

EDITORIAL

Specific allergen immunotherapy: time for alternatives?

Specific allergen immunotherapy (SIT) is a widely used therapeutic option for allergic diseases. It is highly effective in preventing anaphylaxis due to insect venom allergy which constitutes the only absolute indication for this mode of therapy. SIT is most widely used as therapy for respiratory allergies. In allergic rhinitis due to either seasonal or perennial allergens, SIT is used as a treatment alternative or adjunct to pharmacotherapy for patients with sensitivities to unavoidable allergens. Due to the risk of precipitating acute severe asthma or even anaphylaxis, the use of SIT in asthma is more controversial and is not a substitute for conventional pharmacotherapy. Notwithstanding, many well-conducted studies have demonstrated the efficacy of SIT in asthma and SIT is used as an adjunct therapy in carefully selected individuals with allergic asthma [1].

Conventional SIT comprises the delivery of incrementally increasing doses of allergen by subcutaneous injection to achieve a therapeutic benefit. To achieve efficacy a dose of approximately 5–20 µg of the major allergen needs to be tolerated with each maintenance injection that is then administered at regular intervals for a period of 3–5 years depending on the condition [2]. In some regions, where pollen counts are high, pollen immunotherapy may be given only pre-seasonally and discontinued through the subsequent pollen season [3].

The discomfort of repeated subcutaneous injections is a disincentive to conventional SIT, particularly in paediatric age-groups. In addition, the risk of systemic allergic reactions occurring in up to 10% of patients receiving SIT, has led to the exploration of alternative routes for administration of allergens [4]. There is accumulating evidence that the immune system is particularly programmed to induce tolerance to ingested or inhaled allergens ('mucosal tolerance') [5]. Intuitively this might be usefully applied to SIT where the introduction of allergens by the mucosal route ('local immunotherapy') can be employed to invoke regulatory immune responses, including T cell anergy or the induction of CD4⁺ T cell regulatory populations [6]. Such an approach might increase the effectiveness of SIT and diminish side-effects.

Alternative routes for the local administration of SIT have been attracting increased clinical and research interest in an attempt to improve patient acceptability and minimize the risk of serious adverse events. These approaches include bronchial inhalation, sublingual absorption and/or oral ingestion and nasal insufflation [7]. Local bronchial SIT has been disappointing with no significant clinical improvement in symptoms nor late asthmatic response to allergen despite inducing a reduction in the early bronchial response to allergen [8]. Adverse events, in particular bronchospasm, were concerning.

Sublingual immunotherapy (SLIT), which has become quite popular in central Europe, requires administration of allergen under the tongue for 1–2 min followed in some regimens by ingestion of the extract with gastric absorption. SLIT using

several allergens has proven efficacious in double-blind, randomised, placebo-controlled studies by improving symptoms and in some cases reducing medication use. Studies using *Parietaria* have revealed efficacy in reducing symptoms and medication use in adults [9–11] and children [12], as have studies in grass pollen-induced rhinitis and asthma [13–17]. SLIT has also been effective when used for treatment of rhinitis and asthma due to house dust mite sensitivity when administered in adults [18,19] or children [20,21] for 18 months or more. Two studies using SLIT in olive pollen sensitivity reported partial efficacy [22,23]. Moreover, there is some evidence from experimental models of increased gastrointestinal absorption of allergen when allergoid preparations are delivered by SLIT [24] with clinical correlates showing efficacy in well-conducted studies [25,26].

A feature common to these trials of SLIT is the high doses of allergen used, frequently 300 times the dose which would usually be delivered subcutaneously. Treatment is administered as frequently as daily or twice daily and side-effects appear to be minimal compared to placebo patients with no severe hypersensitivity reactions reported. However it is unclear whether sufficient allergen is absorbed by the sublingual route to consistently generate an immune response. A double-blind comparative study of sublingual vs. subcutaneous immunotherapy in seasonal allergic patients demonstrated no specific immunoglobulin (Ig)G or IgG4 antibodies after one year of the sublingual therapy in contrast to the conventional subcutaneous route [27]. In contrast, the double-blind, placebo-controlled study of sublingual-swallow SIT in patients with perennial asthma due to house dust mite allergy that showed objective improvement in lung function elicited increased levels of specific IgE and IgG4 [18].

The use of nasal routes of allergen administration for immunotherapy is another alternative to injection immunotherapy. Nasal-associated lymphoid tissue (NALT) and bronchus-associated lymphoid tissue (BALT) comprise a discrete component of the immune system with the capacity to induce immunity or tolerance. This has been particularly exploited in research involving animal models of autoimmune diseases where nasal administration of specified autoantigens can prevent the onset of experimentally induced autoimmune diseases and alter the progression of established diseases [28]. The administration of dominant T cell epitopes shows clear efficacy in some of these approaches [28]. In studies involving unfractionated allergen or discrete T cell epitope peptides, the timing, dose and structure of an administered allergen is critical to its success in inducing immune regulation, as is the genetic background of the animals used. Importantly there have been reports that some allergen dosage regimens can provoke a more potent pro-inflammatory response, indicating that delivery of allergens via the mucosal route is not without risk of inducing or exacerbating an inflammatory response [5,28].

In this issue of the journal, Winkler and colleagues report that an intranasal treatment regimen with a recombinant form of the major birch pollen allergen Bet v 1 decreased systemic allergic immune responses as well as local airway inflammation in mice sensitized to birch pollen via intraperitoneal inoculations [29]. Pilot experiments were performed to establish the optimal dose and frequency of treatment administration which occurred over 6 days. One week after the final intranasal application of allergen, an aerosol challenge with 1% birch pollen extract was performed on two consecutive days. This immunotherapy protocol resulted in a decrease in both allergen-specific IgG1 and IgE levels in serum in the actively treated animals with an accompanying decrease in skin test reactivity to intradermal Bet v 1. Assessment of T cell function by measurement of lymphoproliferation of spleen and pooled lung cells indicated decreased proliferation in response to Bet v 1 in the actively treated animals compared to controls. Spleen cell cultures and pooled lung cell cultures also secreted less interleukin (IL)-5, while no difference was observed in IL-10 levels. Eosinophils were decreased in broncho-alveolar lavage fluid.

Overall the results show a decrease in allergic inflammation in the lungs and lymphoid tissue following a schedule of intranasal administration of allergen in a previously sensitized animal. As such this study raises the possibility of using intranasal immunotherapy for allergen desensitization in humans, which may be effective locally in the nasal mucosa, but may also result in allergen tolerance systemically. The study also re-emphasizes the critical importance of allergen dose and route of administration for tolerance induction. This finding is consistent with the large number of studies in autoimmune diseases where the genetic background of the animals utilized plays a major role in determining response to treatment. This has particular implications for translating such research into a genetically diverse human population.

Carefully designed studies of local nasal immunotherapy (LNIT) have been performed in humans which show some evidence of efficacy although to date this approach has been limited for human use by a high level of unacceptable side-effects [30]. Seasonal rhinitis due to *Parietaria* has been treated with LNIT administered pre-seasonally, however, the effect was short-lived and probably required annual re-administration to maintain therapeutic benefit [31,32]. Efficacy has also been reported in placebo-controlled trials with a powdered grass pollen extract decreasing symptoms in actively treated patients during the grass pollen season and improving the threshold of nasal allergen challenge compared to control patients [33,34]. Additionally, LNIT administered in powdered form was effective in decreasing symptoms and nasal allergen challenge threshold in the treatment of perennial rhinitis due to house dust mite sensitivity [35]. In these studies side-effects were confined to local symptoms with no reported systemic allergic reactions.

The intranasal administration of T cell epitopes derived from Der p 1 has been shown to prevent primary sensitization to house dust mite allergens in naïve mice [36]. This suggests the potential use of intranasal immunotherapy as a vaccine to prevent the acquisition of sensitization. Evidence from this and other studies in autoimmune diseases also supports the efficacy of selected T cell epitope-based vaccines when administered by the nasal route.

The study by Winkler and coworkers [29], together with previous experimental and clinical trial evidence suggests that

local nasal immunotherapy holds promise as an alternative route of delivery for SIT. However several questions need to be answered in experimental models before promoting additional clinical trials of this mode of treatment. Firstly, the retention of dominant T cell epitopes in allergens or modified allergen preparations is critical to maximize their potency as tolerogens, and therefore their potential to induce clinical desensitization. Secondly, the potential for this mode of therapy to induce systemic allergic reactions, rhinitis or asthma needs to be decreased by allergen modification to abrogate IgE binding [3] or co-treatment with an agent such as anti-IgE [37]. Thirdly, previous studies highlight the importance of well-defined dosage regimens in promoting efficacy of local immunotherapy. Greater understanding of the mechanisms of allergen processing by dendritic cell subsets at different sites may allow further refinement of desensitization regimens [38].

Accumulating evidence of the efficacy of local SIT suggests pathways in which further studies of SIT might be usefully directed. As yet there is little evidence regarding the effects of local SIT compared to conventional SIT. Such evidence needs to be obtained in order to ascertain the relative benefits of local immunotherapy and thereby inform clinical decisions.

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J. DOUGLASS and R. O'HEHIR

Department of Allergy

Asthma and Clinical Immunology

Alfred Hospital and Monash University

Prahran Victoria 3181

Australia

E-mail: j.douglass@alfred.org.au