Sublingual Immunotherapy for Aeroallergens

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Sublingual immunotherapy represents an important progress in the use of personalized medicine in children with allergic asthma. It is a viable option for house dust mite driven asthma and in subjects with the asthma associated with allergic rhinitis.

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1. Introduction

Asthma is a chronic disease affecting 10%–15% of school-aged children. First-line treatment for allergic asthma consists of such medicines as inhaled corticosteroids, long-acting beta2-agonists and short-acting beta2-agonists as needed with the aim of minimizing symptoms, improving lung function, and reducing inflammation. Notwithstanding, some children need additional treatment to improve asthma control. Moreover, in patients who achieve control, symptoms can return upon discontinuation of drugs. Different response to the same therapy can be due to a distinctive asthma endotype that indicates a subtype of the disease with a distinct underlying pathophysiological mechanism. In childhood, two forms of asthma have been conventionally studied. The type2 (T2)-high endotype can be allergic or nonallergic and it is characterized by an eosinophilic airway inflammation, while in the T2-low endotype, a neutrophilic or paucigranulocytic airway inflammation is found. Most children have allergic asthma that may be considered a phenotype, with early onset, atopic background, family atopic history, allergic sensitization to common inhaled allergens, eosinophil inflammation, and bronchial hyperreactivity that overlaps with eosinophilic and T2 asthma. In this promising era of precision medicine, matching asthmatic patients with the T2-high endotype allows “personalizing” more effective therapeutic choices that target the airway T2 pathway. They include biologicals and allergen specific immunotherapy (AIT) in asthmatics who partly respond or do not respond to first-line treatment or have a recurrence after a suspension. AIT has been the first attempt of precision medicine and it is tailored to the specific IgE that elicits the reaction. AIT is the only disease-modifying treatment for patients with IgE-mediated allergy due to airborne allergens. It consists of repetitive administration of the allergen extract that provokes symptoms with the purpose of inducing allergen tolerance in allergic asthma by targeting the underlying mechanisms and modifying the immunological response. Subcutaneous AIT (SCIT) has been the only accepted effective AIT for allergic rhinitis and asthma over several years and it still represents the standard treatment for hymenoptera venom hypersensitivity**.** SCIT may rarely induce unpredictable anaphylactic reactions. Moreover, children can be annoyed by repeated injections that require visiting a doctor’s office. So, alternative safer and more comfortable routes of allergen administration that may allow self-administration at home have been investigated. SLIT has been quickly recognized in official documents as an alternative to SCIT in respiratory allergy at variance from other routes. Furthermore, SLIT has been used for other allergy-driven

diseases, such as atopic dermatitis. Both SCIT and SLIT share similar mechanisms, that involve induction of allergen-specific IgG4, stimulation of IgE-blocking IgG antibodies, T-cell tolerance. These mechanisms suppress the specific Th2 immune response and prevent further exacerbations. In SLIT, an important role for antigen tolerance is played by the uptake of the allergen by dendritic cells of oral mucosa. SLIT is specific for the allergen causing IgE-mediated asthma but not for asthma in itself.

2. Product-Related Considerations

SLIT vaccines are available as liquid drops or tablets that are swallowed after keeping under the tongue for 1–2 min. Sublingual formulations are not equivalent since they vary according to the manufacturer in the diluent, preservatives, unit of measurement of potency, dosage, and schedules. The diversity in marketed products has led to heterogeneity in the way national regulators deal with different products. In most countries, AIT products usually require a marketing permission like other drugs. However, SLIT products are also commercialized and routinely used in many countries as “named patient products” that just need to be prepared according to the Good Manufacturing Practice to be commercialized.

At variance from SCIT, in SLIT, the build-up phase with increasing doses usually lasts a few days, or it is unnecessary, and the treatment starts with the maintenance dose. The maintenance dose can be administered according to the manufacturer: once a day, on alternate days, twice weekly. SLIT for seasonal allergens can be discontinued at the beginning of the season (preseasonal treatment), at the end of the season (pre-coseasonal) or administered continuously. SLIT for perennial allergens is usually administered all year-round. A SLIT course of 3 years is recommended to achieve better long-term results. However, a prospective study found that a treatment of 4 years slightly improved efficacy and long-term benefits in adults.

3. Sublingual Immunotherapy for Asthma

Several systematic reviews and trials have been conducted on the use of SLIT in asthmatic children. Meta-analyses have been hampered by heterogeneity among selected studies in population, allergens, products, outcomes, doses, duration of treatment. It is noteworthy that efficacy and safety should be characterized for each formulation because of differences between sublingual products. Furthermore, meta-analyses have been limited by power of the trials since most of them studied primarily patients with allergic rhinitis. Allergic rhinitis, which affects 60–80% of asthmatic children, is the most frequent comorbidity and it is associated with worse asthma control. Furthermore, not validated instruments were used and asthmatic exacerbations at the time of the studies were not considered as the outcome that the authors should have tried to influence. Even if these shortcomings questioned the conclusions, most meta-analyses and systematic reviews showed the efficacy of SLIT in asthmatic children.

The impact of SLIT on asthma is often assessed as a secondary outcome in studies on IgE-mediated allergic rhinitis. So, SLIT should be used in children with controlled mild and moderate asthma or controlled severe asthma associated with allergic rhinoconjunctivitis. There is a conditional recommendation on the use of SLIT in children

when allergic asthma is isolated because of the moderate or low quality of evidence that does not allow defining a clear recommendation. However, the EAACI Guidelines state that the available evidence support the efficacy of HDM SLIT for pediatric asthma and recommend HDM SLIT drops for children with controlled HDM-driven allergic asthma as an add-on treatment. For other allergens, the prescription clearly depends on the product and the type of the eliciting allergen. SLIT tablets or SLIT drops with documented efficacy should be given to asthmatic children with allergy to grass, birch, or other pollens. Low-quality data support the use of SLIT in children with allergy to Alternaria and cat dander.

In polysensitized children constituting the majority of those with a pollen allergy, the molecular-based diagnosis would permit the identification of genuine sensitizers and cross-reactive panallergens. The effectiveness of AIT would possibly be increased by prescribing AIT only for genuine allergens. In the pollen—food allergy syndrome, SLIT does not improve symptoms to cross-reacting foods. It should be carefully excluded that asthma is elicited by foods.

Besides the severity of manifestations, SLIT should be considered if avoidance of the identified relevant inhalant allergens is not effective or is impracticable as the most advantageous treatment set-up. SLIT should be started when pharmacotherapy is protracted, e.g., for more than 3 months, or induces side effects. The cost and the presumed adherence to SLIT are to be considered. During SLIT, children should always receive correct pharmacotherapy. SLIT efficacy should be ascertained by reduction of frequency and severity of symptoms, use of medication, and improvement of lung function. The evaluation of SLIT results should be made following at least six months of pre-coseasonal SLIT for pollen or six to twelve months for perennial allergens and SLIT can be discontinued when patients get worse. There is no absolute age limitation for SLIT administration. Even though the efficacy and safety of SLIT has been shown in children of 3 years of age, evidence is scarce. Therefore, in preschool children, SLIT should be prescribed after carefully assessing risks and benefits and SLIT drops should be preferred. There are no data suggesting that children receiving SLIT are at a higher risk for the COVID-19 infection. It is recommended to carry on the administration of SLIT during the COVID-19 pandemic. Patients with suspected or confirmed infection with COVID-19 should discontinue the treatment [94]. Finally, in children with rhinoconjunctivitis caused by grass or birch, it has been shown that some SLIT products can be a feasible option not only for controlling symptoms, but also for preventing the onset of asthma. A minimum of 3 years course is generally recommended to obtain a preventive effect.

SLIT is a nice example of precision medicine for allergen-driven asthma. There has been a significant progress in SLIT over the last years with introduction of new formulations. Recently approved SLIT products have been investigated in large trials, mainly in adults with asthma or in patients with allergic rhinitis, and there is a need in studies on their use in asthmatic children. Generally, SLIT appears to be safe and effective as an additional treatment in most children with controlled IgE-mediated asthma due to more common allergens. However, products differ in characteristics and efficacy. A distinction of products is necessary to avoid confusion and predict benefits.

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