Efficacy of Sublingual Immunotherapy with Multiple Allergens in Bronchial Asthma

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Abstract

Background: Specific allergen immunotherapy (SIT) involves the administration of allergen extracts to modify or abolish symptoms associated with atopic allergy. Allergen specific immunotherapy is a cornerstone in the management of respiratory allergy. The traditional subcutaneous route is burdened with the severe adverse reactions. In the present study, an attempt has been made to administer the allergen specific vaccine through oral route using multiple allergens in allergic bronchial asthma. The efficacy and safety with sublingual immunotherapy has already been demonstrated mostly in the treatment of allergic rhinitis.

Setting and Design: Based on clinical history, symptoms presented for at least 3 years with set criteria for immuno-modulation for asthma, failure in allergen avoidance and moderate to severe clinical manifestations.

Material and Methods: A total number of 60 patients with allergic asthma were scrutinized of which 25 were subjected for detailed physical examination family history, pulse, blood pressure, haemoglobin, stool examination and medication. Allergy skin test with various allergens were performed by using modified skin prick test method. Allergens showing reactions equivalent or more than positive control (histamine were incorporated in the formulation of immunotherapy mixture. Symptoms before and after the therapy, Peak expiratory flow rate (PEFR), skin test, side effects and medications were studied.

Results and Conclusions: Our results of sublingual immunotherapy using multiple allergen showed significant reduction in symptoms, medication, and improvement in PEFR by modifying the natural history of the disease and preventing the onset of new sensitization. SLIT could be a viable alternative to SCIT, with the same rationale and indication. It could be used in association with proper pharmaco-therapy at the earlier stages of allergic bronchial asthma for optimal symptomatic relief.

Introduction

Specific allergen immunotherapy (SIT) involves the administration of allergen extracts to modify or abolish symptoms associated with respiratory allergy. The process is specific, in that the treatment is targeted at those allergens responsible for symptoms are recognized by the patient and physician. Hence SIT demands a careful assessment of the patients condition and the role of allergic triggers. Since its discovery, immunotherapy has been commonly given sub-cutaneously (SCIT). Nevertheless, other modalities of allergen administration were proposed and investigated during last century, involving the administration of vaccines via gastrointestinal, nasal or bronchial routes.

The idea of administering the allergenic extracts orally is not so recent as commonly believed; the oral route was first suggested.
in 1900 and the first clinical attempts were made a few years later. In 1998 a panel of experts of the World Health Organization, on the basis of an extensive review of the literature, concluded that both sublingual (SLIT) and local nasal (LNIT) immunotherapy are viable alternatives to the injection route and that their use in clinical practice in adults is justified.

The clinical efficacy and safety with sublingual immunotherapy has already been demonstrated mostly in the treatment of allergic rhinitis. Present study deals with administration of multiple allergens through sublingual route in the treatment of allergic asthma.

**Methods and Subjects**

Sixty subjects with allergic asthma were scrutinized of which, 25 adult subjects with a history of allergic asthma were included in the study. They were subjected for detailed physical examination family history, pulse, B.P., Hb, stool examination and medication To confirm the sensitivity for various allergens in vivo (modified skin prick test) test was employed. Allergens with positive reactions equivalent to histamine (positive control) were incorporated in the formulation of immunotherapy mixture. Symptoms before and after the therapy, Peak expiratory flow rate (PEFR), skin test, side effects and medications were studied.

Glycerinated aqueous allergic extract for specific immunotherapy consisted of major allergens as determined by the sensitivity test. Composition in each case was determined by patient’s individual sensitivity spectrum. Proportions of the various allergens used were specified on each immunotherapy set. Thus, each treatment was individually formulated. The extract suspended in extracting fluid (Coca’s solution) containing 50% glycerine I.P. was standardized according to w/v ratio of native material to the extracting fluid. Each course was provided in multi-dose vial of allergens, with colour code in graded strengths as follows:

**Treatment Set :**  
Strength 1 Black label 0.01% w/v  
Strength 2 Green label 0.1% w/v  
Strength 3 Blue label 1% w/v  
Maintenance Set : 1% w/v

Maintenance dose (strength 3) was continued for three years. Dosage patterns were devised according to patients sensitivity and tolerance.

Composition of sublingual immunotherapy : Glycerinated aqueous extracts consisted of concentration 100 times of the dose administered in subcutaneous immunotherapy. Doses were prescribed in the form of drops. Drops were advised to be taken daily at the same time, preferably on empty stomach. Route of application : sublingual – drops were kept for 2 minutes and swallowed with 1/2 cup of water. Mixture of 5 allergens were administered in all the subjects. Dosage were administered always individually according to the sensitization pattern (Table 1).

<table>
<thead>
<tr>
<th>Table 1 : Treatment Schedule</th>
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<tr>
<td>Days</td>
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<td>-----------------------------</td>
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<tr>
<td>First vial (0.01 w/v)</td>
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<tr>
<td>Second vial (0.1 w/v)</td>
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<tr>
<td>Third vial (1 w/v)</td>
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<td>Maintenance Dose- Top tolerable dose</td>
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Care was taken to increase the dose at regular intervals however, it could be increased provided the previous dose has been tolerated without any reaction. In case there was gap in treatment for more than two weeks, therapy was re-initiated (for safety reasons) with half of the dose last given. In the event of interruption of more than 4 weeks, the therapy was resumed from the initial dose.

**Results**

All the 25 subjects with allergic asthma showed 92% compliance (completed the 3 years course SLIT therapy) with very few side effects (Fig. 1). Most common allergens responsible for allergic asthma were house dust, house dust mites, pollen and fungi (Fig. 2). Commonest pollens were *Amaranthus spinosus, Cocos nucifera, Peltophorum pterocarpum, Prosopis juliflora* and *Ricinus communis*. Among fungal allergens, the most common were *Alternaria alternata, Curvularia lunata, Rhizopus nigricans* and *Aspergillii*. Formulation of immunotherapy mixture was based on individual sensitivity. Allergens in graded strength having not more than 5 allergens were administered sublingually in all the patients. All the subjects completed 3 years course of SLIT. During the treatment, no systemic or bronchospastic reactions occurred except irritation of throat and vomiting in 2 subjects. The mean medication scores in the treated group reached a statistical significance at the end of treatment. The symptom score and use of medication showed year-on-year improvement (Fig. 3). Allergen specific IgE tested by skin prick test showed significant reduction at the end of three years. Peak expiratory flow rates (PEFR) also improved significantly. The overall self evaluations from the patients finishing the entire course of SLIT was significantly better.

**Discussion**

SLIT was first investigated in a DBPC rigorous trial in 1986 and subsequently many studies showing its effect not only on rhinitis but also on asthma symptoms. Outcome of
the therapy showed reduction in symptoms and use of β₂-agonists, intake of systemic steroids and clinical symptoms. The controlled trial conducted have shown unequivocal evidence of efficacy of SIT in selected patient groups.

The oral route (allergen immediately swallowed) represented the starting point for the subsequent diffusion of SLIT. The rationale for giving the allergen orally is that the gastrointestinal tract has an abundant mucosal immune system (so called gut-associated lymphoid tissue [GALT]): hence an effective antigen presentation can be expected. Studies carried out in 1980s on oral immunotherapy (OIT) reported controversial and/or negative results and brought OIT into disfavour. Nevertheless, the subsequent trials with high doses of allergen renewed the interest in oral administration.

Immunotherapy expands allergen specific Th1 immunity and suppresses the Th2 responses resulting in clinical allergy. Durham and Till in their study summarized the biopsy evidence that immunotherapy reduces the CD4+ lymphocyte response to allergen challenge in the nose and skin. It also increases cells expressing mRNA for the Th1 cytokines IFN-γ, IL-2 and IL-12 while reducing cells expressing the Th2 cytokine IL-4.

In the present study only 2 subjects suffered from mild throat irritation which was self resolving and mild vomiting. It included oral/sublingual itching after ingestion of the dose, and gastrointestinal complaints. Sporadically, headache, rhinorrhea, constipation and urticaria were also reported. Andre’ et al recently reported only mild side effects. Pajno et al in a study of 350 children with allergic rhinitis treated with major allergens (extracts) 3-20 times the amount in usual monthly maintenance dose by subcutaneous route observed mild to moderate reactions in 1.5% patients: one patient developed rhino-conjunctivitis, 2 patients developed urticaria and two children developed wheezing. In a series of allergic rhinitis and/or asthma treated with high allergen dose with Ultra rush SLIT, Rossi et al observed mild local symptoms such as pruritus of the buccal cavity in 17.96%. Lombardi with monoallergen (cat epithelia) in perennial allergic rhinitis and/or bronchial asthma observed adverse effects in 7.5% with ultra rush sublingual swallow therapy. There were seven episodes of rhinitis, 3 of oral itching and one of abdominal pain.

Arena et al showed long term effect with allergoid extracts with good effectiveness and safety in mild intermittent asthmatics. Sanchez evaluated the clinical effectiveness of sublingual immunotherapy with cat epithelium extract in monosensitized patients with rhinitis and/or bronchial asthma and found effective after 1 year of treatment. Rossi et al reported mild local symptoms (17.96%) with ultra rush sublingual swallow therapy.

Our results with multiple allergen high dose therapy (100 times the amount in usual monthly maintenance dose by subcutaneous route) showed significant reduction in symptoms, medication, allergen sensitization and improvement in PEFR by modifying the natural history of the disease and preventing the onset of new sensitization.

SLIT could be a viable alternative to SCIT, with the same rationale and indication but noninvasive with lesser risk of side effects. It is intended to be used in association with proper pharmacological treatment at the earlier stages of the disease, for optimal management of asthma.

References


