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Editorial

Allergen Immunotherapy: The Scientific Facts

Allergy affects various systems of the body but primarily involves lung, nose and skin. The mediators released immune reaction of antigens and immuno-globulin (Ig) E produces symptoms of allergy in genetically predetermined system. The methods of combating IgE-mediated allergic disease is allergic immunotherapy.

Immunotherapy, was previously known as desensitisation and/or hyposensitisation is a treatment modality to suppress IgE-mediated symptoms by directing the immune system to produce blocking (IgG) antibodies instead of IgE. This is achieved gradually by administering the increasing doses of antigen(s) from a very diluted amount to the maintenance dose for that particular patient. The maintenance dose varies from person to person. The concept of immunotherapy is very old and goes back to the inducing of *Vish-kanyas* in Indian literature, where a girl was given increasing doses of poison starting from the diluted one and ultimately, she could tolerate the large amount of poison sufficient to kill a strongly built person. In scientific world, first human experiment using immunotherapy for hay-fever was done by Noon and Freeman in 1911. The concept got approval from the Federal Drug Authority (FDA) (USA) in the year 1949.

Since then there have been several trials on immunotherapy and most of them demonstrated favourable results. Laboratory experiments also supported the benefit showing a decrease in IgE, an increase in IgG, a decrease in histamine release by basophil after exposure to antigen, and a decrease in airway reactivity apart from the improvement in the clinical symptoms.

According to recent concept, allergen acts through T-helper 2 (TH2) cells resulting an increase in their number and increased interleukin-4 (IL-4), which then leads to production of more IgE. Simultaneously, there is lowering of interferon-gamma (IFN-γ). It has been demonstrated that specific immunotherapy generates TH1 response reducing IL-4 and IgE production. The TH1 cytokines upregulates cell mediated immune defence mechanisms, promoting phagocytosis and natural killer cell activity (IFN-γ and IL-12) and cross inhibit TH2 responses.[1]

The methods followed for detecting the offending allergens prior to immunotherapy are skin tests. Skin testing is usually done by intradermal injection of antigen or by prick test. The intradermal tests have more chances of false positive, whereas prick tests yield more false negative results. In our opinion, intradermal tests should be done first and prick tests may be performed later for further confirmation. Recently, it has been shown that chances of anaphylaxis is more with prick test method than intradermal method. *In vitro* methods, *e.g.* RAST/ELISA can also be used for appropriate diagnosis alongwith *in-vivo* procedures.

An unbiased approach is very much needed in practising immunotherapy. Unfortunately, as the concept floated in the community more and more misuse, overuse of immunotherapy has started, resulting in the controversies. The believers were sticking to its usefulness, whereas others were having contradictory or unequivocal statements. There was a time when persons laughed as to how an insect as large as cockroach can enter the respiratory tract to produce allergy. Now insect allergy, mainly of antigenic proteins from faeces and urine of the insects is an established identity.

Allergy practice, *i.e.* specific immunotherapy requires plenty of time for probing the patient to record detailed history of illness, proper skin testing, unbiased interpretation, judicious prescription writing, precautions of side effects and adequate follow-up.

Immunotherapy has an important drawback, *i.e.* risk of developing anaphylaxis, though in rare occasions especially while skin testing, during increase in the dose of antigen and/or peak season for that antigen, during acute attacks, injecting antigen intravenously (IV) or intramuscularly (IM) by mistake or by ignoring signs of side effects in previous dose, etc. Deaths due to above reasons has cautioned that person practicing allergy should be trained and the set-up should have requisite facilities for managing anaphylaxis. Safer methods of immunotherapy, like modification of allergen to retain antigenicity and almost negligible allergenicity are being developed, *e.g.* polymerised antigens, which will be quite safe and provide better results. Recently, trials are underway to produce antibodies against IL-4, which is raised after antigen exposure. Use of such antibodies will block IL-4, and thus, IL4 will not be available for further reaction *i.e.* production of IgE.

The safer and easier method for drug delivery in immunotherapy is being tried—oral, nasal, spit methods.[3-6] Presently, sublingual immunotherapy (SLIT) which was introduced in 1986 is providing encouraging results.[7] However, the dose has been uniformly standardised in India. SLIT has been allowed to be used for research purpose to accumulate data for consideration by the Controller-General of India for recommending use of SLIT in population. Guidelines for practicising allergen immunotherapy in India has been published in 2009.[8]

There is no method for the management of bronchial asthma and rhinitis, which can maintain a normal level of airway reactivity even after discontinuation of therapy except immunotherapy, where the airway reactivity was found to be normal upto 3 to 5 years

after discontinuation of immunotherapy. Therefore, the stay should be made to use, achieved through specific immunotherapy. However, the antigens (prescription) should be administered by properly trained persons for adequate period of time. There is no point in arguing about the usefulness of immunotherapy, since it has already been well established by several workers[9]. In support, may we quote a paragraph written by Richard F. Locky (1997) in the Allergy Advocates of American College of Allergy and Applied Immunology:

"Allergen immunotherapy alter the immunological reaction responsible for insect allergy, hay fever and allergic asthma. Such therapy decreases the symptoms and the amount of medication necessary to control the allergic diseases, and in the case of insect allergy, stops the life-threatening reactions from occurring when a patient is stung.[10] Newer methods under investigation will eventually result in better therapy with fewer injections and a prolonged effect that lasts even when the injections are discontinued."

The WHO has endorsed effectiveness of allergen immunotherapy by issuing position statement paper in 1998.[11]

In studies carried out at V.P. Chest Institute, Delhi, specific immunotherapy provided benefit in about 50% cases of nasobronchial allergy in 1 to 2 year's time,[12] with mixed and single insect antigen.[13,14] Standard-isation of allergen extracts will further improve the response of immunotherapy by mini-mising the batch to batch variations of commercially available extracts. There is also a need to reduce the number of allergens used for allergy diagnosis and immunotherapy by isolating common allergenic moieties (proteins). This will also avoid mixing of irrelevant allergens. Storage and transport of extracts is another aspect which needs to be looked after very seriously. We expect few peptides and/or recombi-nant allergens or easy IgE delivery method will be in use for combating allergy ailments through specific immunotherapy.

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