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## Allergen specific immunotherapy in nasobronchial allergy

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### ABSTRACT

**Background:** More than one antigen have been used for immunotherapy of allergic disorders. So far less than five antigens have been employed with variable results. AIM: To evaluate effect of multiple antigens up to six in the immunotherapy of nasobronchial allergy.

**Setting and design:** Based on clinical history, symptoms present for at least 3 years with set criteria of immunomodulation for asthma and rhinitis: documented IgE mediated asthma and rhinitis, failure in allergen avoidance and moderate to severe clinical manifestations.

**Material and methods:** Five hundred cases of various allergic disorders attending allergy clinic of Bombay hospital were screened. Allergen specific immunotherapy was initiated in 131 subjects (56 \_rhinitis and 75 asthma) with prior consent. Patients suffering from allergic disorders secondary to diseases or drug therapy were excluded. Multiple allergen immunotherapy was given at specific intervals up to a period of one year. Allergen extracts were prepared as per standard technique. For statistical analysis "students' t test" was used.

**Results and conclusions:** Significant improvement in PEFR, reduction in skin sensitivity to allergens used in immunotherapy formulation and symptomatic relief without any untoward reaction show that multiple allergen immunotherapy is as effective as monoallergen immunotherapy in nasobronchial allergy.

## INTRODUCTION

Specific immunotherapy (SIT) is one of the treatment modalities available to medical profession for allergic disorders. Immunotherapy which is also known as hyposensitization or desensitization was developed long before immune mechanism involving IgE antibodies was defined. It was introduced by Noon in 1911<sup>1</sup> by inoculating pollen extracts in cases of hay fever. Literature reveals that different methods have been applied from time to time viz. inhalation method<sup>2,3</sup> in asthma sensitive to house dust mite (D pt) and Rinkle method in pollen hay fever.<sup>4</sup> Later Ohman and Bousquet et al<sup>5,6</sup> used the allergen immuno-therapy in asthma and allergic diseases. In India, an array of workers<sup>7-11</sup> reported hyposensitization in respiratory allergy and asthma. New understanding of classical allergic diseases such as rhinitis and asthma has underlined their multiple pathogenesis and wide clinical spectrum.<sup>12</sup> The treatment of allergic diseases involves reducing severity of symptoms by immunomodulating the disease process itself.<sup>13-15</sup>

The purpose of this study, was to have detailed information about the efficacy of allergen specific immunotherapy with mixture of antigens in naso-bronchial allergies.

## MATERIAL AND METHODS

Five hundred cases of various allergic diseases viz. urticaria, rhinitis and asthma referred to the Department of Allergy, Bombay Hospital were screened. Patients have been selected on the basis of following criteria: clinical history, symptoms present for at least 3 years; age of the subject between 10 to 50 years and positive skin prick test. Criteria for immuno-modulation for asthma: documented IgE mediated asthma, failures in allergen avoidance and moderate to severe clinical manifestations. Based on these criteria, allergen specific immunotherapy was initiated in 200 perennial allergic subjects. All the 131 cases (56 rhinitis; 75 asthma) included in this study had given consent. Raised total IgE was found in all the subjects. Allergen source: Dusts were collected from patient's surroundings and were subjected to microscopic examination for presence of mites. Mites were isolated from bed and floor dust and were cultured in laboratory using standardized procedures. Pollen raw material was collected from specific plants species. The polliniferous material was then processed to achieve a purity of 99%. After confirming the purity and identity the purified pollen raw material was defatted with petroleum ether (40-60degrees C) to remove fatty substances. The allergenic raw material was stored at - 20 degree C and was used for preparation of allergen extracts. Identified fungal strains were innoculated and cultured in the Lab. The sporulated mass was used for production of raw material used for preparation of allergen extracts. All the allergens used in this study are approved by Drug Control of India and FDA for skin prick testing and hyposensitization treatment.

In order to confirm the allergic manifestations, specific IgE for all the allergens was estimated by in vivo method (modified prick test) using allergens prevalent in the atmosphere consisting of dusts, house dust mites, pollens, insects, fungi and food. Allergen specific IgE is a better predictor of clinical allergy than total IgE levels or blood eosinophil counts. For assessing allergen specific IgE prick test is preferred method in comparison with various in vitro tests viz. RAST and QUIDEL. Prick test shows an 85% agreement with the above two methods.<sup>16</sup>

All the allergens were standardized and biological activity was determined in relation to histamine equivalent prick test in all individuals. This data was compared with allergen extracts routinely used for immunotherapy.

Allergen extracts were prepared in Cocas solution and were standardized on the basis of protein nitrogen units. Glycerophenol was used as an adjuvant. These extracts were subjected to undue toxicity test and sterility test before use for immunotherapy. Allergen extracts were formulated for SIT as per the prescription and specification on the basis of positive skin test results. Allergen extracts for SIT were grouped as either 1) Dusts and mite or 2) Pollen and fungi. For formulation of immunotherapy treatment extracts, endpoint titration method was used to determine a starting dose. In this method, allergens were diluted in serial dilution and each concentration was injected into the skin of the patient to find out allergen reactivity. The dilution which did not show any reaction was considered as starting/ safe dose. These formulations were supplied by M/s Creative Diagnostic and Medicare Pvt. Ltd. in concentration of 1:25000, 1:2500, 1: 250 and 1: 50 w/v as per procedure of Allergo-Pharma, West Germany.<sup>17</sup> Immunotherapy extracts were administered at different intervals as per recommended guideline provided by the company.<sup>6</sup> Allergy shots were administered in incremental doses starting from lowermost concentration (1:25000) increasing at the interval of biweekly, weekly and fortnightly. Initial therapy was given for a period of 6-8 months until top tolerable dose was achieved. The maintenance therapy was initiated depending on the top tolerable dose. Duration of maintenance dose was one year and allergen shots were administered twice a month . In our study, all the patients received immunotherapy for three to six allergens. None was on single allergen therapy. The concentration of dust mite extract employed for immunotherapy was in the concentration of 0.2% w/v (1000 PNU) for Derp1 and 1500 PNU for Derf1. Allergens which are used for initial immunotherapy, the same were used for maintenance dosage without changing percentage composition (3-6 allergens). On completion of initial therapy, maintenance dose (two to four weeks interval) was advised to their family physicians and to every patient for maintaining the record of attack of asthma/rhinitis, severity of the symptoms and symptomatic treatment. These patients were advised to report back after completion of each vial for follow up. Baseline sensitivity test, peak expiratory flow rate along with symptoms were recorded. These parameters were noted after the treatment to substantiate the efficacy of immunotherapy.

## RESULTS

Study group comprised of 75 asthmatics and 56 cases of rhinitis. In both the groups, number of allergens and mixture for immunotherapy formulation involved ranged from three to six ([Table 1](#)). Patients having rhinitis (44.64%) were found to be strongly positive for five different allergens (multiple allergens) compared to asthmatics (29.33%). Comparative figures for involvement of six different allergens were similar in asthma (42.67%) and rhinitis (41.07%).

Among the patients who had positive history of asthma, sensitivity to house dust (62.7%) and house dust mite (HDM) (82.67%) were higher compared to house dust (42.86%) and HDM (51.78%) in rhinitis. However, sensitivity to pollen prevalent in the atmosphere of Mumbai<sup>18</sup> was comparable in both the groups (72% and 71.43% respectively) ([Table 2](#)).

One year follow up in cases of asthma showed that all of them completed the initial therapy .

Out of the total (75), 13 were on second maintenance dose, 5 were receiving third dose and 2 with fourth dose and one patient having fifth dose. All rhinitis patients' (56), also completed the therapy. Of these, 5 were on second maintenance dose and two on third maintenance dose (Table 1).

Significant symptomatic relief was observed in both the groups. The changes were assessed by way of skin sensitivity test, symptom score and peak expiratory flow rates (PEFR) in asthmatics while in rhinitis all parameters showed significant changes except PEFR (Table 3). Symptomatic therapy was also instituted in 5 \_ 10% cases.

## DISCUSSION

Immuno-therapy is indicated in patients with rhinitis and asthma caused by house dust mite and pollen in whom allergen avoidance and medications fail to control the symptoms.<sup>19,20</sup> Allergen immunotherapy offers long standing relief from allergic diseases unlike mainstay pharmacotherapy, which merely counters the effects of inflammatory mediators. Recent insight into factors polarizing Th responses towards Th1 or Th2 is providing important new directions for refinement of SIT<sup>21</sup> Our results show that the patients receiving SIT had significant symptomatic improvement in nearly 70% of cases (adults and paediatric group). Reports from Western countries showed symptomatic relief between 20-70% in nasobronchial allergy<sup>22</sup> and 80%<sup>23</sup> as well as 92 %<sup>24</sup> in asthma. Similar success rates varying between 80% to 90% have also been reported by others in asthma<sup>25</sup> and rhinitis.<sup>26</sup> One report from India showed: overall seventy five percent improvement:66% in seasonal, 62% in irregular and 48% in perennial asthma.<sup>9</sup> Tiwari<sup>7</sup> in his study (10 to 40 year age group) also showed similar results (75%), however, respective percentages for seasonal, irregular and perennial asthma was low (55.5%, 44%, 40% respectively).

In our series, therapy was planned on the basis of skin sensitivity using modified prick test which is very sensitive and specific<sup>16</sup> and end point titration was attained using standardized allergens unlike previous studies from India<sup>7,9</sup> employing intra-dermal tests. Intradermal tests even with proper negative and positive controls show a considerable number of false positive reactions and difficulty in interpretation.<sup>26</sup> WHO committee on allergen skin testing does not approve intradermal testing as a routine procedure except in special cases.<sup>6</sup> It has been stated that results of hyposensitization varies from place to place and good results depend on immunological state of the patient, degree of exposure to offending allergen and proper interpretation of skin test and methods used.<sup>27</sup>

Aqueous preparations of some allergens including *Dermatophagoides pteronyssinus* standardized against WHO standard are extremely potent but severe local reactions have been reported<sup>28</sup> However, with our purified and standardized aqueous extracts, no such reactions were observed.

It was found that amongst multiple antigens employed for SIT, sensitivity to HDM (82.7%) was higher compared to HD (62.7%) & pollen (72.0%) in asthmatics. Telang et al<sup>11</sup> reported positive intradermal tests for dust (54.7%), pollen (14.1%) and none for HDM. Such studies using multiple antigens have not been reported earlier except one study with less than 5 antigens.<sup>10</sup> Other studies<sup>7,9</sup> did not mention particular local allergens in rhinitis and asthma

who received hyposensitization. Gaur & Gupta<sup>10</sup> observed more than 50% response in 46.8% cases receiving immunotherapy with mixture of less than five antigens in one year. Our results show that 5-6 antigens (Table 1) were used in 72 % asthma cases and 85% in rhinitis during similar period. However, improvement (70-80%) was higher in asthma compared to rhinitis (51.8%) irrespective of number of allergens involved. Thus, multiple (mixture) allergen immunotherapy may be equally efficacious as monoallergen immunotherapy.

Specific allergen immunotherapy was reported to be safe by Norman<sup>29</sup> and subsequently used by others<sup>6,30</sup> although different types of immunotherapy were recommended in allergic asthma viz. inhalation of allergen<sup>2,3</sup> inoculation of allergen-antibody complexes.<sup>31</sup> Immunotherapy was used in nasobronchial allergy<sup>7,32</sup> as well as in pollinosis<sup>9,21,33</sup> for chronic asthma. Lately Patterson<sup>30</sup> used it in respiratory allergic diseases and Telang<sup>11</sup> employed it in bronchial asthma.

We observed that patients sensitive to HD and HDM showed significant improvement: 61.3% asthmatic patients experienced 70-80% symptomatic relief, 12% had 50% relief while 26.7% reported 25% relief. In subjects with rhinitis comparative figures were 51.8% (70-80% relief), 10.7% (50% relief) and 37.5% (25% relief) respectively. Efficacy of the allergen immunotherapy was also evidenced by the decline in allergen specific IgE antibodies by way of decreased skin test reactivity, reduced PEFr and reduction in medication. Immunotherapy has been reported to be beneficial with subjective clinical effect mainly in allergic rhinitis.<sup>27</sup> In our study, patients with both asthma as well as rhinitis responded well to SIT. High efficacy in our study, might be attributed to uninterrupted therapy and use of standardized allergen extracts as reported by Johnstone<sup>34</sup> in a study of pollinosis and pollen asthma. It is possible that continuation of therapy beyond 2-3 years might be more effective. Mital et al in a study comprising of 76 patients<sup>35</sup> reported that 70% subjects with perennial asthma showed significant symptomatic relief with continuous treatment of SIT for 6 months. Complete to slight relief of symptoms was observed in 86.84% while 13.16% had no relief.

In the present study, a mixture of five allergen extracts were used for immunotherapy in rhinitis (44.64%) and another six allergens for same condition (41.07%) for one year. In asthma figures were 29.33% and 42.67% respectively. The results were encouraging in both the groups. Earlier study carried out by Shivpuri<sup>36</sup> showed positive results of hyposensitization with only mite allergen using intradermal test and with 0.01 ml of 1:2000 and prick test with 1:80 concentration. It has been observed that the degree of improvement increases with the period of regular immunotherapy.

The efficacy of immunotherapy in our nasobronchial cases with multiple sensitivities has been shown to be beneficial though it has been reported that such patients (sensitive to pollen, dust mite, animal dander & mould) have more severe or more complex disease and do less well on allergen immunotherapy.<sup>37</sup>

We also observed significant improvement in PEFr, however, no such improvement was recorded in a study carried out at Trivandrum,<sup>37</sup> difference could be due to different method employed.

This study shows that SIT employing multiple allergens is as effective as monoallergen immunotherapy in bronchial asthma as well as in rhinitis in terms of reduced need of pharmaco-therapy.

Since it is the first time up to six allergens have been used, precautions have been taken to assess the side effects as well as therapeutic benefits employing modified prick test, PEFR as well as clinical assessment based on set criteria viz. frequency of symptoms and drug requirement. These patients were followed up at frequent intervals.

We intend to continue the immunization up to a period of three years for all subjects and look for prolonged period of remission. Attempts are being made to improve our understanding in the mechanism of action.

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