Review Article

Immunotherapy approaches for managing allergic conditions in children – A narrative review

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ABSTRACT

Allergic reactions in children are a major concern globally. The ever-changing environment, exposure to new and chemically altered compounds, genetically modified food products, variations in hygiene parameters, and most importantly, questionable immunity, together influence the pattern of allergic diseases in children. The most favorable and convenient mode of treatment sought is the use of over-the-counter drugs like antihistamines. However, they tend to lose their efficacy when used over a long period of time. Immunotherapy, for the management of allergic conditions, is considered a gold standard and is still a promising tool. Subcutaneous immunotherapy and sublingual immunotherapy together comprise the two modes of allergen-specific immunotherapy. Each method differs in its mode of administration and role in allergic diseases, in terms of, efficacy and safety measures. The choice between the two is dependent on the type of allergic disease and personal preferences opted either by the specific patient, or by the health-care professional involved in the treatment. The convenience of administration and compliance are also major grounds to consider while opting for the most appropriate mode of treatment. This review hence highlights new advancements in the field of immunotherapy, the efforts to achieve the goals envisioned and literature focusing on better outcomes in managing allergic reactions.

Key words: Allergic diseases, Allergen-specific immunotherapy, Allergens, Subcutaneous immunotherapy, Sublingual immunotherapy

The term "allergy" originated in 1906, by Clemens von Pirquet, a Viennese doctor, based on his clinical observations of patient hypersensitivity, to harmless substances such as pollen, food, or dust [1,2]. Chronic, inflammatory disorder with anomalous immune reactions to certain environmental substances, referred to as allergens, is termed as an "allergy." Various proteins, having varied origins, can behave as allergens and may cause allergic reactions [3]. According to eminent allergy experts, allergic symptoms may range from mild to moderate, or even be life threatening, depending on the balefulness of the antigen, the immune system, has been exposed to [4]. Allergens may be chemical (skincare or haircare products, fragrances, dyes), food related (peanuts, eggs, genetically modified food products) or air borne (pollens, dust mites, spores). These allergens may result in reactions such as anaphylaxis, skin anomalies, allergic rhinitis (AR), or asthma [5-7]. In 1963, Philip Gel and Robin Coombs proposed a classification in which acute immunoglobulin E (IgE)-mediated Type - I hypersensitivity reaction was termed as an "allergy" [8,9].

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Allergic diseases in children are common health concerns among the pediatric population globally. These diseases include AR, asthma, allergic dermatitis, and food allergies. An epidemiological study by Okubo *et al*., reported about 40% of the children's population suffering from allergic diseases [10]. The extremity and impact of the condition may vary broadly and affect the quality of life, school attendance, and overall health of the child. In a study by Batmaz *et al*., children aged 8 and 18 years were compared, having been divided into two groups, one with severe allergic conditions and the other serving as the control group. The results of the study revealed that the quality of life among the control group was better than the ones having chronic allergic conditions [11].

Allergic diseases in India have seen a recent upsurge. Conditions such as asthma, AR, atopic dermatitis, and food allergies contribute their share in this situation. Causal reasons could be attributed to worsening climatic conditions, increasing levels of pollution, poor hygienic conditions, and low access to health-care facilities, especially in rural areas. According to a study by Singh *et al*., 11.3% of children aged between 6 and 7 years and 24.4% of children aged 13–14 years reported

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the prevalence of AR, in India [12]. However, according to an ISAAC study (2009), overall 2.7% of children aged between 6 and 7 years had eczema and 3.6% of children aged between 13 and 14 years had eczema [13]. Food allergies present a lower prevalence at 0.14% as compared to rhinitis, asthma, and eczema among children in India [14]. There are several studies (Table 1) suggesting the prevalence and rise in the percentage.

Increase in the prevalence and morbidity rate of allergic diseases, such as AR, asthma or food allergies, a need for the development of a disease modifying therapy which targets the underlying pathomechanisms, has become paramount. This has led to the popularity of allergen immunotherapy (AIT), a therapy, which induces immune tolerance to allergens for a long period of time. It reduces allergic inflammation, symptoms, disease severity, and in turn, the need for multiple medications. AIT has also proven to be effective against new sensitization, progression of AR into asthma, and on severity of asthma. The conventional routes to administer this therapy, that is, subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), are in use for the treatment of asthma, AR and venom allergies, since the past many years and with successful results. Other routes of immunotherapy, specifically for food allergies, are currently under research, especially for the pediatric population [20-25]. A room for improvement regarding the efficacy, safety, and adherence of AIT in daily practice, along with the need to develop newer routes of administration, still persists. This review thus, summarizes the immune mechanism of AIT, the protocols to be followed, indications and safety measures to be kept in mind while administering it to children, and the recent developments in the field.

EVOLUTION OF AIT

Around the 20th century, significant advancement started under the work of Leonhard Noon and John Freeman, in 1911 [26], who were the first to observe reduction in conjunctival sensitivity to grass pollen by administering repeated injections of crude grass pollen extract. Frank land conducted the first double-blind trial in 1954 and confirmed the efficacy of subcutaneous grass pollen therapy for seasonal asthma. Norman and Lichtenstein in 1978 were the first to demonstrate that AIT is allergen specific. Hunt *et al*., in the same year, demonstrated the efficacy of purified Hymenoptera venom immunotherapy in cases of severe insect venom allergy. In 1998, the World Health Organization, in a position paper, identified the risks of AIT in uncontrolled asthma cases. It also highlighted the safety of the sublingual route for immunotherapy, which was also supported by the World Allergy Organization (WAO) position paper. In 1999, it was reported that 3 years of continuous SCIT resulted in long-duration benefits even after its discontinuation, for 3 years. In 2009, the epicutaneous route for immunotherapy was tested in grass pollen allergy. The first report of intradermal immunotherapy was reported in 2013. In 2018–2019, oral and epicutaneous immunotherapy for peanut allergy were tested. Several such randomized clinical trials are further needed to test the efficacy of AIT in children [27].

MECHANISM OF ACTION OF AIT

AIT involves several immunological pathways for its mechanism of action, requiring an interplay between adaptive and innate immune responses. The primary goal is to restore immune tolerance to allergens, which is achieved by decrease in the number of effector cells such as mast cells, basophils, eosinophils, and type 2 innate lymphoid cells [28-32], induction of regulatory T and B cell responses [33-38], and regulation of allergen-specific antibodies [39]. There is limited literature on the mechanism of action of AIT in children.

EFFECT ON INNATE IMMUNITY

Basophils and mast cells are the primary cells which play an important role in mediating allergic response. AIT functions by inducing early desensitization of both these cells, resulting in their suppression to respond to allergen-IgE crosslinking [40], thereby causing reduced tissue infiltration and release of mediators by the primary cells. There are studies to support this mechanism of action of AIT on innate immunity [41,42]. Therefore, AIT is considered successful, when the IgG4 antibodies, which

Table 1: Prevalence of allergic diseases in children from India

S.No.	Allergic diseases	Type of study	Authors	Allergic condition	Prevalence of allergic condition and their upsurge
1	Respiratory allergic diseases	Centre hospital-based study	Paramesh [15]	Asthma/severe asthma	From 20% to 27.5% persistent severe asthma 4–6.5% between 1994 and 1999.
		Review	Chandrika [16]		From 6% (1998) to 21.2% (2013)
		cross-sectional questionnaire survey	Singh *et al*. [17]	Asthma	2.4% (6–7 years) 0.1% (13–14 years)
		Cross-sectional questionnaire survey	Sharma and Banga [18]	Asthma	Rural areas (6–7 years 4.4% and 13–14 years 2.7%) Urban areas (6–7 years 6.0% and 13–14 years 5.3%)
2	Atopic dermatitis	Cross-sectional surveys	Odhiambo *et al*. [13]	Eczema	0.90%
		Systemic review	De *et al*. [19]	Atopic dermatitis	3.1–7.21% (0–16 years)
3	Food allergy		Li *et al*. [14]	19% of 5677 children from Mysore and Bangalore. Low at 0·14% (6–11 years)	

compete with IgE for allergen binding, are blocked, resulting in the prevention of activation and degranulation of mast cells and basophils. AIT has shown to have modulatory effect on dendritic cells and innate lymphoid cells as well, apart from mast cells and basophils [28].

EFFECT OF AIT ON ADAPTIVE IMMUNITY

AIT has shown modulatory effects on T and B cells. Local expansion of FOXP3+CD25+Tregs in the nasal mucosa of patients was observed with SCIT [43]. Epigenetic changes in Tregs were seen in SLIT in addition to hypomethylation of FOXP3 promoter region which is responsible for the suppression of Tregs [44]. The mechanism of AIT on adaptive immunity can also be demonstrated by its effect on allergen-specific TH2 cells and TH2-related surface markers [45]. These cells have been demonstrated to have significantly reduced following grass pollen immunotherapy [46] and oral peanut therapy [47].

THE TWO-WAY APPROACH: SUBCUTANEOUS OR SLIT

The conventional routes of administration of AIT in clinical practice currently are SCIT and SLIT, while other routes such as intralymphatic and epicutaneous are under investigation [48].

Administration of SCIT is usually done as a depot adsorbed on aluminum hydroxide or tyrosine (unmodified or modified extracts). Schedules of SCIT may be decided on the basis of number of injections/visit, number of visits/week, and the swiftness with which the patient reaches maintenance dose. In a conventional situation, SCIT is administered as one to three injections per week, for a variable number of weeks, followed by a maintenance phase which involves administering injections every 2–6 weeks over a period of years.

SLIT route has been made use of recently, the first randomized clinical trial having been conducted in 1986 [49], almost 75 years later of SCIT being first reported [50]. SLIT was administered in tablet form for the first time in 2001. Administration technique of SLIT involves use of fast-dissolving tablets or drops, to be retained under the tongue for at least a minute and then swallowed. SLIT is recommended in seasonal AR as either continuously or pre/co-seasonally, commencing at 2 months or better 4 months, before the beginning of pollen season.

Although numerous studies are available on SCIT and SLIT in adults, substantial evidence is lacking in children [51]. Literature supporting the efficacy of prolonged SCIT in children suffering from grass pollen and perennial AR to house dust mites is scarce [22]. SLIT on the other hand has shown to have a safer profile, so much so, that it may be administered at the patient's home itself [52,53]. Studies have shown only 12% poor compliance in patients completing a 3-year SLIT treatment [54]. According to a systematic review of 60 studies, clinical effectiveness of SLIT as a treatment modality in seasonal and perennial AR was less convincing in children as compared to adults [55-57]. Although studies have also shown well tolerance to SLIT tables in children suffering from house dust mites (HDM) perennial AR and resulted in improved symptoms [58-60]. Grazax asthma prevention trial demonstrated that there was marked reduction in asthmatic symptoms and need for asthmatic medication in patients undergoing 5-year grass SLIT treatment, without any changes in the primary outcome, that is, onset of asthma [61,62]. Despite the presence of such clinical trials and results, more studies need to conduct to test AIT in children.

DIAGNOSIS OF ALLERGIC CONDITIONS IN CHILDREN AND TREATMENT PLAN

Diagnostic tests for allergic conditions in children give a scope of approaches pointed toward distinguishing explicit allergens, setting off unfavorably allergic reactions, and surveying the seriousness of the condition (Table 2). Skin prick tests are usually performed to distinguish hypersensitive reaction responses of allergens onto the skin and observe for confined responses. Blood tests, for example, specific IgE examines, and measure the degrees of allergen-specific antibodies in the bloodstream, giving understanding into sensitizing to specific allergens. Moreover,

Table 2: Prevalent allergic diseases, frequency, and immunotherapy options

Allergic disease	Frequency of occurrence	Common allergens	Diagnostic tests	Immunotherapy options
Asthma	High	Dust mites, pollen, mold	Spirometry, peak flow measurement, allergy testing	SCIT, SLIT
Allergic rhinitis	Common	Pollen, dust mites, pet dander	Skin prick test, allergen-specific IgE blood test	SCIT, SLIT, intranasal corticosteroids
Atopic dermatitis	Common	Food allergens (e.g., milk, eggs, peanuts), environmental allergens	Patch testing, Skin prick test	Allergen avoidance, topical corticosteroids
Food Allergy	Increasing	Peanuts, tree nuts, milk, eggs, soy, wheat	Oral food challenge, skin prick test, allergen-specific IgE blood test	Allergen avoidance, OIT, SLIT
Eczema	common	Environmental allergens, irritants	Patch testing, skin prick test	Allergen avoidance, topical Steroids
Allergic conjunctivitis	Common	Pollen, pet dander, dust mites	Eye examination, allergy testing	Topical antihistamines, mast cell stabilizers

SCIT: subcutaneous immunotherapy, SLIT: Sublingual immunotherapy, OIT: Oral immunotherapy, IgE: Immunoglobulin E

allergen challenge tests might be led under controlled conditions to incite unfavorably allergic reactions and affirm analysis. In specific cases, pneumonic capability tests or imaging concentrates on chest X-rays might support diagnosing conditions like asthma. Clinical history and physical examination remain indispensable parts of finding, helping the determination and interpretation of diagnostic tests and therapy to be engaged.

INDICATIONS/CONTRAINDICATIONS OF USING AIT IN CHILDREN

As AIT is an allergen-specific treatment, the indication relies completely on the identification of the allergen(s) causing the symptoms, so that the correct choice of allergen product can be selected for the treatment. Hence, it is recommended in patients with AR/conjunctivitis with or without asthma, when there is clear evidence of inhalant allergens [48]. It is currently recommended in patients with moderate-to-severe AR symptoms according to the AR and its impact on asthma classification [63]. It may also be considered in patients with mild AR, who wish to test its efficacy long term including its potential to prevent asthma [64,65]. The current literature, although, is insufficient to support the use of AIT in cases of asthma in the pediatric population, severe uncontrolled asthma being an absolute contraindication [65]. The trials designed on the other hand to investigate the efficacy on asthma in adults are promising, resulting in the decrease of inhaled corticosteroids for asthma control and reducing asthmatic exacerbations [66,67]. The global initiative for asthma management, recently, documented SLIT as an add on therapeutic option for asthma control in adults associated with AR to HDM [51]. However, the evidence related to preschoolers is limited [68].

Any relative or absolute contraindications should be carefully evaluated before commencing AIT in children. Uncontrolled or severe asthma, any active autoimmune disorders, active malignant neoplasia, or poor adherence are an absolute contraindication. While partially controlled asthma, any beta blocker therapy, systemic autoimmune disorders in remission, severe psychiatric disorders or immunodeficiencies, and any history of severe reactions to AIT are relative contraindications. Any medical or social complication which prevents the patient from frequent visits to the clinic for a long period of time should be treated as an absolute contraindication.

EFFICACY AND SAFETY OF AIT IN CHILDREN

There are several studies to support the safety and tolerance of SCIT and SLIT in the pediatric population with AR and decently controlled asthma. Local reactions seen generally with SCIT in children are redness, itching, or swelling [22]. Measures such as cooling, topical glucocorticoids, or oral antihistamines can be used to overcome it. In cases of redness/swelling >10 cm in diameter, the clinician should adapt the next dose accordingly. Systemic reactions such as anaphylaxis, angioedema, and generalized urticarial have been reported in 2% of the patients due to SCIT. Although very rare, fatal or near fatal systemic reactions have also been documented [69]. Therefore, trained clinicians should administer AIT under well-equipped clinical conditions, to handle adverse conditions like anaphylaxis [22,48].

SLIT, on the other hand, has a better safety profile than SCIT, as reported systemic reactions are fewer and less severe. The reason for this can be partially owed to the amount of immunologically active allergen. Although the amount used, as compared to SCIT, is 50–100 times, but the dose which actually reaches the antigen presenting cells, including the dendritic cells, is diluted and flushed away by the saliva, thereby reducing the initial dose administered. Local adverse reactions have been reported, limited to the oral mucosa, but rarely systemic reactions and no fatalities have been reported due to SLIT, in the three decades since its being used [70].

The WAO has recommended a consistent use of systemic reaction grading and classification [71] and SLIT local reactions grading system [72], to standardize the reporting of adverse effects due to AIT. In cases where AIT is suitable for children, relative and absolute contraindications, as well as, certain risk factors such as current allergy symptoms or infections, mast cell disease, previous systemic reaction to AIT, excess dose escalation during initiation, overdose of allergen extract, etc. [51], should always be considered.

DURATION OF AIT IN CHILDREN

To achieve significant clinical efficacy in children, AIT (both routes, SCIT or SLIT) should be used for 3–5 years, according to the data currently available. Modification in clinical history of allergic respiratory diseases and prevention of its evolution can also be assessed long term with AIT. Therefore, a recommended duration of 3 years for allergic respiratory diseases and 5 years for venom allergies is directed [48,53,70]. A marked improvement in symptoms can be observed in the 1st year of therapy itself. Reasons of treatment failure can be attributed to incorrect diagnosis, shorter duration of treatment, insufficient dosage, or inadequate adherence [51]. Once the efficacy of the treatment has been established, it can be comfortably continued for 3 years, at the least. It may be prolonged for additional 2 years, based on the treatment outcomes and consent of the family and the patient. Thus, the duration of the treatment (3–5 years) is decided on an individual basis.

CURRENT AND NOVEL APPROACHES IN AIT

AIT, although considered as the gold standard, needs to be administered under specialist supervision, owing to the risks of adverse reactions, including anaphylaxis. Use of 50% glycerin as preservative and stabilizer in allergen extracts or alum-precipitates to reduce immediate allergic effects are some of the methods commonly used in practice. Mechanisms to not only improve safety and convenience of patients but also to retain the efficacy of AIT have been an area of research.

The use of glutaraldehyde or formaldehyde to chemically modify allergens, to produce allergoids, which have altered

tertiary structures and reduced allergenicity, have shown modest efficacy.

Alternative routes of immunotherapy such as intralymphatic, oral and epicutaneous are also being explored. Intralymphatic immunotherapy is achieved by injecting allergen extracts into the lymph nodes, generally in the groin, under the guidance of ultrasound. Oral peanut immunotherapy has proven to be effective in children, although the presence of gastric adverse reactions. In a phase 3 trial in children aged 4–17 years, it was observed that 67.2% of the participants responded well to oral peanut immunotherapy as compared to 4.0% treated with placebo, although gastrointestinal symptoms were common in both. The development of the epicutaneous route was to make use of the numerous dendritic cells in the skin to enhance the processing of allergen administered at low concentrations [27]. In a study conducted on children aged 4–11 years having peanut allergy, peanut extract through skin patch was delivered. It was observed that 35.3% of the children compared with 13.6% treated with placebo, showed desensitization and reduced side effects, confined to local site of application [27].

At present, long-term tolerance for AIT through SCIT or SLIT routes has been achieved by standardized whole allergen extracts in inhalant allergies. But mechanisms which are safer, more efficacious, have convenient regimens, are tolerable for a longer duration with minimal side effects, are also being explored. Some of these mechanisms include:

- Combination of allergen extract with monoclonal antibodies (mAbs) or with toll-like receptor agonists.
- Molecular allergology has allowed more precise allergy diagnosis and development of recombinant whole allergens and hypoallergenic variants, resulting in a more individual specific “tailor-made” AIT.
- To target specifically T or B cell-dependent pathways, allergen-derived peptides have been formulated. Their efficacy over whole allergen extracts is questionable.
- Passive immunotherapy, that is, injecting a blend of IgG4 mAbs, directed against IgE epitopes of major allergens can prove to be effective against nasal allergies [27].

WAY FORWARD

AIT remains the gold standard for the treatment of allergic reactions, but the drawbacks like long duration of treatment and anaphylaxis cannot be avoided. The efficacy of AIT has proven to be commendable in cases of AR in adults and children, in the past decades, and extensive clinical trials and studies have been conducted to support the same. Not only has AIT proven to be a long-term disease modifying therapy for AR but also an effective form of preventive therapy in respiratory and food allergies. More studies need to be conducted to explore the benefits of AIT in children to facilitate it as an intervention in the early phases of disease progression. While AIT has progressed as an effective therapy over time, still many aspects need to be explored, especially among the pediatric population, with the primary objective of delivering AIT as personalized medicine. In depth understanding of the underlying mechanisms of action of AIT can pave the way for not only improving the current therapeutic strategies but also for advancing novel development. Parallelly, a more enhanced diagnostic tool can help provide a precise diagnosis for effective AIT prescription. Longitudinal, prospective, and well-designed clinical studies are thus required in the future to authenticate the current therapeutic strategies and explore novel approaches of AIT.

CONCLUSION

Clinically, SCIT and SLIT are the two routes popularly used to administer AIT in children and adults. While there is enough evidence to support its use in adults, more research is needed on the pediatric population. Thus, newer routes, like intralymphatic, epicutaneous or oral, novel approaches like modified allergens, safer and efficacious adjuvants, molecular allergology and further clinical trials can help provide concrete support to the fact that AIT is the gold standard to treat allergic diseases in adults as well as children.

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