

# Allergen Immunotherapy: the Good, the Bad, and the Unknown

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Allergen immunotherapy was initially developed more than a century ago by Leonard Noon and John Freeman [1]. Grass pollen was the first allergen to be studied in 18 patients with hay fever. The two investigators laid the foundation for allergen immunotherapy by choosing a relevant allergen, using standardized allergen extracts, developing a protocol consisting of initial low doses followed by gradual increments in dose and interval, and performing repeated allergen challenges to monitor efficacy. A follow-up paper, published 3 years later, demonstrated that of 113 hay fever seasons, in 34 seasons (30%) the hay fever was cured, in 39 (35%) it was significantly reduced, in 27 (24%) it was slightly reduced, in 13 (12%) it was unchanged, and in 2 patients it was worse [2].

It took another 40 years for the first randomized placebo-controlled trial on allergen immunotherapy to be performed by Frankland [3]. He demonstrated that a whole grass pollen extract and its partially purified proteins were effective, as compared to an ultrafiltrate that contained no protein and to a phenol-containing diluent alone. Since then, numerous well-designed randomized controlled studies have demonstrated the efficacy of allergen immunotherapy in allergic rhinitis and asthma [4], and later on in stinging insect hypersensitivity [5]. The beneficial effects of allergen immunotherapy have been

demonstrated in several aspects, including the reduction of symptom scores, reduction of medication used, reduced response to allergen challenge, and improved quality of life in both children and adults [4]. The clinical benefits of allergen immunotherapy are accompanied by complex immunological changes. These include the generation of T regulatory cells producing inhibitory cytokines such as interleukin-10 and transforming growth factor-beta, an initial increase followed by decrease in specific immunoglobulin E levels, and a delayed increase in levels of allergen-specific IgG4 [6]. However, no consistent association was demonstrated for those immunological changes and the clinical response to treatment. The efficacy of allergen immunotherapy, which was initially demonstrated for grass pollen, was subsequently proven also for fungi, animal allergens, house dust mite, and cockroaches [4]. Furthermore, beyond the direct effect of allergen immunotherapy on the sensitivity to a particular allergen, there are additional long-term benefits with this form of therapy. First, the effect of allergen immunotherapy, on both clinical symptoms and medication use, might extend even after treatment is discontinued [7]. Second, the effect of allergen immunotherapy might extend beyond the particular allergen the patient is immunized for, thus preventing the development of new allergen sensitivities in mono-immunized patients [8]. Moreover, in allergic children with wheezing, allergen immunotherapy was demonstrated to prevent a subsequent development of asthma [9]. Still, despite a century of practice, many unanswered questions regarding allergen immunother-

lg = immunoglobulin

apy remain [10]. Although it is currently recommended that treatment continues for 3–5 years, optimal duration of therapy and whether a longer duration is beneficial remain controversial. In addition, some patients might have sustained remission even after discontinuation of treatment while others might relapse [4,7]. However, markers to identify patients who might relapse upon discontinuation of therapy are lacking.

In the study by Rottem et al. in this issue of *IMAJ* [11], real-life safety and efficacy of subcutaneous allergen immunotherapy was examined in northern Israel in 232 patients. This retrospective study, based on patient records and a computerized database, examined symptom score, quality of life and drug dispensing in patients receiving aeroallergen and stinging insect immunotherapy over a 5 year period. The study is limited by its retrospective nature and the lack of a control group. The authors found that 120 of the 135 patients (88.9%) who reached a maintenance dose exhibited complete or partial improvement, defined as a meaningful reduction in symptoms and increased quality of life as assessed by patients and physicians. A longer duration of treatment resulted in reduced symptoms, as 86.1% of those treated for more than 5 years compared with 60.5% of patients treated for 3–5 years reached complete resolution of symptoms. These findings highlight once more the potential benefit of allergen immunotherapy. Unfortunately, the controversies and yet unanswered questions were not examined in this study.

The beneficial effects of allergen immunotherapy are hampered primarily by its inconvenience. In the study by Rottem et

al., 62 patients (26.7%) dropped out primarily due to inconvenience in attending the allergy clinic to receive treatment (25 patients during build-up and 37 during the maintenance phase). Another limiting factor is the adverse effects, which include local and systemic reactions and in severe cases even anaphylaxis. In their study, the rate of local and systemic side effects was low and most systemic reactions were mild. However, some moderate-severe reactions were recorded. Local reactions occur frequently in the course of allergen immunotherapy in up to nearly 80% of patients and 4% of injections [12]. Still, the majority of these reactions are mild and patients are typically not bothered by them. Systemic reactions, although more rare, still occur [13]. In a 20 year survey of allergen immunotherapy, systemic reactions were observed in 5.2% of patients and 0.06% of injections during the first 10 year period, and in only 1.08% of patients and 0.01% of injections in the second 10 year period [20].

Rottem and co-authors found that local reactions during build-up predict local reactions during the maintenance phase. This is in contrast to a previous single-center retrospective study showing that local reactions and large local reactions were not predictive of similar reactions at the next injection [14]. More importantly, Rottem et al. found an association between local reaction in the build-up or maintenance phase and systemic reactions occurring in the same phase. This is an important finding as it might suggest that dose adjustments should be made in patients with local reactions to try and avoid subsequent systemic reactions. Dose adjustments after local reactions during allergen immunotherapy were indeed recommended in the past after a correlation between local and subsequent systemic reactions was suggested. Although several well-controlled studies performed later found no such association, patients with greater frequency of large local reactions ( $\geq 25$  mm) were indeed found to have a higher frequency of systemic reactions [15]. Rottem and team used a definition of  $> 20$  mm wheal for local reactions. This

definition partially overlaps with what others have previously defined as large local reactions. It could be, therefore, that patients experiencing a high frequency of large local reactions are at increased risk for subsequent systemic reactions, and that dose adjustments for these patients should be considered. Rottem et al. also found that systemic reactions during build-up are a risk factor for systemic reactions during maintenance. A previous prospective multicenter study has shown that there is a subgroup of patients who are at risk for systemic reactions. These patients contribute to up to 40% of systemic reactions [16]. Therefore, some patients with recurrent systemic reactions might need to discontinue immunotherapy or receive a reduced dose as long as the dose is high enough to prevent allergy symptoms.

No fatal reactions were documented in the study by Rottem et al. Previous retrospective surveys of members of the American Academy of Allergy, Asthma & Immunology, conducted before 2002, estimated that a fatal anaphylactic reaction to subcutaneous immunotherapy occurs in every 2 to 2.5 million injections. However, no fatal reactions were directly or indirectly reported from 2008 to 2011 [17]. In the previously mentioned 20 year survey of allergen immunotherapy, no fatal reactions were reported [13]. Possible risk factors for severe reactions during immunotherapy include uncontrolled asthma, injections administered during exacerbations of symptoms, high degree of hypersensitivity, use of beta-blockers, injections from new vials, and dosing errors [4]. The decline in fatal reactions and the fact that no such reactions were described in the study by Rottem et al. is encouraging.

New emerging modes of allergen immunotherapy are currently explored. Sublingual immunotherapy is the most advanced and is already in clinical use. SLIT involves placing an allergen extract under the tongue to allow absorption. The allergen should be taken daily, and the currently recommended length of treat-

ment, like SCIT, is 3–5 years. Although head-to-head studies are lacking, SLIT appears to be as effective as SCIT with fewer side effects [18]. Other new forms of allergen immunotherapy attempt to increase the immunogenicity and reduce the allergenicity of the extract by using adjuvants, Toll-like receptor agonists or modified extracts. Also, alternative routes of delivery, such as intralymphatic, epicutaneous and nasal immunotherapy, are being explored [19].

Oral immunotherapy is a new form of therapy offered to patients with food allergy. It is clinically available worldwide and in Israel [20]. Still, many consider this form of treatment experimental due to several unanswered questions, such as optimal duration of therapy, the risk for recurrence once treatment is discontinued, and the frequency of side effects. As discussed above, most of these questions remain controversial for subcutaneous immunotherapy as well, despite a century of extensive research and clinical use [10].

In summary, allergen immunotherapy is an effective treatment for allergic rhinitis, allergic asthma and stinging insect hypersensitivity. Although systemic reactions may occur, adverse effects are usually mild. Despite that, many avoid this form of therapy due to inconvenience. Several key questions remain unanswered despite the long-term use of this treatment. The study by Rottem et al. has several important observations, emphasizing the efficacy and safety of allergen immunotherapy in patients in Israel. The unanswered questions will require additional studies. Newer treatment modalities, some already in clinical practice, may preserve the beneficial effects of allergen immunotherapy while making it more readily accessible, allowing more patients to benefit from this form of therapy.

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SLIT = sublingual immunotherapy

SCIT = subcutaneous immunotherapy

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