

REVIEW

Preventive capacity of allergen immunotherapy on the natural history of allergy

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Key words

Allergen immunotherapy • Preventive capacity • Mechanisms of action

Summary

Allergen immunotherapy (AIT) is the practice of administering gradually increasing doses of the specific causative allergen to reduce the clinical reactivity of allergic subjects. A bulk of literature demonstrates that AIT is an effective and safe treatment to reduce allergic symptoms and the use of drugs. The preventive capacity of AIT is less investigated. The studies thus far available showed that this treatment, in both forms of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) is able to prevent the development of asthma in patients with allergic rhinitis and the occurrence of new sensitizations in patients monosensitized. Such outcomes demonstrate the ability of AIT to change the natural history of respiratory allergy. Of particular

importance, SCIT with Hymenoptera venom has an invaluable role in preventing potentially fatal anaphylactic reactions to the culprit sting in venom-allergic patients. Ongoing studies are aimed at evaluating the possible capacity of AIT in primary prevention of allergy. All these capabilities are related to the mechanisms of action of AIT. In fact, both SCIT and SLIT are able to modify the allergen presentation by dendritic cells that in turn modify the phenotype of allergen-specific T cells, switching from the Th2-type response, typical of allergic inflammation, to a Th1-type response. An important role is played by allergen-specific T regulatory (Treg) cells, which produce suppressive cytokines such as IL-10 and TGF-beta.

Introduction

Allergen immunotherapy (AIT) is the practice of administering gradually increasing doses of the specific causative allergen to reduce the clinical reactivity of allergic subjects. As stated in the World Health Organization document dedicated to AIT, concerning the products to perform the treatment “The historical term allergen extract was changed to allergen vaccine to reflect the fact that allergen vaccines are used in medicine as immune modifiers similarly to vaccines for infectious diseases” [1]. AIT was introduced more than one century ago, but remained a merely empirical treatment until 1954, when the first controlled trial was published, and was later continuously developed to reach full scientific evidence demonstrated by a number of meta-analyses [2, 3]. The only method to administer AIT was the subcutaneous injection until the 1980s, when a series of fatal adverse reactions both in Europe [4] and in the USA [5] raised the important issue of treatment safety. The sublingual route, introduced by a trial based on very low doses [6] that now we know to be ineffective, has been subsequently the object of thorough investigation and has currently achieved full scientific evidence of efficacy [7-9].

Therefore, today two forms of AIT are available, subcutaneous immunotherapy (SCIT), which is the only treatment recommended in patients with allergic reactions

to Hymenoptera stings, and sublingual immunotherapy (SLIT) which is a valid option to treat patients with allergic rhinitis and allergic asthma. A large literature is accessible evaluating the efficacy and safety of SCIT and SLIT, the aim of this article is to focus the preventive capacity of both treatments.

Prevention of allergic reactions to Hymenoptera stings

Systemic reactions to insects belonging to the order of Hymenoptera, that include honeybees (*Apis spp*), bumblebees (*Bombus spp*), yellow jackets (*Vespula spp*), wasps (*Polistes spp*), and hornets (*Vespa spp* and *Dolichovespula spp*), affect about 3% of the general population, with particular interest for anaphylaxis, that is associated to a risk of potentially fatal reactions [10]. SCIT with Hymenoptera venom, known as venom immunotherapy (VIT) is highly effective in preventing further systemic reactions [11] and is also very well tolerated, as showed by the absence (differently from SCIT with inhalant allergens) of fatal adverse reactions to VIT [12]. In particular, the capacity to prevent fatal reactions to stings is 100%, and the capacity to prevent any kind of systemic reactions is estimated in 90-95% [13]. Of note, the patients not completely protected from stings can achieve full protection by increasing the maintenance

dose over the recommended amount of 100 mcg, being possible to determine the protective dose in each individual [14]. A recent important advance was represented by the recognition that VIT is effective and safe also in patients suffering from mastocytosis, which is a known risk factor for developing particularly severe reactions to insect stings [15, 16]. All these observations make VIT an invaluable treatment to prevent anaphylaxis from insect stings.

Prevention of asthma in patients with allergic rhinitis

Allergic rhinitis and asthma are closely correlated and patients suffering only from rhinitis have a substantial risk to develop asthma [17]. A pivotal experience in demonstrating the ability of AIT to prevent such progression was the Preventive Allergy Treatment (PAT) study [18]. The PAT study evaluated a group of 183 children, aged 6-14 years, with grass and/or birch pollen allergy after a 3-year course of SCIT, and found that the significant improvement in rhinitis symptoms observed at SCIT stopping persisted at a 5-year follow-up. The AIT treated children had, compared with control subjects treated only with drugs, significantly less asthma after 5 years as evaluated by clinical symptoms. In addition, 147 children were followed-up 7 years after termination of AIT: the significant improvement in rhinoconjunctivitis persisted at the follow-up, and significantly less actively treated subjects had developed asthma at the follow-up as evaluated by clinical symptoms. Patients who developed asthma among controls were 24/53 while in the AIT group were 16/64 [19]. The longitudinal treatment effect when adjusted for bronchial hyperresponsiveness and asthma status at baseline including all observations at 3, 5 and 10 years time points was statistically significant ($P = 0.0075$). The odds ratio for no-asthma was 4.6 (95% Confidence Interval [CI] 1.5-13.7) in favour of AIT. The authors concluded that AIT has long-term clinical effects and the potential of preventing development of asthma in children with allergic rhinoconjunctivitis up to 7 years after treatment termination. There are also studies on prevention of asthma by SLIT. Di Rienzo et al. conducted a prospective parallel group study on 60 children (mean age 8.5 years) allergic to dust mites and divided into two matched groups: 35 underwent a 4- to 5-year course of SLIT with standardized extract and 25 received only drug therapy [20]. The patients were evaluated at three time points (baseline, end of SLIT and 4 to 5 years after SLIT discontinuation) regarding presence of asthma and use of anti-asthma drugs. In the SLIT group significant differences were found for the presence of asthma ($P \leq 0.001$) and the use of asthma medications ($P \leq 0.01$), whereas no difference was observed in the control group. Madonini et al showed in a retrospective survey on 302 patients treated with SLIT that, during a 1-year follow-up after stopping the treatment only 1% of non-asthma patients reported an onset of respiratory symptoms. The clinical benefits were as-

sociated with the length of treatment: patients with long-lasting benefits were treated for a mean duration of 29.1 months, while patients showing a return to pre-SLIT condition were treated for a mean 13.3 months [21]. In a more recent study, 216 children with allergic rhinitis, with or without intermittent asthma, were evaluated and then randomized to receive drugs alone or drugs plus SLIT for 3 years; 144 children received SLIT and 72 received only drugs. Asthma was less frequent in SLIT patients (odds ratio, 0.04; 95% confidence interval, 0.01-0.17), and the number of children with a positive methacholine challenge result decreased significantly after 3 years only in the SLIT group [22].

Prevention of new sensitizations

As reported above, the development of new sensitizations following the initial monosensitization is typical of the natural history of respiratory allergy. The issue of preventing new sensitizations by AIT was investigated in various studies. The first investigations concerned small populations of patients. Des Roches et al. studied 22 children monosensitized to dust mites receiving SCIT with standardized allergen extracts and 22 other age-matched controls. Children were followed-up for 3 years, and it was found that 10 of the 22 children monosensitized to dust mites treated with SIT did not have new sensitivities compared with 0 of 22 children in the control group, this difference being significant ($p = 0.001$) [23]. In another small study, 23 patients allergic to grass pollen – 13 treated with SCIT and 10 controls – were prospectively followed for 6 years during the grass pollen season. At the last time point, 61% of the initially pollen-monosensitized children had developed new sensitizations to perennial allergens compared to 100% in the control group [24]. The difference was significant ($p < 0.05$), but not so impressive as in the study by Des Roches. Of course, the modest number of patients make likely a stochastic distribution of data in such studies.

A more robust study evaluated 134 children (age range 5-8 years) with respiratory allergy due to monosensitization to mites, 75 treated with SCIT and 63 children treated with medication only, who were considered as controls. SCIT was administered for 3 years and all patients were followed-up for a total of 6 years. New sensitizations were assessed by skin prick test and serum-specific IgE every year during the follow-up. At the end of the study, 69 SCIT treated and 54 controls were available; of them, 52 (75.4%) in the SCIT group showed no new sensitization, compared to 18 (33.3%) in the control group ($p < 0.0002$). The allergens most common responsible for the new sensitizations were pollens of *Parietaria*, grasses and olive [25].

A retrospective study evaluated a very large number of monosensitized patients, including 7182 patients treated with SCIT for 4 years and followed for further 3 years, and 1214 patients treated only with drugs for the same period years. All patients underwent prick test and specific IgE measurement before and after the 4 years of

SCIT and again 3 years later. The results showed that polysensitized subjects were 23.7% in SCIT-treated and 68% in drug treated after 4 years ($P < 0.0001$) and 26.95% and 76.77%, respectively, after 7 years ($p < 0.0001$). Asthmatic subjects were more prone to develop polysensitization in comparison to subjects suffering only from rhinitis (32.14% instead of 27.29% after 4 years, 36.5% instead of 31.33% after 7 years; $P < 0.0001$) [26]. Concerning SLIT, in the previously cited study by Madonini et al. on 302 patients followed-up for one year after stopping SLIT in only 9.6% of patients were detected by skin tests new sensitizations [21]. In the study by Marogna et al. the rate of new sensitizations was even lower, corresponding to 3.1% of SLIT treated patients and to 34.8% of controls, with an odds ratio to develop new sensitization in controls equivalent to 16.85 [22]. In a further study, the same authors prospectively evaluated the long-term effect of SLIT given for 3, 4, or 5 years on 78 patients, 59 of whom completed the study, compared with 12 control subjects. The total duration of the follow-up was 15 years [27]. According to new sensitizations, all the control subjects over the 15 years period developed positive test to allergens previously negative, while this occurred in less than a quarter of the patients receiving SLIT (21% in treated for 3 years, 12%, in treated for 4 years, and 11% in treated for 5 years, respectively).

Is AIT suitable for primary prevention of respiratory allergy?

The possibility to prevent the sensitization to inhalant allergens is currently under evaluation by Holt, who planned a prospective study of administration to newborns at risk of allergy (because of allergic parents) of sublingual extracts containing a mix of the most commonly sensitizing allergens [28]. The study is ongoing but a long time will be needed to achieve reliable observations on the real capacity to prevent, and not simply to postpone, the onset of allergy. It seems likely that the new method of AIT by intralymphatic injection, based on a very low number of administrations [29, 30], may represent in a near future a more suitable candidate method for primary prevention of allergy.

The mechanisms underlying the preventive capacity of AIT

The first mechanism suggested to explain the effectiveness of AIT was the generation of IgG antibodies. As IgG induced by vaccination neutralize the infectious

agents [31], IgG induced by AIT should block the contact between the specific allergen and the IgE on the surface of mast cells and basophils [32, 33]. However, concerning prevention of anaphylaxis from insect stings, that is the most suitable model for a blocking role of IgG, a firm relationship between the amount of venom-specific IgG and clinical protection was never achieved, especially in the long-term [34]. Thus, finer mechanisms are likely to be involved, such as the inhibition by IgG of effector cells activation through their FC-gamma receptors [35]. In any case, the role of IgG antibodies should currently be viewed in the big picture of the effects of AIT on the immunologic response to the administered allergen, that seem similar in SCIT and SLIT [36-39]. In particular, the traditional, subcutaneous route of administration was first demonstrated to modify the allergen presentation by dendritic cells (DCs) that in turn modify the phenotype of allergen-specific T cells, switching from the Th2-type response, typical of allergic inflammation and characterized by a cytokine pattern including IL-4, IL-5, IL-13, IL-17, and IL-32 to a Th1-type response. This immune deviation is related to an increased IFN-gamma and IL-2 production as well as to the anergy of Th2 or to tolerance, the latter being related to the generation of allergen-specific T regulatory (Treg) cells, which produce cytokines such as IL-10 and TGF-beta. Comparable immunologic changes, with a pivotal role for Dcs in the oral mucosa and IL-10 producing Tregs, were observed during SLIT with administration of high allergen doses [38].

Conclusions

AIT for respiratory allergy, in both forms of SCIT and SLIT, has showed, along with a clinical efficacy starting from a few months from initiation of treatment [1, 2, 7], a clear preventive capacity on the development of asthma in subjects with rhinitis and on appearance of new sensitizations. This capacity is likely to be improved by the introduction of new materials to perform AIT. Valenta, who pioneered the diagnosis and treatment of allergy by using the molecular components of the allergens, suggested that the availability of the structures of the most common allergen molecules allows currently to produce well-defined recombinant and synthetic allergy vaccines able to target more precisely the mechanisms of allergy, and offers new possible allergen-specific strategies for prevention of allergic diseases [40]. However, to the purpose of preventing allergy in a child at risk it is strongly needed to increase the awareness on AIT in both the medical community and the lay, as currently conceived in international initiatives [41].

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