Immunotherapy and Bronchial Asthma in Children

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Abstract

Background: Allergen immunotherapy (AIT) is the administration of the causal allergen to control allergic inflammation and symptoms. AIT has been used for over a century and it is really reflected the only disease-modifying therapy for IgE-mediated allergic diseases, because it induces a persistent immunological and clinical tolerance toward the causal allergen. Both subcutaneous AIT (SCIT) and sublingual (SLIT) are used and accepted as effective treatments for adults and children with allergic rhinitis (AR) with or without asthma. Existing studies recommend that both SLIT and SCIT can induce the same immunologic changes.AIT can modify the upper and lower respiratory allergic symptoms by modulating the IgE-mediated response following the allergen exposure. An important mechanism in achieving immunologic tolerance is the upregulation of allergen-specific T-regulatory (Treg) cells and B-regulatory (Breg) cells, which primarily down-regulate the Th2 response Over the last 20 years, sublingual allergen immunotherapy has expanded popularity based on controlled trails that have revealed a favourable safety profile.

Keywords: Immunotherapy, Bronchial Asthma

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Introduction

Asthma is a chronic disorder of the bronchial tree. Now, bronchial asthma is seen as a complex heterogeneous disorder with variable natural history, severity, comorbidities, and therapeutic response. The disease is thus defined in numerous ways. For example, asthma is described as an airway disorder with underlying chronic inflammation characterized by hyper-responsive airway with different mechanical pathways (endotypes) and variable clinical features (phenotypes), which results in nonspecific symptoms as recurrent wheezing, shortness of breath, nocturnal or early morning cough, and chest tightness. Airway hyper-responsiveness is defined as the narrowing of the airways as response to a various stimuli, such as allergens and nonspecific triggers and infections **(1)**.

A recent Lancet Commission report on asthma called for greater awareness of the various phenotypes, with exclusive underlying pathological mechanisms, frequently grouped under the non-specific label of asthma. The definition of asthma phenotypes is the combination of clinical, demographic and pathological characteristics of asthma, including pathological and inflammatory endotypes as a subset within this definition.**(2)**

Asthma affects approximately 400 million individuals worldwide and its prevalence and burden are increasing in spite of the improvement of novel therapies,

improvement in the design of delivery devices, and new technologies for monitoring and enhancing adherence **(3)**.

Asthma was less prevalent in developing countries, and the highest prevalence was detected in Anglo- Saxon countries, with unexpected northwest to southeast gradient in asthma prevalence within Europe, and this could not be explained by the known risk factors. In addition, asthma prevalence cannot simply be explained by genetic differences: great variations between countries with a similar genetic or ethnic background were seen. The variations in risk factors and time course of the different disease entities between the different countries could provide an explanation **(4)**.

The goal of asthma therapy is to achieve asthma control. According to the data management of allergic diseases, reflect avoidance of the risk factors, treatment, and promoting of tolerance. Keeping this in mind, the management of allergic diseases depends on how it easy is to avoid the trigger agents. Current medications allow children to live a more or less "normal" life, including sharing in sports and other physical and social activities **(5)**.

BIOLOGICAL AGENTS AND ASTHMA

Biologic agents represent a very important advance in the treatment of chronic immune-mediated diseases and have led to significant advances in the management of rheumatoid arthritis, inflammatory bowel disease, and, severe asthma. **(6)**.

Omalizumab is an expensive therapeutic option with the disadvantage of being administered in a hospital, subcutaneously, under supervision. It is a therapeutic option in step 5 for therapy refractory asthma, after the exclusion of all other measures. It has been shown to reduce exacerbations, reduce the dosage of inhaled (and oral) steroids, and develop asthma related QoL. Dupilumab is a monoclonal antibody that atteched to the IL-4 receptor-α and has the ability to block the action of both IL-4 and IL-13. It has revealed promising efficacy in the treatment of allergic rhinitis and nasal polyposis, eczema, and asthma with elevated blood eosinophils. Ligelizumab, second-generation monoclonal antibody to IgE, showed three times more efficacy than omalizumab. **(7)**.

Allergen immunotherapy (AIT) is the administration of the causal allergen to control allergic inflammation and symptoms. AIT has been used for over a century and it is really reflected the only disease-modifying therapy for IgE-mediated allergic diseases, because it induces a persistent immunological and clinical tolerance toward the causal allergen **(8)**.Both subcutaneous AIT (SCIT) and sublingual (SLIT) are used and accepted as effective treatments for adults and children with allergic rhinitis (AR) with or without asthma. Existing studies recommend that both SLIT and SCIT can induce the same immunologic changes. **(9)**. The comparison between SLIT and SCIT is presented in **Table 1**.

HISTORY OF IMMUNOTHERAPY

Although the whole story of immunotherapy appears to be a new one, the first routes of immunotherapy dates back to 1911 when two English researchers used water solution of hay fever pollen extracts for to treat hypersensitized patients. Another very important step in the history of sublingual immunotherapy was the findings of a group of German researchers who showed that sublingual route of allergen-specific immunotherapy of house dust mite (HDM) extract may be similarly clinical effective as subcutaneous route.. A few years later **Scadding's and Brostoff .(10)** proved a clinical efficacy of low dose sublingual immunotherapy in patients with allergic rhinitis sensitized to house dust mites. **(10)**.

Table 1: Comparison of SCIT and SLIT

Treatment	SCIT	SLIT
Dose-effect relationship	Studied for various allergens: multiple mixed, ragweed, HDM, cat, dog, grass, honey bee, wasp, hornet	Studied for various allergens: grass, pollen mix, birch, alder, hazel, ragweed
Definition of optimal dose	Documented in one DBPC trial of HDM allergens	Documented in one DBPC trial of a grass pollen tablet
Efficacy after 1 year of treatment	Determined for multiple allergens in DBPC trials, some on a large scale	Determined in large scale DBPC trials for grass pollen extracts
Efficacy after 2 and 3 years of treatment	Shown in trials of various allergens	Shown in large scale DBPC trials of grass pollen extracts
Sustained therapeutic benefit	Shown in multiple trials, most of which were controlled	Shown in trials of adequate size, for grass pollen extracts for adults
Efficacy for allergic asthma	Shown for various allergens	Small effect in meta-analysis
Asthma prevention	No DBPC trials, positive findings in controlled trials	No DBPC trials, positive findings
Prevention of new sensitization	Shown in controlled trials of individual allergens	No DBPC trials, positive findings

MECHANISMS OF ALLERGEN IMMUNOTHERAPY

AIT can modify the upper and lower respiratory allergic symptoms by modulating the IgE-mediated response following the allergen exposure. An important mechanism in achieving immunologic tolerance is the upregulation of allergen-specific T-regulatory (Treg) cells and B-regulatory (Breg) cells, which primarily down-regulate the Th2 response. Regulatory cells inhibit the activation of allergen-specific Th2 lymphocytes, suppress allergic inflammation, and eventually shift toward a Type 1-mediated immune response, releasing cytokines, interleukin (IL)-10 and transforming growth factor-b (TGF-b) **(11)**.

TABLE 2: Mechanisms of immunologic tolerance mediated by T and B regulatory cells during allergen immunotherapy **(12)**

Treg-mediated mechanisms	Breg-mediated mechanisms
• Release regulatory cytokines (IL-10, TGF-b, and IL-35) • Induce tolerogenic DCs subsets • Reduced number of ILC2 • Suppress activation of allergen-specific Th2 lymphocytes • Downregulate the expression of FC+RI receptors on mast cells, • Decrease allergen-specific IgE synthesis • Promote B-cell production of IgG4 antibody	• Release regulatory cytokines (IL-10, TGF-b) • Induce the synthesis of IgG4 blocking antibodies • Inhibit activation and proliferation of effector T lymphocytes • Suppress Th2-dependent inflammation • Promote T-cell expression of Foxp3 and generation of functional Treg cells

THE MECHANISM OF SLIT

The site of allergen application plays an important role in the mechanism of tolerance induced in the course of SLIT, that is oral mucosa, which is considered to be 'immuno-priviledged' **(13)**.

Antigen-presenting cells (APCs), mainly dendritic cells (DCs), which are densely distributed in the epithelium, lamina propria and submucosal layer of the oral mucosa, are essential for immunotolerance in SLIT. DCs capture antigens that reach the oral epithelium (within 15–30 minutes), migrate to regional lymph nodes (within the subsequent 12 – 24 hours) and at the same time transform (by proteolytic degradation) antigen proteins into fragments that can be presented to T lymphocytes **(8)**.

The critical importance points in activating the tolerogenic function of DCs and thus SLIT effectiveness are: 1) The duration of allergen contact with antigen-presenting cells in the oral mucosa; 2) The dose and frequency of allergen contact (application); 3) Oral mucosa micro-environment; and 4) The effects of contributory

factors that enhance tolerogenic abilities and induce a Th1-type response (e.g. MPL – a TLR-4 agonist) **(13)**.

INDICATIONS AND CONTRAINDICATIONS FOR SLIT

Table 3: Indications for SLIT **(14)**

Immunological indications	**Documented IgE-dependent hypersensitivity to pollen allergens, house dust mites or cat fur**
Clinical indications	**Allergic rhinitis (and conjunctivitis)** **Controlled atopic asthma with mild to moderate course** **Very good alternative therapy when injection immunotherapy not accepted**
Pharmacological indication	**Lack of anticipated effect** **Lack of acceptance of pharmacotherapy on the part of the patient or children family** **Adverse effects after treatment**

Table 4: Contraindications to SLIT **(14)**

Absolute	**Severe immune systemic disorders** **Severe circulatory system disorders** **Neoplastic diseases** **Chronic inflammations** **Severe asthma when FEV1 <70% of normal value in spite of treatment** **β–blocker treatment** **Poor adherence and severe mental disturbances**
Relative	Pregnancy
Temporary	Inflammatory processes in gastrointestinal tract (7-day interval needed around vaccinations)

AIT AND ASTHMA

The definite asthma management is control-based: therapeutic strategies are based on a stepwise approach and adjusted in a continuous cycle including assessment, treatment and review. Though, standard pharmacotherapy does not affect the underlying pathogenetic immune response as it is withdrawn symptoms and inflammation occur again **(15)**.

CLINICAL EFFICACY OF SLIT

Although it passed more than a decade of proven clinical efficacy of SLIT, in addition to the effect of SLIT on quality of life, data of long-lasting effects are still missing. Results from a 15-year-long prospective study by **Marogna *et al.* (16)** showed that long-lasting effects of SLIT are in direct association with the treatment's duration. Some study suggested that 4 years of SLIT may be associated with better out comes after more than 3 years of treatment. Some authors are very doubtful concerning the adherence and tolerability of the treatment mainly in the pediatric population, although the other one claimed that even 1 or 2 years of treatment is sufficient to mediate immunological response **(17)**.

Another important aspect of SLIT is long-lasting effects. After 12 years of follow-up period, **Eng *et al.* (18)** showed preventive effects of SLIT 6

years after the treatment cessation comparing with the standard pharmacotherapy.

SAFETY AND TOLERABILITY OF SLIT

Over the last 20 years, sublingual allergen immunotherapy has expanded popularity based on controlled trails that have revealed a favourable safety profile **(19)**. However, threatening severe systemic reaction related to SLIT were informed. Overall prevalence of systemic adverse events was lower than 20% in DB-PC-RCT, whereas the prevalence of severe systemic reactions was between 1 and 2% of total recorded events. Most commonly post marketing surveys reported mild to moderate commonly self-resolved systemic reactions **(20)**.

Local adverse reactions are most common SLIT-related side effects although it is not very easy to record them as it is not generally including in post marketing analysis nor in DB-PC-RCT. Its prevalence fluctuates from 50 to 80% and they include oropharyngeal and gastrointestinal reactions such as itching, pruritus, and eczema in oral mucosa and/or diarrhoea, vomitus, and abdominal pain. **(21)**.

QUALITY OF LIFE WITH SLT

According to various DB-PC-RCT, real-life studies and meta-analysis quality of life (QOL) is a very important issue for children and adults with allergic diseases. **Cipranci *et al.* (22)** and **Djuric-Filipovic *et al.* (5)** showed the improvement of the QOL in SLIT groups.

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