

Role of immunological mediators in the follow-up of asthma and allergic rhinitis patients on allergen immunotherapy

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Abstract

BACKGROUND: Bronchial asthma (BA) is characterized by chronic airway inflammation. Many studies have shown a significant overlap between BA and allergic rhinitis (AR). Specific allergen immunotherapy (AIT) is effective for the treatment of BA and AR. Only limited studies have evaluated the role of immunological parameters to assess the response in patients on AIT. Hence, this study was done to assess the role of interleukin-4 (IL-4), IL-5, and IL-6 in the follow-up of patients of BA and AR on AIT.

MATERIALS AND METHODS: This study was conducted on diagnosed cases of BA, AR, and BA with AR attending the outpatient department who were started on subcutaneous immunotherapy as per the standard Indian guidelines. Blood samples were collected at the beginning of the treatment and every 3 months thereafter for a period of 51 months, and serum IL-4, IL-5, and IL-6 levels were measured.

RESULTS: In this study, 170 patients were enrolled over a period of 51 months. Out of 170, 80 (47.1%) patients had completed 1 year of treatment with AIT at the end of 51 months of follow-up. Significant reduction was observed in IL-4, IL-5, and IL-6 levels during the treatment with AIT over a period of 12 months.

CONCLUSION: Our study suggests a possible role of IL-4, IL-5, and IL-6 in the follow-up of BA and AR patients; however, further studies are needed in this area.

Keywords: Allergen immunotherapy, allergic rhinitis, bronchial asthma, interleukins

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Introduction



Bronchial asthma (BA) is a heterogeneous disease, usually characterized by chronic airway inflammation. It affects 1%–18% of the population in different countries. Recognizable clusters of demographics, clinical, and pathophysiological characteristics are often called asthma phenotypes. Allergic asthma is the most easily recognizable asthma phenotype. It is associated with past or family history of allergic diseases such as eczema, allergic rhinitis (AR), or food or drug allergy. Many studies have shown a significant overlap between BA and AR. In most studies, 20%–50% of AR patients had asthma, and 30%–80% of asthmatic patients reported AR. Specific allergen immunotherapy (AIT) is effective for the treatment of BA and AR.^[1] AIT is an immunomodulatory method for the treatment of immunoglobulin E (IgE)-mediated allergic diseases to control the symptoms and decrease the sensitivity toward allergens by giving sequentially increasing dose of antigen(s) to induce a shift of the immunological response from TH2 to TH1. AIT can be administered through different routes but currently, only subcutaneous immunotherapy (SCIT) and sublingual immunotherapy are used.^[2]

The role of TH2 cells in asthma is widely accepted. Allergen-specific IgE synthesis is T-cell dependent through cognate activation of B lymphocytes and T cell-derived cytokines. In atopic asthma and allergic rhinitis allergen processing and presentation to allergen-specific T-cells through antigen-presenting cells is a key initiation step for the synthesis of allergen specific IgE.^[3] TH2 cytokines, IL-4, and IL-5 have been detected in airway samples from atopic asthmatics.^[4] IL-4 plays a critical role in switching B-lymphocytes to produce IgE and therefore is of critical importance in the development

of allergic diseases, although other cytokines such as IL-5 and IL-13 have synergistic effects.^[5] IL-6 is a pleiotropic cytokine that acts as a pro-inflammatory mediator. While largely associated with T-cells and macrophages, it is increasingly apparent that the airway epithelium is a major source of IL-6 in the lungs.^[6] Circulating IL-6 is elevated in asthmatic patients and in bronchoalveolar lavage fluid of patients in whom asthma is clinically active.^{[7],[8]} AIT produces a shift of TH2 response toward TH1. This brings the reduction in release of inflammatory mediators, specific IgE levels, and allergen-specific airway hyperresponsiveness apart from producing clinical improvement. It induces a decrease in IL-4 and IL-5 production by TH2 cells and a shift toward increased interferon gamma production by TH1 cells.^[2] Hence, this study was done to assess the role of inflammatory mediators in the follow-up of BA and AR patients on AIT.

Materials and Methods

This was a prospective study conducted on the diagnosed cases of BA, AR, and BA with AR attending the outpatient department of our institute who were started on SCIT. Blood samples were collected at the beginning of the treatment; after this period, serum IL-4, IL-5, and IL-6 levels were measured for every 3 months followed by a period of 51 months.

The diagnosis and treatment of BA and AR was done as per the Global Initiative for Asthma and Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, respectively.^[9] Skin prick testing (SPT) to 58 common aeroallergens was performed in all the patients. Atopy was defined as a positive SPT (wheal diameter of >3 mm as compared to buffer saline as control) for at least ≥1 aeroallergen. SCIT was started based on SPT results as per the standard Indian guidelines. SCIT vials containing causative antigens were decided based on correlation with history, evidence of exposure, precipitation of symptoms after exposure, and skin test positivity. In cases where more than single antigen correlated with history, the amount of individual antigen was decided depending on their skin test positivity.^[2] The patients were followed up with IL-4, IL-5, and IL-6 levels before the initiation of SCIT and subsequently, at every 3 months for a period of 51 months for the purpose of the study. Interleukin levels were measured by enzyme-linked immunosorbent assay method.

All data analyses were performed using the SPSS statistical package version 22.0 for windows (IBM-SPSS, Chicago, IL, USA). The data of IL-4, IL-5, and IL-6 were expressed as mean ± standard deviation and standard error mean. For comparing the inflammatory response, paired sample *t*-test and one-way ANOVA test were applied. A two-tailed *P* < 0.05 was considered statistically significant at 95% confidence interval.

Results

In this study, 170 patients were enrolled from 2014 to 2017. Patients had a mean age of 29.25 years. Most of the patients had the diagnosis of BA with AR [Table 1]. The duration of illness was 1–5 years in 56.4% of the patients at the time of enrollment [Figure 1]. The various antigens positive on SPT were moth (54.7%), housefly (52.9%), mosquito (51%), female cockroach (51.7%), male cockroach (47.6%), rice weevil (34%), house dust mite (30%), wheat dust, (13.5%), and house dust (11.7%).

	<i>n</i> (%)
Patients	
Mean age	29.25 years
Male	95 (55.8)
Female	75 (44.1)
Diagnosis	
Bronchial asthma	24 (14.1)
Allergic rhinitis	32 (18.8)
Bronchial asthma with allergic rhinitis	114 (67.0)
Mean Interleukin levels at 0 months (pg/ml)	
IL-4 levels	7.78
IL-5 levels	12.33
IL-6 levels	7.82
IL=Interleukin	

Table 1: Baseline characteristics of the patients (n=170)

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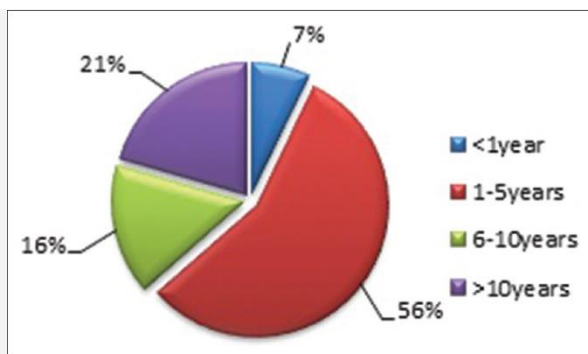


Figure 1: Duration of illness at the time of enrollment

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Patients were enrolled over a period of 51 months; out of 170, 80 (47.1%) patients had completed 1 year of treatment with AIT at the end of 51 months of follow-up [Figure 2]. Out of 80 patients, 45 (56.2%) were male and 35 (43.7%) were female with the mean age of 28.8 years. Fifty-two (65%) had the diagnosis of BA with AR, and for 51 (63.8%) patients, duration of illness was between 1 and 5 years at the time of enrollment. Immunotherapy was initiated with single-antigen extract in 13 patients and with multiple antigen extract in 67 patients.

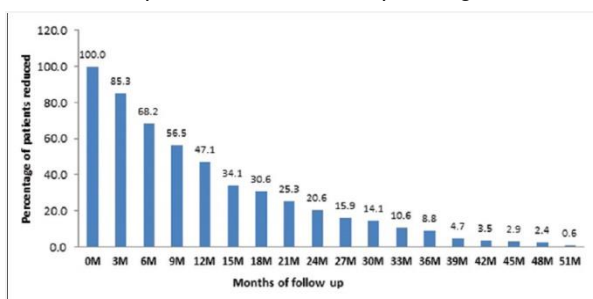


Figure 2: Percentage of patients reduced as per different time of enrollment

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[Table 2] shows the mean levels of IL-4, IL-5, and IL-6 during 12 months of follow-up. Significant reduction was observed in IL4, IL-5, and IL-6 levels during the treatment with AIT [Figure 3]. The decrease in IL-4, IL-5, and IL-6 was statistically significant at 12 months of follow-up with P value of 0.000. In the current study, the reduction in inflammatory markers (IL-4, IL-5, and IL-6) was significant in both single-antigen extract and multiple antigen extract immunotherapy groups [Figure 4] and [Figure 5].

Months of follow-up	Interleukin levels $\pm$ SD (pg/ml)		
	IL-4	IL-5	IL-6
Baseline	6.92 $\pm$ 3.68	9.74 $\pm$ 6.86	8.11 $\pm$ 7.16
3 months	6.13 $\pm$ 3.11	8.76 $\pm$ 6.24	7.26 $\pm$ 4.59
6 months	5.39 $\pm$ 2.84	8.23 $\pm$ 6.25	6.61 $\pm$ 4.08
9 months	4.75 $\pm$ 2.64	6.95 $\pm$ 5.49	5.75 $\pm$ 3.26
12 months	4.71 $\pm$ 5.04	5.73 $\pm$ 4.75	4.94 $\pm$ 3.18

IL=Interleukin, SD=Standard deviation

Table 2: Mean levels of interleukin-4, interleukin-5, and interleukin-6 ($n=80$)

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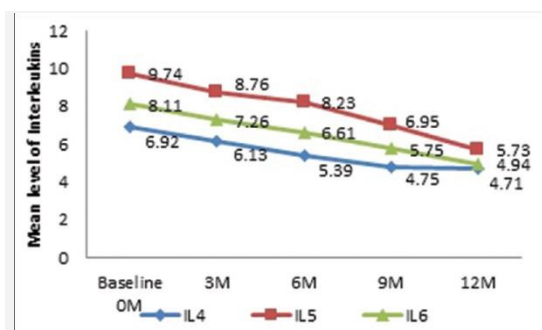


Figure 3: Mean levels of interleukins over a follow-up of 12 months

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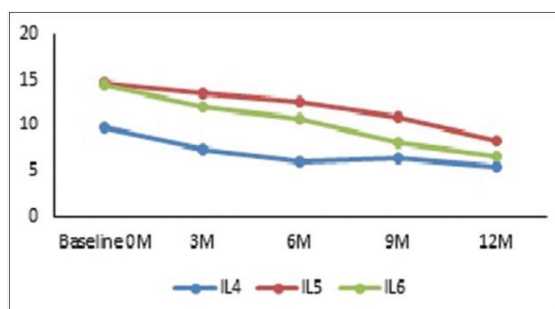


Figure 4: Mean levels of interleukins in patients on immunotherapy with single-antigen extract

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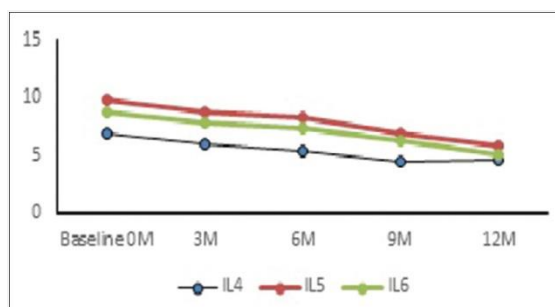


Figure 5: Mean levels of interleukins in patients on immunotherapy with multiple antigen extract

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Discussion



Allergic diseases represent complex innate and adaptive immune responses to environmental antigens leading to inflammatory reactions with a TH2 cell and allergen-specific IgE predominance. Expansion of allergen-specific Th2 cells producing IL-4 and IL-13 is essential in the induction of B cells and the production of allergen-specific IgE antibodies. Allergen-specific IgE binds to receptors, on the surface of mast cells and basophils as well as to antigen-presenting cells which in turn allows for an increased uptake of allergens. During the development of allergic diseases, effector TH2 cells not only produce traditional Th2 cytokines such as IL-4 and IL-5 but also produce novel cytokines with pro-inflammatory functions.^[10] Allergen-specific immunotherapy is the only therapeutic approach that can change the immunologic response to allergens and thus can alter the natural evolution of allergic diseases. The role of AIT is established in the management of BA and AR.^{[11]•[12]•[13]} A Cochrane review, which assessed the role of AIT in asthma, concluded that there were reductions in asthma symptom scores, medication usage, and allergen-specific bronchial hyperreactivity.^[12] Studies have shown that polysensitization is more prevalent in the general population.^{[14]•[15]} In a study by Kumar *et al.* on the pattern of skin sensitivity to various aeroallergens in patients of BA and AR in India, insects (43.90%) were found to be the most common offending allergen.^[16] In our study also, insects were the most common offending allergen. Our study was done to assess the role of inflammatory mediators in the follow-up of asthma and AR patients on AIT. Shorter duration of disease/early initiation is one of the factors that increase the clinical efficacy of AIT.^[2] In our study also, the duration of illness was 1–5 years in most of the patients at the time of enrollment. The assessment of the response to AIT is made clinically either by the improvement of symptoms and reduction for the need of medications or combination of the two and assessment of quality of life. The use of immunological parameters for the assessment of response has also been suggested.^{[2]•[17]•[18]•[19]} In our study, there was a significant decrease in the levels of IL-4, IL-5, and IL-6 at 12 months of follow-up in patients of BA and AR on AIT. Reduction in inflammatory markers was seen in both single-antigen extract and multiple antigen extract immunotherapy groups.

Only a few studies have evaluated the role of immunological parameters to assess the response in patients on AIT. Nasr *et al.* have conducted a study to evaluate the changes in the clinical symptoms and in the level of serum IL-33 before and after pollen immunotherapy in patients with AR and showed clinical improvement associated with a decrease in serum level of IL-33 after pollen AIT.^[20] Wilson *et al.* assessed the relationships between symptomatic improvement after immunotherapy and eosinophil numbers and IL-5 expression in the nasal mucosa during the pollen season and concluded that improvement in symptoms after grass pollen immunotherapy results, at least in part, from inhibition of IL-5-dependent tissue eosinophilia.^[21] Srivastava *et al.* conducted a study to assess the efficacy of cockroach immunotherapy by the change in skin reactivity, clinical parameters, and immunological parameters including IL-4 and found that IL-4 levels were decreased after 1 year of therapy.^[22] Our study suggests a possible role of IL-4, IL-5, and IL-6 in the follow-up of BA and AR patients on AIT; however, further studies are needed in this area.

Conclusion



In patients of BA and AR on AIT, there is a significant reduction in inflammatory markers (IL-4, IL-5 and IL-6) in both single antigen extract and multiple antigen extract immunotherapy group suggesting a possible role of IL-4, IL-5 and IL-6 in follow up of BA and AR patients on allergen immunotherapy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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