Allergy 2006: 61 (Suppl. 81): 20–23

Review article

Sublingual immunotherapy in the treatment of adult allergic rhinitis patients

Sublingual immunotherapy (SLIT) was accepted for clinical use by the medical community only 15 years after the first controlled trial published. The acceptance of SLIT has been driven by the evidence base of a large number of clinical trials confirming the efficacy and a recent meta-analysis study. Although SLIT is self-managed by the patient, this does not generate problems with compliance. The safety profile, assessed in clinical trials and postmarketing surveillance studies, is satisfactory with no reports of systemic adverse reactions. New data are available on the persisting, long-lasting effect of SLIT and on the association with the prevention of asthma in paediatric patients. However, there is only indirect evidence for such persistence and duration of effect in adult patients. Key priorities for further investigation are the mechanisms of action, the efficacy in asthma, the cost/effectiveness and the identification of those patients who will achieve the maximum benefit with SLIT.

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Key words: adults subcutaneous immunotherapy; allergic rhinitis; efficacy; safety; sublingual immunotherapy.

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Introduction

Allergic rhinitis, which is characterized by sneezing, watery nasal discharge, nasal obstruction and itching, affects approximately 20% of the adult population in the Western world (1). Although not normally serious, the disease impacts the quality of life of the sufferer, affecting work and school performance and altering their social life. There is also a considerable economic factor involved because of the costs incurred both from lost productivity and prolonged pharmacotherapy (2). In addition, if left untreated, allergic progression to asthma may occur.

Treatment of allergic rhinitis

Allergen avoidance is always the first-line treatment for allergic rhinitis and, although not completely effective, it may reduce the need for further intervention. The treatment strategy for allergic rhinitis is based on anti-inflammatory drugs and/or specific immunotherapy. The relative advantage of these two interventions is unknown but, theoretically, combining interventions with different modes of action should improve the clinical outcome (2). However, compliance with pharmacotherapy among adult allergy patients is generally low because this otherwise healthy population is disinclined to take too many drugs, particularly steroid preparations (3).

An advantage of using immunotherapy is that it can significantly reduce the severity of allergic disease and the need for anti-allergic drugs, which may lead to improvements in the quality of life of atopic patients. Many rhinitis patients have minimal persistent inflammation during allergen exposure in the lower airways. This inflammation is often under-diagnosed and therefore inadequately treated. Specific immunotherapy might, if used in monotherapy, improve inflammation and disease progression. Therefore, the benefits of instituting specific immunotherapy early in the evolution of the disease, while the severity of the disease remains modest and when the possibility of preventing deterioration to asthma is at its highest, should be considered (2).

Early development of immunotherapy

Early attempts at immunotherapy from 1911 used the subcutaneous route of administration, and for many decades this route continued to be the major mode of administration of immunotherapy, albeit in a substantially empirical form. However, in 1986, the British Committee for the Safety of Medicines reported 26 deaths caused by subcutaneous immunotherapy (SCIT), and raised serious concerns about the safety and the risk/benefit ratio of SCIT. As a consequence, the interest in noninjection routes (formerly called alternative routes) rapidly increased and many trials with oral and nasal

immunotherapy were published in the 1980s. Since the first controlled study (4), the sublingual route appeared the most promising alternative to the traditional SCIT. In 1998, after an extensive review of the literature, a panel of experts of the World Health Organization concluded that sublingual immunotherapy (SLIT) was a viable alternative to the injection route, and that its use in the clinical practice in adults is justified (5).

From an historical perspective, SLIT represents a special case. Whereas SCIT required more than 80 years to achieve recognition together with clearly defined indications and contraindications (5), only 20 years passed between the first double-blind clinical trial of SLIT (4) and its acceptance by the regulatory authorities and medical community (2, 5). Currently, SLIT is marketed and used in routine clinical practice in many European countries and standardized vaccines are available.

Indications for SLIT

The Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines suggest that SLIT may be indicated in carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen, house dust mite or cat allergy. Patients eligible for selection may include those insufficiently controlled by conventional pharmacotherapy, patients who have presented with systemic reactions during SCIT, and those with poor compliance or refusal to have injections (2). The Global Initiative for Asthma (GINA) state that specific immunotherapy, directed at treating an underlying allergy to grass and other pollen, domestic mites, animal dander, or *Alternaria* spores, may be considered when avoiding allergens is not possible or appropriate medications fail to control asthma symptoms. There is no specific mention, however, of the alternative methods of administering specific immunotherapy (6).

There is some evidence that the results of SLIT are less marked in adult patients compared with patients under 18 years (7). This raises the question as to whether the indication for SLIT should only extend to adult patients with pollen-induced rhinoconjunctivitis who are unable to tolerate SCIT, perhaps because of adverse side effects. Nevertheless, some solid scientific evidence is available for SLIT in adults. Looking at the literature, there are more than 50 controlled trials of SCIT and 32 of SLIT but, in general, the SLIT studies are of better methodological quality compared with SCIT trials. In addition, the safety aspects of SLIT have been specifically addressed since its introduction in clinical practice. In addition, a double-blind, double-dummy, controlled trial in patients allergic to birch pollen, provided evidence that no significant difference exists between SLIT and SCIT in terms of symptom improvement and rescue medication use (8). In this trial, SCIT was slightly more effective than SLIT, but with a significantly greater occurrence of side effects. Indeed, there are some other comparative trials of SLIT and SCIT (9, 10) that confirm the equivalence of the two routes, but these studies have methodological biases and cannot be considered conclusive.

Compliance with SLIT

Another important issue is compliance because SLIT is self managed at home by the patient. Classical treatment for SLIT, as with SCIT, involves a build-up period, followed by a maintenance phase where the vaccine is taken daily or on alternate days, according to the manufacturer's instructions. The administration is usually continuous for perennial allergens and pre-seasonal or pre-co-seasonal for pollens.

It is generally supposed that the adherence to treatment is optimal with SCIT that is given by the doctor in his office. However, data from the literature do not support this belief, probably because the inconvenience, discomfort and side effects lead to a high nonadherence rate (11). By contrast, the randomized study by Marogna et al. (7) found that the majority of patients comply with SLIT. In this study in outpatients with respiratory allergy, adherence was calculated from the amount of allergen left in returned vials on follow-up visits. The volume of extract used by each patient was recorded on a scale from insufficient ($<40\%$) to excellent ($>80\%$; Table 1) (7). It would appear, therefore, that although it is difficult to monitor 'in real-life situations', compliance with SLIT regimens is satisfactory (7, 12), probably due to the ease of use and the scarcity of side effects.

Safety and adverse events with SLIT

There is robust evidence to support the excellent safety profile of SLIT. In more than 20 years of clinical trials and use, no severe or life threatening event or fatality has ever been reported (13). Moreover, postmarketing surveillance studies of SLIT-treated adults demonstrated that, overall, side effects occurred in $<10\%$ of the patients and <1 per 1000 doses (14).

Pooled data from 472 adults in eight double-blind, placebo-controlled trials in France, Italy and Greece

Table 1. Adherence to prescribed sublingual immunotherapy treatments over 3 years

Adherence	Number (%) patients ($n = 271$)
Excellent (>80%)	195 (72)
Good (60–80%)	49 (18)
Poor /insufficient (>40%)	27 (10)

Data pooled from six studies; adapted from André et al. (15).

Table 2. Average number of reported adverse events (AEs) in adult patients

AE	SLIT group, average number (%)	Placebo group, average number (%)
Skin	9 (3.2)	8 (3.1)
Mouth	40 (13)	3 (0.8)
Rhinitis	9 (4.6)	3 (2.6)
GI	27 (7.5)	9 (3.6)
Wheezing	8 (1)	15 (2.8)
Conjunctivitis	1 (0.16)	1 (0.16)
Laryngeal oedema	1 (0.16)	0 (0)
Aphthous ulcers	1 (0.16)	0 (0)
Headache	0 (0)	4 (1.3)
Muscle spasm	1 (0.16)	0 (0)

Data adapted from Marogna et al. (7, 15).
SLIT, sublingual immunotherapy.

showed the number of adverse events in those receiving active treatment was 39% compared with approximately 23% in the placebo group. These adverse events were for the most part minor, nonspecific and mild systemic reactions, and were never major systemic or anaphylactic reactions (Table 2) (15). Drop-out while on active treatment was recorded in 14 adult patients compared with 10 patients on placebo. The major reasons for stopping treatment were repeated buccal and abdominal complaints. These are the organs in direct contact with the allergen and this reaction is not unexpected. The development of these complaints in approximately one-third of patients is reminiscent of the local cutaneous reactions (erythema < 5 cm in diameter) at injection site in SCIT, which is considered acceptable (15). Indeed, the most frequent side effects with SLIT are the oral itching/swelling that usually disappears after the first doses, followed by gastrointestinal adverse events, such as stomach-ache, nausea and diarrhoea. These latter side effects seem to be at least in part dose-related, whereas there is no clear evidence for a dose-dependence of the other local or systemic adverse events (16).

Does SLIT have a long-term effect on disease progression in adults?

Because of long history of SCIT in clinical use, there are several well-documented characteristics of SCIT that still need to be confirmed for SLIT. One such characteristic is the persistence of treatment effect after treatment discontinuation. This effect has been repeatedly observed for the injection route (17) but, to date, only a single SLIT study has demonstrated a 5-year persistence of effect, and this study was performed in children (18).

Indirect evidence for a long-lasting effect with SLIT in adults was provided by studies that showed a decrease in incidence of asthma in SLIT-treated patients. For instance, a study of 136 patients with grass-pollen rhinitis and mild asthma found significantly less asthma attacks in the SLIT group than in the placebo group (19). In addition, compared with the placebo group, the SLIT group used less medication, including antihistamines, betamethasone and steroids at peak pollen count. This suggests that SLIT treatment modified the systemic immune response.

Significant improvements in conjunctivitis symptoms and prevention of asthma symptoms have been seen in other grass-pollen studies (20). A review of eight studies showed that the number of asthma attacks in the actively treated groups was lower than in the placebo groups, which indicates that SLIT is effective in reducing asthma attacks in allergic patients with moderate asthma (15). Serum IgG4 and IgE increased in these studies but there was no correlation with clinical assessment (19).

Further evidence of systemic immune response modification can be inferred from skin test measurements following SLIT. One study found 5.9% of SLIT patients had one or more new skin-test reactivities compared with 38% of patients in the placebo group. This finding, coupled with the dramatic decrease in patients positive to the methacholine challenge, led these researchers to the conclusion that SLIT is acting as a biological response modifier (7).

Conclusion

Use of SLIT to treat allergic rhinitis is supported solid experimental and clinical evidence but there is potential to improve SLIT further. The priorities for improvements include the definition of the optimal dose (and the dose–response relationship), and the identification of the patients who will achieve the maximum benefit with SLIT. In parallel, a more detailed knowledge of the mechanisms of action would lead to improved efficacy and safety. From a clinical and practical point of view, there is an increasing interest in simplified and/or accelerated up-dosing regimens. Therefore, future controlled studies are needed to elucidate the mechanisms underlying the effectiveness and the persistence of efficacy of SLIT in adult patients.

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