

Sublingual immunotherapy

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Recent claims have been made that sublingual immunotherapy (SLIT) may be a viable alternative to injection immunotherapy (SIT). Animal studies show that when allergens are administered topically, they are handled differently, and IgE responses can be reduced. Most published studies of human SLIT have been small but show fairly consistent benefits on symptom scores, with few systemic side effects. Objective measures of allergen reactivity usually do not change. Relatively few subjects have been treated in SLIT trials compared with the numbers that would be required to validate new drug therapies. On the plus side, SLIT appears to work in adults and in children; it offers some logistic advantages and seems to be safe. Giving allergen by mouth rather than by injection should decrease the costs of immunotherapy, but the cumulative dose of allergen used in SLIT has been between 20 to 375 times the dose given in conventional SIT. Further cost-benefit analysis is needed. On the other hand, standard SIT is effective and is supported by better clinical and experimental evidence. The balance sheet for SLIT is improving, but on the current evidence, SLIT requires further evaluation before it could be recommended for use in routine clinical practice. (*J Allergy Clin Immunol* 2001;107:441-4.)

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The concept of specific desensitization lies at the heart of our specialty. Throughout much of the developed world, injection immunotherapy is accepted as a practical and effective means of reducing sensitivity to allergens,¹ although there remain disagreements about the best way to achieve clinical benefit. In particular, North American allergists tend to use multiple allergen vaccines, whereas Northern Europeans often prefer to use single allergen vaccines. Despite these differences in immunotherapy practice, there is general agreement that this form of therapy should only be prescribed and administered by professionals who are familiar with its use. All current guidelines emphasize the need for careful patient selection to ensure that those treated are likely to benefit and that the risks of adverse effects are minimized. While recognizing the efficacy of current

Abbreviations used

EAACI: European Academy of Allergology and Clinical Immunology
SIT: Specific immunotherapy
SLIT: Sublingual immunotherapy

regimens, work continues to find alternative forms of immunotherapy that are either more effective or more easily administered.

One area that has attracted considerable attention in recent years is the use of sublingual immunotherapy (SLIT). High-dose oral regimens were used in the first half of the 20th century^{2,3} but then lost ground to injection immunotherapy in conventional medical practice. Low-dose regimens for desensitization have been widely used in alternative medical practice,⁴ and they have occasionally been evaluated by mainstream allergists,⁵ although their effectiveness is disputed. In the last few years, there has been a resurgence of interest in the possibility of achieving desensitization by giving high doses of allergen topically. In a number of countries, particularly Spain, Italy, and France, this has become increasingly common in office practice, but there is now also an increasing body of evidence from academic studies to support the practice of local immunotherapy. A recent position statement from the European Academy of Allergology and Clinical Immunology (EAACI) has given some support to this approach,⁶ and it seems timely to examine the evidence for this form of therapy.

The theoretic basis for topical immunotherapy rests on 2 concepts. First, it is proposed that allergens given through the mucosal surface are handled differently from allergens given parenterally, leading to a special form of immunologic tolerance. Second, it is proposed that giving the allergen directly to the target organ may lead to downregulation of local effector responses. Clearly, both mechanisms could apply when the allergen is given directly to the target organ (eg, nasal immunotherapy), whereas indirect routes, including the sublingual approach, rely on the first of these propositions.

It is well established in animal models that IgE responses to allergens can be reduced or prevented by prior administration of allergen by the oral or inhalation routes.^{7,8} The precise mechanisms by which this oral tolerance is induced remain unclear, but it seems likely that the route of allergen processing and presentation is a crit-

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ical determinant of the subsequent T-cell response. From a theoretic perspective, the mucosal surface has to deal with regular exposure to a wide range of innocuous material, and its default response is set to nonresponse.^{9,10} This contrasts with the internal immune defenses, which are not normally exposed to foreign material because of the barrier epithelial defenses. Anything that reaches the internal defenses must have breached the external barriers and can therefore be considered dangerous, whereas most material seen at the surface may not be going anywhere and can be ignored. The more complex question regards what determines that some foreign material will elicit an immune response at the mucosal surface, despite being incapable of invasion, and furthermore why some materials elicit allergic-type responses while others drive more conservative (IgG) responses. This issue lies at the heart of what makes an allergen allergenic and also determines whether we may be able to achieve desensitization by means of the topical route.

Experimental support for this theory is available. It has been shown that locally administered allergen is taken up by mucosal dendritic cells, and at least in nonsensitized mice, the allergen is then presented to T cells together with IL-12, thereby biasing the response toward a T_H1 profile and away from the pro-IgE T_H2 profile.¹¹⁻¹⁴ It is less clear whether this mechanism can suppress established allergic responses, which is the situation that we would wish to achieve with SLIT. It is clear, however, when allergen is given by the sublingual route to allergic human subjects, that the allergen is retained in the buccal region much longer than if the allergen is simply placed in the mouth and then swallowed, suggesting that allergens are indeed taken up locally after sublingual administration.¹⁵ In contrast to animal models, the immunologic response to SLIT in human studies has been relatively modest. Some changes have been found in skin sensitivity,¹⁶ but most studies have not found any change in systemic parameters, such as specific IgE, specific IgG, or T cell-cytokine balance.¹⁶⁻²⁰

The 1998 EAACI position paper⁶ identified 31 studies of local immunotherapy, of which 14 used nasal immunotherapy, 2 administered the allergen directly into the airways, 9 used the oral route, and 6 used the sublingual route. Most of these studies were quite small, and various methodologies were used, but by means of careful meta-analysis, some conclusions could be drawn. First, it was apparent that nasal immunotherapy was effective, with a benefit found in 13 of 14 studies. The benefit appeared to be sustained only while the therapy was continued: after 2 years of successful therapy, the level of symptoms in the subsequent season was similar to that found in untreated patients.²¹ Local side effects were common, and it is arguable that nasal immunotherapy might be working by causing repeated degranulation of local mast cells and subsequent local tolerance of allergic inflammation rather than through a true immunologic effect. Oral immunotherapy seemed to be ineffective, with 7 of 9 eligible studies showing no benefit.⁶ Only 6 eligible sublingual studies were identified, 4 in adults and 2 in children. All of these found a benefit for active ther-

apy. All 6 of these studies used the sublingual-swallow method in which the extract was placed under the tongue, held there for a period of minutes, and then swallowed. Systemic side effects were relatively rare, except in one study,¹⁶ and none of the side effects were judged to be life-threatening. A significant reduction in skin test reactivity was found in one study,¹⁶ but there were no measurable changes in bronchial responsiveness to allergen or methacholine.^{16,22,23} The EAACI position paper concluded that SLIT has been shown to be efficacious in patients with rhinitis, but insufficient information was available to draw any conclusions for its use in asthma.

A number of criticisms can be made against the EAACI position paper analysis: 7 SLIT sublingual studies had to be excluded from the analysis for various reasons; several different allergens were studied (3 house dust mite, 2 grass pollen, and 1 weed pollen) with varying treatment regimens; and, most importantly, only 117 patients received active extracts in the 6 eligible studies, far less than would be required in comparable drug therapy trials.

Since 1998, a number of further studies have been published. A 2-year study of SLIT in children aged 6 to 14 years with allergic rhinoconjunctivitis caused by *Parietaria judaica*²⁴ found a benefit for active treatment, bolstering the evidence base for use of SLIT in younger patients. Over 85% of the subjects' symptoms improved, as did half of the symptoms of those in the placebo-treated group, with reductions of at least 30% in symptom scores. Interestingly, this improvement was not accompanied by any reduction in the use of concomitant medication in either group. This contrasts with studies of conventional (injection) specific immunotherapy (SIT), where there is usually a parallel reduction in symptoms and in medication use.²⁵⁻³² However, this study also illustrates several of the methodological problems associated with SLIT trials. This study was relatively small (41 patients, of whom 20 were randomized to active treatment), and almost one quarter of the patients failed to complete the trial period.

An even higher proportion of dropouts was reported in another recent SLIT study, which started with 72 patients but had 36 dropouts, 23 of whom cited lack of efficacy as the reason for discontinuing their participation.³³ Two thirds of these were in the placebo group, where lack of efficacy is to be expected, but this raises some concerns about the recruitment process for these studies. After all, the participants agreed to take part in the trials knowing that half of them would receive placebo therapy. Clinical trials rely heavily on the altruism and motivation of potential subjects, but if subjects are recruited who will not remain in the study when they receive placebo therapy, the whole basis of the study is undermined. This then wastes the contribution of the participants who adhere to the study protocol, as well as the clinical and financial resources put into the study. This is a significant ethical issue that has not yet been properly addressed by ethics committees (institutional review boards) to date.

Another recurrent problem in analysis is the existence of baseline differences between the active and placebo groups. In the study by La Rosa et al,²⁴ the active group

had a shorter duration of symptoms before therapy and also higher symptom and drug scores at the start of the 1996 pollen season. This means that there was more scope for improvement in the actively treated group and hence an increased chance of the active treatment showing benefit. Moreover, some parameters were unchanged in the active group but deteriorated in the placebo-treated group. Although we would all have accepted the data if the active group had symptom improvement but symptoms in the placebo group had remained the same or deteriorated, it is less clear how to interpret this type of reverse change.³⁴

The value of proper baseline evaluation is highlighted by a recent study of the efficacy of house dust mite SLIT in 24 children aged 8 to 15 years.³⁵ This study included a full year of baseline measurements, thereby ensuring the groups were well matched before entering the active phase. Twenty-one subjects completed the study, with the 3 dropouts being in the placebo group. Asthma episodes, nighttime asthma symptoms, and medication use were all relatively stable in the placebo group but improved significantly after 1 year of active SLIT. Although this study was relatively small, the conclusions are much clearer than in many larger studies because of the careful baseline assessment. This careful approach to studies of controversial therapies is to be commended.³⁴

The body of evidence supporting SLIT has been expanded considerably in the past 2 years. A recent safety analysis reported data on 347 patients who had received active therapy in placebo-controlled trials.³⁶ Most of these data are now published, although some of the studies cited were only available in abstract form at the time of analysis. One of these newer studies found differential effects on symptoms in patients with allergic rhinitis treated with grass pollen SLIT.³⁷ This was a large study, with 63 patients in each arm. The actively treated group showed a 30% reduction in rhinitis symptom scores, a 10% to 15% reduction in conjunctivitis scores, and no detectable effect on asthma symptom scores during the pollen season. This raises the possibility that the mechanisms driving asthma and rhinitis symptoms may be different, or else the asthma process may be less sensitive to the immunologic mechanism targeted by SLIT.

Giving allergen by mouth rather than by injection should decrease the costs of SIT by reducing the need for medical and nursing time, as well as costs of consumables, such as syringes and needles. However, the cumulative dose of allergen used in SLIT studies has been between 20 to 375 times the usual cumulative dose of allergen given to patients for conventional injection SIT.³⁸⁻⁴⁰ The increased cost of the allergen extracts is in part offset by reduced consumable and staff costs, but formal cost-benefit analysis is still needed.

Data on safety aspects of SLIT are encouraging. Local side effects seem to have been quite common in some studies,^{16,22,24} but the investigators do not seem to have regarded this as a problem. Local gastrointestinal symptoms were the most common adverse feature in these studies and are usually classified as local side effects because the allergen is given into the gastrointestinal tract. Sys-

temic side effects have also been reported, but there have been no episodes of full-blown anaphylaxis.^{6,36}

Therefore the arguments in favor of SLIT are first that it works in adults and in children, as evidenced by a number of independent trials of single agents; second that it seems safe; third that it may be cheaper, although the reduced costs of administration and reduced need for medical supervision are offset by increased costs of allergen extracts; and fourth that it offers some logistic advantages in countries where access to allergy specialists is difficult.

In argument against the use of SLIT, it has to be acknowledged that there are good alternatives: standard injection SIT is effective, and the evidence to support this form of therapy is much better than the evidence for SLIT, especially in the treatment of rhinitis. Direct comparisons with SIT and with standard drug therapy are also needed. Of course, SLIT may have some additional long-term benefit, but the evidence to date suggests that SLIT remains effective only while it is being given.²¹ This is in contrast to SIT, which is effective for several years after cessation^{41,42} and reduces the risk of development of new sensitizations when given to allergic children.⁴³ The changes in T_H1/T_H2 balance and cytokine production after injection SIT are consistent with a disease-modifying effect. Our current understanding of the action of SIT is that it works through modifying the cellular response to allergen. There are clear immunologic correlates in the form of shifts in T_H1/T_H2 balance⁴⁴⁻⁴⁶ and the induction of allergen-specific IgG. These have not yet been demonstrated after SLIT,^{16-20,47} although some effect is seen on inflammatory parameters, such as adhesion molecule expression⁴⁸ or serum eosinophil cationic protein values.⁴⁹ It is fair to say that we do not know whether the responses to SIT are connected to the mode of action. They could simply reflect the vaccination schedule, without being the direct means of efficacy.

In conclusion, SLIT has a degree of efficacy in allergic disease and significant logistic advantages over conventional SIT in terms of patient acceptability and reduced need for medical supervision. This could make it an attractive option, especially in those areas where access to allergists is limited, either through distance or because of limited numbers of specialists. Few direct comparisons with SIT have been made, but thus far it seems that SLIT is less effective than SIT. Therefore the decision to use SLIT has to be supported by reductions in costs and improvements in patient acceptability and compliance. The balance sheet for SLIT is improving, but on the current evidence, SLIT requires further evaluation before it can be recommended for use in routine clinical practice.

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