review article

Allergen immunotherapy: Basic concepts

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Access this article online

Website: www.ijaai.in

DOI: 10.4103/0972-6691.116606

Quick Response Code:

ABSTRACT

Allergen-specific immunotherapy is the therapeutic approach for allergic disorders with dysregulated immune responses, working through down-regulation of predominant T-cell and IgE mediated reactions by inducing immune tolerance by long-lived decrease in allergen-specific T-cell responsiveness through administration of allergen extracts in incremental doses. The potential candidates include mainly those with uncontrolled symptoms despite avoidance measures and medication use. Traditionally, immunotherapy is administered subcutaneously, although sublingual, mucosal, intranasal, intrabronchial, intralymphatic, and epicutaneous routes are also in existence. Currently, it has an established role in the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and insect sting hypersensitivity. Other disorders demonstrating significant improvement on immunotherapy include atopic dermatitis, food allergies, etc., Newer therapies, such as anti-IgE (omalizumab) used in combination with immunotherapy, have improved the safety and efficacy of immunotherapy. Future studies involving scientific research with the aim of improving patient outcome using safer forms of immunotherapy through recombinant technology, including allergens with reduced allergenicity and T-cell epitope based allergy vaccines without reducing immunogenicity, are in process.

Key words: Allergen, allergen-specific immunotherapy, allergic asthma, allergic rhinitis, subcutaneous immunotherapy, sublingual immunotherapy

INTRODUCTION

Allergen immunotherapy is defined as the repeated administration of specific allergens to patients with IgE-mediated conditions for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.[1-3] It represents the specific modality of treatment that alters the natural course of allergic disorders through increasing doses of allergen extracts.[2,4] The practice of allergen immunotherapy is going on for over 100 years now since 1911.[3,5,6] Besides its established role in treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect venom hypersensitivity,[2] the spectrum of usage with encouraging results has recently extended to other allergic disorders like food allergies and atopic dermatitis with aeroallergen sensitization.[7] Recent advances in allergen immunotherapy have expanded on the improved

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understanding of the IgE-mediated immunological mechanisms, characterization of specific antigens and allergies, and the standardization of allergen extracts.[2] Currently, recombinant technology allergen extracts are being modified to reduce their allergenicity without reducing their immunogenicity.[4,7] Although the clinical response to immunotherapy has been proven to be allergen-specific, there is now enough evidence to support that administration of appropriate monotherapy to monosensitized patients can reduce the likelihood of the patients developing additional sensitivities.[8,9]

In this article, every effort has been made to review most of the aspects of the subject in a simplified manner for better understanding by the primary care physicians.

SPECTRUM OF AEROALLERGENS IN INDIA

In this country, the work on pollen allergy was initiated in the 1950s, and based upon the clinico-immunological studies, important pollens carrying allergenic potential have been identified [Table 1]. The knowledge about allergens has progressed with particular reference to structure, function, and cross-reactivity. Aeroallergens play a major role in pathogenesis of respiratory allergic diseases, particularly rhinitis and asthma. Besides pollens, fungi, house dust mites, animal dander, domestic pets, and insects as triggering factors are of importance as well.[10,11]

CLINICAL INDICATIONS

Candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures and those experiencing unacceptable adverse effects of medications or who wish to reduce the long-term use of medications. Immunotherapy is also recommended for patients with history of systemic reactions to insect stings. There is also evidence that venom immunotherapy (VIT) might be effective in reducing large local reactions that might cause significant morbidity and impaired quality of life.[2,7,12]

MECHANISM

Allergic diseases represent a complex disturbance in innate and adaptive immune responses to natural environmental allergens existing in the form of proteins derived from pollens, molds, dust mites, cockroaches, etc.[13,14] Immunological changes associated with immunotherapy are complex, and better understanding necessitates knowledge of the basic mechanisms of the allergic reactions. The allergic response is a mast cell–immunoglobulin E (IgE) dependent process requiring previous exposure and sensitization to a specific allergen. The degree of sensitization depends on several factors including genetic predisposition, load and duration of allergen exposure, and other environmental factors. Initial interaction of specific allergen takes place with antigen presenting cells (APCs) such as dendritic cells. Activated APCs make contact with T cells whose specific antigen receptors recognize one of the peptides in their major histocompatibility complex (MHC) class II. After a productive interaction, antigen-specific T cells get activated that are then capable of activating antigen-specific B cells to produce IgE. Once released by the plasma cells, antigen-specific IgE binds to the high-affinity receptors known as FCεRI on the surface of mast cells and basophils, leading to degranulation after triggering calcium transmemberane fluxes, with eventual release of mediators such as histamine, prostaglandins, proteoglycans, and some enzymes causing immediate (type 1) hypersensitivity reactions. The unleashing of the allergic response is biphasic: the early response lasts for up to 30 min and is

Table 1: Important aeroallergens in different parts of India

Central India	North India	South India	East India	West India
Poaceae family	*Prosopis juliflora*	*Cassia*	*Lantana*	*Solanum sisymbriifolium*
Asteraceae family	*Ricinus communis*	*Ageratum*	*Cucurbita maxima*	*Crotolaria juncea*
Apocynaceae family	*Morus*	*Salvadora*	*Cassia fistula*	*Ricinus communis*
Rosa	*Mallotus*	*Ricinus*	*Cocos nucifera*	*Mallotus phillippensis*
Cicer	*Alnus*	*Albizia lebbeck*	*Calophyllum inophyllum*	*Prosopis juliflora*
Ricinus communis	*Quercus*	*Artemisia scoparia*	*Phoenix*	
Ailanthus	*Argemone*	*Parthenium hysterophorus*	*Ricinus communis*	
Holoptelea	*Amaranthus*	*Casuarina equisetifolia*	*Aegle marmelos*	
Cheno/Amaranth	*Chenopodium*	*Spalhotrodia*		
Cyperus	*Holoptelea*	*Peltophorum* cyperaceae		
Cocos mucifera	*Poa species*			
Hibiscus	*Rumex acetosa*			
	Alianthus excelsa			
	Trewia nudiflora			
	Argemone mexicana			
	Cedrus doedara			
	Populus deltoides			
	Dodonaea viscosa			
	Bauhinia variegata			

characterized by rapid release of preformed histamine, proteases, and production of tumor necrosis factor alpha (TNFα), prostaglandins, and leukotriens from mast cell degranulation; the *late phase response* is characterized by release of mediators such as TNFα, interleukin (IL)-4, and IL-13, which are critical for cellular phase of the allergic response in which leukocyte recruitment promotes additional tissue inflammation and allergy.[13] In the airway inflammatory response in asthma, eosinophil-derived mediators of inflammation, including major basic protein, eosinophil cationic protein, and lysophospholipase, are toxic to the respiratory epithelium and contribute to the pathogenesis of allergen-triggered inflammation in diseases like asthma.[15] The naive T cells on activation proliferate and differentiate into T helper 1 (Th1) or T helper 2 (Th2) cells, depending upon the presence of certain cytokines. For example, in the presence of IL-12 secreted by macrophages, activated T cells differentiate into Th1 cells, whereas in the presence of IL-4 produced by mast cells, these differentiate into Th2 cells. Interferon (IFN)-γ produced by Th1 cells not only promotes Th1 differentiation but also inhibits the proliferation and production of Th2 cells [Figure 1]. In contrast, IL-10 produced by Th2 cells blocks the production of Th1.[16,17] More recently, Th17 cells producing IL-6, IL-17, IL-22, and TNFα have been described.[13,17,18] Similarly, Th22 cells are found in T-cell populations from the skin of patients with psoriasis, atopic eczema, and contact dermatitis.[19] In humans, Th1 cells produce IL-2, IFN-γ, and possibly small amounts of IL-6, IL-10, and IL-13. On the other hand, Th2 cells produce IL-4, IL-5, IL-6, IL-9, and IL-13 required for differentiation, survival, and activity of mast cells, basophils, eosinophils, and mucus-producing cells. Normally, Th1 cells support cell-mediated immune response and suppress the proliferation of Th2 cells, whereas Th2 cells support humoral and allergic responses.[13,17] When one pathway is underway, the other one is suppressed. The mechanisms by which immune responses to non-pathogenic environmental antigens lead to either allergy or harmless immunity depend upon T regulatory (Treg) subset of $CD4^+$ T cells that are dominant in healthy individuals. Accordingly, a change in dominance and the balance between Th2 and Treg cells may lead to either allergy or development of recovery.[1,20] Thymic stromal lymphopoietin (TSLP) is IL-7 like cytokine that triggers dendritic cells and mast cells to induce Th2 inflammatory response. It is expressed by epithelial cells (mainly lung- and skin-derived epithelial cells), producing CCL17 and CCL22 following exposure to TSLP, and these cytokines affect Th2-type cells. Recent studies in both humans and mouse models have demonstrated the role of TSLP in development and progression of atopic diseases like allergic rhinitis, asthma, atopic dermatitis, and food allergy.[21]

Allergen-specific immunotherapy (SIT) is the most effective therapeutic approach for dysregulated immune response toward allergens and works through enhancing immune tolerance mechanisms and reduction in the lymphoproliferative responses to allergens.[13] The earliest effect of SIT leads to decrease in the number and mediator release of mast cells, basophils, and eosinophils, improved

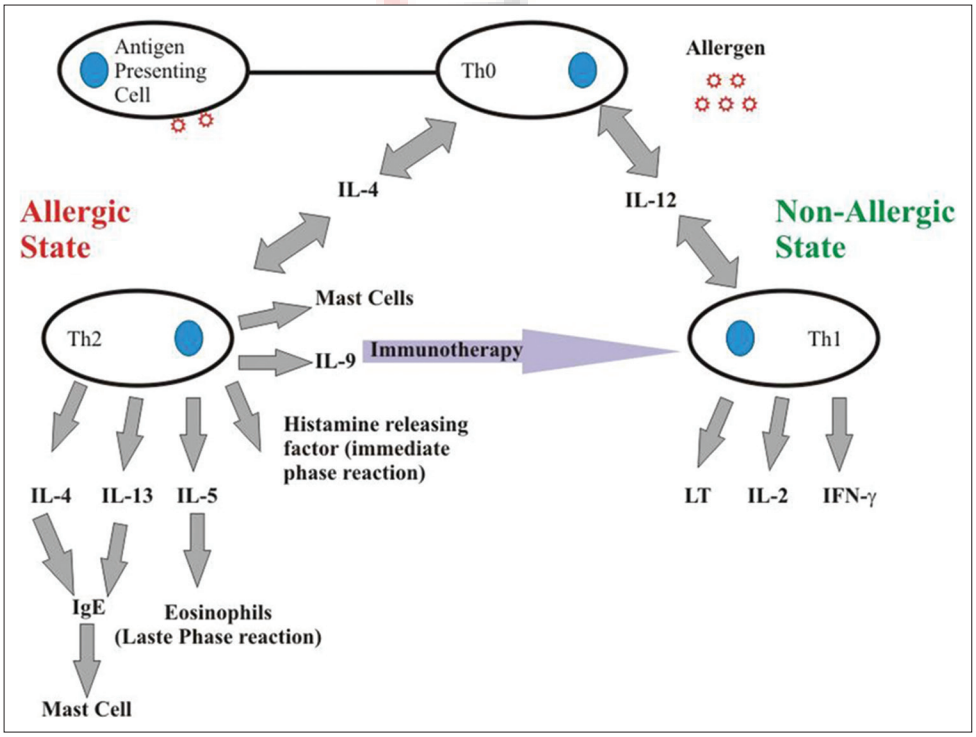

Figure 1: Schematic diagram of the Th1 and Th2 paradigm in allergic diseases and mechanism of immunotherapy to shift Th2 toward Th1 response

clinical symptoms, and decreased tendency for systemic anaphylaxis despite exposure to the allergens.[1,17,22] This is followed by increase in Treg cells secreting IL-10 and transforming growth factor beta (TGF-β) associated with immunological tolerance and shifting of immune response from the *allergic* Th2 to *non-allergic* Th1. IL-10 induces a decrease in B-cell antigen-specific IgE production and simultaneously increases IgG4 production. It significantly reduces mast cell density and local histamine concentration, and prevents mast cell degranulation, also down-regulating eosinophil function and activity. An increase in serum allergen-specific IgA and IgG levels, particularly of the IgG4 isotype, occurs with SIT from 10- to 100-fold.[7,13,23,24] The serum-specific IgA again leads to the induction of IL-10 released from monocytes.[25] The levels of specific IgE initially increase, which then gradually decrease, and a significant decrease in the allergen-specific IgE/IgG4 ratio occurs after several months of SIT.[1,7] Proliferative response of T-cell clones is also inhibited by IgG4 antibodies through prevention of IgE-facilitated allergen binding to B cells and subsequent presentation to allergen-specific T-cell clones.[26] Following SIT, significant reduction in IgE levels occurs in years in spite of early generation of Treg cells.[13] For sublingual immunotherapy (SLIT), contact of the antigen with oral mucosa is important and oral Langerhans cells are critically involved in this process.[27] The allergen is captured within the oral mucosa by these cells that after maturation migrate to the proximal draining lymph nodes. These nodes favor the production of blocking IgG antibodies and the induction of lymphocytes with suppressive function. IL-10 secretion is enhanced leading to induction of T cells with regulatory phenotypes. Serum IgG4 is increased fairly more compared to subcutaneous immunotherapy (SCIT).[28] High dose regimens of SLIT facilitate capture of sufficient amounts of allergens by dendritic cells, and the oral mucosa represents a critical step in inducing adequate and long-lasting T-cell response.[29] As per the published guidelines, SLIT requires further evaluation before it can be recommended in routine clinical practice.[2,7]

ALLERGEN EXTRACTS

Immunotherapy is effective against hypersensitivity to pollens, animal allergens, dust mites, molds/fungi, and insect stings (level A evidence).[7] Allergen extracts to prepare allergen immunotherapy are complex mixtures of allergenic and non-allergenic macromolecules (proteins, glycoproteins, and polysaccharides) and low–molecular-weight compounds.[7,30] *Pollen extracts* are proved safe as evidenced by the Cochrane Database reviews of several clinical trials.[31] Extracts for some clinically important fungi are abundant as airborne bioparticulate during certain seasons. Among the animal dander, cat and dog antigens are abundant even in the absence of these animals indoors, and immunotherapy has been found effective for both.[32,33] Immunotherapy with standardized dust mite antigens is generally more effective compared to crude allergens. Cross-reactivity between the two species, *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, and with other species as well is known and this needs to be taken into account while preparing extracts of other species.[34] Again, immunotherapy with *Hymenoptera* venom is highly effective in dramatic reduction of anaphylaxis to honey bee, yellow jacket, hornet, and wasp stings, and the same holds true for immunotherapy using whole-body extracts of imported fire ants.[35] There is limited data available on the immunotherapy against cockroach antigens; some trials have demonstrated encouraging results.[36] The commercially available extracts are relatively low in potency. If immunotherapy is prescribed, only glycerinated extracts should be used, and regionally relevant species should be included in the extracts.[7,36]

Multiallergen extracts

Vast majority of immunotherapy trials have used single allergens, whereas some clinical trials using multiallergen extracts also have demonstrated significant clinical efficacy.[33] There is evidence that proteolytic enzymes in some mold extracts could destroy other antigens such as pollens and dust mites when combined in mixtures. For this reason, it is desirable to separate pollen and other extracts from those with high proteolytic activity in mixtures.[7,37]

Allergen extract selection

As per the latest practice parameter update of the American Academy of Allergy, Asthma and Immunology,[7] and the guidelines prescribed by the Indian College of Allergy, Asthma and Immunology,[2] the selection of components of an allergen immunotherapy extract should be based on a careful history and correlation with positive allergy skin test results or serum-specific IgE antibodies, and the extract should contain only clinically relevant allergens. In choosing the components for a clinically relevant allergen immunotherapy extract, the physician should be familiar with local and regional aerobiology and indoor and outdoor allergens, paying special attention to potential allergens in the patient's own environment. The extract preparations should be performed by persons experienced and trained in handling allergenic products. Standardized extracts should be used to prepare the allergen immunotherapy treatment sets. While mixing allergen extracts, cross-reactivity of allergens, optimization of the dose of each constituent, and enzymatic degradation of allergens should be taken into consideration. For many botanically related pollen allergens that are cross-reactive, selection of single pollen within the cross-reactive genus or subfamily might suffice. When pollen allergens are not cross-reactive, testing for and treatment with multiple locally prevalent pollens might be necessary (evidence B).

Allergen extract handling and expiration dates

Allergen immunotherapy extracts should be stored at 4°C-8°C to reduce the rate of potency loss. In case of

electricity failure (>2 h), the vaccines should be kept in ice box or any other cooling device; also, for transportation, cooling devices should be used. In case of withdrawal of more antigens from the vial, it should not be injected back into the vial to avoid contamination. Consideration should be paid to the potency loss over time influenced by factors such as storage temperature, presence of stabilizers and bactericidal agents, presence and concentration of proteolytic enzymes, and volume of the storage vial.[2,7] Description of details regarding labeling of different dilutions, record keeping, etc., is beyond the scope of this article.

ROUTES OF ADMINISTRATION

The standard allergen immunotherapy is administered as subcutaneous injections (SCIT) at frequent intervals (described below). Currently, there are no FDA-approved formulations for non-injection immunotherapy extracts; however, besides subcutaneous administration, allergen extracts are being prescribed to be administered through many routes.[2,7] SLIT that was introduced in 1986 is demonstrating encouraging results.[38] In India, it has been allowed to be used for research purpose to accumulate data for consideration by the Controller General of Drugs for recommending SLIT in this country.[3] Several meta-analyses demonstrated significant improvement with SLIT administration of the allergen extracts for allergic rhinitis[39] and asthma[40] both in adults and children, and for food allergies and mild atopic dermatitis in children.[4,41] As the standard SCIT is relatively contraindicated in pre-school age, recent data have demonstrated that SLIT is safe in young children, offering new possibilities of treating pediatric allergies.[40,41] Compared to SCIT, vaccination by the sublingual route requires at least 50-100 times more allergens to reach similar levels of efficacy as those of SCIT.[41] Several other studies have revealed encouraging results with immunotherapy using intranasal,[42] oral,[43] intralymphatic,[44] intrabronchial,[45] and epicutaneous[46] routes.

DOSING

According to the prescribed guidelines of the American Academy of Allergy, Asthma and Immunology and the Indian College of Allergy, Asthma and Applied Immunology, allergen immunotherapy should be prescribed under the direct supervision of a trained allergist/immunologist in the office having facilities with appropriate equipment, medications, and personnel to deal with anaphylaxis.[2,7] For conventional SCIT, injections should be given with a calibrated small volume syringe using a 26- to 27-gauge 1/2- or 3/8-inch non-removable needle in the lateral or posterior portion of the arm using safety precautions.[7] The mixing of the antigens in a syringe is not recommended because of potential treatment errors and cross contamination of extracts. Again, the risk of errors of administration may be reduced by maintaining patients' identifiers (at least two from patients name, birth date, identification number, or other person-specific identifier) on labeling of patient-specific vials.[7] Allergen immunotherapy dosing consists of two treatment phases. The *build-up phase* involves administration of injections with progressive increase of allergen dose. *Maintenance dose* is the highest concentration projected to provide the therapeutically effective dose. The starting dose for buildup is usually a 1000- or 10,000-fold dilution of the maintenance concentrate, although lower build-up dosing is advisable for highly sensitive patients. If too dilute, it will need unnecessarily large number of injections to achieve a therapeutically effective dose, and if the starting dose is too concentrated, the patient might be at increase risk of having systemic reactions. The frequency of administration during build-up phase generally includes one to three injections per week. It is customary to either reduce the dose if a systemic reaction has occurred or to discontinue immunotherapy if the reaction has been severe. During treatment gaps, it is customary to reduce the dose when the interval between injections is prolonged. The maintenance is usually achieved after 3-6 months. The *rush* or *cluster* schedule can achieve a maintenance dose more quickly.[2,7] Again, *ultra rush* immunotherapy schedules have also been described for stinging insect hypersensitivity to achieve the maintenance dose in as little as 3.5-4 h.[47] Once the maintenance phase is achieved, the interval for injections varies from 2 to 6 weeks, but is individualized for each patient.[2] If a patient receiving immunotherapy transfers from one physician to another, the decision by the latter has to be followed by the patient. Usually SCIT is not recommended to be administered at patient's home; however, exceptionally in such circumstances, consideration of potential benefits and risks should be made on an individual basis.[7] The most common way to decide about doses used in SLIT is to compare the cumulative amount administered sublingually over a period of 1 month to that administered for monthly maintenance dose of SCIT.[6] Patients should be evaluated at least every 6-12 months while they receive immunotherapy.[2,7] The VIT injections are generally administered at weekly intervals, beginning with doses of 0.1-0.5 μg and increasing to a maintenance dose of up to 100 μg per venom. The interval between maintenance dose injections can be increased to 4-week intervals during the first year, and 6-8 weekly during subsequent years of VIT. VIT is usually continued for 3-5 years, although some patients may need to continue it indefinitely.[12] A decision about continuation of effective immunotherapy should generally be made after the initial period of 3-5 years of treatment. Some patients might experience sustained clinical remission after discontinuation of immunotherapy, but others might relapse. The severity of disease, benefits sustained from treatment, and patient's convenience of treatment are the factors to be considered in determining whether to continue or stop immunotherapy for an individual patient.[2,7]

EFFECT OF CONCURRENT MEDICATION USE DURING IMMUNOTHERAPY

Antihistamines may mask the occurrence of minor reactions that would otherwise alert a physician to impending systemic reactions, if taken before the injections during the build-up phase.[7] However, these agents have been demonstrated to reduce local and systemic reactions during VIT.[47] Premedication with *montelukast* delays the onset and decreases the size of reactions during VIT, but no controlled studies have investigated the effect of leukotriene antagonists on the occurrence of systemic reactions.[48] Combination pretreatment with *ketotifen*, *methylprednisolone*, and *H1*- and *H2*- *receptor antagonists* has demonstrated decreases in the frequency of systemic reactions.[49] *Omalizumab* used in combination with immunotherapy is effective in improving the symptom scores, compared to immunotherapy alone. It also improves the safety and tolerability of cluster and rush immunotherapy regimens for patients with allergic rhinitis and asthma.[14] Patients with bee venom allergy who are unable to tolerate VIT because of anaphylaxis are subsequently able to tolerate it in combination with omalizumab.[50] Concomitant use of β-blockers and allergen immunotherapy should be carefully considered, as these agents pose an increased risk for more serious and treatment-resistant anaphylaxis.[7,51] Similarly, patients on angiotensin converting enzyme (ACE) inhibitors have been associated with greater risk for more severe reaction from VIT as well as insect stings. This leads to inhibition of metabolism of angiotensin, bradykinin, and substance P. Bradykinin, being a potent vasoactive mediator, contributes to the hypovolemia and hypotension in patients with severe anaphylaxis.[7]

ADVERSE EFFECTS

Local reactions

Local reactions associated with allergen immunotherapy are fairly common and include redness, swelling, and warmth.[2,14] These can be lessened with oral antihistamines, both during cluster and rush protocols, whereas leukotriene antagonists are more effective in rush protocols. However, during VIT, local reactions are decreased with both. Large local reactions usually do not appear to be predictors of future systemic reactions, although this may happen in more than 10% injections, requiring dosage adjustments.[7,47,48]

Systemic reactions

Although there is low risk of severe systemic reactions with appropriately administered doses, life-threatening and fatal reactions do occur in less than 1% patients receiving conventional immunotherapy to greater than 34% following rush immunotherapy protocols. Risk factors for systemic reactions such as urticaria, angioedema, respiratory symptoms, or hypotension include errors in dosing, uncontrolled severe asthma, high degree of allergen hypersensitivity, and concomitant use of β-blockers or ACE inhibitors.[4,7] Premedication with agents including ketotifen, H1- and H2-blockers, and omalizumab, as already mentioned, has been found effective in decreasing the frequency of systemic reactions.[49,50] Allergen immunotherapy should be administered in a setting where all arrangements to tackle with anaphylaxis are in place and prompt recognition and treatment is ensured.[2,7] There is no robust evidence to support the excellent safety profile of SLIT and no life-threatening events or fatalities have been reported over more than 20 years of clinical trials.[41] Local reactions, primarily oral mucosal pruritis and edema, are common with SLIT, usually not persisting with continued treatment.[7]

RELATIVE CONTRAINDICATIONS AND SPECIAL CONSIDERATIONS

Immunotherapy is contraindicated in *poorly controlled patients with asthma* (Peak expiratory flow rate i.e., PEFR < 70%) and immunotherapy should not be initiated unless the patient's asthma is stable.[2,7,52] Medical conditions that reduce the patient's ability to survive the systemic allergic reactions or the resultant treatment are relative contraindications for allergen immunotherapy. Examples include: markedly compromised lung function (acute or chronic), unstable angina, recent myocardial infarction, significant arrhythmias, and uncontrolled hypertension; however, immunotherapy might be indicated for high-risk patients, such as insect hypersensitivity and cardiac disease being treated with β-blocker medications.[7] Again, patients who are *mentally or physically unable to communicate clearly* with the physician and those with history of non-compliance might be poor candidates for immunotherapy. Inability of a patient to communicate will make it difficult for the patient to report signs and symptoms, especially early symptoms suggestive of systemic reaction.[7] Also, it is contraindicated in *very young and old* patients. Immunotherapy is also contraindicated in patients with *epinephrine sensitivity* because such patients cannot tolerate life-saving treatment.[52]

Pregnancy is a state where medications have to be prescribed carefully.[53] Immunotherapy is not as such indicated is the pregnant patients. It is not usually initiated during pregnancy because of concerns about potential adverse effects of systemic reactions and their resultant impact on the fetus, mother, or both. However, if pregnancy occurs during the build-up phase and the patient is receiving a dose unlikely to be therapeutic, discontinuation of immunotherapy should be considered.[2,7,54] If pregnancy occurs during the maintenance phase, immunotherapy can be continued but the dose is usually not increased. Initiation of immunotherapy might be considered during pregnancy when the clinical indication

is a high-risk condition such as anaphylaxis caused by *Hymenoptera* hypersensitivity.[7] Two studies suggest that allergen immunotherapy during pregnancy might prevent allergic sensitization in the child.[55,56] Both studies revealed similar levels of allergen-specific IgG in paired cord blood and maternal blood samples. However, more research is needed to elucidate the effect of allergen immunotherapy during pregnancy on the subsequent development of allergen sensitization in the child. Currently, there is no evidence of increased risk of prescribing or continuing allergen immunotherapy for a mother while breastfeeding and for the breast-fed child. Although there are no controlled studies about the effectiveness or risks in patients with *immune deficiency* (HIV/AIDS) and *autoimmune disorders*, on the basis of current guidelines, immunotherapy can be considered in such situations.[7]

CLINICAL EFFICACY AND OUTCOMES

Immunotherapy is highly effective for the treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity (evidence A).[7] In children, it has been shown to prevent the new onset of allergen sensitivities in monosensitized patients,[9] as well as progression from allergic rhinitis to asthma (evidence B).[7] The clinical efficacy of SCIT has been validated by 75 double-blind, placebo-controlled trials demonstrating clinically relevant decrease in symptom medication scores.[2] Similarly, in a systematic review of 88 trials involving 3459 asthmatic patients, significant reduction in symptoms, medication use, and improved bronchial hyperresponsiveness were seen.[31] As yet, the efficacy of immunotherapy is confirmed for the treatment of inhalant allergy due to pollens,[57] fungi,[58] animal allergens,[32,33] dust mites,[59] and cockroaches.[36] There is a cluster of meta-analyses showing highly significant improvement in patients with allergic rhinitis.[60] Although at present, there is no FDA-approved formulation for non-injection immunotherapy,[7] randomized controlled clinical trials with dust mite and pollen SLIT have demonstrated significant improvement in patients with allergic rhinitis[39] and allergic asthma,[40] especially in children. Insect sting hypersensitivity reactions are fairly common; systemic reactions occur in 0.4-0.8% of children and 3% of adults. VIT is extremely effective in reducing the risk of subsequent reactions from insect stings to less than 5%, and such reactions are even milder is those experiencing subsequent exposures.[12] Also, some studies have found no increase in the frequency of systemic reactions in patients taking β-blockers[61] or ACE inhibitors,[62] demanding further studies. Ultra rush immunotherapy protocols[47] have been formulated to achieve the maintenance dose in a period of around 3.5-4 h (as mentioned above), making susceptible individuals at reduced risk of systemic reactions after future stings. There are some data favoring that immunotherapy is effective for *atopic dermatitis* associated with aeroallergen sensitivity.[7,63] Clinical improvement has also been observed during one more double-blind, placebo-controlled study of 48 children with atopic dermatitis using dust mite SLIT, where significant improvement occurred in children with mild but not with moderate or severe disease.[64] Yet, clinical trials do not support the use of SCIT for food hypersensitivities,[7] although studies using SLIT with hazelnut[65] and milk,[66] and oral immunotherapy with peanut,[67] egg,[68] and milk[69] have demonstrated encouraging results.

Novel therapies

With the advent of recombinant DNA technology, hypoallergenic variants with a potential of having reduced risk of side effects are currently under study, showing encouraging results.[70] Similarly, T-cell epitope based allergy vaccines with reduced allergenicity and maintained immunogenicity are also being clinically evaluated. Synthetic peptides representing immunodominant T-cell epitopes of major allergens can modulate allergen-specific T-cell responses in the absence of IgE cross-linking and activation of effector cells. Such newer modalities are expected to improve the outcome of allergy treatment in the near future.[71]

Non-adherence to the specific allergen immunotherapy contributing to poor outcome is a critical issue. In India, studies reveal various factors associated with non-adherence, which include gender, allergic conjunctivitis, family history, progression of disease, perception of immunotherapy, medicine requirements, and frequently missed doses.[72] In a similar way, other factors like psychiatric illnesses, systemic allergic reactions, lack of insurance coverage, etc., have been described.[73] These factors may vary between different settings and countries, demanding specially designed awareness programs for better outcome of allergen immunotherapy.

Immunotherapy – Indian scenario

In more than the last two decades, there has been tremendous progress in the field of allergy in India. Research regarding characterization of various aeroallergens and the effectiveness of immunotherapy of significant value has taken place.[10,11] There are several trials published so far, but a detailed description of all is beyond the scope of this write-up. Karmakar and co-workers studied the effectiveness of *Cocos nucifera* pollen extract immunotherapy in a placebo-controlled population. Significant clinical improvement and serological reduction in allergen-specific IgE and elevation in of IgG in the treated population compared to placebo-treated patients was observed.[74] Gaur and Gupta (1996) demonstrated that 50% of the seasonal allergic rhinitis cases showed considerable reduction in their symptom score and drug intake after 2 years of immunotherapy with mixed allergen vaccines[75]. In 1997, Shaikh compared the effectiveness of budesonide (an inhaled corticosteroid) with immunotherapy in patients with

perennial asthma. Budesonide was found to result in faster and more striking improvement compared to immunotherapy; however, immunotherapy resulted in slow but steady improvement that was long lasting and did not decline as rapidly as budesonide therapy.[76] Worth appreciable is the research work conducted by Srivastava and co-workers,[77,78] as encouraging results were found with immunotherapy derived from *Culex quinquefasciatus* (mosquito). Again, they studied the clinico-immunological profile of rhinitis and asthma, where they found significant improvement in the symptom score, forced expiratory volume in first second i.e., FEV1, and immunological parameters among the studied population. As already mentioned, significant contribution in the field of allergy regarding the study of various aeroallergens and formulating the aerobiology profile of various regions of India has been made by Singh,[10,11] whose advancement in the field of allergy will overall improve the outcome of various allergy disorders in this country.

SUMMARY AND CONCLUSIONS

Allergen immunotherapy is the available treatment serving the purpose of altering the natural course of allergic disorders. Currently, it has an established role in the therapy of allergic rhinitis, allergic conjunctivitis, allergic asthma, and insect sting hypersensitivity, based on evidence obtained through randomized controlled trials. Other than conventional SCIT, the role of non-injection routes of immunotherapy such as SLIT and oral immunotherapy is not yet established, although there are several observations available showing therapeutic trend. Newer modalities like anti-IgE therapy (omalizumab) used in combination with immunotherapy have significantly reduced the risk of systemic reactions. Novel immunotherapy approaches through recombinant technology and development of T-cell epitope based allergy vaccines leading to the production of low-allergenicity extracts are the future goals of improving the outcome of allergic disorders.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the generous help provided by Mr. Vivek Tiwari, Ishrat-ul-Hamid Lone, and Adil Moheen Hakim, who tirelessly devoted their time for typing and designing this manuscript.

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How to cite this article: Hassan G, Kant S, Prakash V, Verma AK, Saheer S, Singh A, *et al*. Allergen immunotherapy: Basic concepts. Indian J Allergy Asthma Immunol 2013;27:9-18.

Source of Support: Nil, **Conflict of Interest:** None declared.