

Allergen Immunotherapy in Asthma: Still Promising Approach

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ABSTRACT

Background: Asthma a common and important respiratory problem with considerable morbidity and mortality outcome had been thoroughly studied problem and despite being effective and safe in ameliorating asthma course, steroid treatment, usually through inhalation, remains unsatisfactory as their withdrawal will be followed with relapse of asthma. **Aim:** To revise the rule of Allergen Immunotherapy in the form of Subcutaneous Immunotherapy (SCIT) or Sublingual Immunotherapy (SLIT) in asthma. **Results and Conclusions:** Allergen immunotherapy has a disease-modifying property and may prevent asthma onset and worsening and improves asthma symptoms in a good fraction of patients and because of safety of both procedures trial of AIT has to be considered in patients with chronic mild and moderate asthma.

Keywords Allergen Immunotherapy, Asthma and Immune diseases.

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INTRODUCTION

Introduction: Asthma; a chronic inflammatory disease with a wide spectrum of presentation ranging from a very mild occasional episodes of symptomatology referred to airway hyperreactivity to a severe intractable chronic disabling state, nevertheless the variability of airway obstruction dominates the whole picture of asthma, being a chronic inflammatory disease, every effort should be met to suppress this process for the hope of improving the quality of life, preventing the exacerbations and decreasing the airway remodeling and consequently the irreversible airway changes^(1,2). Steroids

remain the cornerstone in this concept and inhaled corticosteroids treatment is considered the best option for the control of asthma severity and ameliorating inflammation and clinical severity, however the natural course of the disease doesn't change fully even with prompt treatment and relapse after cessation of ICS is noticeable, Takaku Y. et al in a study of 11 well-controlled asthmatics according to GINA on low-dose ICS, 10 (91%) had increased airway hyperreactivity (AHR) and four (36%) had relapse of asthma symptomatology during the year following stopping ICS⁽³⁾. A newer study by [Jung-Hyun Kim](#) et al

documented an earlier loss of asthma control in patients with mild chronic asthma who discontinued ICS after stabilization of the disease compared to those who remain on regular ICS and more over there was a significant increase in allergic and inflammatory markers in the those who lost control in both groups based on inhaled nitric oxide levels, sputum eosinophils counts and serum immunoglobulin E concentration. Accordingly long term remission is supposed to be achieved by different procedures of immunotherapy including the well established allergen immunotherapy^(4,5,6).

Allergen Immunotherapy

Allergen immunotherapy (AIT) and in other terminologies desensitization, hyposensitization, specific immunotherapy (SIT), allergen-specific immunotherapy (ASIT) is the administration of a well-documented allergen in a stepwise increase in doses planning to abolish IgE-mediated allergic element through sublingual or subcutaneous route.

Mechanisms of modulating immune response

- 1- AIT induces the production of IgG or more specifically IgG4 (in subcutaneous administration) and IgA (in sublingual route) Abs in serum instead of IgE, thus preventing IgE mediated release of allergic mediators of mast cells
- 2- AIT decreases the numbers of Th2 cells and consequently decreases Th2-related cytokines like IL-4 and IL-5 which are involved in

recruitment of eosinophils and production of IgE

- 3- AIT increases the output of regulatory T cells (Tregs) which increases the production of IL-10, transforming growth factor (TGF)- β , and IL-35 these help decrease the allergic and immune responses^(3,7-11)

Key Milestones:

1911: The first successful case of allergen immunotherapy was managed in London by Dr. Noon in London using pollen extracts to treat hay fever⁽¹²⁾.
1950s-1960s: Standardization of allergen extracts and protocols making

Indication of AIT in asthma

AIT is indicated for patients with chronic disabling Mild-Moderate severe asthma in whom atopic features are assessed according to one or more of these factors:

- 1- Patient's history (Presence of other atopies, specially allergic rhinosinusitis, and or a clear family history of asthma of asthma and other atopies)
- 2- High levels of blood or sputum eosinophils and or increased IgE
- 3- Positive skin testing for common allergens especially house dust mites⁽¹³⁾

The followings are justified needs for AIT

- 1- Poor response to medical pharmacotherapy
- 2- Intolerance for the medical pharmacotherapy

- 3- The will of the patient to achieve long term remission

AIT is contraindicated in:

- 1- Severe asthma with acute severe exacerbation(Absolute)
- 2- Age <5>70years (Relative)
- 3- Patients with acute coronary syndrome, chronic poorly controlled ischemic heart disease and arrhythmias, and inadequately controlled hypertension (Absolute)
- 4- Previous important reaction to AIT(Absolute)^(3,13)

Subcutaneous Immunotherapy (SCIT) in Asthma

The sessions of SCIT has to be done by an expert personnel, usually an immunologist or respiratory physician and the treatment session has to be done in an area where medical interference including intensive care management is available at times of emergency

After selection of the patients requiring SCIT a patients consent must be obtained and careful and thorough discussion of the process of SCIT has to be done with the patient stressing on the possible risk of acute anaphylaxis and the need to supervise the patient after each session for a certain period of time, and to discuss the interval and duration of AIT and the need for adherence to the therapy as the clinical response will need time to appear , the possibility of treatment failure has to be explained for the patient and the causes of failure including high allergen burden, the side effect of treatment and the patient's adherence and the presence of important

comorbidities including cardiac problems, unremittable GERD and obesity^(14,15)

Procedure

Choosing Allergen extracts depends on individual characterizations which may be subject to evaluation by history and subcutaneous testing though this procedure has false positive and negative results many of the extracts are commercially available (like house dust mites and pollen). The quality of the allergen extracts used has to be evaluated carefully by the administrator as the outcome and the possible complications are related to this issue, following the individual's environment and the regional allergens distribution is crucially important. The available allergens extracts include HDM, grass and birch in addition to cat dogs and cockroaches antigens.

SCIT is administered in two phases

- A- Induction phase: During this phase, 2-3 weekly injections of gradually increasing doses starting with a very low dose , starting with a very low dose reaching the maximal dose in around 3–6 months.
- B- Maintenance phase: Satisfactory tolerance to the allergen is expected to be reached the injection of inhalant antigen is usually given monthly for 3-5 years after that the patirnt may acquire a long lasting remission of his symptomatology ^(3,14,15)

More rapid or accelerated courses may be applied such as rush immunotherapy where the increasing doses are given every

quarter to one hour at 1-3 daily intervals to achieve early maintenance period but this is usually associated with increased risk of complications as anaphylactic reactions

After the end of the maintenance phase the patient will be assessed clinically for the continuity of remission as there is no specific laboratory test to assess the response.

Sublingual immunotherapy (SLIT)

SLIT has several advantages over SCIT including the no need for injections, self-administration at home and the better safety profile. In SLIT the allergen extract is placed sublingually as a rapidly dissolved tablet or a liquid formula in rapidly dissolving tablet or liquid formula, the first dose has to be administered under physician supervision. It is valuable for HDM, grass and birch

At present, there are no specific tests or clinical markers that will distinguish between patients who will relapse and those who will remain in long-term clinical remission after discontinuing allergen immunotherapy. Therefore, the decision to continue immunotherapy beyond 3 to 5 years should be based on individual patient factors such as the severity of the disease, benefits sustained from treatment, reaction history, patient preference, and treatment convenience⁽³⁾

Safety and precautions

Generally SCIT is a safe procedure with a low incidence of serious reactions and negligible mortality if the procedure is performed under strict supervision and competency⁽¹⁶⁾.

Acute allergic events can be divided in:

- A- Local reactions where by redness and or itching occur at the site of injection these are very common (>30% of the patients) and it is not necessarily predict more severe systemic reactions in the next procedures. These reactions are usually treated with local soothing agents, local corticosteroids application and may need oral antihistamine
- B- Systemic reactions are less frequent following inhalant SCIT, the incidence according to several reports ranges from about 0.1% to 5% of procedures ranging from mild reaction of urticaria and angioedema to severe allergic reactions (SARs) that occur in < 0.2%, the most severe is the anaphylactic reaction, never the less the mortality is near zero% and in one big study there was no single mortality after 8 million injection, care must be taken at the 30 minutes following the dose as this the most common time for the reaction., intramuscular epinephrine at a dose of 0.5 mg is effective and safe, it can be supplemented with antihistamine and or corticosteroid, saline infusion may be needed to support the circulation and on rare instances vasopressor agents infusion and assisted ventilation may be required for severe reaction⁽¹⁶⁾.

The outcome of AIT

In a large scale metanalysis of more than 50 RCTs, SCIT seems to improve the quality of life, decrease the need for rescue medications (as short-acting bronchodilators), decrease the need for systemic corticosteroids, and improve spirometric values including FEV1 (low evidence) while there was no sufficient evidence regarding the effect on symptoms and health care but overall, there was a decrease of the need for long-term control medications (moderate evidence)⁽¹⁷⁾

On the other hand, SLIT improves asthma symptoms, decreases need for of long-term control medication and improves spirometric values including FEV1 (moderate evidence). To lesser extent SLIT may decrease rescue medication use, and may improve quality of life, while, again there was no sufficient evidence regarding the effect on symptoms and health care. Local and systemic allergic reactions occurred commonly but required no changes in treatment schedule, and life-threatening reactions were not reported^(17,18).

CONCLUSION

Allergen Immunotherapy, both SCIT and SLIT have a practical rule in ameliorating asthma outcomes in patients with mild and moderate severity states with negligible mortality and manageable morbidity.

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