

Review article

Future developments in sublingual immunotherapy

The increasing prevalence of allergic rhinitis and its progression to asthma has severe implications for patients and health care systems in many countries. An ideal therapy is one that is effective not only against symptoms but also towards the natural progression of the allergic disease. Immunotherapy is recognized to achieve both these aims. Administration of allergens by the sublingual route, a modality with a very low rate of systemic reactions, is widely considered a treatment of choice. However, if it is to be universally accepted, more developments are required. Although, it is effective against grass and other seasonal pollens, further controlled trials are needed to confirm its efficacy against perennial allergens. Additional studies, particularly in paediatric populations, are needed to confirm its long-term effects on disease progression. New vaccine developments, which take into account the increasing understanding of the underlying immune mechanisms and that exploit molecular engineering techniques will create allergens that are effective, stable, risk free and easy to administer.

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The prevalence of IgE-mediated hypersensitivity has steadily increased over the past few decades from 5% to 30% (1). Consequently, in some countries as many as one in five of the adult population suffer from allergic rhinitis (2, 3). Although, not life-threatening in itself, up to 20% of people with allergic rhinitis go on to develop asthma as a natural progression of their disease (4). Current pharmacotherapy is effective in addressing common symptoms, such as sneezing, nasal discharge and congestion. However, although mainly satisfied with their conventional drug therapy, patients often wish to have a treatment that is also active in preventing progression to more serious complications (5).

Allergen-specific immunotherapy is considered to be the only treatment to combine both improvement of symptoms and alteration of natural history of the allergic disease (6). Conventionally administered by subcutaneous injection, it is now thought that sublingual immunotherapy (SLIT) might prove a better treatment modality than subcutaneous immunotherapy (SCIT), because its risk to benefit ratio is greater (7). This review explores the recent advances in SLIT and discusses the future developments that are necessary to confirm that this type of treatment will satisfy the needs of both patients and healthcare providers.

Meta-analysis indicates safety and efficacy of SLIT

To ensure that SLIT becomes accepted as a first-choice allergy treatment, further large-scale, controlled clinical

trials are needed to establish not only its safety but also its efficacy. Over the past 15 years at least 25 randomized, double-blind, placebo-controlled trials have been carried out to determine the efficacy and safety of SLIT (8). These have consistently confirmed the excellent safety profile of allergens administered by the sublingual route (8, 9). The efficacy results, however, lack such clear outcomes and, due to variations in trial procedures, can be open to interpretation.

Nevertheless, a meta-analysis performed on 22 double-blind, placebo-controlled trials involving 979 patients was able to conclude, despite the wide heterogeneity in scoring systems, SLIT significantly reduced both symptoms and medication requirements in allergic rhinitis, particularly when the allergy was because of pollen from grass and other widespread plants (2).

Many allergens have been tested in SLIT trials, including common perennial allergens, such as house dust mite and cat dander (2). The reductions in symptom and medication scores of house dust mite allergens failed to reach statistical significance in trials so far, but a clear trend for improvement in the treated group was noticed. However, despite these results, it should not necessarily be assumed that SLIT is efficacious only for the treatment of seasonal allergies. Studies with SCIT indicated that the duration of treatment was crucial for efficacy against the mite allergen. Such findings also appear to be true for SLIT, where improvements in symptoms were only seen after at least 2 years of therapy (10). The dosage of allergen used, as well as the duration of treatment, may be important for perennial allergen immunotherapy; from

the data available it is difficult to determine how much antigen was used in these SLIT trials (2), and it is possible that the dosage was simply too low to produce a statistically significant effect. The influence of dosage on SLIT efficacy is discussed in more detail later.

The long-lasting and disease-modifying effects of SLIT

The long-lasting effect of SCIT on the symptoms of rhinitis after treatment discontinuation is well documented (11). Similarly, SLIT also appears to have a sustained effect on rhinitis symptoms (4).

Several studies clearly indicate that SCIT can also prevent the onset of asthma in rhinitis patients thereby modifying the course of allergic disease (12, 13). Because of the relatively recent introduction of SLIT, there are few long-term confirmatory data available and, therefore, it is unclear whether it produces a similar duration of effect. There are data showing a reduction in the number of days with asthma symptoms with less need for beta-agonists and intake of systemic steroids, which suggests that SLIT may have an equivalent effect on the natural progression of allergy (10). This finding is supported by a recent prospective study in which 35 children, followed-up for 4–5 years after SLIT cessation, showed a reduced incidence of asthma compared with the control group ($P < 0.001$) (14). Likewise, Novembre et al. (4) also found that SLIT reduces the development of seasonal asthma in children with hay fever. More large-scale trials are necessary to confirm the efficacy of SLIT in altering the natural progression of allergic disease in paediatric populations because it is in this population that the clinical effects of immunotherapy are the most marked (15).

Allergen dosage

Another noticeable difference between published controlled trials of SLIT was in the amount of allergen administered. It is clear that, compared with SCIT, vaccination by the sublingual route requires more allergen (at least 50–100 times more) to reach similar levels of efficacy (6). One reason for this may be that current SCIT protocols include the use of an adjuvant (such as calcium phosphate or aluminium hydroxide), which is not incorporated in sublingual administration (16). Although, it has been suggested that reaching a threshold cumulative dose of allergen is important for successful SLIT, it is also possible that current vaccines do not target immune cells efficiently, most particularly dendritic cells. Thus, it is only with high-dose regimens that sufficient amounts of allergen are captured by sentinel dendritic cells within the oral mucosa. Therefore, this suggests that high-doses are critical for inducing a strong and long-lasting T-cell response.

Numerous studies have shown that the dose of antigen has an effect on T-lymphocyte stimulation. One of the

major aims of immunotherapy is to reorient the pattern of T-cell specific response from T helper (Th) 2 to Th1 patterns in atopic patients. Exposure to high doses of allergen during immunotherapy may promote the trafficking of Th1 over Th2 cells by selectively modulating the surface expression of adhesion molecules and chemokine receptors on these cells. However, the influence of antigen dosage on regulatory T cells is unclear at present, and this area of immunotherapy has become of interest because of the ability of regulatory T cells to down-regulate both the Th1 and Th2 response (16).

Regulatory T cells are poorly reactive with antigen *in vitro*, so, strong antigenic stimulation may be necessary to induce proliferation and activation of this group of T cells. Importantly, high doses of antigen will provide a strong initial burst of T-lymphocyte stimulation, leading to the establishment of T-cell mediated immune memory and long-term tolerance (16). Future SLIT vaccine development should therefore take into account both clinical observations from controlled trials and also the latest experimental data on the mechanism of the action of immunotherapy.

Future prospects for SLIT development

In the majority of cases, SLIT is administered in the form of drops with only occasional use of tablet formulation (2). The change from drops to tablet formulation could provide a major advance in improvement in SLIT dosing and vaccine development, which has been otherwise limited by drop administration. From a pharmacological view point the two formulations are equivalent because, in the tablet, the allergen is released unchanged as the tablet dissolves (17). However, tablets are easier to take than drops, which should increase compliance and may, in turn, lead to lower doses of allergen being required (17). In addition, the tablet formulation increases the stability of the product and ensures standardization of doses.

Recent trials of grass allergen tablets have demonstrated the safety profile of this formulation in high doses (18–20). The efficacy of grass allergen tablets in symptom prevention and reducing medication usage was recently demonstrated in asthmatic patients with rhinoconjunctivitis (18, 20).

The current understanding of the immune mechanisms underlying allergen-specific immune responses can be harnessed to optimize allergen presentation for SLIT. Added to this, the power of molecular engineering and innovative antigen delivery systems should offer the opportunity to design rational second-generation recombinant vaccines specifically tailored for the sublingual route. Such vaccines would be explicitly designed to elicit a strong allergen-specific regulatory T-cell response without exacerbation of the potentially dangerous Th2 allergic response.

While today's sublingual vaccines are based on natural biological extracts, new vaccines are being developed which rely upon selected recombinant allergens (21). There are almost unlimited possibilities to engineer the type of molecules designed to elicit the immune pathway required (22). The best approach for immunization by the sublingual route may be to rely on recombinant allergens presented in their most native conformation, which would allow maximal IgE-mediated targeting and capture of allergens by the Fc portion of IgE (Fc-epsilon receptor-type I, or FcεRI+) dendritic cells in the oral mucosa of atopic patients (16). It is the stimulation of oral dendritic cells through IgE-dependant epitopes that elicits directly the Th1 or regulatory T-cell response, and this action is probably unique to the oral mode of administration.

Other vaccine preparation strategies should perhaps consider the use of biological or synthetic adjuvants and formulations to improve allergen presentation to oral

Langerhans cells. This approach would help to enhance SLIT efficacy, reduce allergen dosage and simplify immunization schemes. Regulatory T-cell adjuvants specifically designed for SLIT might be used to target the allergen to Langerhans cells. They would be used to trigger the production of interleukin-10 and/or transforming growth factor-beta by antigen-presenting cells, while enhancing their capacity to migrate to local lymph nodes to ensure T-cell priming. They could also help orientate T-cell responses towards regulatory T cells by engaging surface particular receptors, such as ICOS, CD46 or specific Toll-like receptors (16).

These molecularly defined vaccines may also help identify immunological markers of clinical efficacy, which would, in turn, be useful in the development of future vaccines, with the long-term goal of tailoring treatment to patient-specific antigen patterns.

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