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Article *in* International Journal of Molecular Medicine · May 2022

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Immunotherapies in the treatment of immunoglobulin E-mediated allergy: Challenges and scope for innovation (Review)

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Received December 24, 2021; Accepted February 28, 2022

DOI: 10.3892/ijmm.2022.5151

Abstract. Immunoglobulin E (IgE)-mediated allergy or hypersensitivity reactions are generally defined as an unwanted severe symptomatic immunological reaction that occurs due to shattered or untrained peripheral tolerance of the immune system. Allergen-specific immunotherapy (AIT) is the only therapeutic strategy that can provide a longer-lasting symptomatic and clinical break from medications in IgE-mediated allergy. Immunotherapies against allergic diseases comprise a successive increasing dose of allergen, which helps in developing the immune tolerance against the allergen. AITs exerttheirspecial effectiveness directly or indirectly by modulating the regulator and effector components of the immune system. The number of success stories of AIT is still limited and it canoccasionallyhave a severe treatment-associated adverse effect on patients. Therefore, the formulation used for AIT should be appropriate and effective. The present review describes the chronological evolution of AIT, and provides a comparative account of the merits and demerits of different AITs by keeping in focus the critical guiding factors, such as sustained allergen tolerance, duration of AIT, probability of mild to severe allergic reactions and dose of allergen required to effectuate an effective AIT. The mechanisms by which regulatory T cells suppress allergen-specific effector T cells and how loss of natural tolerance against innocuous proteins induces allergy are reviewed. The present review highlights the major AIT bottlenecks and the importantregulatory requirements for standardized AIT formulations. Furthermore, the present reviewcalls attention to the problem of 'polyallergy', which is still a major challenge for AIT and the emerging concept of 'component-resolved diagnosis' (CRD) to address the issue. Finally, a prospective strategy for upgrading CRD to the next dimension is provided, and a potential technology for delivering thoroughly standardized AIT with minimal risk is discussed.

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Key words: allergen-specific immunotherapy, allergen extract, allergen engineering, component-resolved diagnostics, polyallergy

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1. Introduction

There is a delicate balance between immune tolerance and responsiveness against foreign assault. If the balanceis shifted towardstolerance it may underpin the development of pathological conditions, such as cancer. However,if the immune system is overly responsive, this may induce autoimmune diseases and allergic disorders (1,2). Hyper responsiveness of the immune system is responsible for different allergic conditions in atopic individuals (3). Studies have estimated that >25% of the population in developed countries suffers from immunoglobulin (IgE)-mediated allergies or 'type I hypersensitivity' (4-6). Allergen-specific immunotherapy (AIT), also known as 'allergy vaccination' or 'desensitization', is a treatment that fine-tunes the defense system of the body to become tolerant to a specific allergen over a period of time (7,8). AIT is accompanied by several potential drawbacks, such as local and systemic immune reactions during AIT administration, and variable patient outcome (9,10). Despite the risk and differential response among individuals, AIT is still the most effective approach and the only therapeutic approach that is specific for the treatment of allergy. AIT reduces the activation and proliferation of lymphocytes in response to allergenic stimulus and further enhances the immune tolerance mechanisms towards specific allergens (11). Principally, during AIT, the allergen

is administered to the host via different routes at increasing concentrations to achieve an effective immunotherapy (12). Theprocessis divided into twophases: The 'build up phase'and the 'maintenance phase' (13).

During the first phase, or 'build up phase' of immunotherapy, an increasing dose of the therapeutic formulation is administered to the host 2 or 3 times in a week, which enhances the allergen tolerance over time (14). The length of this phase varies based on the frequency of injections and effectiveness of the therapeutic formulation but generally ranges between 3 and 6 months (14,15). After achieving an effective dose in the 'buildup phase', the second phase of AIT is started as a 'maintenance phase' (15). The gap between therapeutic injections throughout the maintenance phase varies and may range from 2-4 weeks to 2-5 years (15,16). This desensitization process increases the threshold dose of the allergen to cause allergic reactivity (13). Several studies have provided evidence that administration of a suitable allergen for immunotherapy not only provides protection against its own allergenicity but also reduces the probability of developing sensitization against other allergens (17,18). The first specific immunotherapy for grass pollen-induced hay fever was introduced in 1903 (19). However, over time, the treatment options with different routes for AIT expanded the scope of immunotherapy to other allergic diseases (20-24). The identification of IgE and a blocking antibody of IgE, IgG4, provided a leap forward in the field of AIT (25,26). With further advances in technologies in later years, such as the synthesis of chemically modified and genetically engineered allergens with low allergenic activity and their use for AIT, the scope of modifying the allergens for an improved clinical outcome broadened (27,28). In addition, novel biomarkers have been identified that could be useful for monitoring the effectiveness and predicting the safety of immunotherapy (29). The practices of allergen immunotherapy have been knowingly or unknowingly used for several decades. Fig. 1 provides a roadmap of findings associated with AIT (19-30). The present review attempts to provide a comprehensive overview of the history and diverse clinical applications of AIT, and to explore developments in the scientific understanding of therapy along with future perspectives.

2. Allergen extracts for immunotherapy

Allergens are a complex mixture of allergenic and non-allergenic ingredients comprising single or multitudinous combinations of proteins, carbohydrates, lipids and glycoproteins (31). The allergenic ingredients that are responsible for induction of allergy could potentially also be used for the diagnosis and specific immunotherapy of the same allergy (32). Usually, the therapeutic formulations are directly prepared from a natural source of allergen, which contains allergenic as well as non-allergenic components (31,32). The concentration of an allergen for inducing effective immunotherapy depends on several bio-variable factors, such as the ratio of allergic and non-allergic ingredients, their quantity, processes used for their isolation and purification, and genetic makeup of the affected atopic individual (33). Crude allergenic extract is extensively used for immunotherapy; however, four major problems are often witnessed during the course of this method: i) Allergen extracts comprise a variety of allergenic as well as non-allergenic proteins, other macromolecules and toxic ingredients, which is often difficult to standardize involving high batch-to-batch variability; ii) development of specificities against newer proteins; iii) unpredictable clinical response due to systemic administration of intact allergens through extracts; and iv) effective therapeutic doses are often difficult to achieve due to a lack of standardized extracts (33-35). Therefore, the standardization of allergen extracts from their natural source is necessary to diminish their allergenic potential and to ensure their consistent composition and potency for AIT (36). At present, various injectable and non-injectable, Food and Drug Administration (FDA)-approved allergen extract-based therapeutic formulations are used for the diagnosis and treatment of different allergic diseases (37-39). However, the majority of the FDA-approved allergen extract-based therapeutic formulations are non-injectable. For example, to treat allergic rhinitis and conjunctivitis, the FDA-approved GRASTEK (timothy grass pollen allergen extract), ODACTRA (house dust mites allergen extract), RAGWITEK (short ragweed pollen allergen extract) and ORALAIR (sweet vernal, orchard, perennial rye, Timothy and Kentucky bluegrass mixed pollens allergen extract) are available as tablets for sublingual AIT (37,40-42). Similarly, PALFORZIA (peanut allergen powder) is also an FDA-approved allergen extract-based therapeutic formulation that is used for the treatment of peanut allergy through oral immunotherapy (OIT) (38,43). In addition, numerous other injectable and non-injectable allergen extract-based therapeutic formulations are being investigated in different phases of clinical trials (39,44,45). Table I provides an overview of allergen extracts approved by the FDA or undergoing clinical trials.

At present, novel ways are being developed to introduce chemical modifications in the allergenic extracts intending to lower their allergenic potential without affecting the immunogenicity, and such modified extracts are termed as 'allergoids' (27,46,47). To enhance the efficacy of the immunotherapeutic approaches and decrease the allergenic properties of a given protein, different chemical, structural and recombinational modifications can be introduced in the allergen (34). The generation of hypoallergenic hybrid molecules through conjugation of allergens to adjuvant substances activating innate immune cells, such as CpG oligonucleotides, carbohydrate-based particles, or nanosized therapeutic formulations are examples of these modifications (48-50). These alterations are primarily intended to modify the IgE-specific epitopes present on allergens, while keeping the T cell epitopes intact (51). Methods of chemical modifications to prepare hypo allergens are advantageous over others as they can be applied on different homogenous as well as heterogeneous types of allergens. For example, coupling of allergens with polyethylene glycol, glutaraldehyde and formaldehyde has been illustrated to modify the IgE epitopes of allergens (34,51). Similarly, treatment of allergens with maleic acid anhydride generates recognition sites for different scavenger receptors in allergens, thereby facilitating their intake by phagocytic cells, and immunotherapy with these hypo allergens has been observed to induce the type 1 helper cell (Th1) dominated immune response (52,53). Similarly, conjugation of allergens with synthetic oligo-deoxy nucleotides carrying

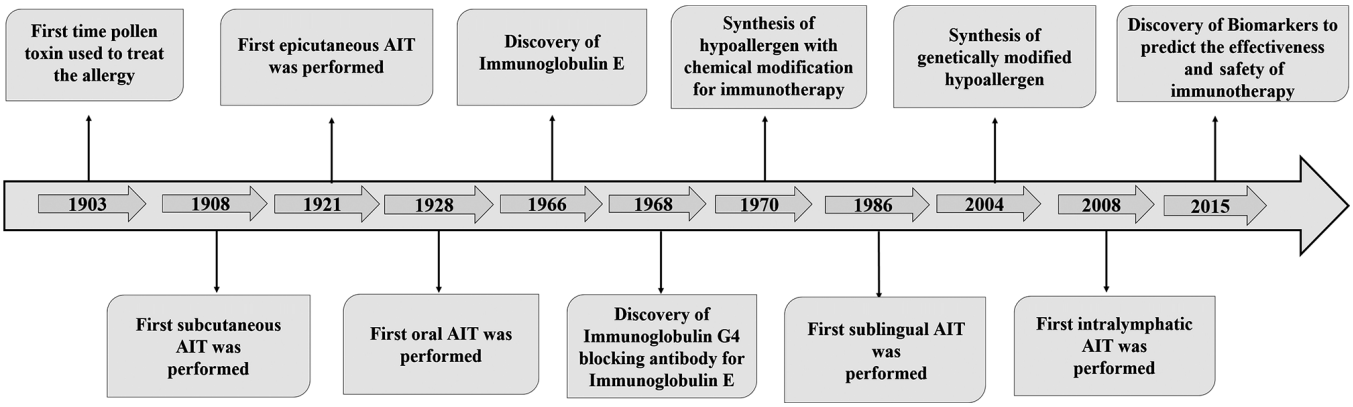

Figure 1. Timeline of major scientific advances during the history of AIT. Injection of crude pollen extract to ameliorate the allergenic response of pollen was first described in 1903, representing the initial breakthrough in AIT. Since then, numerous advances in experimental methods and innovations have fueled the transition of AITs from fundamental research to clinical trials and have contributed to the identification of AIT-associated biomarkers. AIT, allergen-specific immunotherapy.

immune-stimulatory CpG sequences from bacterial DNA can mask IgE-specific epitopes on allergens and could potentially block the cross-linking between allergens and IgE bound to high affinity IgE receptor (FcεRI) present on the surface of mast cells and basophils (54). In order to further refine this strategy, further investigations that compare the relative efficiency of the chemical modifications and determine their potential synergistic or additive effects are required.

Recombinant DNA technology has also been used for targeted alteration in allergenic proteins by means of mutations, deletions, fusion, site-directed mutagenesis and hybridization (32). Recombination of the genes of allergens requires knowledge of their sequences and positions of amino acids, as well as their three-dimensional conformation, which is helpful for targeted modification (34,55). Using this approach, hypo allergens for the timothy grass Phil p 5b and American Cockroach Per a 1 allergen have been successfully prepared by deleting the IgE epitopes present in the corresponding gene segments, and the consequent hypo allergens were observed to have reduced IgE binding properties, reduced histamine-releasing activity and reduced skin reactivity (56,57). After modification, allergens may exhibit low allergenicity but also carry the risk of generating new epitopes that may induce allergic reactions (48). Therefore, it is important to subject the newly synthesized hypo allergens to pertinent *in vitro* and *in vivo* evaluation tests before approving them for therapeutic applications.

3. Mechanisms of AIT

Allergy is fundamentally an undesirable hyperactive immune response to allergens, which occurs due to a breach of peripheral tolerance and dysregulation of immune homeostasis mediated by cellular and molecular factors, such as TLR4 or TLR8, regulatory T cells (Tregs), T cell, immunoglobulin and mucin and allergen-specific MHC class II tetramer$^+$ cells (58,59). Forkhead box P3 (FoxP3)-positive Tregs are pivotal for generating tolerance against self-antigens and harmless non-self-antigens (60,61). Usually, Tregs present at the mucosal surfaces suppress the immune cells involved in the mediation of allergic responses, such as type 2 CD4$^+$ helper cells, mast cells and eosinophils (62,63). Distinct approaches have been used in various AIT studies; however, there is a profound overlap in the mechanism underlying these AITs and their allergen-specific tolerogenic features (64,65). The major differences among various approaches primarily involve the role of antigen presenting cells (APCs) associated with differentroutes of immunotherapy, memory cell or Treg responses, characteristic immunoglobulins produced, and interaction with other immune cell types present at the interface niche, where the primary encounter of the tolerogenic protein occurs with the host (12,66,67). Notably, the APC phenotype present at the host-environment interface servesan important role in peripheral insensitivity or immunogenicity to innocuous antigens (68,69). For example, dendritic cells (DCs) are specialized antigen-presenting cells, which initiate and sustain allergic inflammation, or support tolerance induction (70,71). After being triggered by an antigen, immature DCs polarize into either dendritic cells-1, dendritic cells-2 (DC2s), dendritic cells-17 or regulatory dendritic cells (DCregs), which induce the differentiation of naïve T cells into Th1, type 2 helper (Th2) or T helper 17 cell (Th17), or Tregs, respectively (29,71,72). Compared with immature DCs, DCregs or tolerogenic DCs represent an intermediate stage of DC maturation characterized by higher expression levels of class II major histocompatibility complex (MHC) and co-stimulatory molecules, but often lack the capacity of proinflammatory cytokine secretion (73,74). The DCs involved in AIT are primarily myeloid DCs (mDCs) and Langerhans cells (LCs), which are also characterized by expression of FcεRI on their surface (75,76). mDCs secrete IL-12, which tilts the Th1/Th2 balance towards Th1 responses, whereas LCs promote the development of T helper 3 regulatory cells via production of IL-10 and TGF-β, thereby attenuating the Th2 immune responses (71,75). The induction of allergen-specific Tregs is the central factor in all types of AITs; however, how the allergen-specific effector T cells or naïve T cells transform into allergen-specific Tregs is not well understood. It would appear that the myriad of signals present in the microenvironment of immature DCs after the phagocytosis of allergens orchestrates the development of the Th2-mediated allergic response or tolerogenic response against allergens spearheaded by Tregs (76,77). It has been demonstrated in several models that

Table I. Allergen-specific immunotherapies approved by the FDA or undergoing clinical trials.

First author/s, year	Allergic diseases	Immunotherapy	Proper name	Tradename	FDA approval	(Refs.)
Köberlein and Mösges, 2013; Rizvi and Panchal, 2015; Cho *et al*, 2018; Nelson, 2018	Allergic rhinitis and conjunctivitis	Sublingual immunotherapy	Timothy grass pollen allergen extract	GRASTEK	Approved	(37,40-42)
			House dust mites allergen extract	ODACTRA		
			Short ragweed pollen allergen extract	RAGWITEK		
			Sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass mixed pollens allergen extract	ORALAIR		
Thompson *et al*, 2020	Allergic rhinitis and conjunctivitis	Intralymphatic immunotherapy	Conifer mountain cedar pollen extract	TX-SMILE	Undergoing clinical trial	(44)
Dougherty *et al*, 2021; Erlich, 2022	Food allergy (peanut allergy)	Oral Immunotherapy	Peanut allergen extract	PALFORZIA	Approved	(38,43)
Senti *et al*, 2012	Food allergy (peanut allergy)	Epicutaneous immunotherapy	Peanut allergen extract	Viaskin® EDS with peanut allergen	Undergoing clinical trial	(45)
Zuidmeer-Jongejan *et al*, 2015	Food allergy (fish allergy)	Subcutaneous immunotherapy	Recombinant fish parvalbumin	FAST-Fish	Undergoing clinical trial	(39)

FDA, Food and Drug Administration.

coincident exposure of pathogens or endotoxin with allergen may lead to onset of IgE-mediated allergic responses (78,79). However, in the absence of pathogenic signals during AIT, the immature DC sunder go tolerogenic interaction with T cells of the lymph node (80). This promotes the development of IL-10, TGF-β and IL-35-secreting Tregs, thereby inducing allergen-specific peripheral tolerance (81-83).

These suppressive cytokines (IL-10 and TGF-β) are known to inhibit the differentiation, proliferation and activation of effector T cells, and further bring about desensitization of mast cells and basophils (84). IL-10 acts by decreasing the production of allergen-specific IgE, while increasing the levels of immunoglobulin G4 (IgG4) and immunoglobulin G2a (IgG2a) secretion from B cells (85). In addition, TGF-β is also involved in the induction of allergen-specific tolerance during AIT (86). Tregs are the major source of TGF-β, which affects T cell proliferation and differentiation, and inhibits Th2 differentiation by suppressing GATA binding protein 3 (GATA-3) expression and IL-4-mediatedSTAT6 activity (87-89).

Apart from the suppressive Tregs and DCregs, a population of IL-10-secreting suppressor B cells has also been identified, and this is known as regulatory B cells (Bregs) (90,91). The primary function of Bregs is to support immunological tolerance and inhibit unwanted inflammation (92). IL-10-secreting Bregs serve an important role in the tolerance induction during AITs (93). IL-10 is a key suppressive cytokine associated with Bregs; however, TGF-β and IL-35 have also been identified as Breg-associated suppressor molecules (94,95). Different subsets of Bregs have been described in humans and a defective development and function of Bregs may result in various chronic inflammatory diseases, such as collagen-induced arthritis and chronic hepatitis B virus infection (96,97). Although IL-10 secretion is common to all Bregs, they are further grouped into different subsets based on their differential functions (98). The immature/transitional Bregs ($CD19^{+}CD24^{hi}CD38^{hi}$) suppress effector T cells but enhance Treg function (99). Similarly, another sub-population of Bregs, known as memory B Cells/B10 Bregs ($CD19^{+}CD24^{hi}CD27^{+}$), enhance and stabilize the expression of FoxP3 in Tregs (100,101). Another subset of Bregs ($CD25^{high}CD71^{high}CD73^{low}$) prevents peripheral tolerance by producing IL-10 and blocking antibody IgG4 (93,102). Notably, it has been reported that the relative percentage of $CD19^{+}$ $CD24^{hi}CD27^{+}$ Bregs was decreased in patients with allergic rhinitis, whereas an increase in the percentage of $CD19^{+}CD24^{hi}CD38^{hi}$ Bregs was observed in comparison with healthy individuals; however, the significance of this finding is unclear (103). It has been noted that Bregs serve a critical role in effective AIT. After AIT, the percentage of IL-10 and IgG4-secreting Bregs increases, which suppresses the allergen-specific $CD4^{+}$ T-cell proliferation and further ameliorates the allergic airway inflammation via FoxP3-positive T regulatory cells (93,104). In another study conducted on bee venom antigen allergic patients subjected to AIT, an enhanced percentage of IL-10 and IgG4-secreting $CD25^{hi}CD71^{hi}CD73^{low}$ Bregs, which potently suppress allergen-specific $CD4^{+}$ T-cell proliferation and produce increased amounts of IgG4, was found (93). Notably, a 10-100-fold increase in serum allergen-specific IgG4 isotype has been observed for AITs (85). IgG4 functions as a blocking antibody for IgE and

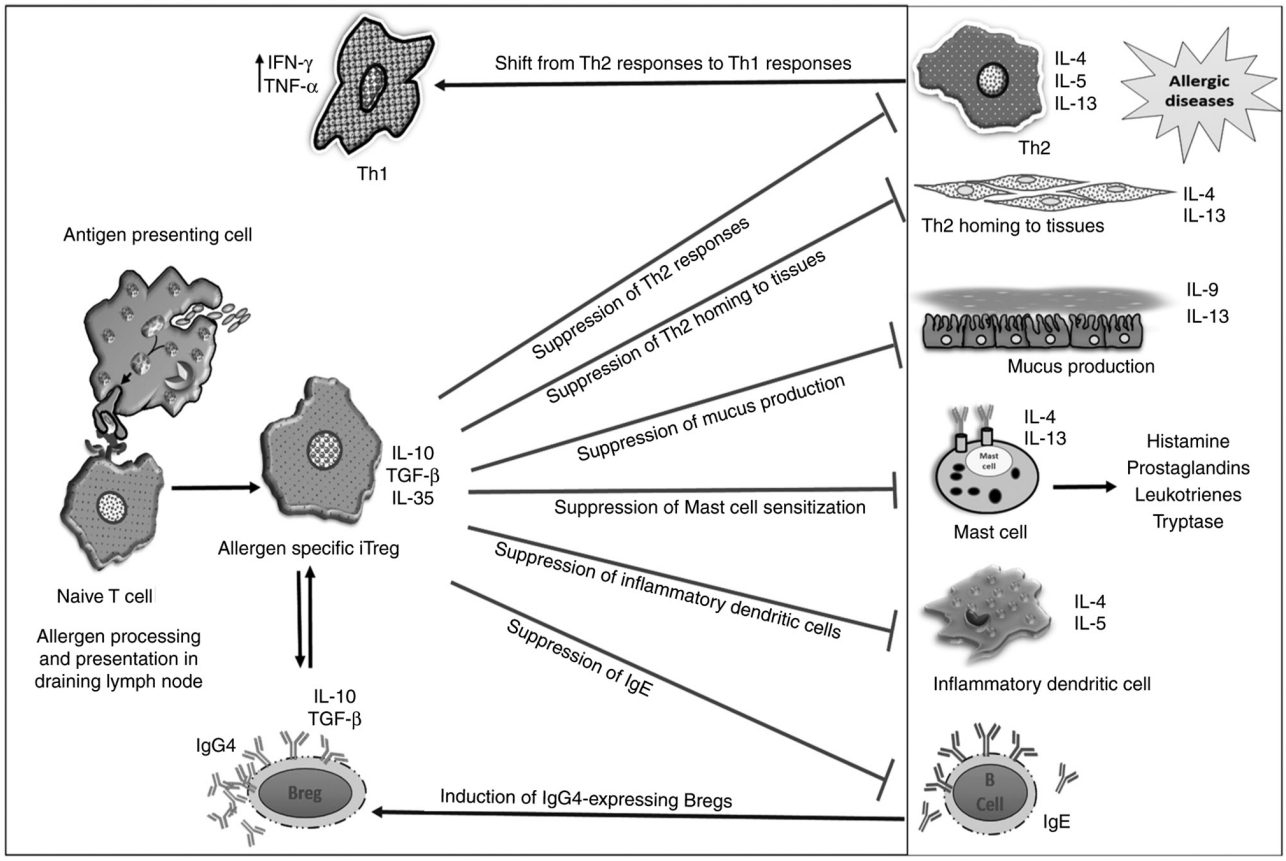

Figure 2. Mechanism underlying allergen-specific immunotherapy. Following immunization, the allergen is captured by local antigen presenting cells, processed as small peptides and presented in association with the MHC and iTregs. The iTregs secrete suppressive cytokines, including IL-10, TGF-β and IL-35, which further suppress different allergic components in either a contact-dependent or independent manner. Allergen-specific iTregs can shift the Th1/Th2 balance towards the Th1 (IFN-γ and TNF-α secreting T cells) type from the predominant Th2 (IL-4, IL-5 and IL-13-producing T cells) type. Furthermore, iTregs can also inhibit tissue homing of Th2s, mucus secretion and sensitization of mast cells. In addition, IL-10 and TGF-β secretion by iTregs inhibits the inflammatory dendritic cells and IgE production from B cells, and induces IgG4 (IgE blocking antibodies) secretion from Bregs. These modulations by iTregs result in the development of tolerance against the allergen. Breg, regulatory B cell; IgE, immunoglobulin E; IgG4, immunoglobulin G4; iTreg, inducible regulatory T cell; MHC, major histocompatibility complex; Th1, type 1 helper cell; Th2, type 2 helper cell.

considerably reduces the binding of IgE to its receptor present on the surface of mast cells and basophils (105). This process prevents mast cell degranulation, which in turn downregulates the activity of eosinophils and neutrophils (106). IgG4 antibodies also inhibit the proliferative response of T-cell clones by blocking IgE-facilitated allergen binding to B cells and thereby inhibiting the presentation of allergenic peptides by B-cells to allergen-specific T-cell clones (93). Additionally, an increase in IgG2 a in the serum shifts the Th1/Th2 immune response towards a Th1-dominated immune response (107). Despite early generation of Tregs following AIT, it may still take years to effectuate a marked reduction in IgE levels in the allergic individuals (108). An analysis of the mechanisms of AIT has been summarized in Fig. 2, and a comparison of various AITs is presented in Table II.

4. Routes of administration in AIT

The most important factor, which contributes to the duration of AIT, is the route of administration and this has a marked influence on the clinical outcome of immunotherapy (12). There a large variations in the immune niche present at various external tissue interfaces associated with different AITS, which serve a major role in fine orchestration of immune responses (12,109,110). The routes of administration of AIT can be categorized into subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT), OIT, intralymphatic immunotherapy (ILIT) and epicutaneous immunotherapy (EPIT).

SCIT. Historically, SCIT has been the first form of immunotherapy, where in a small amount of allergen extract is administered by injectioninto the subcutaneous layer of skin and this is commonly called an'allergy shot' (111). It was used for the first time approximately a century ago by Noon (20,112) in 1911 as a useful measure to tackle hay fever symptoms (20,112). Until the discovery of IgE in 1965, SCIT was used without having a proper understanding of the primary allergic mediators and the regulatory mechanisms targeted by immunotherapy (20,113). However, in a number of cases, the therapy proved effective in reducing the symptoms of allergic diseases for a prolonged period (114). Previous studies have demonstrated that improvements can be observed within 3 months after initiation of therapy, and those benefits may be long lasting with decreases in seasonal symptoms and use of anti-allergic medications, which further persisted for at least 2 years even after discontinuation of immunotherapy (115,116).

Table II. Comparative analysis of different allergen-specific immunotherapies.

First author/s, year	Immunotherapy	Targeted APCs	Mechanism	Disadvantages	(Refs.)
Lawrence *et al*, 2016; Cox *et al*, 2012; Hesse *et al*, 2018; Jacobsen *et al*, 2012; Jongkhajornpong and Laisuan, 2017; Aasbjerg *et al*, 2014	Subcutaneous immunotherapy	DCs of non-vasculature part of subcutaneous layer	Decrease in inflammatory mediators (i.e., histamine and PGD2); migration of mast cells, eosinophils and basophils within target organs (skin, nose and lung); induction of Th1s and Tregs; duration, >100 injections in 3-5 years	Redness at the site of injection, swelling and itchiness (local reactions); shortness of breath; occasionally severe anaphylactic reactions, which may cause death	(71,111,114,115,117,118)
Okamoto *et al*, 2017; Lim *et al*, 2017; Frati *et al*, 2010; Allam *et al*, 2008; Di Bona *et al*, 2010	Sublingual immunotherapy	Oral LCs	Decrease in the recruitment of mast cells, eosinophils and basophils; progressive decline of serum IgE; increase in allergen-specific serum IgG4 and mucosal IgA; decrease in Th2 responses, while promoting Th1 and Treg responses; duration, 1 drop daily/5 drops three times per week for 1-3 years	Only a few local reactions but no mortality has been reported so far	(127-129,131,213)
Smaldini *et al*, 2015; Vickery *et al*, 2014; Sampson, 2013; Harrison and Powrie, 2013	Oral immunotherapy	Macrophages and DCs of GI lumen	Induction of various $FoxP3^{high}CD4^{+}CD25^{+}$ Tregs (e.g., TGF-β^{+}, IL-10^{+} and IL-35^{+} Tregs); increased IgG4 with decline in serum IgE; duration, daily for 2-5 years	Local and systemic reactions along with risk of anaphylaxis	(146,149,150,214)
Dioszeghy *et al*, 2018; Dupont *et al*, 2010; de Chaisemartin, 2015; De Calisto *et al*, 2012	Epicutaneous immunotherapy	LCs of the superficial skin layer	Induction of $FoxP3^{+}$/IL-10^{+}-producing Tregs; decreased eosinophils in BAL; reduced Th2 responses; duration, 3-4 months	Few local reactions	(153,161,215,216)
Hylander *et al*, 2013; Martínez-Gómez *et al*, 2009; Freiberger *et al*, 2016; Rajakulendran *et al*, 2018	Intralymphatic immunotherapy	DCs of lymph node	Shifting of Th2 responses towards Th1 type; generation of allergen-specific Tregs; increase in the serum titers of allergen-specific IgG antibodies, particularly IgG4; duration, only 4 injections within 12 weeks	Mild local adverse reactions, such as throat irritation, and oral and ear pruritus, are common; rarely severe adverse reactions	(163,166,167,169)

AHR, airway hyperresponsiveness; APCs, antigen presenting cells; BAL, broncho alveolar lavage; DCs, dendritic cells; FoxP3, forkhead box P3; GI, gastrointestinal; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG4, immunoglobulin G4; LCs, Langerhans cells; PGD2, prostaglandin D2; Th1, type 1 helper cell; Th2, type 2 helper cell; Treg, regulatory T cell.

A case study of apatient with atopic keratoconjunctivitis revealed that SCIT was fairly successful in controlling the allergic symptoms and disease exacerbation (117). The therapeutic benefits of SCIT are attributed to different types of regulatory mechanisms. In a study comparing the efficacy of SLIT vs. SCIT against grass allergy, it was demonstrated that SCIT could induce comparatively high levels of IgE blocking antibody IgG4, by suppressing Th2 cytokine production more efficiently (114,118). The subcutaneous administration of allergens activates IL-10-secreting DCs, which further induces IL-10 or TGF-β secretion from Tregs, thereby establishing the homeostatic balance between Th1 and Th2 cytokines. IL-10 secreted by Tregs induces B cells to secrete allergen-specific IgE-blocking antibodies, such as IgG4 andimmunoglobulin A, which further trap allergens before their binding to receptor-bound IgE (119-121). The enhanced IL-10 also leads to induction of specific non-reactivity of allergen-specific T cells during the later phase of therapy either by inducing clonal anergy in allergen-specific effector T cells or by generating immunosuppressive Tregs (114,122). Principally, in SCIT, the target APCs are DCs of the non-vasculature part of the skin, i.e., subcutaneous administration of allergens modulates the distribution of various subpopulations of DCs and their ability to produce different proinflammatory cytokines, such as IFN-α and IL-6 (71,123). In addition, SCIT alters the distribution of type 2 innate lymphoide cells (ILC2s), which have been recognized to servean important role in the initiation and establishment of allergic responses through production of thetype 2 cytokines IL-5 and IL-13 (124). ILC2s also empower DCs to potentiate memory T helper 2 cells, and thus may enforce the recall immune response against allergens (125).

Despite its potential efficacy, SCIT has been found to trigger adverse allergic reactions, including rashes at the site of injection, swelling, itchiness, breathlessness and even anaphylaxis leading to death, numerous times (126). Furthermore, it takes a long time (>50 injections in 3-5 years) to achieve the effective therapeutic dose for sustained allergen tolerance (114).

SLIT. Unlike during SCIT, where allergy shots are administered through injection, during SLIT, a minute amount of allergen extract is kept under the tongue of the patient, held for 2 min and then swallowed, thus avoiding the irritation of injection (127-129). However, the doses administered during SLIT are restricted by the available concentration of the allergen extract and the volume of liquid that can be held under the tongue (129,130). During the initial 4-6 months of SLIT, the allergen extract with a low allergenic potential is administered to the patients at gradually increasing doses, followed by a constant maintenance dose administered daily for up to 3 years (115). Compared with SCIT, where subcutaneous DCs are important, LCs are central to tolerance development during SLIT (71,131). The LCs prominently express high affinity IgE receptor (FcεR1), MHC class I and II, and other co-stimulatory and co-inhibitory receptors on their surface, which makes them suitable for receptor-mediated IgE-dependent allergen uptake and subsequent presentation to T cells (132). This triggers the transformation of naive T-cells into Tregs implicated in allergen-specific immune tolerance (133,134). In addition, cross-linking of allergen-bound IgE with FcεRI on oral LCs results in the production of IL-10, which facilitates inflammation resolution (135). Notably, during the early phase of SLIT, IL-10 is also contributed by allergen-specific IL-10-producing Tregs, thus establishing a concordance between the innate and adaptive arms of immunity for induction of a tolerogenic microenvironment (136,137). In a clinical study, it was observed that 12 months of SLIT against house dust mite allergy was advantageous in inducing allergen tolerance (127). Several clinical trials have also illustrated the clinical efficacy of single allergen tablets (grass and ragweed) and extract solution (ragweed) at the primary level (37,42). After getting clinical approval from the FDA, SLIT has been commercialized in several parts of the world (127,128,131).

Compared with SCIT, SLIT delivers a more satisfactory clinical outcome in children and adults as demonstrated by its efficacy to prevent reoccurrence of allergic symptoms for a longer period (118). According to World Allergy Organization, SLIT is the most innocuous immunotherapy that is used as an alternative to injection-based immunotherapy (46,138). Importantly, considering the relative safety of SLIT in clinical trials over the years and standardization of modalities with several allergen extracts, such as ragweed and grass pollen, certain SLIT tablets have also been permitted to be taken at home without medical supervision (138). At present, this is the only form of immunotherapy that provides this flexibility to allergic patients. The local reactions during SLIT are mild and resolve themselves without requiring any allergen dose adjustment or adjunct medication (129). In an observational safety study evaluating the safety of SLIT, only 11 out of 65 children subjected to SLIT were reported to exhibit adverse reactions, and even the observed reactions were not severe enough to necessitate modification or discontinuation of therapy (129,139). At present, there has been no report of mortality associated with SLIT (140).

OIT. OIT was reported for the first time in 1928 (141). Primarily, OIT was conceived to attain immune tolerance against food allergens; however, later it was observed that the potential scope of immunotherapy might also cover allergic asthma (142). OIT is easily administrable and requires less time to achieve tolerance against an allergen compared with other immunotherapies (143). This advantage may be attributed to the presence of the microbial flora in the intestine, which are responsible for facilitating allergen-specific oral tolerance (144). It is known that secretion of certain microbial metabolites, such as short chain fatty acids, acetate, propionate and butyrate, facilitates the differentiation and expansion of Tregs in the gut mucosa (144).

In OIT, an allergen extract is taken either in encapsulated form or administrated with an aqueous solution (145). The swallowed allergen extract is adsorbed by the gut mucosal membrane and phagocytosed by APCs in the gastrointestinal tract, which further stimulates gut mucosal Tregs (146,147). OIT has been observed to provide symptomatic relief in allergic asthma through induction of blocking antibody (IgG4) with concurrent reduction in serum IgE levels (148). In a study monitoring the sustained clinical efficacy of OIT, wherein 24 volunteers were subjected to 5 years of peanut OIT, half of the volunteers developed the capability to tolerate 5 g in a double-blind, placebo-controlled food challenge and could successfully incorporate peanut into their diet (149). In spite of

several reports demonstrating the therapeutic efficacy of OIT, there is also a considerable risk of serious allergic reactions and anaphylaxis involved with OIT, which has restricted the over-the-counter sale of OIT allergy shots (150-152).

EPIT. EPIT for the treatment of allergies was first introduced in early 1917. The procedure of EPIT requires administration of an allergen to the epicutaneous layer of the skin, where large numbers of professional antigen presenting LCs facilitate the trafficking of allergens into the lymph nodes (153). EPIT is a strategy gradually evolving for the treatment of different allergic conditions and particularly food allergy, considering the potential risk associated with OIT (154). In the context of food allergy, another important phenomenon which requires particular mention is 'gut homing', which is migration of T and B cells from primary lymphoid organs to the inflamed and non-inflamed regions of the intestine (155). Food allergy is characterized by a disturbed gastrointestinal immune environment and gut homing, which hampers the movement of tolerogenic Tregs into gastrointestinal immunological tissues. This compromises the body's ability to cope with local and systemic immune responses induced by the oral administration of harmless antigens, such as food proteins (156). EPIT can regenerate gut-homing via selective expansion of unique TGF-β^+ Tregs, which impart protection against anaphylactic reactions (157,158). Furthermore, EPIT provides a naturally safer alternative to other AITs, because the allergen delivered through the epicutaneous layer of the skin reaches the systemic circulation in minute amounts compared with other routes of administration (159). The epicutaneous Viaskin® Patch- (EV patch) system has been developed for EPIT, which enhances the allergen delivery across intact skin (160). Therapeutic formulation or allergen extract can be directly applied on the groove of the EV patch, which facilitates allergen exposure to APCs in the superficial layers of the skin (161). Repeated application of the EV patch in mice for 8 weeks resulted in desensitization with no significant increase in histamine after oral challenge with allergen (160). The advancements indicate that the epidermal layer of the skin with a non-vasculature system could be exploited as amoresuitable route for immunotherapy with fewer side effects.

ILIT. ILIT is characterized by the delivery of allergen directly into lymph nodes, which generates immune tolerance earlier compared with other AITs (162). ILIT came into consideration when it was observed that only a minute amount of allergen was channelized into the lymph node when administered through other routes (163). In this regard, intralymphatic administration of allergens is associated with a marked enhancement in the effectiveness of allergy vaccination, even with a low dose of allergen (164,165). In a murine model, it has been demonstrated that ILIT induces higher levels of serum cytokines, such as IL-10, IL-4 and IL-2, compared with SCIT (166). In congruence, ILIT also encourages the switching of Th2-dependent hyperactive allergic responses to Th1 phenotype, which boosts the production of IgG2a and IgG4, albeit with a markedly lower dose of allergen compared with SCIT (167). In an open trial study to determine the safety and efficacy of ILIT, 6 patients were subjected to intralymphatic inguinal injections of either birch or grass-pollen extract, and all patients stayed healthy and reported symptomatic relief from allergy alongside decreased medicinal requirement (24). In another study comparing the therapeutic outcome of SCIT vs. ILIT in patients with pollen allergy, ILIT was observed to be more efficacious in reducing the frequency of rescue medication and provided improved symptomatic relief with reduced skin-prick sensitivity in patients (168). Furthermore, allergen tolerance is induced markedly faster in the ILIT, as early as by 4 months, compared with other AITs, which take 2-5 years (169,170).

5. Disadvantage of AITs

Since the fundamental process of immunotherapy involves challenging the sensitized patients with increasing doses of allergen, there is always an acute possibility of undesirable minor to severe allergic reactions. Furthermore, during the 'build up' or 'escalation' phase of immunotherapy, local and systemic reactions are often witnessed with increasing doses, which impedes the procedural efforts to achieve a therapeutically active 'maintenance' dose (15). Furthermore, due to huge variations in the sensitivity of different patients to an allergen, the therapeutic formulation applicable for one atopic individual may not be promising for others (10). Another confounding factor is the variation in the composition of allergenic extracts available for immunotherapy from different manufacturers, which may arise due to differences in allergen sources and allergen extract preparation protocols (171). Allergen extracts prepared from divergent natural sources may get contaminated with pathogens and allergens from other sources, which yields undesirable immunogenicity and even new IgE-mediated allergies (46). One of the causes underlying the limited success and variable outcome of immunotherapeutic approaches so far is the absence of standardized procedures and regulatory guidelines for preparation of allergen extracts and their characterization (10,172). Another major bottleneck hindering the progress of AIT is the lack of appropriate biomarkers that can predict the efficacy of AIT (29).

Lack of uniform regulatory guidelines for AIT. The present review summarizes a consensus on the AIT guidelines followed by regulators on a global scale, which are fundamentally based on the factors influencing the therapeutic efficacy of AIT (Table III). These guidelines are largely based on meta-analyses, which include reports published over the past two decades, and primarily aim to ascertain the efficacy and safety of AIT (10,126,173-177). However, at present, the drug and vaccine safety monitoring system for AIT is poorly organized and is only based on the voluntary reporting of side effects and efficacy. In this regard, there is a clear need to institutionalize dedicated monitoring systems of allergen immunotherapy outcomes and to further streamline uniform regulatory guidelines on the modalities of AIT.

Lack of successful AIT biomarkers. At present, no surrogate biomarkers that can predict the effectiveness of AIT have been identified (178). Decreased levels of allergen-specific IgE and increased levels of serum IgG4 have been acknowledged as biomarkers to predict the clinical efficacy of AIT (179,180). Increased numbers of IL-10 and TGF-β-producing Tregs during and after immunotherapy are also crucial emerging

Table III. Guidelines for allergen-specific immunotherapy.

First author/s, year	Essential factors	Description	(Refs.)
Gaur, 2017; Pajno *et al*, 2018; Weinberg, 2011; Ansotegui *et al*, 2020	Selection of diagnostic tests for allergy	World Allergy Organization has approved SPT as the best diagnostic method to detect allergen-specific IgE in the serum sample of the allergic individual; if an allergic individual is suffering from any skin diseases, whether allergic or non-allergic, SPT should not be performed or postponed until the skin problem is resolved; an intradermal test for the detection of allergen-specific IgE can also be performed but it is susceptible and may also provide false-positive results compared with SPT; SPT should not be performed in a pregnant woman; *in vitro* detection of serum IgE against a particular type of allergen should be used as a diagnostic tool where SPT cannot be performed; radio/enzyme immunoassays can be used to detect total and specific IgE as an *in vitro* diagnostic test; clinically, a basophil-activation test can also be used to measure the progress of AIT and diagnosis of allergy by detecting cross binding of the allergen to IgE; presence of allergen-specific IgE (either on *in vivo* or *in vitro* testing) in serum does not always mean that the individual is suffering from IgE-mediated allergy, and thus, before starting any immunotherapy, family history analysis regarding allergies is always required	(10,174,217,218)
Gaur, 2017; Pajno, *et al*, 2018; Pfaar *et al*, 2014; Pitsios *et al*, 2015	Selection of patients for immunotherapy	Allergen-specific IgE must be present in the patient serum; the minimum age of the patient is >5years, with no upper limit; moderate to severe allergic rhino conjunctivitis, persistent rhinitis, large local reactions to insect venom and atopic dermatitis in a patient aeroallergen sensitivity, allergic asthma and symptoms are of sufficient duration and severity; AIT should be performed in that case if allergen avoidance is not possible or if symptom relief is inadequate with treatment; for a particular age group (children, young adults and adults), AIT formulation and duration should be different; improvement in medical symptoms should be observed periodically after the escalation phase; therapy should be stopped if there is a lack of clinical improvement even after 1year of immunotherapy and the possibility of other cures should be explored	(10,174,176,219)
Gaur, 2017; Ring *et al*, 2014; Pfaar *et al*, 2014; Halken *et al*, 2017; Pitsios *et al*, 2015	Selection of allergens to use for immunotherapy	The allergenic ingredient which is responsible for the induction of allergy, is also used for the diagnosis and specific immunotherapy of the same allergy. Furthermore, the atmospheric condition and history of allergen exposure of the atopic individual directly affects their quality of life. Therefore, for an effective immunotherapy, the selection of the allergen must be local, and according to allergy, it should also be seasonal as climate affects protein-lipid content and therefore allergenicity of the allergen; allergen extracts used for immunotherapy can be used with different types of modification to decrease the allergenicity; the mixing of allergens during the preparation of therapeutics formulation for polysensitization should be decided after allergy diagnosis against more than one allergen. If allergens are non-homologous, then	(10,126,176,177,219)

Table III. Continued.

First author/s, year	Essential factors	Description	(Refs.)
		compatibility of each (cross-reactivity and enzymatic degradation) should be kept in consideration before mixing allergens; allergens with high proteolytic enzyme activities (such as dust mites, fungal and insects) should not be mixed with any other allergen and should be prescribed preferably in separate vials	
Pfaar *et al*, 2014; Wollenberg *et al*, 2018; Lommatzsch, 2018; Wollenberg *et al*, 2018	Selection of AIT for patient	Important factors for selecting AIT are that it should be able to build and maintain long-lasting immunity against an allergen without triggering any local or systemic reaction. It should have the potential to prevent new allergic sensitivities; patients with skin diseases should not be allowed to undergo SCIT and EPIT; AIT should not start in a pregnant woman; there is some possibility of local allergic reactions at the site surrounding the route of AIT administration, for example erythema, pruritus and swelling are common for SCIT and EPIT, while oropharyngeal pruritus is common for OIT and SLIT. However, immunotherapy should not provoke a systemic reaction (anaphylaxis). Allergen injections (vaccine) should be administered separately from other vaccinations for infectious diseases with a gap of at least 1 week; AIT, if required, should be used in combination with pharmacotherapy to control the clinical symptoms of a local reactions, the AIT in combination with pharmacotherapy can also increase the efficacy of AIT; AIT for respiratory allergy should not start when the chances of getting in contact with the allergen are high or during a peak pollen spell; injections should not be administered when the patient has clinical symptoms, or the symptoms should be controlled by adequate medication	(176,220-222)

AIT, allergen-specific immunotherapy; EPIT, epicutaneous immunotherapy; IgE, immunoglobulin E; SCIT, subcutaneous immunotherapy; SPT, skin prick test.

biomarkers to assess the clinical response of AIT (29,181). In addition, AIT induces other molecular markers in DC2s, such as CD141, GATA-3 and receptor-interacting serine/threonine kinase 4, as well as in DCregs, such as complement C1q chain receptor variant IIIA of IgG Fc, which can also be used as a potential biomarker to predict the efficacy of AIT (182-184). However, neither of these biomarkers is appropriate to precisely predict the prognosis and clinical efficacy of immunotherapy in all AIT-receiving patients. Therefore, it is further required to refine the understanding of the specific mechanistic involvement of these biomarkers in the successful progression of AIT. This will help in monitoring the progress of therapy and integrating appropriate solutions, which will improve the clinical outcome.

6. Polyallergy

Another growing concern is the problem of 'polysensitization', which is a sensitivity of atopic individuals to two or more allergens, and this condition is referred to as 'polyallergy' after clinical confirmation (185). According to estimates, 60-80% of allergic patients are polysensitized (186). An increasing prevalence of polyallergy has been documented with age, which necessitates the development of immunotherapeutic approaches that can take care of more than one allergen simultaneously (186,187). However, an additive preparation of mixture of allergens for simultaneous AIT may not yield the desirable outcome, as one allergen may affect the stability and optimal dose of the other allergen, thus affecting its immunotherapeutic potential, efficacy and even safety (188-190). In this regard, the European Medicines Agency has suggested that AIT should not be performed with a mixture of two non-homologous allergens, and should be performed separately for seasonal or perineal allergens (10). This creates the problem and annoyance of enduring separate immunotherapeutic procedures by patients for addressing multiple allergen sensitivities on an individual basis (190). The polyallergic condition in patients may arise due to 'cross-reactivity' or 'co-sensitization' (186). Cross-reactivity is defined as IgE reactivity against structurally related proteins when the sequence homology is often >70%, whereas co-sensitization may involve multiple IgE sensitizations against structurally unrelated allergen groups (191). It is essential to understand the nature of polyallergy with respect to 'cross-reactivity' or

'co-sensitization' to design a safe and effective AIT (192). With the advancement in science and technology, it is now possible to isolate the pure allergic components from their natural source for refined diagnosis and treatment of allergies. Component-resolved diagnosis (CRD) utilizes purified native or recombinant allergens to detect IgE sensitivity against individual allergen molecules and has assumed increasing importance in clinical investigation of IgE-mediated allergies (193). The CRD technique quantifies serum specific IgE against individual allergenic proteins or even allergenic peptides present in natural sources, rather than quantifying IgE against the whole natural extract (194). At present, CRD diagnosis is used in laboratory practices as single plex and multiplex arrays and offers a promising technology that could replace conventional serum specific IgE assays in the near future (195). One of the major advantages of CRD is that it can discriminate true allergens from the cross-reactive allergen molecules and polyallergy of other related allergens (196). However, CRD analysis utilizes intact proteins or random peptides in its present form, which makes the data interpretation complex and ambiguous (192,196). A more refined CRD approach could entail the use of individual IgE epitope-based recombinant fragments present in a protein, rather than using the whole allergenic protein components (192). *In silico* analysis in conjunction with wet lab validation allows determination of specific IgE epitopes present in an allergen, which can be further employed for predicting epitope specific IgE reactivity of patient serum (197). The present review describes a strategy for developing allergy arrays with potential application for AIT in patients with polyallergy (Fig. 3).

The strategy offers a simple and robust tool with a high resolution for predicting IgE cross-reactivity or co-sensitization from single or multiple allergenic sources. After a thorough characterization of the IgE sensitivity profile of a patient, the same IgE epitope-based recombinant fragments can also be used for generating hypoallergens intended for use in AIT (198,199). The hypoallergen could be prepared by modifying the IgE specific epitopes of the particular allergen either by coupling them with chemical modifiers or by altering the coding sequence of the allergy-responsive component of the allergen using recombinant DNA techniques (46,200,201). A combination of these hypoallergenic epitope-based proteins may be employed for AIT through a single dosing regimen plan (202). However, before the onset of AIT, it should be ensured by a skin prick test that the serum of the patient shows IgE reactivity towards the allergens but not the hypoallergens (202).

7. Future prospects

There is a need for devising strategies aiming at improved predictability of AIT, minimization of side effects, annoyance of injection, irritability, fatal outcomes and a shorter immunotherapeutic duration along with sustenance of life-long tolerance for the allergen. Several combinatorial therapies, which involve administration of allergen extracts with immunomodulatory or suppressive cytokines, such as TGF-β, IL-35 and IL-10, have yielded encouraging results; however, these approaches may markedly escalate the cost of immunotherapy (203,204). Different endogenous specialized proresolving lipid mediators (SPMs) have also shown promise as therapeutic agents in the resolution of allergic inflammation. Results from several experimental systems indicate that SPMs, including lipoxins, resolvins, maresins and protectins, are multi-pronged and potent regulators of inflammation and stimulate resolution (205,206). For example, a combination of resolvin D1 (RvD1) and 17-hydroxydocosahexaenoic acid has been demonstrated to inhibit IgE production by human B cells and it also suppresses the differentiation of naïve B cells into IgE-secreting cells by specifically blocking epsilon germline transcript (207). Furthermore, other studies have also investigated the roles of SPMs in murine models of allergic airway inflammation and have revealed their protective role in allergic asthma (208-210). RvD1 is also known to reduce the allergic airway inflammation by targeting eosinophils and proinflammatory mediators involved in the Th2 signaling pathway, while resolvin E1regulates the development of Th17 cells and IL-23 production (205). Similarly, exogenous administration of maresin1 (MaR1) during the allergen challenge phase attenuates allergen-triggered inflammation by decreasing the multiple allergy-associated parameters, such as numbers of eosinophils, allergen-specific IgE levels and type 2 cytokines in bronchoalveolar lavage fluid (BALF), and increasing TGF-β levels (211). The MaR1-mediated increase in BALF TGF-β triggers Tregs to limit type 2 innate lymphoid cell activation, and thus, promotes resolution of lung inflammation. In addition, MaR1 promotes lung catabasis for allergic asthma by suppressing ILC2-derived IL-5 and IL-13, while stimulating the expression of amphiregulin (211). Furthermore, amphiregulin itself contributes to a constitutive, low-level release of bio-active TGF-β within tissues, leading to continuous tissue regeneration and to an immunosuppressive environment, which may keep inflammation-prone tissues in the homeostatic state (212). Considering the multi-pronged beneficial actions of SPMs, they are important potential candidates for combinatorial AITs.

Furthermore, as aforementioned, the lack of appropriate biomarkers indicating successful progression of AIT is a major bottleneck affecting the clinical outcome of allergy immunotherapy. Clinical investigations examining the expression levels and biosynthesis of SPMs in relation to efficacious AIT may help to identify prospective biomarkers. In a model of allergic lung inflammation, MaR1 production declined upon allergen challenge but increased with resolution of allergic inflammation (211). This finding suggests that levels of MaR1 in tissues before and after allergen-specific immunotherapy may be tested as a biomarker of successful immunotherapy.

8. Concluding remarks

The knowledge gathered in the past decades has helped in developing an improved understanding of the mutual interaction between immune cell types presents in diverse immunological niches, thereby propelling the evolution of different AIT routes of administration and improved therapeutic formulations. As a noteworthy breakthrough, the over-the-counter sale of certain AIT formulations is also now possible, the self-administration of which does not require any special hospital supervision. However, there is still much to be done to address the issues of standardizing AIT formulations, the risk of frequent adverse

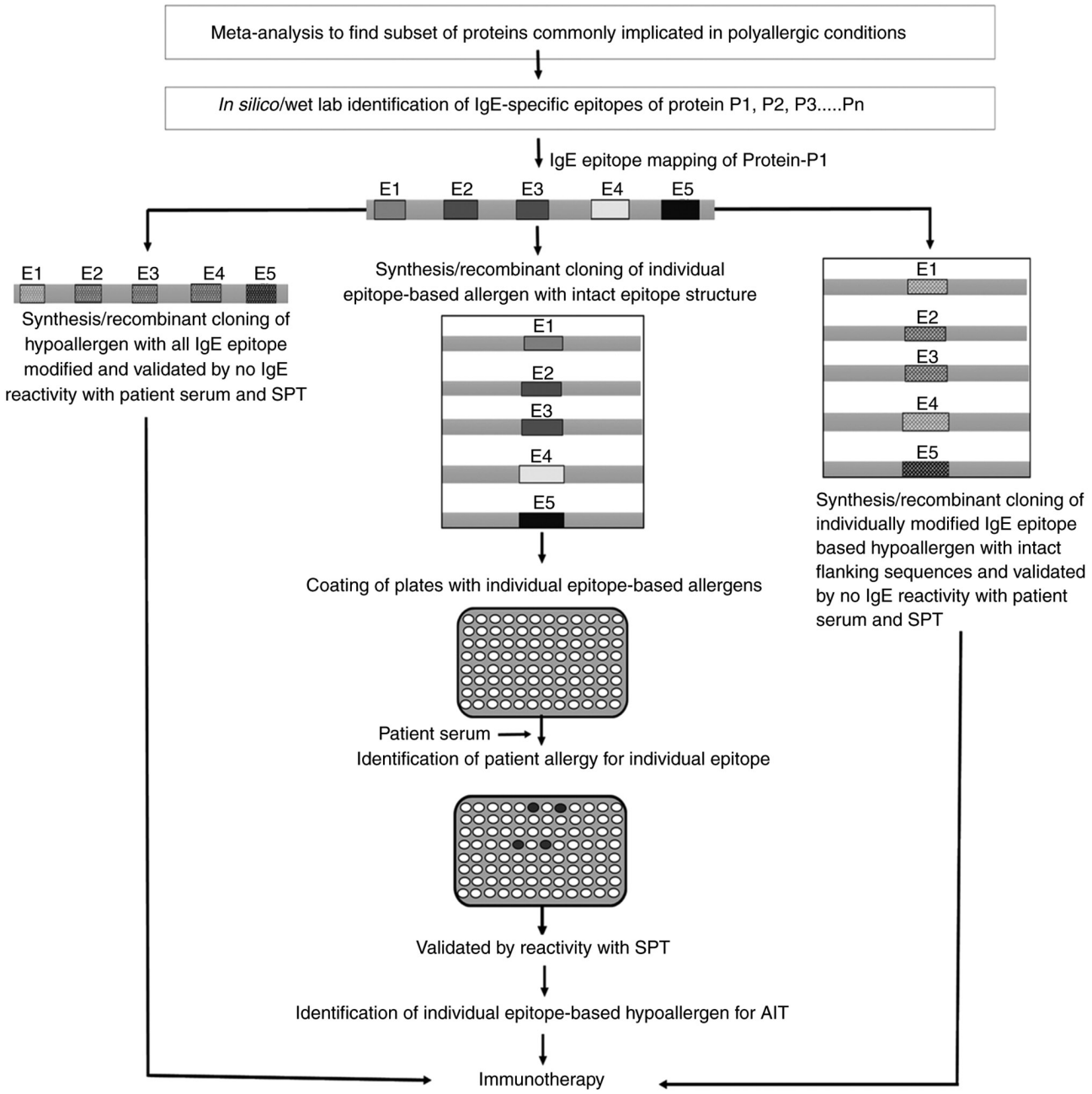

Figure 3. Schematic representation of the potential strategy for developing unique IgE epitope-based allergy arrays for conducting AIT in patients with polyallergy. It has been attempted to illustrate the plan for an example protein P1. The subset of proteins involved in a polyallergic condition (P1, P2, P3…Pn) would be derived from meta-analysis, followed by subjecting each protein to an algorithm as per the schematics depicted for protein P1. First, an *in silico* and wet lab analysis would be carried out to map and validate all IgE epitopes (E1, E2, E3, E4, E5) in an allergenic protein (P1). The middle path depicts the method for the synthesis of an individual IgE epitope-based allergenic peptide with intact epitopes and flanking sequences. These peptides would be used to coat the allergen array plates and these plates can be employed to determine the sensitivity profile of the patient against an individual IgE epitope or multiple IgE epitopes. The left path in the figure illustrates the synthesis of hypoallergen carrying all IgE epitopes present in the allergen but modified for minimum IgE reactivity. This hypoallergen can be used for immunotherapy when a patient is found to be allergic to different epitopes of a single allergen. On the other hand, the right path in the figure shows the synthesis of a hypoallergen carrying the individual IgE epitope, where the epitope would be modified for minimum IgE reactivity. Subsequently, these peptides can be used for immunotherapy, when a patient is found to be sensitive to single or multiple IgE epitopes present in one or more allergens. AIT, allergen-specific immunotherapy; IgE, immunoglobulin E; SPT, skin prick test.

reactions, the maintenance of tolerance to allergens, the reduction in the duration of AIT, and other concerns, such as polyallergy. Developing immune tolerance against allergens is the primary aim of AIT but the current understanding of the precise mechanism underlying the induction of allergen-specific Tregs is still in its infancy. An improved scientific understanding of key events guiding antigen-specific tolerance would pave the way for the advent of novel non-invasive technologies targeting induction of allergen-specific Tregs for an improved prognosis of AIT and complete cure of allergies.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

AT conceptualized the review article and was thoroughly involved in the critical review of the manuscript for important intellectual content. SY carried out the literature survey and prepared the review. SS and PM drafted the tables and figures. Data authentication is not applicable. All authors participated in the design and revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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