

Oral, Nasal and Sublingual Immunotherapy: Do They Work, Are They Safe?

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General aspects

Since the first documented empirical attempt (1), the subcutaneous administration of allergens (allergen-specific immunotherapy, SIT) resulted in effective relieving symptoms of hayfever and asthma; therefore, SIT was subsequently largely prescribed both in Europe and USA. Actually, attempts to give the allergenic extracts by different routes had been made: oral route (2), bronchial route (3), intranasal route (4) and sublingual route (5). These approaches have remained anecdotal and of speculative interest only, because the use of the subcutaneous route was widespread and well supported. In 1986, a detailed report of 26 deaths due to SIT was published, thus raising serious concerns about the safety and the risk/benefit ratio of this treatment (6). Although the majority of life-threatening events resulted to be avoidable (7), the interest in the non-injection routes for immunotherapy rapidly increased, and a large number of clinical trials were published within a few years. In fact, the non-injection routes have the primary aim of minimizing the risk of adverse events.

In 1998, a panel of experts of the World Health Organization, based on an extensive and critical review of the literature, concluded that both sublingual (SLIT) and local nasal (LNIT) immunotherapy were viable alternatives to the injection routes and that their use in the clinical practice was justified (8). These conclusions were further confirmed in a position paper prepared by the European Academy of Allergology and Clinical Immunology (EAACI) (9).

Clinical efficacy and safety

The pure oral route (OIT), with the allergen immediately swallowed, seemed to be poorly effective (only two studies out of nine reported significant benefits), despite

some immunological effects. In some studies, the oral route gave no effects, mainly gastro-intestinal. The bronchial route gave no effects. Therefore, the clinical use of these routes is not recommended (8,9).

The efficacy and safety of LNIT in a blind placebo-controlled trial were evaluated by reducing nasal symptoms. Nevertheless LNIT is a non-injection technique (practically painless). Moreover, LNIT is a progressive treatment (11) and there may be a risk of progression. LNIT is progressive and long-term schedules have been proposed. LNIT is patient-friendly. LNIT is a treatment for pollinosis. LNIT is virtually devoid of side effects. LNIT is reported only in one study. LNIT is a technique.

SLIT (extract kept in the mouth) has recently appeared to be a promising alternative. It has been extensively studied from different points of view. A paper (9) published in 1998 reported 20 studies, most of them

Almost all the controlled trials showed a reduction of allergic symptoms and a significant improvement of quality of life of patients. In a recent study, it was demonstrated that SLIT (5 yrs) which is similar to SIT.

SLIT resulted to be a safe treatment. No fatal adverse events were reported. In controlled trials were conducted. The occurrence of adverse events. In a recent review, the incidence of adverse events ranged between 0% and 10% (18), the available data on the safety of SLIT even in a long-term study.

Some studies attempted to compare SLIT and traditional SIT. In a rigorous criterion, SLIT was found to be comparable to SIT. In a study comparing SLIT and subcutaneous immunotherapy, SLIT was found to be comparable to SIT.

some immunological systemic changes induced by OIT could be seen. Moreover, in some studies, the oral administration of high doses of allergen provoked untoward effects, mainly gastrointestinal. Also, in the two randomized studies available, the local bronchial route gave inconclusive results, but displayed a quite high rate of side effects. Therefore, the clinical routine use of oral IT and local bronchial IT is not presently recommended (8,9).

The efficacy and safety of the nasal route (LNIT) is now supported by 14 double-blind placebo-controlled studies (10). The majority of them confirmed their efficacy in reducing nasal symptoms induced by grasses, birch, ragweed, *Parietaria*, and mites. Nevertheless LNIT acts only on rhinitis symptoms and requires a specific administration technique (pre-medication with cromolyn, vocalizing during spraying etc). Moreover, LNIT is effective only when administered before each allergenic exposure (11) and there may be problems in giving it to children. For these reasons, the use of LNIT is progressively decreasing. On the other hand, new simplified administration schedules have been recently proposed (12) in order to make the treatment more patient-friendly. LNIT is still used in a minority of patients, for instance as preseasonal treatment for pollinosis. Its safety is anyway satisfactory since the new powder extracts are virtually devoid of local side effects. Asthmatic attacks following LNIT were reported only in one study and they were probably due to an incorrect administration technique.

SLIT (extract kept under the tongue for 1-2 minutes and then swallowed), immediately appeared to be the most promising and effective route and therefore it was extensively studied from different viewpoints. The efficacy evaluation in the EAACI position paper (9) published in 1998 was based on 8 studies, whereas we have presently available 20 studies, most of them published between 1998 and 2002 (for review see 13-14).

Almost all the controlled randomized studies agree on the efficacy of SLIT in reducing symptoms and/or medication intake in rhinitis and asthma. A significant effect on quality of life of patients receiving SLIT has been demonstrated as well (15). Very recently, it was demonstrated in asthmatic children that SLIT has a long-lasting efficacy (5 yrs) which is similar to that described for injection IT (16).

SLIT resulted to be safer than subcutaneous immunotherapy, since no fatal or near-fatal adverse event has ever been reported. All the side effects reported in the controlled trials were of grade I-II and in the majority of the cases they were self-resolving. The occurrence of side effects is quite higher with subcutaneous SIT. In a recent review, the incidence of severe systemic adverse events with subcutaneous SIT resulted to range between 1% and 50% of the patients (17). Apart from the controlled trials (18), the available post-marketing surveys on SLIT confirm the optimal safety profile of SLIT even in a real situation (19,20).

Some studies attempted to compare the clinical and immunological effects of SLIT and traditional SIT (21-25) and they provided controversial results. If we want to use a rigorous criterion, there are only two double-blind, double-dummy controlled studies comparing SLIT and traditional subcutaneous SIT (24,25). Those trials showed that SLIT and subcutaneous SIT are virtually equivalent as far as efficacy is concerned.

Immunological aspects

Local IT have been studied mainly from a clinical point of view. Only few observations concerning its mechanisms of action are presently available. In humans, SLIT has been demonstrated to be capable of reducing the proliferative response of T lymphocytes from atopic subjects (26), and the same effect has been seen also with local nasal immunotherapy (27). On the other hand, some convincing data have been provided *in vivo*, by means of the nasal/conjunctival challenge with allergens. It has been shown that both SLIT (28,29) and LNIT (30) exert a measurable modulatory effect on inflammatory cell infiltration and adhesion molecule expression on the target organ. Noteworthy, these results are consistent with the experimental data showing the tolerogenicity of the mucosal antigen administration (31-33).

It should be remembered that the sublingual administration was first proposed with the rationale of achieving a prompt absorption of the allergen through the mucosa. Indeed, the clinical studies showed that the allergen immediately swallowed (oral route) performs poorly, whilst the sublingual administration is clinically effective. Therefore, the sublingual epithelium seems to play an important role in the process. Very recently, the pharmacokinetics of local routes in humans was studied using a radiolabeled purified allergen (Par j 1) (34,35). After the administration (sublingual or intranasal) of the ¹²⁵I-radiolabeled allergen, sequential scintiscans, plasma radioactivity, and plasma chromatographies were evaluated at different times. No direct absorption of the allergen through the mucosa could be observed, since plasma radioactivity increased only after the allergen was swallowed. Moreover, the allergen was retained for a long time (up to 24 hours) at the mucosal level, both in the nose and the mouth. These observations, taken together, lead to the conclusion that the contact of the allergen with the oral mucosa is a crucial step, but that the allergen is not absorbed in the mouth.

Points to be developed

The results from the clinical trials are encouraging and lead to the official approval of SLIT and LNIT for routine clinical use. Nevertheless, the studies of SLIT are a matter of ten years only and, therefore, several points need to be better addressed. One of the most important aspects is the optimal dose of allergen to be administered. It is known that the use of very high amounts of allergen is associated with gastrointestinal symptoms, although severe side effects have never been described. Based on the available data, the effective dose should be between about 3-5 and 300 times higher than the subcutaneous route, but this interval is wide and dose-ranging studies lack.

Another problem with SLIT is the difficulty to assess the adherence to the treatment, which is self-administered (the same problem exists with drugs), whereas the subcutaneous IT is given by the physician and it is believed to achieve an optimal compliance. Nevertheless, looking at the few studies assessing the compliance with subcutaneous IT, the rate of discontinuation of the treatment ranged between 10 and 34% (36) and up to 50% of the patients were noncompliant because of the side effects (37).

Finally, at variance with the development of asthma, no clear demonstration has been demonstrated for SLIT.

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Finally, at variance with injection IT that has been shown capable of preventing the development of asthma from rhinitis (38), this preventive effect has not yet been demonstrated for SLIT, although it is reasonable to expect it.

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Discussion

Blaser: You briefly mentioned that there is a gastro-intestinal absorption of the allergens in sublingual therapy. Do these patients have gastro-intestinal problems?

Passalacqua: No, the patients we started with in the pharmacokinetic study did not have any relevant problems. We asked for stomach ache and past diseases. The described effect was observed in all patients and it was interesting to see that when we administered the native allergen, we could only find peptides in the plasma. When we used the allergoid, that is a modified allergen, we could also find a fraction of the intact molecule in the plasma. Thus, a gastro-intestinal absorption probably occurs anyway.

Jäger: I have a question concerning the 10-year study. You mentioned that the drop-out rate is about 50%, but you have the same number of patients over the whole 10 years. Did you look for the intention to treat patients?

Passalacqua: No, because... You have to consider... equal immunotherapy... could happen and co... form a double-blind... is a clinical study with...

Malling: We have seen... on some things and p... is a safe treatment b... completely agree with y... mentioned 22 studies... Among these studies... ding to the criteria th... other aspect is that it... rather unusual to ha... more information ab... ventive aspects, that... generally recommen... patients.

Passalacqua: I absol... for that, because we... tude of efficacy I onl... notherapy studies, th... negative, I referred... cacy in our study is n... we cannot say that s...

Malling: No, I comp... other comment that... I were a grass pollen... histamines daily dur... therapy, I would hav... year round. I am no...

Passalacqua: It is th...

Malling: Yes, for pe...

Passalacqua: Okay... anti-histamines is al...

Malling: Does that...

Passalacqua: No, w... the whole season.