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Review

Allergen immunotherapy in children and adolescents with respiratory diseases

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Abstract. To date, the only disease-modifying treatment strategy for allergic rhinitis and asthma is allergen immunotherapy (AIT). There is evidence that AIT improves allergic rhinitis and asthma, such as reducing symptom severity and medication use and improving of quality of life, with a long-lasting effect after the end of the course. The recent clinical trials evidenced AIT effectiveness and safety in allergic asthma. Consequently, the current version of the GINA (Global Initiative for Asthma) guidelines recommend AIT as an add-on therapy for asthma. There is also evidence that AIT may exert preventive activity on the possible progression from allergic rhinitis to asthma in children and the onset of new sensitizations. (www.actabiomedica.it)

Key words: allergen-specific immunotherapy, subcutaneous immunotherapy, sublingual immunotherapy, allergic asthma, children

Allergen immunotherapy (AIT) is the only disease-modifying treatment strategy for IgE-mediated diseases (1-3). AIT damps allergic response and relieves symptoms. Subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are the most used and accepted route of administration. Both are effective for both adults and children with respiratory allergies, such as allergic rhinitis (AR) and asthma, and are recommended by guidelines (4,5). However, the risk of SCIT systemic reaction is more considerable in uncontrolled asthma and with rush schedules. Therefore, SLIT could be a reliable alternative to SCIT, mainly in children, as at home, self-administration is possible, and the risk of severe systemic reactions is reduced (6). In clinical practice, the route choice depends on several factors, including product availability or approval, geographic location, cost, patient's characteristics, physician attitude, and patient preference. There is evidence that both SCIT and SLIT induce superimposable immunologic effects (7, 8). Rough allergen extracts are used for SCIT as aqueous or physically-adsorbed (depot) products. There are also chemically-modified allergens (allergoids) as depot extracts. SLIT is available as aqueous solutions or tablets. Pending harmonized and international rules to regulate AIT products, there are two

situations: distribution as "named patient products" (NPP), which only require to be prepared in compliance with Good Manufacturing Practice, or formal marketing authorization. According to EMA directives, SLIT tablets for grass pollen and house dust mite (HDM) have been recently registered for use in children, adolescents, and adults. AIT induces allergen tolerance, and consequently affects the natural course of allergy, preventing clinical disease progression, such as from rhinitis to asthma. Moreover, AIT controls allergic symptoms when not responsive to avoidance or pharmacotherapy, reduces medication use, improves the quality of life, and has long-lasting effects after the end of treatment (9). The most recent clinical trials strengthened the evidence concerning the AIT effectiveness and safety to treat allergic asthma, so that asthma guidelines recommend SLIT as an add-on therapy for asthma in adults and adolescents with house dust mite allergy, under well-defined conditions (5). Furthermore, AIT has preventive effects preventing asthma in AR subjects, mainly if early started in childhood (10). AIT modulates the immune response consequent to the causal allergen exposure. Through complicated mechanisms involving both innate and adaptive immunity, AIT regulates T- and B-cells, changes antibody isotypes, and decreases mediator release, and migration of eosinophils, basophils, and mast cells to inflamed tissues (11). AIT-induced immunologic tolerance is based on the upregulation of allergen-specific T-regulatory (Treg) cells and B-regulatory (Breg) cells, and the consequent down-regulation of the T helper 2 (Th_2) response (10). Treg and Breg cells produce interleukin (IL)-10 and transforming growth factor-β (TGF-β), regulatory cytokines inhibiting the activation of allergen-specific Th_2 lymphocytes, suppressing type 2 inflammation, and ultimately shifting toward a physiological Type 1-mediated immunity (12, 13).

High-dose AIT induces many immunological modifications: dendritic cells (DCs) produce IL-12, IL-27, and IL-10, that generate and activate distinct phenotypes of Treg cells, in particular, forkhead box P3 $(Foxp3)^+$ Treg and inducible Treg (iTreg) cells (10,11). Both $Foxp3^+$ Treg and iTreg cells suppress allergic reaction releasing regulatory cytokines (IL-10, TGF-β, and IL-35), inducing tolerogenic DCs subsets, suppressing allergen-specific Th_2 lymphocytes, downregulating the expression of FCεRI receptors on mast cells, decreasing allergen-specific IgE, and promoting IgG_4 synthesis (10). IL-10 exerts inhibition of IL-4 and IL-5, allergen-specific IgE, but increases IgA and IgG_4 (11). The competitive effect of IgG_4 toward IgE antibodies is an "immunologic blockade" that inhibits mast cell and basophil degranulation. TGF-β suppresses Th_2 and innate lymphoid cells type 2 (ILC2), thus reducing type 2 inflammation. Breg cells promote allergen immune tolerance, by producing IL-10 and TGF-β, blocking IgG_4, inhibiting effector T cells, suppressing type 2 inflammation, and restoring allergen-specific Treg cells (14). AIT is indicated in patients suffering from AR with or without conjunctivitis, and/or asthma, after documenting a true allergy to the causal allergen (15). Candidates for AIT are patients whose symptoms are not controlled adequately by medications and environmental measures or those experiencing unacceptable adverse effects of medications or who wish to reduce the long-term use of medications (16). There is evidence that AIT is effective, safe, and preventive in AR and/or asthma both in adults and children, even though there is considerable heterogeneity among the study populations enrolled, the different schedules, the different AIT products, and the outcomes (17).

In clinical practice, there is convincing evidence about efficacy and safety of AIT in adults and children with allergic asthma, as confirmed by meta-analyses, mainly concerning the impact of SLIT in asthmatic children, even though there were variable results due to the heterogeneity of tested products and clinical outcomes. Combined AR and asthma symptom and medication scores significantly diminished in asthmatic children with comorbid AR after SLIT treatment. These outcomes also persisted after AIT discontinuation. There is evidence that a prospective study showed fewer asthma episodes, the use of relievers, and improved lung function in asthmatic children after five years of AIT discontinuation (17). Meta-analyses of randomized clinical trials concerning the asthma treatment by SCIT demonstrated a significant reduction in asthma symptoms, asthma medication use, and airway hyperreactivity both in children and adults. SCIT exerts a long-term impact on childhood asthma, as, af-

ter a 3-year SCIT, a global remission of asthma was obtained. Moreover, children re-evaluated nine years after the SCIT discontinuation, had three times lower risk of frequent asthma symptoms than controls (15). SCIT and SLIT are, therefore, useful to treat AR and asthma in children. Notably, AIT could reduce ICS doses, also guarantying asthma control. AIT added to ICS maintenance therapy reduced ICS doses while still maintaining asthma control. The pivotal immunomodulating role of AIT consists of controlling and inducing remission of disease activity. This aspect differentiates AIT from other anti-allergic therapies that are short-lasting.

It has to be underlined that AIT is allergen-specific. Therefore, a thorough clinical history and appropriate allergy diagnostic tests are essential to accurately identify the causal allergen(s) (4). In the case of polysensitized patients, the identification of the major allergens should also be supported by the use of component-resolved diagnostics (18). Benefits and the risks, and the ability to comply/cooperate with AIT, should always be assessed.

As regards the monitoring of AIT efficacy, it has to be considered that the combined assessment of symptom severity and medication use represents the most reliable tool. In particular, the visual analog scale could be an easy way to measure the patient's perception of AIT improvement.

The safety of AIT has always been a crucial issue in all clinical trials. Many aspects should be considered in clinical practice. If AIT is correctly prescribed and administered, AIT, mainly SLIT, is safe and well-tolerated also in children with allergic asthma.

In conclusion, AIT is a valuable therapeutic option, especially in childhood, to modify the progression of respiratory allergic disease. Both SCIT and SLIT are useful in pediatric allergic rhinitis and asthma, having an intriguing steroid-sparing effect. However, uncontrolled asthma must be a definite contraindication for AIT treatment. Coupling novel biological therapies with AIT could represent a promising approach to potentially avoiding adverse reactions. At present, AIT should be considered the best expression of Personalized Medicine in clinical allergy.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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