspects(53) 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 document (56) 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-centre, randomised, 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 being marketed as NPP and as such will allow more flexibility regarding mixing with i.e. related allergens and/or dose adaption resembling a “personalized” approach in AIT.

In addition, several aspects of AIT beyond market authorisation 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).

Conclusion:

Current regulations of allergen products by competent authorities have successfully integrated

This article is protected by copyright. All rights reserved

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.

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 1960's-1970's 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 characterised 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 adults (70) have confirmed the efficacy and safety of SLIT with tablets. Efficacy and safety have also been established with ragweed(71) 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).

This article is protected by copyright. All rights reserved

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 prevention of asthma development in children. Two landmark papers have been published. The open controlled PAT study(76) showed less asthma in children treated with SCIT in the 7 years 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 exacerbations (81) 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).

This article is protected by copyright. All rights reserved

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.

Guidelines in allergen immunotherapy

Need for guidelines

Every year more data on different approaches to allergen immunotherapy is published. Some publications to should lead to a change in practice while others shouldn't. 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 Parameters (97) 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.

Approach to developing guidelines

Clinical guidelines 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

This article is protected by copyright. All rights reserved

Accepted Article

tool, particularly in terms of applicability, rigour 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).

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 summarised in Table 2. 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/paper 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 e.g., 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.

This article is protected by copyright. All rights reserved

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.

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 modelling 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 modelling 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

This article is protected by copyright. All rights reserved

Accepted Article

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.

Future directions of AIT

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).

This article is protected by copyright. All rights reserved

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, whilst 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 (aluminium hydroxide, calcium phosphate, microcrystalline tyrosine, monophosphoryl lipid (MPL) A; all of which act to some degree through activation of the inflammasome (118)), 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 has 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 disulphide 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 1-10kDa), 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).

This article is protected by copyright. All rights reserved

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 AIT (127) 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).

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, whilst 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 be effective to date.

This article is protected by copyright. All rights reserved

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.(129) 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, and slower asthma progression. (130) Similar data were found for birch AIT(131) and for mite allergoids.(132) These studies are of importance but are only hypothesis-generating.

Using the MASK-air (Mobile Airways Sentinel Network) approach,(133, 134) it was recently found that AIT was improving allergic symptoms and work productivity.(135)

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(136). 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(137).

Conclusion:

The delivery of cost-effective modern health care is challenging for the allergic diseases.

This article is protected by copyright. All rights reserved

Accepted Article

Innovative solutions - based on mobile health devices- are required to support authorities and they should foster transformation of health and care towards integrated care with organizational health literacy.

AIT and the COVID pandemic

The pandemic of COVID-19(138) has led to an increased uncertainty regarding the applicability of immuno-modulating therapies such as AIT. Several guidelines and position papers have been published by learned societies aimed to optimize treatment of allergic patients in daily routine(139-144). One early ad-hoc statement of the EAACI and the ARIA-initiative provided practical recommendations on AIT(145) and recommended temporal interruption of AIT in suspected or confirmed COVID-19 in accordance with recommendations with infectious diseases in general(146-148). However, in case of a patient without any signs of a COVID-19 infection or *severe acute respiratory syndrome coronavirus type 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(149). 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.

Conclusion

This article is protected by copyright. All rights reserved

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 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 e.g., 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.

Accepted Article

This article is protected by copyright. All rights reserved

Tables

Common allergen sources* for AIT or in vivo allergen diagnosis in Europe
• Pollen of the group of sweet grasses of the *Poaceae (Gramineae)* family
• Pollen of the birch group
• Pollen of 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)

Table 1 : Common allergen sources* for AIT or in vivo allergen diagnosis in Europe. *****Full documentation and market authorisation considered mandatory (from Annex I of Recommendations on common regulatory approaches for allergen products(51)). Abbreviations: *AIT, allergen immunotherapy.*

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

• 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 paediatric populations (also outlined in the paediatric investigation plan (150) including preventive effects regarding disease progression, i.e. asthma development and new sensitizations

Table 2: Important aspects of AIT post market authorisation. *AIT, allergen immunotherapy*

This article is protected by copyright. All rights reserved

Accepted Article

Indication	Key recommendations	References
Allergic rhinoconjunctivitis	• 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	(11)

This article is protected by copyright. All rights reserved

	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	
House dust mite (HDM) related Allergic Asthma	• 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	• 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	(13)

Accepted Article

This article is protected by copyright. All rights reserved

	with incidentally detected sensitization and no systemic symptoms	
Prevention properties	• 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	• 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)

Accepted Article

This article is protected by copyright. All rights reserved

Table 3: Key recommendations from EAACI AIT guidelines (101). Abbreviations: *AIT, allergen immunotherapy; EAACI, European Academy of Allergy and Clinical Immunology; HDM, house dust mite; SCIT, subcutaneous AIT; SLIT, sublingual AIT*

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

Figures

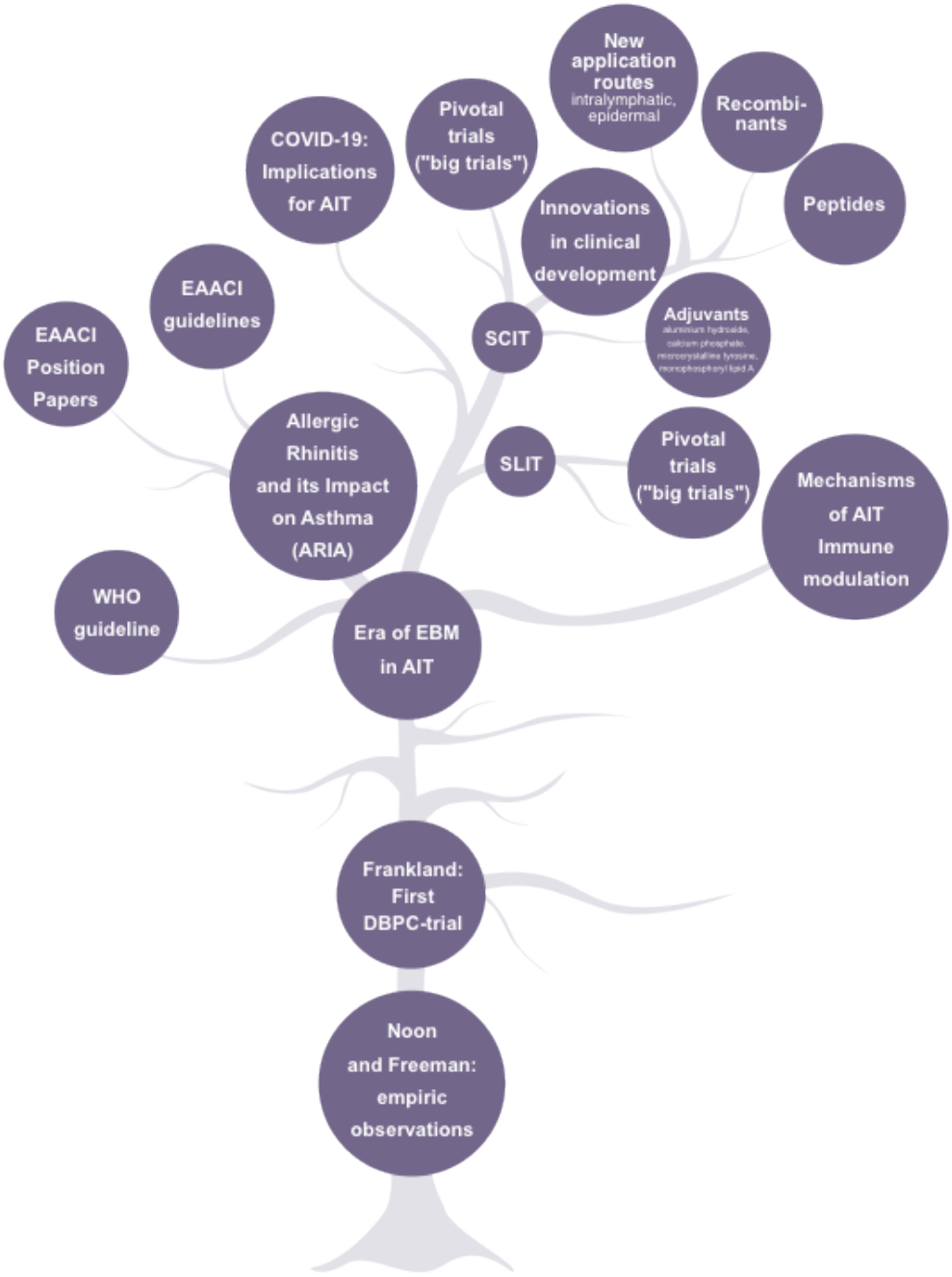


Figure 1_Pfaar et al.

Figure 1: Allergen immunotherapy: 110 years of evidence-based evolution and innovations. Abbreviations: *AIT, allergen immunotherapy; ARIA, Allergic Rhinitis and its Impact on Asthma;*

This article is protected by copyright. All rights reserved

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.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

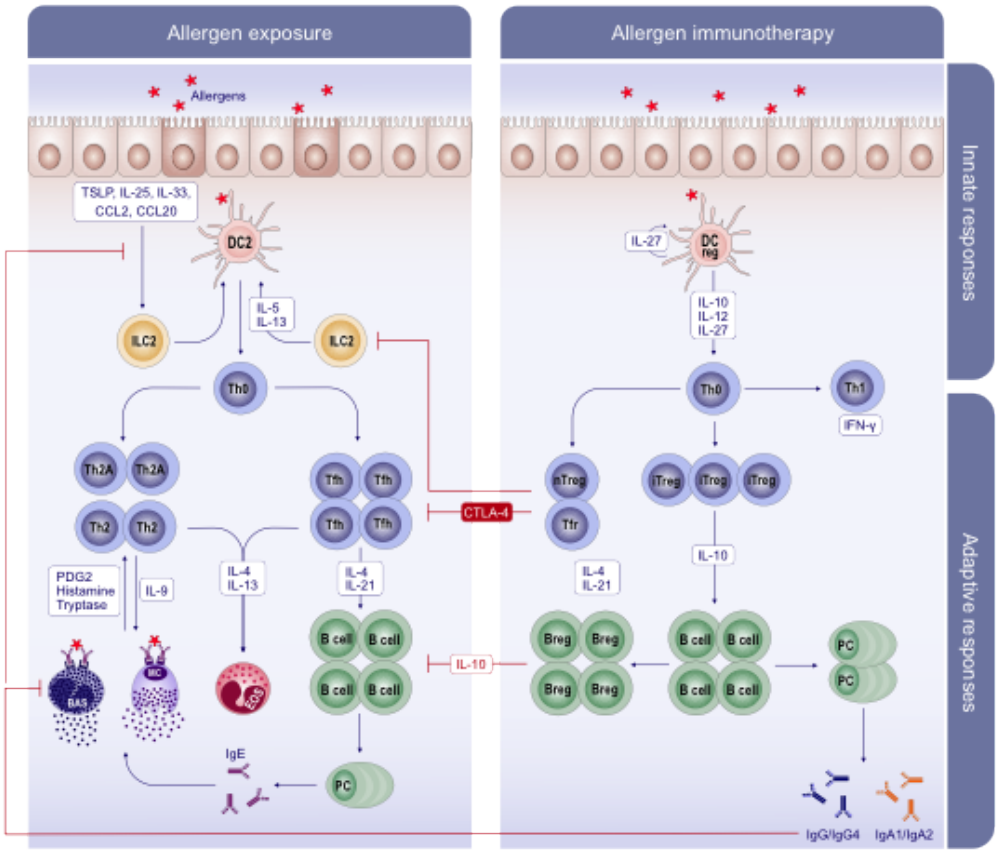


Figure 2_Pfaar et al.

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; FAB, fragment antigen-binding; Ig, Immunoglobulin; IL, Interleukin; IFN-*

This article is protected by copyright. All rights reserved

y, Interferon-Gamma; iTreg, induced regulatory T-cells; nTreg, natural regulatory T-cells; PDG2, prostaglandin D2; Tfr, FOXP3^{+}-T follicular regulatory cells; TGF-ß, Transforming growth factor-beta; Th, T-helper; TLR, toll-like-receptor; Treg, regulatory T-cell; TSLP, thymic stromal lymphopoietin.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

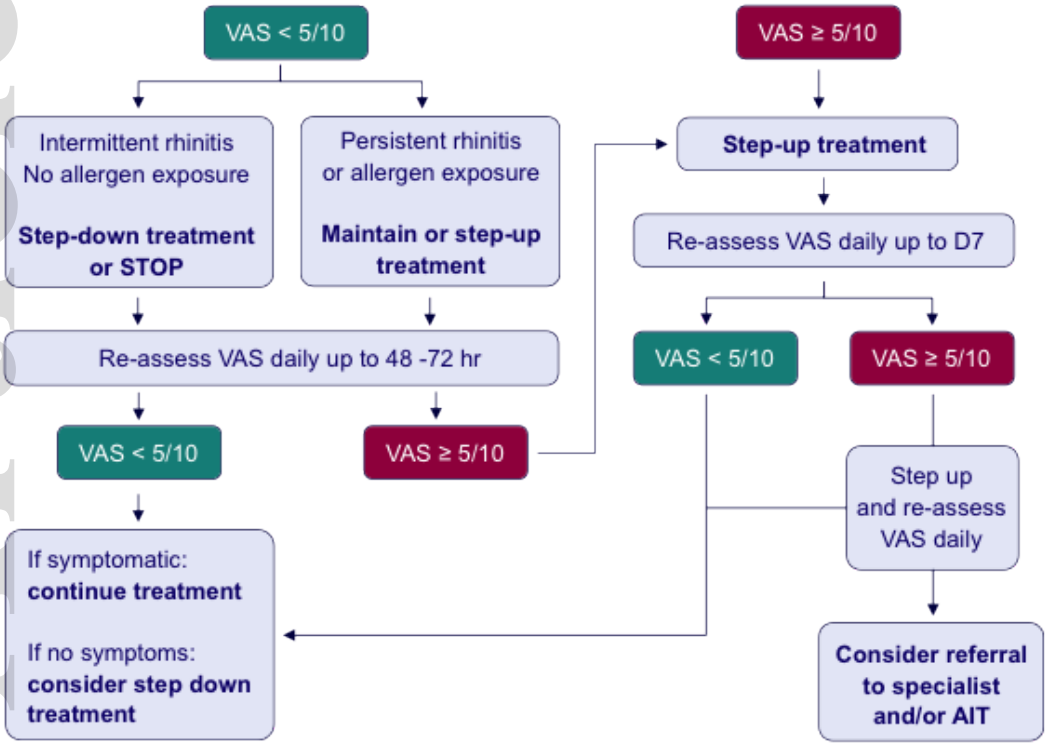


Figure 3_Pfaar et al.

This article is protected by copyright. All rights reserved

Figure 3: Step-wise algorithm for the optimal care of untreated patients as proposed by ARIA. Reproduced with permission from (136) and (151). Abbreviations: *AIT, allergen immunotherapy; ARIA, Allergic Rhinitis and its Impact on Asthma; VAS, visual analogue scale.*

Author contribution: OP and RGW provided the first conceptualisation 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.

Disclosure of interest:

Dr. Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Circassia, grants and personal fees from ASIT Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from MEDA Pharma/MYLAN, grants and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Indoor Biotechnologies, grants and personal fees from GlaxoSmithKline, personal fees from Astellas Pharma Global, personal fees from EUFOREA, personal fees from ROXALL Medizin, personal fees from Novartis, personal fees from Sanofi-Aventis and Sanofi-Genzyme, personal fees from Med Update Europe GmbH, personal fees from streamedup! GmbH, grants from Pohl-Boskamp, grants from Inmunotek S.L., personal fees from John Wiley and Sons, AS, personal fees from Paul-Martini-Stiftung (PMS), personal fees from Ingress-Health HWM, personal fees from Regeneron Pharmaceuticals Inc. outside the submitted work.

Dr. Bousquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed-Innov, personal fees from Purina, outside the submitted work.

Dr. Durham reports personal fees from ALK, non-financial support from ALK, personal fees from Allergy Therapeutics, personal fees from Anergis, personal fees from Stallergenes, personal fees from Allergopharma, outside the submitted work.

Dr. Kleine-Tebbe reports personal fees from AllergenOnline (Nebraska, USA), personal fees from Allergy Therapeutics, personal fees from Allergopharma, personal fees from ALK-Abelló, personal fees from AstraZeneca, personal fees from Bencard, personal fees from Dr. Pfleger, grants and personal fees from GSK, personal fees from HAL Allergy, personal fees from InfectoPharm, personal fees from LETI, grants and personal fees from Lofarma, grants and personal fees from Novartis, personal fees from Merck US, personal fees from Sanofi Genentech, grants and personal fees from Stallergenes-Greer, personal fees from Springer International Publishers, personal fees from ThermoFisher Scientific, personal fees from Thieme Publishers, Germany, non-financial support from American Academy Allergy Asthma and Immunology, non-financial support from European Academy of Allergy and Clinical Immunology, personal fees and non-financial support from German Society of Allergy and Clinical Immunology, non-financial support from WHO/IUIS Allergen nomenclature subcommittee, outside the submitted work.

Dr. Larche reports grants and personal fees from Adiga Life Sciences Inc, other from Circassia Ltd, other from Adiga Life Sciences Ltd, other from Circassia Pharmaceuticals PLC, grants, personal fees and other from Aravax Pty, other from Vaxerna Ltd., outside the

This article is protected by copyright. All rights reserved

submitted work; In addition, Dr. Larche has a patent 17 patent families held by Circassia Pharmaceuticals PLC/Adiga Life Sciences Ltd licensed to Circassia/Adiga.

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

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

References

1. Noon L. Propylactic inoculation against hayfever. Lancet. 1911;1(1572).

2. Pfaar O, Creticos PS, Kleine Tebbe J, Canonica GW, Palomares O, Schulke S. One Hundred Ten Years of Allergen Immunotherapy: A Broad Look Into the Future. J Allergy Clin Immunology Pract 2021;9:1791-803.

3. Dhami S, Nurmatov U, Arasi S, Khan T, Asaria M, Zaman H, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis. Allergy. 2017;72(11):1597-631.

4. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, et al. Allergen immunotherapy for allergic asthma: A systematic review and meta-analysis. Allergy. 2017;72(12):1825-48.

This article is protected by copyright. All rights reserved

5. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. Allergy. 2007;62(3):317-24.

6. Bousquet PJ, Calderon MA, Demoly P, Larenas D, Passalacqua G, Bachert C, et al. The Consolidated Standards of Reporting Trials (CONSORT) Statement applied to allergen-specific immunotherapy with inhalant allergens: a Global Allergy and Asthma European Network (GA(2)LEN) article. J Allergy Clin Immunol. 2011;127(1):49-56, e1-11.

7. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. Allergy. 2014;69(7):854-67.

8. Gleich GJ, Zimmermann EM, Henderson LL, Yunginger JW. Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: a six-year prospective study. J Allergy Clin Immunol. 1982;70(4):261-71.

9. Akdis CA, Blesken T, Akdis M, Wuthrich B, Blaser K. Role of interleukin 10 in specific immunotherapy. J Clin Invest. 1998;102(1):98-106.

10. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. J Allergy Clin Immunol. 2017;140(6):1485-98.

11. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy. 2018;73(4):765-98.

12. Agache I, Lau S, Akdis CA, Smolinska S, Bonini M, Cavkaytar O, et al. EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma. Allergy. 2019;74(5):855-73.

13. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilo MB, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. Allergy. 2018;73(4):744-64.

14. Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018;73(4):799-815.

15. Halken S, Larenas-Linnemann D, Roberts G, Calderon MA, Angier E, Pfaar O, et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. Pediatr Allergy Immunol. 2017;28(8):728-45.

16. Licona-Limon P, Kim LK, Palm NW, Flavell RA. TH2, allergy and group 2 innate lymphoid cells. Nat Immunol. 2013;14(6):536-42.

17. Schroeder JT, Lichtenstein LM, Roche EM, Xiao H, Liu MC. IL-4 production by human basophils found in the lung following segmental allergen challenge. J Allergy Clin Immunol. 2001;107(2):265-71.

This article is protected by copyright. All rights reserved

18. Gueguen C, Bouley J, Moussu H, Luce S, Duchateau M, Chamot-Rooke J, et al. Changes in markers associated with dendritic cells driving the differentiation of either TH2 cells or regulatory T cells correlate with clinical benefit during allergen immunotherapy. J Allergy Clin Immunol. 2016;137(2):545-58.
19. Mjosberg JM, Trifari S, Crellin NK, Peters CP, van Drunen CM, Piet B, et al. Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nat Immunol. 2011;12(11):1055-62.
20. Francis JN, James LK, Paraskevopoulos G, Wong C, Calderon MA, Durham SR, et al. Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG4 inhibitory antibody activity. J Allergy Clin Immunol. 2008;121(5):1120-5 e2.
21. Jutel M, Akdis M, Budak F, Aebischer-Casaulta C, Wrzyszcz M, Blaser K, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. Eur J Immunol. 2003;33(5):1205-14.
22. O'Hehir RE, Gardner LM, de Leon MP, Hales BJ, Biondo M, Douglass JA, et al. House dust mite sublingual immunotherapy: the role for transforming growth factor-beta and functional regulatory T cells. Am J Respir Crit Care Med. 2009;180(10):936-47.
23. Heeringa JJ, McKenzie CI, Varese N, Hew M, Bakx A, Aui PM, et al. Induction of IgG2 and IgG4 B-cell memory following sublingual immunotherapy for ryegrass pollen allergy. Allergy. 2020;75(5):1121-32.
24. Nouri-Aria KT, Wachholz PA, Francis JN, Jacobson MR, Walker SM, Wilcock LK, et al. Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. J Immunol. 2004;172(5):3252-9.
25. Pilette C, Nouri-Aria KT, Jacobson MR, Wilcock LK, Detry B, Walker SM, et al. Grass pollen immunotherapy induces an allergen-specific IgA2 antibody response associated with mucosal TGF-beta expression. J Immunol. 2007;178(7):4658-66.
26. Shamji MH, Kappen J, Abubakar-Waziri H, Zhang J, Steveling E, Watchman S, et al. Nasal allergen-neutralizing IgG4 antibodies block IgE-mediated responses: Novel biomarker of subcutaneous grass pollen immunotherapy. J Allergy Clin Immunol. 2019;143(3):1067-76.
27. Lalek N, Kosnik M, Silar M, Korosec P. Immunoglobulin G-dependent changes in basophil allergen threshold sensitivity during birch pollen immunotherapy. Clin Exp Allergy. 2010;40(8):1186-93.
28. Shamji MH, Layhadi JA, Scadding GW, Cheung DKM, Calderon MA, Turka LA, et al. Basophil expression of diamine oxidase: a novel biomarker of allergen immunotherapy response. J Allergy Clin Immunol. 2015;135(4):913-21 e9.

Accepted Article

This article is protected by copyright. All rights reserved

29. van Neerven RJ, Wikborg T, Lund G, Jacobsen B, Brinch-Nielsen A, Arnved J, et al. Blocking antibodies induced by specific allergy vaccination prevent the activation of CD4+ T cells by inhibiting serum-IgE-facilitated allergen presentation. J Immunol. 1999;163(5):2944-52.
30. Shamji MH, Wilcock LK, Wachholz PA, Dearman RJ, Kimber I, Wurtzen PA, et al. The IgE-facilitated allergen binding (FAB) assay: validation of a novel flow-cytometric based method for the detection of inhibitory antibody responses. J Immunol Methods. 2006;317(1-2):71-9.
31. Ebner C, Siemann U, Bohle B, Willheim M, Wiedermann U, Schenk S, et al. Immunological changes during specific immunotherapy of grass pollen allergy: reduced lymphoproliferative responses to allergen and shift from TH2 to TH1 in T-cell clones specific for Phl p 1, a major grass pollen allergen. Clin Exp Allergy. 1997;27(9):1007-15.
32. Bohle B, Kinaciyan T, Gerstmayr M, Radakovics A, Jahn-Schmid B, Ebner C. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. J Allergy Clin Immunol. 2007;120(3):707-13.
33. Hamid QA, Schotman E, Jacobson MR, Walker SM, Durham SR. Increases in IL-12 messenger RNA+ cells accompany inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy. J Allergy Clin Immunol. 1997;99(2):254-60.
34. Matsuoka T, Shamji MH, Durham SR. Allergen immunotherapy and tolerance. Allergol Int. 2013;62(4):403-13.
35. Wambre E, DeLong JH, James EA, LaFond RE, Robinson D, Kwok WW. Differentiation stage determines pathologic and protective allergen-specific CD4+ T-cell outcomes during specific immunotherapy. J Allergy Clin Immunol. 2012;129(2):544-51, 51 e1-7.
36. Renand A, Shamji MH, Harris KM, Qin T, Wambre E, Scadding GW, et al. Synchronous immune alterations mirror clinical response during allergen immunotherapy. J Allergy Clin Immunol. 2018;141(5):1750-60 e1.
37. Luce S, Batard T, Bordas-Le Floch V, Le Gall M, Mascarell L. Decrease in CD38(+) TH2A cell frequencies following immunotherapy with house dust mite tablet correlates with humoral responses. Clin Exp Allergy. 2021.
38. Varricchi G, Harker J, Borriello F, Marone G, Durham SR, Shamji MH. T follicular helper (Tfh) cells in normal immune responses and in allergic disorders. Allergy. 2016;71(8):1086-94.
39. Shamji MH, Layhadi JA, Achkova D, Kouser L, Perera-Webb A, Couto-Francisco NC, et al. Role of IL-35 in sublingual allergen immunotherapy. J Allergy Clin Immunol. 2019;143(3):1131-42 e4.

Accepted Article

This article is protected by copyright. All rights reserved

40. van de Veen W, Stanic B, Yaman G, Wawrzyniak M, Sollner S, Akdis DG, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. J Allergy Clin Immunol. 2013;131(4):1204-12.

41. Boonpiyathad T, van de Veen W, Wirz O, Sokolowska M, Ruckert B, Tan G, et al. Role of Der p 1-specific B cells in immune tolerance during 2 years of house dust mite-specific immunotherapy. J Allergy Clin Immunol. 2019;143(3):1077-86 e10.

42. Sharif H, Acharya S, Dhondalay GKR, Varricchi G, Krasner-Macleod S, Laisuan W, et al. Altered chromatin landscape in circulating T follicular helper and regulatory cells following grass pollen subcutaneous and sublingual immunotherapy. J Allergy Clin Immunol. 2021;147(2):663-76.

43. Lao-Araya M, Steveling E, Scadding GW, Durham SR, Shamji MH. Seasonal increases in peripheral innate lymphoid type 2 cells are inhibited by subcutaneous grass pollen immunotherapy. J Allergy Clin Immunol. 2014;134(5):1193-5 e4.

44. Golebski K, Layhadi JA, Sahiner U, Steveling-Klein EH, Lenormand MM, Li RCY, et al. Induction of IL-10-producing type 2 innate lymphoid cells by allergen immunotherapy is associated with clinical response. Immunity. 2021;54(2):291-307 e7.

45. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med. 1999;341(7):468-75.

46. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol. 2012;129(3):717-25 e5.

47. Scadding GW, Calderon MA, Shamji MH, Eifan AO, Penagos M, Dumitru F, et al. Effect of 2 Years of Treatment With Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis: The GRASS Randomized Clinical Trial. JAMA. 2017;317(6):615-25.

48. Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. Allergy. 2017;72(8):1156-73.

49. Pfaar O, Agache I, de Blay F, Bonini S, Chaker AM, Durham SR, et al. Perspectives in allergen immunotherapy: 2019 and beyond. Allergy. 2019;74 Suppl 108:3-25.

50. Bonertz A, Roberts GC, Hoefnagel M, Timon M, Slater JE, Rabin RL, et al. Challenges in the implementation of EAACI guidelines on allergen immunotherapy: A global perspective on the regulation of allergen products. Allergy. 2018;73(1):64-76.

Accepted Article

This article is protected by copyright. All rights reserved

51. Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human Recommendations on common regulatory approaches for allergen products. CMDh/399/2019. 2019 [Available from: https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/01_General_Info/CMDh_399_2019_clean_Rev0_2020_07.pdf. Accessed per Mar 05, 2021.52. Bonertz A, Mahler V, Vieths S. New guidance on the regulation of allergen products: key aspects and outcomes. Curr Opin Allergy Clin Immunol. 2020;20(6):624-30.

53. Committee for medicinal products for human use (CPMP). Guideline on allergen products: production and quality issues. EMEA/CHMP/BWP/304831/ 2007. London, 20 November, 2008 [Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-allergen-products-production-quality-issues_en.pdf. Accessed per Mar 5, 2021

54. Lorenz AR, Luttkopf D, May S, Scheurer S, Vieths S. The principle of homologous groups in regulatory affairs of allergen products--a proposal. Int Arch Allergy Immunol. 2009;148(1):1-17.

55. Bonertz A, Mahler V, Vieths S. Manufacturing and quality assessment of allergenic extracts for immunotherapy: state of the art. Curr Opin Allergy Clin Immunol. 2019;19(6):640-5.

56. European Medicines Agency. Commitee for medicinal products for human use (CHMP): Guideline on the Clinical Development of Products for Specific Immunotherapy for The Treatment of Allergic Diseases (CHMP/EWP/18504/2006). 2008 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf. Accessed per March 5, 2021

57. Frankland AW, Augustin R. Prophylaxis of summer hay-fever and asthma: a controlled trial comparing crude grass-pollen extracts with the isolated main protein component. Lancet. 1954;266(6821):1055-7.

58. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. Clin Allergy. 1986;16(5):483-91.

59. Creticos PS. Legends in allergy: Philip S. Norman and Lawrence M. Lichtenstein--the Hopkins experience. J Allergy Clin Immunol. 2007;119(4):1031-8.

60. Frew AJ, Powell RJ, Corrigan CJ, Durham SR, Group UKIS. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006;117(2):319-25.

61. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006;118(2):434-40.

This article is protected by copyright. All rights reserved

62. Didier A, Malling HJ, Worm M, Horak F, Jager S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. J Allergy Clin Immunol. 2007;120(6):1338-45.
63. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. J Allergy Clin Immunol. 2009;123(1):167-73 e7.
64. Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2009;123(1):160-6 e3.
65. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol. 2011;127(1):64-71, e1-4.
66. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol. 2016;137(2):444-51 e8.
67. Nolte H, Bernstein DI, Nelson HS, Kleine-Tebbe J, Sussman GL, Seitzberg D, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2016;138(6):1631-8.
68. Okubo K, Masuyama K, Imai T, Okamiya K, Stage BS, Seitzberg D, et al. Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite-induced allergic rhinitis. J Allergy Clin Immunol. 2017;139(6):1840-8 e10.
69. Nolte H, Amar N, Bernstein DI, Lanier BQ, Creticos P, Berman G, et al. Safety and tolerability of a short ragweed sublingual immunotherapy tablet. Ann Allergy Asthma Immunol. 2014;113(1):93-100 e3.
70. Biedermann T, Kuna P, Panzner P, Valovirta E, Andersson M, de Blay F, et al. The SQ tree SLIT-tablet is highly effective and well tolerated: Results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol. 2019;143(3):1058-66 e6.
71. Creticos PS, Esch RE, Couroux P, Gentile D, D'Angelo P, Whitlow B, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2014;133(3):751-8.
72. Worm M, Rak S, de Blay F, Malling HJ, Melac M, Cadic V, et al. Sustained efficacy and safety of a 300IR daily dose of a sublingual solution of birch pollen allergen extract in adults with allergic rhinoconjunctivitis: results of a double-blind, placebo-controlled study. Clin Transl Allergy. 2014;4(1):7.

This article is protected by copyright. All rights reserved

73. Pfaar O, Bachert C, Kuna P, Panzner P, Dzupinova M, Klimek L, et al. Sublingual allergen immunotherapy with a liquid birch pollen product in patients with seasonal allergic rhinoconjunctivitis with or without asthma. J Allergy Clin Immunol. 2019;143(3):970-7.

74. Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. Clin Transl Allergy. 2015;5:12.

75. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. J Allergy Clin Immunol. 2010;125(1):131-8 e1-7.

76. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol. 2002;109(2):251-6.

77. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sorensen HF, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. J Allergy Clin Immunol. 2018;141(2):529-38 e13.

78. Johnstone DE, Crump L. Value of hyposensitization therapy for perennial bronchial asthma in children. Pediatrics. 1961;27:39-44.

79. Warner JO, Price JF, Soothill JF, Hey EN. Controlled trial of hyposensitisation to Dermatophagoides pteronyssinus in children with asthma. Lancet. 1978;2(8096):912-5.

80. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev. 2010(8):CD001186.

81. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial. JAMA. 2016;315(16):1715-25.

82. Global Initiative for Asthma. Global strategy for asthma management and prevention 2020 [Available from: www.ginasthma.org.] Accesssed per 26 April 2021

83. Loveless MH. Immunization in wasp-sting allergy through venom-repositories and periodic insect stings. J Immunol. 1962;89:204-15.

84. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. N Engl J Med. 1978;299(4):157-61.

85. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol. 1992;90(2):256-62.

This article is protected by copyright. All rights reserved

86. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367(3):233-43.
87. Caminiti L, Pajno GB, Crisafulli G, Chiera F, Collura M, Panasci G, et al. Oral Immunotherapy for Egg Allergy: A Double-Blind Placebo-Controlled Study, with Postdesensitization Follow-Up. J Allergy Clin Immunol Pract. 2015;3(4):532-9.
88. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol. 2008;121(2):343-7.
89. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol. 2015;135(5):1275-82 e1-6.
90. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Ann Allergy Asthma Immunol. 2010;105(5):376-81.
91. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. J Allergy Clin Immunol. 2015;135(3):737-44 e8.
92. Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol. 2005;116(5):1073-9.
93. Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, Diaz de Durana MD, Garcia BE, Gonzalez-Mancebo E, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy. 2009;64(6):876-83.
94. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011;127(3):640-6 e1.
95. Fleischer DM, Greenhawt M, Sussman G, Begin P, Nowak-Wegrzyn A, Petroni D, et al. Effect of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Ingestion Among Children With Peanut Allergy: The PEPITES Randomized Clinical Trial. JAMA. 2019;321(10):946-55.
96. Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, et al. Effect of Varying Doses of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Exposure Among Patients With Peanut Sensitivity: A Randomized Clinical Trial. JAMA. 2017;318(18):1798-809.
97. Practice parameters for allergen immunotherapy. Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy,

Accepted Article

This article is protected by copyright. All rights reserved

Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 1996;98(6 Pt 1):1001-11.

98. Bousquet J, Lockey R, Malling HJ, Alvarez-Cuesta E, Canonica GW, Chapman MD, et al. Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American academy of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol. 1998;81(5):401-5.

99. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108(5 Suppl):S147-334.

100. Larenas-Linnemann DES, Antolin-Amerigo D, Parisi C, Nakonechna A, Luna-Pech JA, Wedi B, et al. National clinical practice guidelines for allergen immunotherapy: An international assessment applying AGREE-II. Allergy. 2018;73(3):664-72.

101. Muraro A, Roberts G, Halken S, Agache I, Angier E, Fernandez-Rivas M, et al. EAACI guidelines on allergen immunotherapy: Executive statement. Allergy. 2018;73(4):739-43.

102. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.

103. Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health Technol Assess. 2013;17(27):vi, xi-xiv, 1-322.

104. Asaria M, Dhami S, van Ree R, Gerth van Wijk R, Muraro A, Roberts G, et al. Health economic analysis of allergen immunotherapy for the management of allergic rhinitis, asthma, food allergy and venom allergy: A systematic overview. Allergy. 2018;73(2):269-83.

105. Di Bona D, Bilancia M, Albanesi M, Caiaffa MF, Macchia L. Cost-effectiveness of grass pollen allergen immunotherapy in adults. Allergy. 2020;75(9):2319-29.

106. Zuberbier T, Lotvall J, Simoens S, Subramanian SV, Church MK. Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review. Allergy. 2014;69(10):1275-9.

107. Bousquet J, Anto JM, Bachert C, Haahtela T, Zuberbier T, Czarlewski W, et al. ARIA digital anamorphosis: Digital transformation of health and care in airway diseases from research to practice. Allergy. 2021;76(1):168-90.

108. Bousquet J, Hellings PW, Agache I, Amat F, Annesi-Maesano I, Ansotegui IJ, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) Phase 4 (2018): Change management in allergic rhinitis and asthma multimorbidity using mobile technology. J Allergy Clin Immunol. 2019;143(3):864-79.

109. Farmanova E, Bonneville L, Bouchard L. Organizational Health Literacy: Review of Theories, Frameworks, Guides, and Implementation Issues. Inquiry. 2018;55:46958018757848.

Accepted Article

This article is protected by copyright. All rights reserved

110. Hunter DJ, Erskine J, Small A, McGovern T, Hicks C, Whitty P, et al. Doing transformational change in the English NHS in the context of "big bang" redisorganisation. J Health Organ Manag. 2015;29(1):10-24.

111. Russell J, Greenhalgh T. Affordability as a discursive accomplishment in a changing National Health Service. Soc Sci Med. 2012;75(12):2463-71.

112. Stenberg K, Lauer JA, Gkountouras G, Fitzpatrick C, Stanciole A. Econometric estimation of WHO-CHOICE country-specific costs for inpatient and outpatient health service delivery. Cost Eff Resour Alloc. 2018;16:11.

113. Bousquet J, Anto JM, Bachert C, Baiardini I, Bosnic-Anticevich S, Walter Canonica G, et al. Allergic rhinitis. Nat Rev Dis Primers. 2020;6(1):95.

114. Dorofeeva Y, Shilovskiy I, Tulaeva I, Focke-Tejkl M, Flicker S, Kudlay D, et al. Past, present, and future of allergen immunotherapy vaccines. Allergy. 2021;76(1):131-49.

115. Pechsrichuang P, Jacquet A. Molecular approaches to allergen-specific immunotherapy: Are we so far from clinical implementation? Clin Exp Allergy. 2020;50(5):543-57.

116. Rodriguez-Dominguez A, Berings M, Rohrbach A, Huang HJ, Curin M, Gevaert P, et al. Molecular profiling of allergen-specific antibody responses may enhance success of specific immunotherapy. J Allergy Clin Immunol. 2020;146(5):1097-108.

117. Komlosi ZI, Kovacs N, Sokolowska M, van de Veen W, Akdis M, Akdis CA. Highlights of Novel Vaccination Strategies in Allergen Immunotherapy. Immunol Allergy Clin North Am. 2020;40(1):15-24.

118. Jensen-Jarolim E, Bachmann MF, Bonini S, Jacobsen L, Jutel M, Klimek L, et al. State-of-the-art in marketed adjuvants and formulations in Allergen Immunotherapy: A position paper of the European Academy of Allergy and Clinical Immunology (EAACI). Allergy. 2020;75(4):746-60.

119. Johnson L, Duschl A, Himly M. Nanotechnology-Based Vaccines for Allergen-Specific Immunotherapy: Potentials and Challenges of Conventional and Novel Adjuvants under Research. Vaccines (Basel). 2020;8(2).

120. Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. J Allergy Clin Immunol. 2010;125(2):383-9.

121. Nelson HS. Allergy immunotherapy: Future directions for the 2020s. Allergy Asthma Proc. 2020;41(5):314-25.

122. Tulaeva I, Kratzer B, Campana R, Curin M, van Hage M, Karsonova A, et al. Preventive Allergen-Specific Vaccination Against Allergy: Mission Possible? Front Immunol. 2020;11:1368.

This article is protected by copyright. All rights reserved

123. Jensen-Jarolim E, Roth-Walter F, Jordakieva G, Pali-Scholl I. Allergens and Adjuvants in Allergen Immunotherapy for Immune Activation, Tolerance, and Resilience. J Allergy Clin Immunol Pract. 2021;9(5):1780-9.

124. Kirtland ME, Tsitoura DC, Durham SR, Shamji MH. Toll-Like Receptor Agonists as Adjuvants for Allergen Immunotherapy. Front Immunol. 2020;11:599083.

125. Wraith DC, Krishna MT. Peptide allergen-specific immunotherapy for allergic airway diseases-State of the art. Clin Exp Allergy. 2021.

126. Su Y, Romeu-Bonilla E, Anagnostou A, Fitz-Patrick D, Hearl W, Heiland T. Safety and long-term immunological effects of CryJ2-LAMP plasmid vaccine in Japanese red cedar atopic subjects: A phase I study. Hum Vaccin Immunother. 2017;13(12):2804-13.

127. Pfaar O, Gehrt F, Li H, Rudhart SA, Nastev A, Stuck BA, et al. Anti-IgE: A treatment option in allergic rhinitis? Allergol Select. 2021;5:119-27.

128. Pfutzner W, Schuppe M. Use of biologics in allergen immunotherapy. Allergol Select. 2021;5:108-18.

129. Paoletti G, DiBona D, Chu DK, Firinu D, Heffler E, Agache I, et al. Allergen immunotherapy: the growing role of observational and randomisedtrial "Real-World Evidence". Allergy. 2021.

130. Zielen S, Devillier P, Heinrich J, Richter H, Wahn U. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: A retrospective, real-world database analysis. Allergy. 2018;73(1):165-77.

131. Wahn U, Bachert C, Heinrich J, Richter H, Zielen S. Real-world benefits of allergen immunotherapy for birch pollen-associated allergic rhinitis and asthma. Allergy. 2019;74(3):594-604.

132. Jutel M, Bruggenjurgen B, Richter H, Vogelberg C. Real-world evidence of subcutaneous allergoid immunotherapy in house dust mite-induced allergic rhinitis and asthma. Allergy. 2020;75(8):2050-8.

133. Bedard A, Basagana X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al. Treatment of allergic rhinitis during and outside the pollen season using mobile technology. A MASK study. Clin Transl Allergy. 2020;10(1):62.

134. Bousquet J, Anto JM, Haahtela T, Jousilahti P, Erhola M, Basagana X, et al. Digital transformation of health and care to sustain Planetary Health: The MASK proof-of-concept for airway diseases-POLLAR symposium under the auspices of Finland's Presidency of the EU, 2019 and MACVIA-France, Global Alliance against Chronic Respiratory Diseases (GARD, WH0) demonstration project, Reference Site Collaborative Network of the European Innovation Partnership on Active and Healthy Ageing. Clin Transl Allergy. 2020;10:24.

Accepted Article

This article is protected by copyright. All rights reserved

135. Pfaar O, Sousa-Pinto B, Devillier P, Canonica GW, Klimek L, Zuberbier T, et al. Effects of allergen immunotherapy in the MASK-air study: a proof-of-concept analysis. Allergy. 2021.
136. Bousquet J, Pfaar O, Togias A, Schunemann HJ, Ansotegui I, Papadopoulos NG, et al. 2019 ARIA Care pathways for allergen immunotherapy. Allergy. 2019;74(11):2087-102.
137. Bousquet J, Bedbrook A, Czarlewski W, Onorato GL, Arnavielhe S, Laune D, et al. Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma. Clin Transl Allergy. 2019;9:16.
138. Coronavirus disease (COVID-2019) situation reports [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed on 13 Apr, 2021
139. EAACI. COVID-19 reports in Allergy. 2020 [Available from: https://onlinelibrary.wiley.com/doi/toc/10.1111/(ISSN)1398-9995.COVID-19 Accessed on 13 Apr, 2021
140. Cardinale F, Ciprandi G, Barberi S, Bernardini R, Caffarelli C, Calvani M, et al. Consensus statement of the Italian society of pediatric allergy and immunology for the pragmatic management of children and adolescents with allergic or immunological diseases during the COVID-19 pandemic. Ital J Pediatr. 2020;46(1):84.
141. Pfaar O, Klimek L, Jutel M, Akdis CA, Bousquet J, Breiteneder H, et al. COVID-19 pandemic: Practical considerations on the organization of an allergy clinic-An EAACI/ARIA Position Paper. Allergy. 2021;76(3):648-76.
142. Pfaar O, Torres MJ, Akdis CA. COVID-19: A series of important recent clinical and laboratory reports in immunology and pathogenesis of SARS-CoV-2 infection and care of allergy patients. Allergy. 2021;76(3):622-5.
143. Shaker MS, Oppenheimer J, Grayson M, Stukus D, Hartog N, Hsieh EWY, et al. COVID-19: Pandemic Contingency Planning for the Allergy and Immunology Clinic. J Allergy Clin Immunol Pract. 2020;8(5):1477-88 e5.
144. Kahwash BM, Deshpande DR, Guo C, Panganiban CM, Wangberg H, Craig TJ. Allergy/Immunology Trainee Experiences During the COVID-19 Pandemic: AAAAI Work Group Report of the Fellows-in-Training Committee. J Allergy Clin Immunol Pract. 2021;9(1):1-6 e1.
145. Klimek L, Jutel M, Akdis C, Bousquet J, Akdis M, Bachert C, et al. Handling of allergen immunotherapy in the COVID-19 pandemic: An ARIA-EAACI statement. Allergy. 2020;75(7):1546-54.
146. Balekian DS, Banerji A, Blumenthal KG, Camargo CA, Jr., Long AA. Allergen immunotherapy: No evidence of infectious risk. J Allergy Clin Immunol. 2016;137(6):1887-8.

Accepted Article

This article is protected by copyright. All rights reserved

147. Pfaar O, Angier E, Muraro A, Halken S, Roberts G. Algorithms in allergen immunotherapy in allergic rhinoconjunctivitis. Allergy. 2020;75(9):2411-4.
148. Pitsios C, Demoly P, Bilo MB, Gerth van Wijk R, Pfaar O, Sturm GJ, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy. 2015;70(8):897-909.
149. Pfaar O, Agache I, Bonini M, Brough HA, Chivato T, Del Giacco SR, et al. COVID-19 pandemic and allergen immunotherapy - an EAACI survey. Allergy. 2021.
150. Mahler V, Mentzer D, Bonertz A, Muraro A, Eigenmann P, Bousquet J, et al. Allergen Immunotherapy (AIT) in children: a vulnerable population with its own rights and legislation - summary of EMA-initiated multi-stakeholder meeting on Allergen Immunotherapy (AIT) for children, held at Paul-Ehrlich-Institut, Langen, Germany, 16.1.2019. Clin Transl Allergy. 2020;10:28.
151. Bousquet J, Schunemann HJ, Hellings PW, Arnavielhe S, Bachert C, Bedbrook A, et al. MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis. J Allergy Clin Immunol. 2016;138(2):367-74 e2.

Accepted Article

This article is protected by copyright. All rights reserved