

Sublingual immunotherapy for allergic rhinitis: an update

Samuele E. Burastero

Purpose of review

The inter-relationship between allergy and nasal diseases has long been known. Failure to address when allergy is a contributing factor diminishes the possibility of a successful surgical intervention. Sublingual immunotherapy is recommended by the World Health Organization to treat allergic rhinitis and is widely used in Europe. Many clinical trials and rigorous meta-analysis support its efficacy. The criteria, however, for the integration of this treatment (with the surgical management of those allergic patients who suffer chronic nasal obstruction, severe drug-resistant hypertrophy and increase in glandular structures of the inferior turbinates) are not fully established. We review here the most recent literature on the efficacy and safety of sublingual immunotherapy. The purpose is to stimulate the use of complementary approaches by ear, nose and throat doctors and allergologists, and to improve the management of patients with persistent allergic rhinitis.

Recent findings

In addition to the results of clinical trials, postmarketing surveillance has confirmed the high safety profile of sublingual immunotherapy in adults and children, its positive impact on the quality of life, and the reduction of the personal and social cost of allergy. Sublingual immunotherapy can prevent new allergic sensitizations and maintain its beneficial effect for years after its discontinuation.

Summary

Sublingual immunotherapy is a highly efficacious and well tolerated form of immunotherapy for allergic rhinitis, and it is capable of interfering with disease progression. Sublingual immunotherapy should be integrated with surgical intervention to achieve optimal outcomes in allergic subjects with chronic nasal obstruction.

Keywords

allergic rhinitis, efficacy, safety, sublingual immunotherapy

Abbreviations

SCIT subcutaneous immunotherapy
SLIT sublingual immunotherapy

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Introduction

Allergy plays a central role in the clinical practice of otolaryngology. Around 50% of patient complaints encountered by ear, nose and throat specialists have an allergic component [1] and inhalant allergy is particularly prevalent. The World Health Organization acknowledged that allergen-specific immunotherapy is a cornerstone in the management of respiratory allergy [2] as it affects the immunologic response towards allergens at its earliest stages [3•]. In fact, immunotherapy not only reduces the symptoms load in the short term, but also has a favorable impact on the natural history of the allergic disease (the so-called 'allergy march'). Allergy march is defined as the progression from food allergy and atopic dermatitis (in infancy) to rhinitis and then asthma [4]. These achievements have been established initially with subcutaneous immunotherapy (SCIT) and subsequently extended to sublingual immunotherapy (SLIT). Both forms of treatment can prevent the onset of asthma in subjects with allergic rhinitis [5].

The natural history of allergic subjects with nasal diseases is suitable for therapeutic modification, even in cases in which initially only surgical treatment could remove patient-specific complaints, particularly those depending on nasal blockage. In fact, subjects undergoing surgery related to anatomical problems, such as septal deformity or turbinate hypertrophy of polyp disease, could have a diminished probability of subsequent surgical intervention if allergy is addressed as a contributing factor to the nasal disease itself [6].

A relevant problem with traditional SCIT is the risk of potentially severe adverse events, which can limit its indications. This problem occurs particularly in small children or in adults in the care of medical centers in which appropriate resuscitative measures are not promptly available. SLIT represents a dramatic improvement in the possibility of treating larger numbers of allergic patients with rhinitis. With SLIT, the allergen extract is kept under the tongue for 1–2 min and then swallowed. Systemic side effects are rare and never severe enough to require resuscitative measures.

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San Raffaele Scientific Institute, Milan, Italy

Correspondence to Samuele E. Burastero MD, San Raffaele Scientific Institute, via Olgettina, 58, 20132 Milan, Italy
Tel: +39 02 2643 4730; fax: +39 02 2643 4723; e-mail: s.burastero@hsr.it

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In most cases, a minority of patients (the proportion depends on the allergen source, allergen concentration, and on individual factors) suffers short-term local (i.e. oral and lingual) effects that are self-resolving. Notably, allergen ingestion (oral immunotherapy) is not efficacious [7], indicating that the absorption of the allergen via the mucosal surface, although minimal [8,9], is nevertheless the crucial event in obtaining the subsequent immunomodulation of the allergic response. These events are detailed in a seminal work [9] that unveiled the critical issue of absorption of allergen through the oral mucosa in the course of SLIT.

The first randomized controlled study of SLIT dates back to 1986 [10], but in the last few years the literature on the safety and the efficacy of this treatment has grown enormously. Importantly, as with SCIT, SLIT also has a preventive effect on the insurgence of further sensitization. The long-lasting action of SLIT, in the years following its discontinuation, has been fully documented. A formal Cochrane review was elaborated on this subject [11] and a systematic review and meta-analysis has been published recently [12**].

We will review here the most important and recent clinical studies on SLIT for the treatment of allergic rhinitis, with a particular focus on its efficacy and safety profile.

Clinical efficacy

The Allergic Rhinitis and its Impact on Asthma (ARIA) [2] consensus document recommends replacing the term 'seasonal' and 'perennial' allergic rhinitis with 'intermittent' and 'persistent' allergic rhinitis, respectively. Nasal obstruction is the most common symptom of persistent allergic rhinitis and is characterized by insufficient air-flow through the nose, which can be either a subjective complaint or the result of objective disease [13**]. International guidelines for the management of rhinitis recommend combining treatment of the upper and lower airways with patient education, allergen avoidance, pharmacological treatment, and specific immunotherapy [2]. Surgery may be needed as an adjunctive intervention in patients with chronic obstruction related to the hypertrophy of glandular structures of the inferior turbinates. Unless nasal surgery is properly indicated, however, and performed with skill, outcomes may be poor. The control of nasal obstruction in persistent allergic rhinitis patients by these measures has been recently, and thoroughly revised by Wang *et al.* [13**]. In this review we will focus specifically on the effect of immunotherapy performed via the sublingual route.

Twenty-two trials involving 979 patients have been included in a recent rigorous meta-analysis of SLIT

based on the attainment of the strict requirements for entering the Cochrane collaboration criteria [11]. These trials were all double-blind placebo-controlled studies involving participants with symptoms of allergic rhinitis and proven allergen sensitivity, treated either with SLIT or corresponding placebo. It was concluded that SLIT is a well tolerated treatment that significantly reduces symptoms and medication requirements in allergic rhinitis. Although the size of the benefit, as compared with SCIT, is uncertain, caused by the paucity of dedicated studies [14*], the safety profile is far more favorable with SLIT.

In the last year more controlled studies have been published that further support SLIT efficacy. Marogna *et al.* [15**] reported that SLIT achieved a significant clinical benefit in birch pollinosis, reduced the eosinophil infiltration in nasal mucosa, and significantly improved pulmonary function during the pollen seasons. Rolinck-Werninghaus *et al.* [16] reported that SLIT had a positive effect on the reduction of a multiple symptom-medication score in children with rhinoconjunctivitis to grass pollen. Novembre *et al.* [17**] found that 3 year' treatment of coseasonal SLIT improves seasonal allergic rhinitis symptoms and reduces the development of seasonal asthma in children with hayfever. Data have been recently reviewed supporting the notion that SLIT has a positive impact on the quality of life of treated patients [12**], as well as on the growing personal and social cost of allergy in western countries [18,19].

Safety profile

The most frequently reported side effects in SLIT-treated patients are oral and/or lingual itching after taking the dose. In some cases, nonspecific gastrointestinal complaints follow. These complaints may include nausea, vomiting, abdominal pain, and diarrhea. There is some controversy about the dose dependence of the more annoying of these (never severe) side effects. I am convinced, based on proper evaluation [20] of available data from extensive meta-analyses [21*], that vaccines using higher doses of allergens are also associated with a relatively high occurrence of gastrointestinal side effects, as largely expected and previously indicated by Canonica and Passalacqua [7]. Moreover, in a single study in which the amount of administered allergen was particularly high (above 300 times greater than the amount administered in standard SCIT), the rate of gastrointestinal complaints was particularly high [22].

Indeed, also in terms of efficacy, it is rather unclear if a dose-response relationship exists. Although this relationship is supported by some studies [23*], a too narrow dose range was considered to reach definite conclusions. This was in comparison with the wide range of doses

(over 100 times difference in the total amount of administered allergen) that have been reported to be efficacious [7]. This issue will be clarified when allergen standardization is performed by the different manufacturers, who only recently have started to do so, by indicating the major allergen content for each immunotherapy preparation. For the time being, it is preferable to use SLIT with an allergenic content at 10–50 times that of standard SLIT, which allows the achievement of efficacious clinical results without significant side effects.

Noticeably, no systemic severe side effect has ever been reported in the literature for over 15 years, neither in SLIT-treated adults nor in children [24]. More consistent information on safety issues has recently become available and was obtained from postmarketing surveys that involved larger numbers of subjects, as compared with clinical trials. Among these surveys, Di Rienzo *et al.* [25] found an overall incidence of systemic side effects in 3% of patients and 1/12 000 doses. Similar figures were reported in very young children aged 3–5 years, whose rate of side effects was 5% and 0.7/10 000 doses [26**].

Biological mechanisms

Recent data suggest immunotherapy acts by modifying the T-cell response to allergens either by immune shift in up-regulation of Th1 responses (increased IL-12 and IgG response) [27] or by decreasing Th2 responses (T-cell anergy) resulting in decrease in IgE, IL-4, IL-5 and proinflammatory cytokines [28], or both. Increase in IL-10 secretion seems to be important and has been shown to confer allergen-specific hyporesponsiveness and to suppress allergen-specific Th2 responses [29,30,31*].

Criteria for enrolling patients with allergic rhinitis to immunotherapy

Here, I propose a simplified checklist for deciding if, and to what extent, specific immunotherapy is going to provide a significant improvement in rhinitis symptoms. Published clinical trials on the efficacy of immunotherapy are performed on carefully selected patients, that is, mostly mono-sensitized subjects with clear-cut phenotypic characteristics. In real life, many patients do not comply with these criteria, and this situation may affect relatively the efficacy of vaccination. For instance, polysensitized patients often cannot be vaccinated, as in these cases it is difficult to define the most suitable extract to properly immuno-modulate the allergen-specific immune response. In these instances, clinical and in-vitro criteria are usually associated to decide what, if any, allergen can be used. In particular, in some centers, in-vivo challenge tests are performed. These include nasal, conjunctival, or bronchial provocation tests with candidate allergens that allow the clinician to single

out the ones that are functionally more relevant to the patients in triggering their symptoms. Moreover, analysis of allergen IgE-specific responses with the recombinant allergen technology [32] allows the clinician to identify patients whose polyreactivity does not derive from the sum of single sensitizations, but from the presence of IgE to panallergens [33]. Panallergens are conserved protein components (e.g. profilins, lipid transfer proteins) present in several inhalant allergen extracts [34,35*]. Only when panallergens are available as isolated (purified or recombinant) proteins will these patients be offered a properly tailored immunotherapy. For the time being, however, they are not likely to benefit from available immunotherapy [36]. Besides these highly specialized approaches, simple clinical criteria can help decide if, in a polysensitized subject, one allergen is prevalent over the other. A criterion may be, for example, the period of the year when symptoms are fully expressed. A preliminary diary of symptoms in patients with a good compliance can help in this specific effort.

Phase 1: anamnesis

The following are symptoms and signs highly suggestive of allergic rhinitis:

- (1) aqueous rhinorrhea, with or without blockade;
- (2) season-specific symptoms, or symptoms triggered upon exposure to a specific allergen source (e.g. house dust, cat dander, etc);
- (3) associated ocular signs (redness, itching, hyperlacrimation);
- (4) associated ear and throat signs (itching);
- (5) associated bronchial signs (asthma).

Phase 2: skin prick test

2A – has positivity to one allergen;

2B – has positivity to two or more allergens, but with important quantitative differences and/or with the possibility of identifying the clinically prevalent one (e.g. a patient with a positive skin test to grass and dust mites, with only springtime symptoms and a prevalent skin positivity to the former allergen);

2C – has positivity to two or more allergens, without the possibility of identifying the prevalent one(s) on clinical grounds.

Phase 3: serum-specific IgE

These must be determined with a validated test with the allergen absorbed on a high-capacity solid-phase matrix:

3A – has positivity to one allergen;

3B – has positivity to two or more allergens, but with important quantitative differences allowing the possibility of identifying the one that is clinically prevalent;

3C – has positivity to two or more allergens, without the possibility of identifying the prevalent one(s) quantitatively.

Decision-making: common scenarios**1 + 2A + 3A**

These are patients who can benefit at the highest extent from specific immunotherapy, in particular those patients with allergy to a perennial (house dust mite) or to a quasi-perennial (pellitory in the Mediterranean countries) allergen. Patients who underwent surgical removal of nasal polyps should be treated to prevent relapses. Further dedicated studies are needed to clarify what level of exposure to an environmental perennial allergen may support the development of nasal polyps. Polyps are certainly more frequently found in allergic subjects and could interfere with their relapse following immunotherapy. It is highly probable, however, that chronic inflammation, supported by the exposure to a perennial environmental allergen, can favor the formation and the relapse of chronic inflammatory lesions.

1 + 2B + 3B

These are patients with a clear-cut polysensitization, but a relative prevalence of one or two allergens over others in triggering symptoms. The allergologist has to balance carefully the indications from in-vitro and in-vitro tests, as well as clinical evidence, to decide the proper vaccine extract to be used. Up to three extracts can be used for vaccination, but these can be mixed only if they have the same seasonal pattern (e.g. grass and birch). If this is not the case (e.g. birch and mites) each single extract has to be given separately, which implies a higher compliance on the patient's side.

1 + 2C + 3C

These are patients who often cannot be vaccinated, although they have a severely allergic phenotype. In some centers, specific challenge test and/or analysis of IgE antibody to recombinant allergens can sometimes allow a reasoned immunotherapy to be prescribed. The success rate, however, is much lower than in the above reported scenarios.

Although intermediate situations are not considered here for the sake of simplicity, the previous paragraphs outline the paradigmatic situations that the specialist can face, with a growing level of difficulty.

Immunotherapy has to be continued for at least 3, and up to 5, years. Therefore, patient's motivation and expected compliance should be carefully checked case by case. In addition, with these limits in mind, a much higher proportion of patients with allergic rhinitis should benefit from specific immunotherapy than is currently found. This immunotherapy would primarily serve the patient's interest, by permanently counter-acting the biologic mechanisms supporting allergy, rather than offering transient symptomatic relief.

Conclusion

SLIT is a well tolerated and efficacious approach to treat the basic mechanisms of allergic rhinitis. SLIT modifies the biological mechanisms supporting allergic inflammation, in contrast to symptomatic treatment. This clinical tool has, until now, been underexploited for improving symptoms and drug consumption in the growing population of allergic patients of western industrialized countries. This approach has advantages affecting both the quality of life and the socioeconomic impact of allergic rhinitis. Patients with persistent allergic rhinitis and chronic lesions of the nasal cavity, such as nasal polyps that require surgical treatment, should benefit primarily from SLIT. In fact, the biological effects of SLIT pose the basis for down-modulating the local immune response and favoring the polyp relapse.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 212).

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