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REVIEW ARTICLE

Immunotherapy in all aspects

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Abstract Allergen immunotherapy is a form of long-term treatment that decreases symptoms for many people with allergic rhinitis, allergic asthma, conjunctivitis (eye allergy) or stinging insect allergy. In this review, we presented the important topics in immunotherapy. The important aspects of immunotherapy are considered to be "Immunologıcal responses to immunotherapy"; "The principal types of immunotherapy"; "Effectiveness"; "Indications"; "Contraindications"; "Allergen immunotherapy in children"; "Safety"; and "Anaphylactic reactions after immunotherapy". The principal types of immunotherapy are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy. Both of them can be used in indicated cases. When using SCIT, physicians must be more careful because of reported rare fatal cases. The risks and benefits of continuing allergen immunotherapy in patients who have experienced severe systemic reactions should be carefully considered.

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Introduction

Allergen immunotherapy is a form of long-term treatment that decreases symptoms for many people with allergic rhinitis, allergic asthma, conjunctivitis (eye allergy) or stinging insect allergy. It decreases sensitivity to allergens and often leads to lasting relief of allergy symptoms even after treatment is stopped. This makes it a cost-effective, beneficial treatment approach for many people [1].

The principal types of immunotherapy are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). The success of immunotherapy, as compared to placebo, is based on the immunological responses to immunotherapy. The important aspects of immunotherapy are considered to be "Immunologıcal Responses to Immunotherapy"; "The Main Types of Immunotherapy"; "Effectiveness"; "Indications"; "Contraindications"; "Allergen Immunotherapy in Children"; "Safety"; and "Time to Anaphylactic Reactions after Immunotherapy Injections".

Immunological responses to immunotherapy

Immunological changes associated with immunotherapy are complex, and the precise mechanism or mechanisms responsible for the clinical efficacy thereof are under continual examination. Immunotherapy creates immunological tolerance, defined as a relative decrease in antigen-specific responsiveness that may be accompanied by

immune deviation, T cell anergy, and/or T cell apoptosis. Successful immunotherapy generates a population of regulatory T cells, which are CD4+ CD25+ T lymphocytes, as an early event (occurring within days or weeks). Regulatory T cells can produce inhibitory cytokines, including IL-10, TGF-β, or both [2–7]. Increases in the levels of such cytokines have been described upon allergen immunotherapy with *Hymenoptera* venom [8], grass pollen [4], and house dust mite (HDM) allergen extracts [5]. IL-10 can decrease B cell antigen-specific IgE production and increase IgG4 levels; reduce proinflammatory cytokine release from mast cells, eosinophils, and T cells; and elicit tolerance of T cells, by selectively inhibiting the CD28 costimulatory pathway. As a consequence, lymphoproliferative responses to allergens are reduced after immunotherapy [9]. The data also support the concept of a later (thus more delayed) allergen-specific immune deviation from a TH2 to a TH1 cytokine profile [10–12]. The results indicate that an increase in the production of IL-12, a strong inducer of TH1 responses, may contribute to this later shift [13].

During natural allergen exposure, eosinophils and mast cells increase in number in the respiratory mucosa, and the levels of secretions rise. These cellular infiltrations are reduced by immunotherapy [14]. Upon immunotherapy, an initial increase in specific IgE antibody levels is evident [15], followed by a gradual and progressive decrease in IgE levels to the baseline level (or below); this may persist for several years. Clinical improvement occurs prior to the decrease in IgE antibody levels, and it is clear that treatment efficacy is not dependent on such a decrease [16]. Thus, lower levels of specific IgE do not explain the clinical responses to immunotherapy [17]. Despite the persistence of significant levels of specific IgE antibodies, immunotherapy usually reduces the release of mediators such as histamine from basophils and mast cells; this is very relevant in the immediate phases of allergic reactions. Suppression of late-phase inflammatory responses in the skin and respiratory tract are also usually noted upon allergen immunotherapy [18].

The principal types of immunotherapy

Subcutaneous immunotherapy

Subcutaneous immunotherapy in patients with pollen rhinitis is associated with transient increases in allergen-specific IgE levels, blunting of seasonal increases in such levels, and increases in allergen-specific IgG levels (particularly IgG4 [19]), and IgA [20]. Serum antibody concentrations seem to be determined more by the dose of allergen administered than the extent of clinical improvement [20]. Immunoreactive IgG populations include antibodies exhibiting wide ranges of clonalities and/or affinities. In contrast, functional assays of IgG are more likely to detect the proportion of circulating IgG that is biologically (and therefore clinically) relevant. For example, serum obtained after SCIT has been shown to inhibit allergen-IgE binding to B cells [21], an effect that is largely mediated by IgG4. This system has been used as an in vitro assay of the ability of "blocking" antibodies to inhibit IgE-facilitated antigen presentation.

Subcutaneous immunotherapy has been shown to decrease the numbers of effector cells at mucosal sites, both during seasonal allergen exposure [22] and after allergen challenge [23], and to reduce effector cell reactivity in vitro [24]. It has been suggested that allergic disease may be caused by a relative imbalance between the effects of T regulatory (Treg) and TH2 cells [25]. The former cells can be divided into "naturally occurring" thymus-derived CD4+ CD25+ cells, which are positive for the transcription factor Foxp3; and regulatory cells of IL-10-producing Tregs [26].

A recent Cochrane systematic review of SCIT to treat seasonal AR [27] showed that the approach was efficacious, as revealed by reductions in seasonal symptoms and the need for rescue medication, compared with placebo. Many controlled studies have shown that both SCIT and SLIT improve asthma symptoms in atopic asthmatic adults and children clinically sensitized to seasonal and perennial allergens [28–30]. Meta-analyses [31–33] of placebo-controlled trials in asthma patients suggest that small but significant improvements in symptoms and lung function develop upon active therapy, compared with placebo. The problem is that very few studies have explored whether, or under what circumstances, immunotherapy aids conventional anti-asthma therapy in terms of reduced drug consumption, improved lung function, or indeed any other outcome measure. In one such study [34], HDM SCIT administered for 3 years to adult atopic asthmatics sensitized them to mites slightly but significantly reduced "as required" bronchodilator usage, and increased lung peak flow compared with placebo, although the cumulative inhaled corticosteroid dosages, symptoms, lung volumes, and bronchial responsiveness to methacholine did not change.

Sublingual immunotherapy

Sublingual immunotherapy involves the regular self-administration and retention of allergen extract under the tongue for 1–2 min before the extract is swallowed. Systemic reactions and fatalities associated with immunotherapy were reported by Lockey et al. [35]. After that Cochrane meta-analysis including a total of 42 double-blind placebo-controlled studies showed significant

reductions in rhinitis symptoms and medication requirements were evident [36]. Recent systematic review with meta-analyses has demonstrated the efficacy of SLIT in children [37]. It is not yet clear whether SCIT and SLIT are of equivalent efficacy. Optimal regimens for administration of both types of treatment may be refined in future and, therefore, comparisons of their relative effectiveness will continue to evolve.

Mechanisms of sublingual immunotherapy

- Allergen immunotherapy provides an opportunity to study antigen-specific tolerance in humans [38].
- The ability of SLIT to elicit allergen-specific tolerance is linked to the peculiar biology of oral antigen-presenting cells. In the absence of danger signals, Langerhans cells, myeloid dendritic cells, and macrophages located in oral tissues, tonsils, and draining cervical lymph nodes are biased toward the induction of TH1 and IL-10-producing CD4D regulatory T cells, thus supporting tolerance as opposed to inflammation [39].
- Successful SLIT is associated with the decrease of allergen-specific CD4 TH2-cell responses (via either apoptosis and/or anergy) paralleled with the induction of TH1 cells (immune deviation) [40–42].
- In addition, SLIT also elicits IL-10-producing CD4+ Treg cells (immunosuppression) [40, 41, 43–48].
- The modulation of allergen-specific CD4+ T cell responses has a profound effect on antibody responses, as a consequence of alterations in immunoglobulin isotype switching linked with cytokines produced [49–51].
- During SLIT, an increase in allergen-specific IgE seric titers, before a progressive decline (after 6 months to 1 year of treatment) or a significant blunting of recall responses during allergen re-exposure is commonly observed [49–54].
- SLIT induces modest systemic changes consistent with those triggered by SCIT, but additional local mechanisms active in the oral mucosa and/or regional lymph nodes are likely to be important [38].

Effectiveness of immunotherapy

Subcutaneous immunotherapy

Few studies have explored the long-term efficacy of SCIT with aero-allergens. One randomized, double-blind placebo-controlled study examined the effects of cessation of grass pollen immunotherapy [55]. After 3–4 years of SCIT, no significant change in either symptom or medication score was evident during the subsequent three pollen seasons. The other studies were open in nature. One monitored 40 patients with asthma, treated with HDM SCIT for 1–8 years. Half relapsed in the subsequent 3 years [56], but the extent to which this reflects the possible loss and subsequent re-acquisition of clinical allergy to the HDM cannot be determined. The data suggest that 3 years of grass pollen SCIT afford benefits that persist for a further 3 years after discontinuation, whereas any potential long-term benefit after discontinuation of SCIT using perennial allergens remains to be determined.

Sublingual immunotherapy

SLIT may also have long-term effects. A double-blind, randomized controlled trial of grass allergen tablet immunotherapy in adults with moderate/severe persistent seasonal AR showed that 3 years of treatment resulted in an approximately 30 % reduction in symptoms and a 40 % decrease in the use of anti-allergic drugs; these reductions were maintained for 1 year after treatment cessation. A disease-modifying effect was also evident [57].

Indications for immunotherapy

Selection of patients for immunotherapy requires accurate identification of the underlying allergic trigger via a combination of clinical history taking, and skin and/or blood tests for allergen-specific IgE. Although IgE sensitization to additional inhalant allergens is not a contraindication, immunotherapy for one allergen is less likely to be effective if exposure to other allergens contributes to the ongoing symptoms. Initial management should focus on pharmacotherapy and allergen avoidance measures. Where such measures achieve adequate symptom control, there is no proven medical advantage in proceeding to immunotherapy. A clearer mandate for immunotherapy emerges when patients have persistent symptoms despite best practice use of anti-allergic medication. The decisions of a patient and his/her clinician to embark on immunotherapy should be founded on an understanding of the necessary commitment involved, as well as on the scope and effectiveness of immunotherapy used to treat the disease in question. Patients should be aware that immunotherapy with any allergen is unlikely to be curative; clinical trials typically show a 30–40 % reduction in symptoms, with a similar reduction in medication use, in the first year of treatment, although pharmacotherapy may control symptoms much more effectively when applied after immunotherapy. The available data also suggest that immunotherapy may afford long-term benefits after

discontinuation, particularly where treatment has been continuous over several years. Any benefit of immunotherapy for AR triggered by perennial allergens, particularly HDM, is less well established than the benefit afforded to patients allergic to seasonal allergens. Nevertheless, clinical trials have shown definite benefits provided that subjects are appropriately selected [58].

Considerations for initiation of immunotherapy (updated from the WHO Position Paper on Allergen Vaccines) [59–62]

1. Presence of a demonstrated IgE-mediated disease: Positive skin tests and the presence, in serum, of IgE specific for an allergen known to trigger clinical symptoms.
2. Proof that a specific sensitivity is involved:
   - Exposure to the allergen(s) confirmed by positive allergy tests associated with appearance of symptoms.
   - If required, allergen challenge with the relevant allergen(s) (optional).
3. Severity and duration of symptoms:
   - Subjective symptoms of rhinoconjunctivitis: patients should have symptoms marked in terms of both severity and duration.
   - For asthma: questionnaire data should not reveal uncontrolled asthma.
   - Objective parameters (for example, work loss, school absenteeism).
   - Pulmonary function tests in asthmatics (essential): Exclude patients with severe asthma.
   - Monitoring of pulmonary function.
4. Availability of standardized or high-quality vaccines.
   - Specific immunotherapy prescribed by specialists.
   - SCIT to be administered by physicians trained to manage systemic reactions if anaphylaxis occurs.
   - SLIT is administered at home and patients should be informed of the possible risks and how to control any side effects.
   - Patients with multiple sensitivities may not benefit from specific immunotherapy as much as will patients with a single sensitivity. More data are required.
   - Patients with non-allergic triggers will not benefit from specific immunotherapy.
   - It is essential, for safety reasons, that asthmatic patients should be asymptomatic at the times of injections because lethal adverse reactions develop more often in asthma patients with severe airway obstructions.
   - In asthmatics, the FEV1 upon pharmacological treatment should attain at least 70 % of the predicted value, for both efficacy and safety reasons.

Sublingual immunotherapy patient selection

To be eligible for SLIT, patients should have:

- SLIT is commonly used in 5- to 65-year-old patients [63].
- Patients are classically selected on the basis of a positive skin prick test and/or a positive IgE in vitro assay (using as a threshold of >0.7 kU/L specific IgEs) [64].
- SLIT with single extracts provides a clear symptom improvement, with a potential cumulative benefit when treating with the two-allergen extracts [65].
- Special SLIT indications exist in the following patients: Patients who remain uncontrolled upon optimal pharmacotherapy [severe chronic upper airway diseases (SCUAD)]; in whom pharmacotherapy induces undesirable side effects; who refuse injections; and who do not want to be on constant or long-term pharmacotherapy [38].

Contraindications to allergen immunotherapy

Very rare serious and fatal adverse reactions to SCIT have occurred in patients with uncontrolled or unstable asthma [66]. In United States practice, asthma is not considered to be such an important contraindication. Patients with asthma should be referred for treatment to a tertiary center. Allergen immunotherapy for rhinitis should not be initiated in patients receiving beta-blockers, as such drugs may enhance the end-organ cardiac, respiratory, and cutaneous effects of type-1 hypersensitivity reactions and render anaphylaxis difficult to treat [67–69]. Several contraindications for immunotherapy include comorbidities, such as autoimmune diseases and malignancies, concomitant drug treatments, particularly β-blockers and angiotensin-converting enzyme inhibitors, pregnancy, patient's age, the severity of asthma, allergen polysensitization and the period of starting the treatment [70]. A careful risk/benefit assessment should be undertaken in such patients. Although allergen immunotherapy has no known teratogenic effects, immunotherapy must not be initiated during pregnancy. However, patients who have not experienced

systemic events during maintenance therapy may be allowed to continue their treatment [71].

Allergen immunotherapy in children

Specific allergen immunotherapy is effective in children with moderate-to-severe allergic rhinitis, and who do not respond to environmental control or optimal medication. SLIT with a grass pollen extract is licensed in the United Kingdom for children aged 5 years and above [72]. However, only limited evidence supports the use of immunotherapy in children under 5 years of age, although both SCIT and SLIT have been employed in this age group [73]. SCIT [73–76] and SLIT [77, 78] improve AR symptoms. In children, the evidence shows that immunotherapy can prevent, or at least delay, the onset of asthma. In a controlled trial of subcutaneous pollen immunotherapy, improvements in AR symptoms lasted for at least 7 years after discontinuation of treatment [74, 75]. In the same study, a reduction in progression from rhinitis to physician-diagnosed asthma was evident (with an OR of 2.5 in favor of active treatment); this also persisted for 7 years. Two trials of subcutaneous HDM immunotherapy in monosensitized children provided further evidence of a disease-modifying effect, with prevention of the onset of new allergic sensitizations [79, 80]. In a single open study, sublingual grass pollen immunotherapy was associated with a reduction in the development of seasonal asthma during the 3-year active treatment period, and a reduced risk of new sensitizations [81]. Pre-seasonal, and pre- and co-seasonal treatment with seasonal allergens was also effective [82]. Subcutaneous cluster updosing is a safe alternative to conventional regimens of HDM and grass pollen administration; clinical efficacy is achieved sooner [83]. Ultra-rush updosing with sublingual drops, and also immunotherapy with tablets containing pollen extracts, may be well tolerated and effective [84].

Safety

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines on immunotherapy were the first to develop an evidence-based model [61, 62]. Adequately powered well-designed double-blind, placebo-controlled-randomized clinical trials (DBPC-RCTs) have been performed on both SCIT [85] and SLIT [86, 87] in patients suffering from pollen-induced AR. The efficacy of immunotherapy was confirmed in selected populations [88]. Practice parameters for immunotherapy have been published by the European Academy of Allergy and Clinical Immunology (EAACI) [89, 90] and the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology (AAAAI/ACAAI) [91]. SLIT is safer than SCIT, although severe reactions may occur rarely [92, 93]. SLIT is administered at home and patients should be educated on how to recognize and treat a reaction if it occurs. It is also important to explore the time course of severe reactions developing after immunotherapy [93].

Safety of subcutaneous immunotherapy

SCIT is safe when performed on selected individuals, in a specialist clinic with adequate facilities, by trained healthcare professionals. Patients treated with SCIT are at risk of both local and systemic adverse reactions but, in the vast majority of cases, the symptoms are readily reversible if they are recognized early and treated promptly. Recently, a standardized grading system for the reporting of systemic allergic reactions developing during SCIT has been developed by the World Allergy Organisation [94]. This should facilitate global standardized reporting of systemic reactions in future. Side effects may occur with all allergen preparations, including standardized extracts [85], allergoids [95], and recombinant allergens [96]. In a Cochrane meta-analysis of 2,007 patients undergoing SCIT for seasonal AR [27], 22 % on immunotherapy vs. 8 % on placebo experienced mild, grade II allergic reactions at some time during immunotherapy, and 7 % of immunotherapy vs. 1 % of placebo-treated patients had grade III allergic reactions (EAACI) [97]. In all, 0.72 % of patients (three) in the immunotherapy group vs. 0.33 % (one) in the placebo group suffered grade IV reactions. Adrenaline (epinephrine) was given to 3.4 % of participants (19/557 patients, equivalent to 0.13 % of the 14,085 injections) in the treated group vs. 0.25 % (1/404 patients, equivalent to 0.01 % of 8,278 injections) in the placebo group. There were no fatalities. Pre-treatment with oral H1 antihistamines during the induction phase reduced the frequency and severity of systemic side effects [98]. In a North American survey of events from 1990 to 2001, involving 646 practices, 41 fatal (20 directly and 21 indirectly reported by physicians) and 273 near-fatal reactions to SCIT were reported. The survey estimated that fatal reactions occurred at a rate of 1 per 2.5 million injections [99].

Safety of sublingual immunotherapy

The safety profile of SLIT appears superior to that of subcutaneous therapy in terms of the incidence of severe systemic reactions, the caveat being that such incidents typically occur away from expert care. Reported serious adverse effects such as anaphylaxis during sublingual treatment have been infrequent [100–103]. Most patients develop discomfort in the early phase of treatment;

oropharyngeal pruritus and angioedema are not uncommon. These symptoms may respond to antihistamines given on an ad hoc or prophylactic basis, and often settle as vaccine administration continues [104, 105]. Uncommonly, local reactions are sufficiently severe to cause treatment discontinuation. Other relatively rare adverse reactions include nausea and/or abdominal pain (particularly in children), rhinitis, conjunctivitis, headache, urticaria, cough, and bronchospasm [104–106].

As SLIT is self-administered, it is important to give patients and their carers clear information on the nature and likelihood of unwanted events, and simple written instructions on the steps to be taken if they arise, as well as advising that sublingual vaccines must be securely stored out of the reach of children. All patients should have access to telephone advice and opportunities to be seen at short notice. Antihistamines should be available to all patients. Where primary care practitioners agree to share the care of patients undergoing SLIT, all should be fully briefed about side effects and how to manage them [104–106].

Anaphylactic reactions after immunotherapy

Most safety data on allergen immunotherapy reactions were obtained in the 30 min following injection. As most serious systemic reactions to immunotherapy occur within this time, patients should remain in the physician's office/medical clinic for at least 30 min after injection [107].

Most systemic reactions occurred within 30 min after injection [108, 109]. Although some studies reported that up to 50 % of systemic reactions occurred after 30 min [110–112], almost all severe systemic reactions commenced within 30 min of injection [109, 110, 113]. In a review of 14 studies, the timing of systemic immunotherapy reaction rates was reported as greater or less than 30 min in 10 studies [108]. The other two studies reported systemic reaction times as averages with ranges; one reported an average time 20 min (range 1–60 min) and the other reported that six reactions occurred between 20 and 55 min. Few studies have provided comparative safety data on the incidence of systemic reactions in the first 20 min vs. the 20- to 30-min period. In the AAAAI fatal reaction and non-fatal reaction (NFR) survey (discussed above), 10 (77 %) patients with fatal reactions and 65 (96 %) patients with NFRs, for whom information on the timing of symptom onset was available, developed symptoms within 30 min of injection [114]. In an earlier AAAAI survey, 17 fatalities associated with allergen immunotherapy were reported over the years 1985–1989 [115]. Onset of anaphylaxis occurred within 20 min in 11 patients, within 20–30 min in 1, and after more than 30 min in 1. Four patients did not wait in the physicians' offices after injection, and the times of onset of their systemic reaction symptoms could not be determined.

Most manufacturers of extracts recommend a wait-and-see period of 20–30 min, or 30 min, after administration of immunotherapy. The EAACI recommends an observation period of 30 min after allergen immunotherapy injection [116]. Most safety data on allergen immunotherapy reactions refer to a 30-min window and, thus, 30 min remains the recommended wait period after immunotherapy injection. Patients should remain in physicians' offices/medical clinics for at least 30 min after receiving an injection, but longer waits are appropriate if directed by the physician.

Some physicians may request that those considered at increased risk of serious systemic reactions outside of the office/medical clinic should carry injectable epinephrine. Such patients should be instructed in the use of epinephrine to treat systemic reactions developing after they have left the physician's office, or the other location where the injection was given. The risks and benefits of continuing allergen immunotherapy in patients who have experienced severe systemic reactions should be carefully considered.

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