

Allergen-Specific Sublingual Immunotherapy for Respiratory Allergy

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Abstract

Present knowledge regarding the clinical efficacy and safety of sublingual immunotherapy (SLIT) for the treatment of respiratory allergy is reviewed. Allergen-specific immunotherapy is presently considered a ‘biological response modifier’ for the treatment of respiratory allergy, to be used in association with drug therapy and allergen avoidance. Its value in the treatment of these conditions has been established in position papers from the World Health Organization and the European Academy of Allergology and Clinical Immunology. Immunotherapy is usually administered subcutaneously (SCIT), and with this route several severe adverse events and fatalities have been described. Therefore, in the last 15 years, novel and safer routes of administration (local routes) have been developed. SLIT, in particular, has been investigated in 18 randomised controlled clinical trials. SLIT’s clinical efficacy (improvement in symptoms and reduction in drug intake) in both asthma and rhinitis has been clearly assessed in 16 of these studies and for the most common allergens. SLIT’s safety profile, derived from the clinical trials and from post-marketing surveillance studies, was shown to be satisfactory in both adults and children. The most frequently reported adverse events are gastrointestinal complaints, which can be avoided through appropriate dosage adjustment. For these reasons, SLIT has been accepted as a viable alternative to SCIT in recent position papers.

The main advantages of SLIT are its safety (no severe systemic adverse event has ever been described) and good patient acceptance, especially in children; in addition, SLIT is a self-administered treatment that can be carried out at home by the patient. In contrast to injection immunotherapy, knowledge of the mechanisms of action of SLIT is still developing, albeit rapidly, although interesting

data about its pharmacokinetics in humans are available. Data are also required concerning the possible preventive and long-lasting effects.

SLIT is a viable alternative to SCIT, with the same rationale and indications. It is intended to be used in association with proper pharmacological treatment, at the earliest stages of the disease, for optimal management of respiratory allergy.

1. Historical Background and General Aspects

Allergen-specific immunotherapy or allergen vaccination is the practice of administering to patients with allergy increasing amounts of allergens in order to achieve hyposensitisation and to reduce the symptoms occurring during the natural exposure to the allergen itself. Since the first empirical attempts,^[1] immunotherapy has been administered subcutaneously. The clinical effectiveness of immunotherapy favoured its widespread use, sometimes leading to improper prescription or incorrect administration. The idea of administering allergen extracts orally is not recent: the first attempts, with favourable results, were made at the beginning of the last century.^[2,3] During the 1950s several trials on local bronchial immunotherapy appeared,^[4] in the 1970s some studies focused on local nasal immunotherapy,^[5] and in the 1980s the sublingual route was proposed. All these approaches remained almost anecdotal and of speculative interest only, since the use of the subcutaneous route was widespread and well supported. In the mid-1980s, the British Committee on the Safety of Medicines^[6] reported six deaths caused by injection immunotherapy and raised serious concerns about the safety and risk/benefit ratio of this treatment, particularly in the light of the availability of new and increasingly effective drugs. Although most life-threatening events were subsequently demonstrated to be avoidable,^[7,8] interest in non-injection routes of administration for immunotherapy rapidly increased, and a large number of clinical trials were published within a few years. In fact, these routes of administration have the primary aim of minimising the risk of adverse events and of improving patient compliance with and acceptance of the treatment.^[9] Current use favours the equiva-

lent terms 'non-injection' or 'local routes'; the term 'alternative routes' should be abandoned.

In 1998 a panel of experts of the World Health Organization (WHO), based on an extensive review of the literature, concluded that both sublingual (SLIT) and local nasal (LNIT) immunotherapy are viable alternatives to the injection routes and that their use in clinical practice is justified.^[10] These conclusions were further confirmed in a position paper prepared by the European Academy of Allergology and Clinical Immunology (EAACI).^[11] The standard oral route (allergen swallowed immediately) seems to be minimally effective and the bronchial route involves important adverse effects, therefore clinical use of these routes is not recommended. The effectiveness and safety of LNIT is supported by 14 double-blind, placebo-controlled studies.^[11,12] Nevertheless, LNIT acts only on rhinitis symptoms, it requires a particular administration technique, and it is difficult to administer to children; therefore its use is progressively decreasing. LNIT is still used in a small number of patients as preseasonal treatment for pollen-associated seasonal allergic rhinitis.

In SLIT, the extract is usually kept under the tongue for 1 to 2 minutes and then swallowed, thus this route is also called the sublingual-swallow route. In recent years SLIT has been extensively studied and investigated from a clinical viewpoint: all the trials performed so far aimed mainly at demonstrating the clinical efficacy and the safety of SLIT; consequently our knowledge of the immunological aspects and the mechanisms of action is still in the early stages. Nevertheless, interesting preliminary data about the possible mechanisms of action and the pharmacokinetics involved in this treatment are available.

2. Immunological Considerations

Much information and data are available for subcutaneous immunotherapy (SCIT) on the possible mechanisms of action both *in vitro* and *in vivo*. These data include: (i) modulation of the synthesis of allergen-specific antibodies, (ii) down-regulation of cytokine and mediator release, (iii) inhibition of activation and recruitment of effector cells, and (iv) modulation of T helper type 1/type 2 (T_H1/T_H2) balance.^[13-17] This latter aspect seems to be of primary relevance for the immunomodulatory effect exerted by immunotherapy.^[18,19]

However, since local immunotherapy has been studied over the last 10 years mainly from a clinical point of view, only minimal information concerning its mechanisms of action *in vitro* is presently available.^[20,21] In an animal model it has been demonstrated that mucosal administration of the antigen could select a functionally disabled population of CD4⁺ cells.^[22] In humans, SLIT has been demonstrated to be capable of reducing the proliferative response of T-lymphocytes from atopic individuals,^[21] and the same effect has been seen with LNIT.^[20] These effects were dissociated from the behaviour of serum specific immunoglobulin (Ig) E and IgGs. This is consistent with what is observed *in vivo*: as opposed to SCIT, SLIT usually does not induce a prompt decrease of IgE and an increase of IgG1 and IgG4, or, at least, these changes are not constant and reproducible. However, it must be borne in mind that almost all the clinical trials available were short term trials, and that as with SCIT, antibody changes can often only be appreciated after long periods of time.

When the inflammatory phenomena (cellular infiltration and adhesion molecule expression on epithelia) were studied in the target organs (nose and conjunctiva) by means of allergen challenge, a significant modulatory effect of SLIT could be observed.^[23,24] These effects were apparent after 4 months of treatment for *Parietaria* pollen, whereas for house dust mites the immunomodulatory action was measurable after 1 year. Similar effects on local allergic inflammation in humans

were seen with intranasal administration.^[25] Finally, a reduction of eosinophil cationic protein levels, which is a marker of allergic inflammation, was also described.^[23] Therefore, it is possible to hypothesise that the immunological effects of SLIT should be measured using parameters other than those used traditionally (IgE, IgG1 and IgG4).

A number of basic immunology studies, especially in animal models, have provided interesting data. The 'tolerogenicity' of the oral route has been demonstrated in several studies;^[26-28] it seems to involve the T_H1/T_H2 differentiation^[29] and the regulation of IgE production.^[27] In addition, the dendritic cells of oral mucosa are known to be able to act as efficient antigen-presenting cells^[30,31] and to produce interleukin-12, which affects the T_H1/T_H2 equilibrium.^[32] Interestingly, consistent data have also been provided for desensitisation through the inhalation route.^[33,34]

In conclusion, the majority of immunological data concerning the mucosal route for immunotherapy come from animal models and, although they are interesting from a speculative viewpoint, they cannot be immediately extrapolated to humans. Studies in humans are just beginning: the few available data do suggest, however, that SLIT does exert immunological changes to some extent.

3. New Pharmacokinetic Aspects

Interestingly, after about a century of clinical use, no data are available on the pharmacokinetics of subcutaneous allergen extracts. Indeed, this aspect would be of particular relevance in the case of antigens administered to the mucosae. Knowledge of the absorption and fate (where the antigen interacts with the immune system) of the allergen is important in order to devise hypotheses on the possible mechanisms of action. It has to be remembered that sublingual administration was proposed with the rationale of achieving prompt absorption of the allergen through the mucosae. Furthermore, clinical studies show that the allergen immediately swallowed (i.e. standard oral route) performs poorly, while sublingual administration is clinically

effective. Therefore the sublingual epithelium seems to play an important role in the process.

Few data concerning the pharmacokinetics of orally administered allergen extracts are presently available.^[35-39] Almost complete degradation of the allergen extract in the duodenum seems to occur in humans,^[35] thus absorption of the native antigen through the gastroenteric mucosa appears unlikely. On the other hand, experiments performed in rats and rabbits suggest significant absorption of the allergen through sublingual and nasal mucosae;^[37,38] this could relate to the increased permeability of nasal epithelium to macromolecules that may be present in allergic individuals.^[40] In fact, as reviewed by Falagiani and Mistrello,^[36] data concerning the pharmacokinetics of allergens are, in general, controversial and not conclusive, since they are mostly derived from animal models. Very recently, the pharmacokinetics of local routes of administration were studied in humans using a radiolabelled purified *Parietaria* pollen allergen (Par j 1) and a special procedure.^[41] After administration (sublingual or intranasal) of the ¹²³I-radio-labelled allergen, sequential scintiscans, plasma radioactivity and plasma chromatographies were evaluated at different times. It was observed that no direct absorption of the allergen through the mucosae occurs, therefore the claimed risk of a too rapid absorption is not supported by the experimental evidence; in fact, plasma radioactivity increased only after the allergen was swallowed. Moreover, the allergen was retained for long periods (up to 40 hours) at the mucosal level, in both the nose and the mouth. Finally, gastrointestinal absorption was relevant but no trace of the native allergen could be detected in the bloodstream, whereas if a modified allergen is administered via the sublingual/swallow route, traces of the allergen can be detected in the plasma. Superimposable results were subsequently obtained using a commercial preparation, in patients with allergy.^[42]

These observations, taken together, lead to the conclusion that contact of the allergen with the oral mucosa is a crucial step, but that the allergen is not

absorbed in the mouth. It can be hypothesised that drainage of the allergen into regional lymph nodes occurs; however, it is difficult to verify this hypothesis, since administration of a beta-emitter with long half-life would be required. At present, based on the available pharmacokinetic data, the sublingual/swallow method of administration seems to be the more correct one, and preferable to simple oral administration.

4. Experimental Evidence: Clinical Efficacy

The clinical efficacy of immunotherapy can be properly judged only on a clinical basis (i.e. symptomatic improvement and drug intake reduction). We do not at present have available surrogate parameters that correlate well with the clinical effect. The so-called paraclinical parameters (skin reactivity, specific and nonspecific organ responsiveness, soluble and local markers of inflammation) are supportive of the clinical data but can never replace them.

The available literature on SLIT has been reviewed according to the restrictive criteria established by WHO and EAACI:^[10,11] only double-blind, placebo-controlled trials published in peer-reviewed journals and with adequate methods and statistical analysis were considered.

Twenty-four clinical trials of SLIT have been published thus far.^[23,24,43-64] Six of these trials^[43-48] have major study limitations: open design,^[46] lack of a placebo group,^[44] too few patients,^[43] drug score not provided,^[45] dose of allergen too low^[47] or dose of allergen not provided.^[48] Their results, although globally encouraging, cannot be considered valuable to demonstrate the effectiveness of the treatment. Therefore, we can rely on 18 double-blind, placebo-controlled studies, performed with adequate methods and samples,^[23,24,49-64] as summarised in table I. Five of these studies were performed in paediatric patients.^[53,56,61,63,64] Almost all the studies confirmed the effectiveness of SLIT with grass pollen, house dust mite, birch pollen and *Parietaria* pollen extracts in terms of symptomatological improvement and/or reduction

Table I. Double-blind, placebo-controlled studies of sublingual immunotherapy

Reference	Age range (y)	Allergen	Time-frame	Dose ^a	Patients (A/P)	Disease	Result	Adverse effects (frequency, severity)
Tari et al. ^[49]	5-12	House dust mite	18mo	365 STU	30/28	R/A	R < 0.001 A < 0.001	3 severe
Sabbah et al. ^[50]	13-51	Grass pollen	17wk	4.500 IR	19/29	R	< 0.05	3 severe
Feliziani et al. ^[52]	14-48	Grass pollen	3.5mo	25 BU	18/16	R	< 0.01	None severe
Troise et al. ^[51]	17-60	<i>Parietaria</i> pollen	10mo	105 BU	15/16	R	< 0.05	Rare, mild
Hirsch et al. ^[53]	6-16	House dust mite	1y	570g Der p1	15/15	R/A	R = NS A < 0.05	Rare, mild
Passalacqua et al. ^[23]	15-46	House dust mite	2y	10.000 AU	10/9	R	< 0.01	None
Vourdas et al. ^[56]	7-17	Olive pollen	2y	4mg Ole e 1	33/31	R/A	R < 0.05 A < 0.04	Rare, mild
Clavel et al. ^[54]	8-55	Grass pollen	6mo	28g Phl p 5	62/28	R/A	< 0.01 A and R	Rare, mild
Horak et al. ^[55]	16-48	Birch pollen	4mo	250 STU	18/16	R	< 0.01	None
Hordijk et al. ^[58]	18-45	Grass pollen	6mo	100.000 BU	30/27	R/A	< 0.05	None
Bousquet et al. ^[57]	15-37	House dust mite	2y	25mg Der p 1	15/15	A	< 0.05 (also FEV ₁ , QOL)	None severe
Passalacqua et al. ^[24]	15-42	<i>Parietaria</i> pollen	8mo	16g Par j 1	15/15	R/A	< 0.01	None
Pradaliere et al. ^[60]	6-25	Grass pollen	4mo	5.000 STU	59/61	R/A	R = NS A < 0.05	None severe
La Rosa et al. ^[61]	6-14	<i>Parietaria</i> pollen	6mo	4.000 STU	20/21	R/A	< 0.01	None severe
Purello D'Ambrosio et al. ^[59]	14-50	<i>Parietaria</i> pollen	8mo	12g Par j 1	14/16	R/A	< 0.01	None
Pajno et al. ^[63]	8-15	House dust mite	2y	2.4mg Der p 1	12/12	A	< 0.001	Rare, mild
Guez et al. ^[62]	6-51	House dust mite	2y	2.2mg Der p 1	24/18	R	NS	None
Caffarelli et al. ^[64]	4-14	Grass pollen	3mo	32.000 AU	24/20	R/A	< 0.05	None

a Dose refers to the maintenance dose administered.
A = asthma; A/P = active/placebo; AU = allergy unit; BU = biological units; FEV₁ = forced expiratory volume in 1 second; IR = internal RAST; mo = months; QOL = quality of life; R = rhinitis; RAST = radioallergosorbent test; STU = standard units; wk = weeks; y = years.

of the intake of medications. In addition, systemic immunological effects (i.e. increase in IgG1-IgG4, reduction in skin reactivity) were observed,^[49,51,54] and a decreased responsiveness of target organs was also described.^[23,24,49,53] In two studies,^[53,62] both conducted with mite extracts, SLIT performed poorly: a trend towards clinical improvement was seen in the active groups but it did not reach statistical significance. This can also be observed with SCIT, which is usually less effective in patients with mite allergy than in patients with pollen allergy. In patients allergic to mites, the duration of the treatment seems to be crucial: treatments lasting at least 2 years provided positive results.^[23,63] Immunotherapy was associated with reductions of between about 20 and 50% in symptom and/or medication scores, indicating the clinical efficacy of immunotherapy was superior to the effects of placebo.

It is important to note that SLIT exerts its effect not only on rhinitis symptoms but also on asthma symptoms. Results from the more recent studies^[57,59,60,63] have shown that SLIT is associated with a clearcut reduction of the days with asthma symptoms,^[60] of the use of β_2 -adrenoceptor agonists,^[57,61] the intake of systemic corticosteroids^[54] and improvement of the clinical symptom score.^[57,60,63] This aspect has been confirmed in an open controlled study showing that SLIT with grass pollen extracts can significantly reduce the nonspecific bronchial hyperresponsiveness to methacholine.^[65]

With regard to the direct comparison between SLIT and SCIT, we have presently available a single double-blind, placebo-controlled study published as a full paper,^[66] which showed that SLIT has a clinical efficacy superimposable to SCIT (symptoms and need for rescue drugs). Two

open, comparative studies have shown that SLIT, compared with SCIT, is better accepted and tolerated by patients.^[67,68] The first of the latter studies, conducted in patients with *Alternaria tenuis* allergy, confirmed that SLIT is as effective as SCIT. The second study, conducted in patients with house dust mite allergy, showed that clinical improvement in asthma symptoms was more prompt with the subcutaneous route compared with SLIT, although equivalent efficacy of SLIT and SCIT for rhinitis symptoms was seen. Finally, a well-designed rigorous placebo-controlled trial with birch pollen extract has been recently published, in abstract form,^[69] showing that SLIT and SCIT have similar efficacy. There are no studies directly comparing the efficacy of SLIT versus that of drugs. At present, since it is accepted that immunotherapy in general is a complementary treatment to be used in addition to drugs, such studies (which are very difficult to perform) are not considered of primary interest.

5. Experimental Evidence: Safety

The primary goal of SLIT is to minimise the risks of adverse events; therefore particular attention has been paid to tolerability in all the studies. The adverse effect most frequently reported in the published controlled trials was the onset of oral /sublingual itching; this phenomenon was always described as mild and self-resolving. Headache, rhinorrhoea, constipation or urticaria were described only sporadically and their incidence did not differ from that in the placebo groups. Notably, no severe systemic adverse events have been reported in the literature over 15 the last years. An early pharmacovigilance study^[70] reported that the incidence of adverse effects was indeed low: oropharyngeal itching represented about 50% of the untoward effects, followed by rhinorrhoea and constipation. Urticaria and asthma were very rare. More than 90% of the effects were mild-to-moderate in intensity and no cases of systemic anaphylaxis were reported.

The safety aspect is of primary importance in paediatric patients. A recent pharmacosurveillance

study performed in 268 children showed that the incidence of all adverse events was 8% and that the adverse events were mild in nature and in no case required discontinuation of the treatment.^[71] Similarly, in more recent paediatric studies, the occurrence of adverse events was low in frequency and events were not troublesome to the patients.^[62-64] In another study a significant occurrence of gastrointestinal complaints was noted, but in this study the amount of allergen extract used was very high: about 375 times the amount usually administered in a standard subcutaneous course.^[61]

It has been claimed that SLIT could induce local oedema in patients suffering from oral allergy syndrome. However, a controlled study performed in patients (n = 30) with documented oral allergy syndrome with an allergoid in orosoluble tablets did not confirm this hypothesis.^[72]

Finally, André et al.^[73] reviewed the safety aspects of the controlled trials performed with the extracts of a single manufacturer. 690 individuals were enrolled (347 active and 343 placebo), including 218 children (103 active and 115 placebo). Most events were mild. All events, with the exception of gastrointestinal effects, had similar incidences in the active and placebo groups. Gastrointestinal events were more frequent in SLIT patients, although they were mild in intensity. The occurrence of adverse events and dropouts was similar in adults and children, and only the cumulative gastrointestinal side effects were more frequent in the SLIT population. At present, the results of the randomised controlled clinical trials and the pharmacosurveillance studies do not support the claimed potential risks attributed to SLIT.^[74]

6. Practical Aspects

Similar to SCIT, SLIT should be used in order to modify the immunological response to allergens, acting at an early stage. For this reason, it is not indicated in the late course of the disease when non-reversible tissue damage is present and when the disease itself cannot be modified.^[75] In fact, immunotherapy may be useful in patients with

mild to moderate asthma. Moreover, SLIT must be used in association with environmental care and with proper pharmacological treatment (antihistamines, topical corticosteroids, bronchodilators, etc.) in order to achieve optimal control of symptoms.^[76] As with SCIT, SLIT is especially indicated in patients with rhinitis or rhinoconjunctivitis with concomitant asthma.

The sublingual route would appear particularly suitable for paediatric patients in terms of safety and since oral therapy is better accepted than injections. SLIT is, in general, suggested in patients showing low compliance with SCIT or with previous severe adverse reactions to SCIT. As with SCIT, SLIT must not be considered as a last-choice treatment.^[75] Since SLIT is self-administered, its prescription can only be made by a specialist, after a detailed diagnosis has been established and the expected cost/benefit ratio has been carefully evaluated.^[6,7,77] Patients must be instructed to carefully follow the manufacturer's schedule of administration and to undergo a clinical visit at least every 3 months. Only extract for which efficacy has been proved (grass pollen, *Parietaria* pollen, house dust mites, olive pollen extract, birch pollen) must be used, and standardised extracts should always be given preference.^[78]

Different administration schedules may be provided by the manufacturers, but usually a SLIT course includes a build-up phase, where the extract is administered at increasing doses, and a maintenance phase, where the maximal dose is administered 2 or 3 times a week. Furthermore, SLIT can be administered either preseasonally, before and during the season, or continuously, based on the type of allergen. Rush schedules for preseasonal immunotherapy are also available. In general, administration of immunotherapy before and during the allergy season are the schedules of choice for pollen allergy, whereas for perennial allergens continuous treatments are preferred. Since no data are available, it is empirically suggested that a successful SLIT course should be continued for 3 to 5 years.

The extract has to be maintained sublingually for 1 or 2 minutes and then swallowed in order to take advantage of both local immunity and enteric absorption. At least in Italy, SLIT is available both as drops and as soluble tablets. Which one to use is a matter of patient preference: tablets are easily manageable, although with drops it is easier to reduce or modify the doses. If the patient reports systemic (e.g. urticaria) or local (gastrointestinal complaints, oral itching) adverse effects, dose reduction or no increase is indicated.^[11]

Finally, from a socioeconomic point of view, considering the indirect costs of the treatment (injections, time loss), SLIT is less expensive than SCIT over the long term (table II).

7. Open Questions

Results from clinical trials are quite encouraging and have led to the official endorsement of SLIT for routine clinical use.^[10,11] Nevertheless, the SLIT studies have only been performed over about the last 10 years and several aspects still 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 extract are associated with gastrointestinal symptoms, although severe adverse effects have not been described. Based on the available data, the effective dose should be between about 20 and 375 times higher than that for the subcutaneous route, but this interval is wide, dose-ranging studies are lacking, and the methods of standardisation used do not allow an exact comparison among the different extracts. The use of allergen extracts with a known major allergen content will solve the problem in the future.

Another problem with SLIT is the difficulty in assessing adherence to the treatment, which is self-administered (the same problem exists with drugs), whereas SCIT is administered by the physician. In any case, from the few studies assessing compliance with SCIT, it is easy to observe that the rate of treatment discontinuation ranges between 10% and 34%,^[79] and that up to 50% of the patients are noncompliant because of the occurrence of intol-

Table II. Estimated costs (\$US) of immunotherapies per year (continuous treatment)

	Sublingual immunotherapy		Injection immunotherapy	
	cost	comment	cost	comment
Treatment	300	2 refills	150	1 refill
Specialist's visit	100	2 interim visits		Patient seen at every injection
Injections		No injection	120	\$10 per injection × 12 injections
Time lost		Self-administered	240	\$10 per hour 2 hours per injection × 12
Total	400		510	

erable adverse effects.^[80] Thus, the safety of SLIT would imply better compliance, although this aspect needs specific studies.

SCIT has been shown to be capable of modifying the course of the disease (i.e. onset of asthma in patients with rhinitis)^[81] and of preventing the onset of new sensitisations.^[82] Moreover, a long-lasting effect of SCIT after discontinuation has been seen in several clinical trials.^[18,83, 84] At present, due to the newness of the approach, such data are still lacking for SLIT and need to be documented.^[85] Finally, although safety in children has been well documented, more conclusive data are needed to establish detailed indications in paediatric patients, and for determining the optimal age for prescribing a SLIT course.

8. Conclusions

Adequate training in allergology is necessary for physicians who prescribe immunotherapy and specialist supervision is required to avoid the risk of poor or inadequate management of the disease. The treatment of respiratory allergy is based on allergen avoidance, pharmacological treatment, and immunotherapy. Immunotherapy and drugs have different actions and aims. Pharmacotherapy (e.g. inhaled corticosteroids, β_2 -adrenoceptor agonists, antihistamines) acts directly on symptoms and allergic inflammation and, depending on the drug, can have a very short onset of action (hours). Immunotherapy is an allergen-oriented immunomodulator that affects the immune response to allergens and its action develops over long periods (days to months). One of the most frequent errors with immunotherapy in the past years has been to

consider it as an alternative to drugs for controlling symptoms, whereas it is now accepted that immunotherapy has to be used in combination with drugs. The effect of immunotherapy is specific for the allergen and not for the disease, considering that allergic rhinitis and asthma are now regarded as two aspects of a unique disease.^[86,87]

SLIT represents a significant step towards optimal allergy management because of its safety, self-administration and ease of use, although several aspects need to be elucidated by further experiments. The characteristic of SLIT itself (self-administration) requires a careful and detailed follow-up of the patients. It is important to remember, however, that SLIT must not be regarded as a substitute for SCIT, but rather as an additional choice or therapeutic tool.

The clinical efficacy of SLIT in both asthma and rhinitis is now supported by a large number of controlled trials. For these reasons SLIT appears particularly suitable for paediatric patients, where an optimal safety profile is required. This latter fact has been highlighted in the recent WHO document.^[75] Finally, it has to be considered that non-injectable immunotherapy may afford a significant socioeconomic impact, since it is self-administered and thus devoid of the time and expense usually incurred with injection immunotherapy.

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