SUBLINGUAL IMMUNOTHERAPY: SAFE ALLERGEN IMMUNO-MODULATION BEYOND THE SPECIALISED CENTRES

There is increasing interest in sublingual immunotherapy around the world.

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The oral route for the administration of allergen immunotherapy has been explored since the early 1900s. With the development of purified and well-characterised vaccine extracts in 1998 the World Health Organization (WHO) and the European Association of Allergy and Clinical Immunology (EAACI) approved the use of sublingual immunotherapy (SLIT) for selected allergic diseases based on the publication of double-blind placebo-controlled studies, which confirmed efficacy and safety.[1]

Since 1998 there has been a worldwide surge in interest in SLIT, because it can be administered by allergy specialists and non-specialists and is particularly suitable for the administration of allergen immunotherapy in developing countries where specialist facilities in the field of allergy are often non-existent.

Immunotherapy is currently the only treatment modality which can alter the natural history of allergic diseases and, in well-selected patients, effect a cure. This has been firmly established for patients sensitive to bees and more recently via the sublingual route for patients suffering from house dust mite and grass pollen allergies.

The sublingual route is also effective for the treatment of asthma and reports of its effectiveness for the suppression of latex allergy and certain food allergies (e.g. kiwi fruit anaphylaxis) emphasise the power of SLIT as a potential new means of immunomodulation for life-threatening allergies.

MODE OF ADMINISTRATION

SLIT involves the daily administration of incremental amounts of a purified allergen which is held under the tongue for 2 minutes and then swallowed. A maintenance dose is usually achieved within 4 weeks and the allergen may be administered as drops, oral sprays or a rapidly dissolving tablet.

Maintenance is continued for 3 years and treatment can be continued throughout the pollen seasons without dosage reduction in pollen-sensitive individuals. Using I^{125} - labelled purified parietaria allergen (Parj1) Bagnusco *et al.*[2] found that allergen was retained up to 40 hours in the oral mucosal and that native allergen was not detected in the blood stream after swallowing the drops. The oral dendritic cells retain the allergen and Fcε receptor-bearing cells in the oral mucosa may be important in the induction of tolerance to allergen during SLIT.

Phases of tolerance induction

Clinical observations and recent immunological studies suggest that the long-lasting allergen tolerance achieved over a period of 3 - 4 years appears to be occurring in several phases, which may be invoking different immunological mechanisms, either simultaneously or sequentially, and possibly related to dosing.
The cumulative doses of allergen eventually given during a course of SLIT are up to 375 times greater than the total doses given during a course of subcutaneous immunotherapy (SIT).

Oral tolerance

The first phase is oral tolerance which occurs within days or weeks of initiating SLIT.

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Sublingual immunotherapy involves the daily administration of incremental amounts of a purified allergen which is held under the tongue for 2 minutes and then swallowed.

Patients who initially react to the sublingual allergen with oral itching report that the itching goes away and even higher doses are tolerated without any local clinical effects. This loss of oral reactivity occurs long before any demonstrable relief of nasal or asthma symptoms is observed.

Short-lived tolerance

The next phase appears to be an intermediate phase of short-lived tolerance and is typically observed in patients receiving pre-seasonal SLIT for pollen allergies. In these patients, within 3 months of initiating SLIT, a reduction in seasonal symptoms is achieved. A similar acquisition of significant protection and tolerance to latex[3] allergen has been reported within 3 months of SLIT.

Long-lasting tolerance

A late phase of long-lasting tolerance is achieved after 2 - 4 years of SLIT, typically for perennial allergies (house dust mite), manifesting as asthma and/or rhinitis, but also for seasonal allergies. Tolerance is sustained for as long as 10 years after SLIT has been discontinued.

In addition there is currently some debate as to whether SLIT activates the same immunological mechanisms to induce tolerance, as has been observed during SIT. In Table I[4-6] recently published immunological changes observed during the three clinical phases of SLIT are listed.

An attenuation of certain Th2 responses appears to be induced early, resulting in early-reduced mast cell responses to allergen. A reduction in late-phase responses and immunoglobulin subclass switching seems to occur later and may be dependent on the cumulative total allergen dose administered.

Table I. **Changes on inflammatory markers during SLIT**[8]

A	Early (6 months)	Fall in serum ECP[4] Fall in IL-13[4] Increased PHA-stimulated IL-12 Increased Der p 1-stimulated IFNγ
B (10-12 months)	Intermediate	Fall in nasal allergen-specific IgE[5] Reduction in nasal tryptase levels[5]
C	Later (>18 months)	Reduction in late-phase SPT responses (p - < 0.003)[6]

ECP = eosinophil cationic protein; PHA = phytohaemagglutinin;
Der p1 = dermatophygoides pteronyssinus antigen 1;
SPT = skin prink test; IL-12 = interleukin 12;
IL-13 = interleukin 13.

Some studies show that the immune responses to SLIT are similar but weaker than those observed during SIT.[6,7] It is possible that the utilisation of the mucosal route by SLIT may envoke additional and more powerful immunosuppressive mechanisms, yet to be identified.

Long-lasting protection resulting from SLIT has been confirmed by Di Rienzo *et al.*[9] After a 3 - 4-year treatment period patients were still protected 5 - 10 years later and a dramatic reduction in treatment requirements for asthma was sustained.

EVIDENCE-BASED CLINICAL INDICATIONS FOR SLIT

Rhinitis

The results of 23 randomised SLIT trials were recently summarised in a Cochrane meta analysis of 22 of the studies[10] involving 970 patients, which has confirmed that SLIT is effective in reducing both the symptoms of allergic rhinitis and allergy medication.

Mild asthma in children

SLIT is also effective for the treatment of mild-to-moderate asthma in patients who are monosensitive to mites, particularly children. In a study by Pajno *et al.*[11] 24 mild-to-moderate asthmatics who were monosensitised to house dust mite received vaccine or placebo for 2 years. There was a significant reduction in asthma symptoms and the use of asthma medication in the actively treated group, which was only seen in the second year of treatment.

When assessing efficacy of a new therapy such as SLIT it is important not to compare the magnitude of the clinical improvement with that of SIT. A recent randomised, placebo-controlled double-dummy study comparing subcutaneous with sublingual pollen immunotherapy over a 3-year period found that the clinical efficacy was not significantly different from SIT – only local side-effects were noted in the SLIT group, whereas SIT resulted in a few serious systemic side-effects.[12]

Allergic conjunctivitis

Efficacy has also recently been demonstrated in 60 adults with severe house dust mite-sensitive perennial allergic conjunctivitis. This was demonstrated by a significant increase in the antigen concentration required to obtain a positive conjunctival challenge test with house dust mite allergen after 18 months of SLIT.[13]

Experimental use

Recently there have been some exploratory studies investigating the efficacy of SLIT for latex and fruit (oral) allergy. A small study[3] of 24 patients provides evidence that within 3 months the 12 subjects who underwent desensitisation via the sublingual route showed significant improvement in symptom scores and could tolerate latex exposure, wear latex surgical gloves and undergo gloved medical procedures without any symptoms.

In another study successful sublingual desensitisation was demonstrated in a patient with a severe anaphylactic reaction to kiwi fruit.[12]

SIDE-EFFECTS OF TREATMENT

Over the past 10 years the safety record of SLIT has resulted in this form of immunotherapy becoming accepted and used in specialised centres and it is a preferred therapy beyond specialised centres worldwide. SLIT is currently a therapeutic option in Europe, South America, South East Asia (e.g. Malaysia), southern Africa and Australia.

Although many thousands of patients have received SLIT worldwide, serious systemic side-effects have never been reported. Reported side-effects from published studies fall into the following eight groups: lip, mouth and tongue irritation, eye itching, gastrointestinal cramping, rhinitis, asthma (mild and easily reversible using a bronchodilator), urticaria, angioedema, and other (non-specific).

The safety of sublingual swallow immunotherapy was investigated by Andre *et al.*[14] Eight double-blind, placebo-controlled studies carried out in France, Italy and Greece involving 690 subjects receiving the Stallergenes SLIT vaccines were reviewed.

In these studies only mild adverse events were found and they occurred in both placebo and actively treated groups in both children and adults. Unusual events mainly involved the buccal cavity (61 in SLIT and 13 in placebo) and the gastrointestinal tract (47 in SLIT and 15 in placebo).

Interestingly, however, wheezing was more frequent in placebo-treated subjects. In most cases the reported side-effect occurred only once. Analysis of the cases dropping out of the studies revealed that the main causes were buccal phenomena and abdominal pain.

In another post-marketing survey by Di Rienzo *et al.*,[15] 268 children aged 2 - 15 years who received ALK-Abello vaccines were studied. SLIT had been administered between 3 months and 7 years (mean 36 months) involving 96 000 doses of the extracts. Overall, mild side-effects (oral itching) occurred in 3% early in the course of treatment.

Seven systemic side-effects occurred, including abdominal pain, conjunctival itching and rhinitis. One of these required specific treatment. One case of urticaria requiring antihistamine treatment was reported. Rhinitis as a side-effect always occurred within 30 minutes of vaccine administration and all the others occurred after 30 minutes. The outcome of SLIT was judged to be excellent or good by 80% of the patients.

Although SLIT has been found to be safe in mild-to-moderate asthmatics included in the published trials, there are no studies of SLIT in severe asthmatics. It is therefore recommended that asthma should be optimally controlled pharmacologically before commencing SLIT. SLIT is therefore given as a combination therapy with the usual asthma medications with a view to modifying the natural history of the disease, reducing asthma medications and effecting a cure.

Co-seasonal immunotherapy also reduces the risk of developing asthma after 3 years in children with allergic rhinoconjunctivitis.[16]

SELECTION AND FOLLOW-UP

- Sublingual immunotherapy is effective if patients are carefully selected. Skin tests or radioallergosorbent tests (RASTs) should be done to confirm monosensitivity to either house dust mites or grass pollen.
- In South Africa, a 50% Rye/50% Bermuda grass mix is ideal for most pollen-allergic patients.
- Patients with autoimmune diseases, severe asthma or other serious medical conditions, especially those who have coronary artery disease or hypertension and are on beta blockers, are not suitable. Pregnancy is not a contraindication to continuing immunotherapy once initiated.
- Patients need to be able to measure improvement. This encourages compliance and justifies long-term use over 3 years.

Patients should maintain telephonic contact with their medical practitioners, particularly in the first month of SLIT, as the treatment is given at home. Baseline symptoms and allergy and asthma medications should be carefully recorded in the patient's clinical notes and reviewed at 1 month and then at 3-monthly intervals. A diary card is useful to document side-effects and reduction in medication requirements.

It is also informative to record quality of life issues at the 3 - 6-month follow-up visits to encourage adherence to medication.

In a recent study of 500 patients with rhinitis and/or mild intermittent asthma, randomised to receive SLIT or pharmacological treatment, adherence was found to be > 80% in 72% of patients, > 60% in 18% and < 60% in 10%. Interestingly, the rate of occurrence of new sensitisations was 5.8% in the active group and 38% in the control group and the prevention of asthma in children with allergic rhinoconjunctivitis has been demonstrated.[16]

References available on request.

ADDENDUM

Note. Although SLIT vaccines are widely used in South Africa, permission must be obtained from the MCC on a named-patient basis until the new SLIT vaccines are registered (hopefully in the near future).

IN A NUTSHELL

Immunotherapy is the only treatment modality that can alter the natural history of allergic diseases.

SLIT is an effective and safe new treatment for allergic subjects with monosensitive grass pollen or mite allergies and is given at home.

Evidence-based reviews (Cochrane) confirm both efficacy and safety of SLIT in children and adults.

The effects of SLIT are sustained for up to 10 years after discontinuation.

SLIT prevents the progression of rhinitis to asthma and the development of new allergic sensitisations.