Allergen specific immunotherapy, together with drugs and allergen avoidance, is a cornerstone in the management of respiratory allergy. The traditional subcutaneous route is burdened with the risk of severe adverse events; therefore, safer routes of administration (noninjection or local routes) have been investigated and developed. Controlled trials failed to demonstrate the clinical efficacy and the safety of oral and bronchial administration, and these routes have been abandoned. Local nasal immunotherapy proved effective and safe in 17 of 18 controlled trials; thus it is considered a viable route of immunotherapy. Nevertheless, nasal immunotherapy is effective in rhinitis only and requires a particular administration technique; therefore its use is slowly declining. The sublingual route is supported by numerous controlled trials showing its efficacy in asthma and rhinitis in adults and children. The safety profile, assessed in clinical trials and postmarketing surveillance studies, is satisfactory; most frequent side effects are gastrointestinal complaints, which can be easily managed by proper dose adjusting. Sublingual immunotherapy is now accepted by the World Health Organization as a valid alternative to the subcutaneous route also in children. Although the long-lasting efficacy has been recently documented for the sublingual route, several points still need to be elucidated, including mechanisms of action, optimal dosage, cost-effectiveness, and adherence. (J Allergy Clin Immunol 2003;111:437-48.)

Key words: Allergen immunotherapy, sublingual immunotherapy, local nasal immunotherapy, noninjection routes

Noninjection routes for immunotherapy

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Allergen specific immunotherapy, together with drugs and allergen avoidance, is a cornerstone in the management of respiratory allergy. The traditional subcutaneous route is burdened with the risk of severe adverse events; therefore, safer routes of administration (noninjection or local routes) have been investigated and developed. Controlled trials failed to demonstrate the clinical efficacy and the safety of oral and bronchial administration, and these routes have been abandoned. Local nasal immunotherapy proved effective and safe in 17 of 18 controlled trials; thus it is considered a viable route of immunotherapy. Nevertheless, nasal immunotherapy is effective in rhinitis only and requires a particular administration technique; therefore its use is slowly declining. The sublingual route is supported by numerous controlled trials showing its efficacy in asthma and rhinitis in adults and children. The safety profile, assessed in clinical trials and postmarketing surveillance studies, is satisfactory; the most frequent side effects are gastrointestinal complaints, which can be easily managed by proper dose adjusting. Sublingual immunotherapy is now accepted by the World Health Organization as a valid alternative to the subcutaneous route also in children. Although the long-lasting efficacy has been recently documented for the sublingual route, several points still need to be elucidated, including mechanisms of action, optimal dosage, cost-effectiveness, and adherence. (J Allergy Clin Immunol 2003;111:437-48.)

Key words: Allergen immunotherapy, sublingual immunotherapy, local nasal immunotherapy, noninjection routes

Allergen-specific immunotherapy or allergen vaccination is the practice of administering to subjects with allergy increasing amounts of allergen(s) (the allergenic extract or vaccine) to achieve a hyposensitization and to reduce the symptoms occurring during the natural exposure to the allergen(s) itself. Since its discovery, immunotherapy has been commonly given subcutaneously (SCIT). Nevertheless, other modalities of administration were proposed and investigated during the last century, involving the administration of vaccines via gastrointestinal, nasal, or bronchial routes. Those routes have been variously named, i.e., alternative, nonparenteral, noninjection, or local routes.
Presently, it is agreed that the most proper terms are local and noninjection, which are equivalent, whereas the word alternative has been abandoned because it might generate confusion with other unconventional medicines.

The characteristics of the local routes are summarized in Table I. It is important to distinguish between the “pure” oral route and the sublingual. In fact, the experimental evidence showed that only this latter one is clinically effective. In sublingual immunotherapy (SLIT), the extract is usually kept under the tongue for 1 to 2 minutes and then swallowed; thus this route is also called sublingual-swallow. Indeed, in some studies a different method was adopted: the allergen was kept under the tongue and then spat out (sublingual-spit). Presently, on the basis of clinical results and pharmacokinetic considerations, only the sublingual-swallow route is used; therefore throughout the text SLIT will indicate the sublingual-swallow modality.

### Table I. Characteristics of the noninjection (local) routes for immunotherapy

<table>
<thead>
<tr>
<th>Route</th>
<th>Acronym</th>
<th>Preparation</th>
<th>Comments</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>OIT</td>
<td>Drops, tablets, capsules</td>
<td>Vaccine immediately swallowed</td>
<td>Buildup + maintenance</td>
</tr>
<tr>
<td>Bronchial</td>
<td>LBIT</td>
<td>Solution, suspension, dry powder</td>
<td>Allergen extract inhaled into bronchial tree</td>
<td>Buildup + maintenance</td>
</tr>
<tr>
<td>Nasal</td>
<td>LNIT</td>
<td>Solution, dry powder</td>
<td>Allergen extract sprayed into a nostril while vocalizing</td>
<td>Buildup + maintenance, steady dosage without buildup</td>
</tr>
<tr>
<td>Sublingual</td>
<td>SLIT</td>
<td>Drops, soluble tablets</td>
<td>Vaccine kept under the tongue for 1-2 min and then swallowed (SLIT-swallow) or spat (SLIT-spit)</td>
<td>Buildup + maintenance, rush build-up</td>
</tr>
</tbody>
</table>

### Abbreviations used
- DBPC: Double-blinded, placebo-controlled
- LBIT: Local bronchial immunotherapy
- LNIT: Local nasal immunotherapy
- OIT: Oral immunotherapy
- SCIT: Subcutaneous immunotherapy
- SLIT: Sublingual immunotherapy

### HISTORICAL BACKGROUND

Since the first empirical attempts, immunotherapy was administered subcutaneously and its clinical efficacy rapidly favored a widespread use. The idea of administering the allergenic extracts orally is not so recent as commonly believed; the oral route was first suggested in 1900, and the first clinical attempts were made a few years later. Subsequently, other routes of administration were proposed (Fig 1): the local bronchial during the 1950s, the local nasal during the 1970s, and the oral at the beginning of the 1980s. Except for local nasal immunotherapy, which was extensively studied starting from 1977, all the mentioned approaches remained substantially anecdotal, because the use of the subcutaneous route was well established. In 1986 the British Committee for the Safety of Medicines reported several deaths caused by SCIT and raised serious concerns about the safety and the risk/benefit ratio of immunotherapy, also because of the availability of cheap and effective drugs. Indeed, it was subsequently demonstrated that, in most cases, life-threatening events were due to avoidable human errors (wrong dose, improper prescription, incorrect administration). Nonetheless, the interest in noninjection routes of immunotherapy rapidly increased; several studies with the oral route were published in the 1980s, and the sublingual route appeared on
TABLE II. Summary of the DBPC studies of LNIT

<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Age range (y)</th>
<th>Patients (A/P)</th>
<th>Allergen</th>
<th>Duration</th>
<th>Type of extract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansson, 1979 (39)</td>
<td>Adolescence</td>
<td>12/11</td>
<td>Grass</td>
<td>14 wk</td>
<td>Aqueous, modified</td>
</tr>
<tr>
<td>Nickelsen, 1981 (40)</td>
<td>16-66</td>
<td>38/34</td>
<td>Ragweed</td>
<td>3 mo</td>
<td>Aqueous, modified</td>
</tr>
<tr>
<td>Welch, 1981 (41)</td>
<td>13-58</td>
<td>18/15</td>
<td>Ragweed</td>
<td>20 wk</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Schumacher, 1982 (42)</td>
<td>20-53</td>
<td>8/7</td>
<td>Grass</td>
<td>10 wk</td>
<td>Powder, modified</td>
</tr>
<tr>
<td>Georgitis, 1983 (43)</td>
<td>16-67</td>
<td>31/13</td>
<td>Grass</td>
<td>10 wk</td>
<td>Aqueous, modified</td>
</tr>
<tr>
<td>Georgitis, 1984 (44)</td>
<td>Adolescence</td>
<td>29/16</td>
<td>Parietaria</td>
<td>18 wk</td>
<td>Powder, modified</td>
</tr>
<tr>
<td>Andri, 1992 (46)</td>
<td>14-54</td>
<td>8/8</td>
<td>Parietaria</td>
<td>12 mo</td>
<td>Powder</td>
</tr>
<tr>
<td>Andri, 1993 (45)</td>
<td>15-54</td>
<td>11/10</td>
<td>Mite</td>
<td>5 mo</td>
<td>Powder</td>
</tr>
<tr>
<td>Passalacqua, 1995 (48)</td>
<td>20-56</td>
<td>9/9</td>
<td>Parietaria</td>
<td>8 mo</td>
<td>Powder</td>
</tr>
<tr>
<td>D’Amato, 1995 (47)</td>
<td>13-37</td>
<td>10/10</td>
<td>Parietaria</td>
<td>8 mo</td>
<td>Powder</td>
</tr>
<tr>
<td>Andri, 1995 (49)</td>
<td>17-56</td>
<td>14/14</td>
<td>Birch</td>
<td>22 wk</td>
<td>Powder</td>
</tr>
<tr>
<td>Andri, 1996 (50)</td>
<td>14-52</td>
<td>13/15</td>
<td>Grass</td>
<td>4 mo</td>
<td>Powder</td>
</tr>
<tr>
<td>Ciria, 1996 (51)</td>
<td>17-44</td>
<td>11/11</td>
<td>Birch/alder</td>
<td>4 mo</td>
<td>Powder</td>
</tr>
<tr>
<td>Bardare, 1996 (52)</td>
<td>5-15</td>
<td>19/20</td>
<td>Grass</td>
<td>3 mo</td>
<td>Powder</td>
</tr>
<tr>
<td>Bertoni, 1999 (53)</td>
<td>18-43</td>
<td>10/10</td>
<td>Grass</td>
<td>3 mo</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Motta, 2000 (54)</td>
<td>13-55</td>
<td>55/47</td>
<td>Grass/mite</td>
<td>8 mo</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Pocobelli, 2001 (55)</td>
<td>16-45</td>
<td>22/21</td>
<td>Grass</td>
<td>4 mo</td>
<td>Powder, modified</td>
</tr>
<tr>
<td>Marucci, 2002 (56)</td>
<td>4-15</td>
<td>16/16</td>
<td>Mite</td>
<td>18 mo</td>
<td>Powder, modified</td>
</tr>
</tbody>
</table>

A/P, Active/placebo.

The oral route (allergen immediately swallowed) represented the starting point for the subsequent diffusion of SLIT. The rationale for giving the allergen orally is that the gastrointestinal tract has an abundant mucosal immune system (so-called gut-associated lymphoid tissue [GALT]); therefore, an effective antigen presentation can be expected. As mentioned, a few studies on oral immunotherapy (OIT) in the early 1980s reported controversial or negative results and brought OIT into disfavor. Nevertheless, the subsequent trials performed (mainly by Scandinavian authors) with high doses of allergen renewed the interest in oral administration. Presently there are 9 double-blind, placebo-controlled (DBPC) trials of OIT, performed with various allergens and conducted in a rigorous fashion. All those trials evaluated the effects of OIT on rhinitis (symptoms and drug intake), and the majority of them were conducted in pediatric patients. Only 3 of the 9 studies showed a statistically significant improvement of symptoms. Of note, in a dust mite study a clinical improvement of rhinitis could be seen only after 2 years of treatment, and improvement of asthma symptoms became significant only at the third year. Moreover, in several studies, many untoward effects (not life-threatening) were noticed. These side effects were mainly gastrointestinal, and they seemed to increase with the increasing of the dosage of allergen. The use of gastroresistant capsules did not enhance the performance of the therapy. It is true that systemic/local immunologic changes (eg, increase of IgG subclasses, reduction of specific reactivity at the target organs) resembling those provoked by SCIT could be demonstrated, but the real clinical efficacy was marginal and achievable only with high dosages. For these reasons OIT appeared to be not cost-effective, and its clinical use was virtually abandoned starting from the early 1990s.

Local bronchial hyposensitization was proposed as early as 1951, but DBPC trials were performed only in the 1990s. There are 2 controlled studies of local bronchial immunotherapy (LBIT), both performed with dust mite extracts. In one study (22 adult patients, treated for about 3 months) no significant clinical improvement was found, although a significant decrease of bronchial specific reactivity (early and late phase at allergen bronchial challenge) was noticed. The majority of patients had a significant fall in their FEV$_{1}$ after LBIT administration, and 1 of them experienced overt bronchospasm. In the other study (24 adult patients, treated for 2 years), significant clinical improvement of symptoms and decrease of medication intake were seen. The authors reported that some patients (figures not provided) experienced bronchospasm and needed bronchodilator therapy.

The results of those trials suggested that the clinical efficacy is unproven and the risk/benefit ratio is unfavorable. These are the reasons why LBIT has been completely abandoned, although it remains an interesting speculative and experimental model.
As mentioned, the first attempts to achieve a selective hyporesensitization of the nasal mucosa were made at the beginning of the 1970s. The rationale for doing that was the observation that a hyporesponsiveness of the nasal mucosa after repeated stimulations with low doses of allergen can be obtained. This fact is, from a clinical viewpoint, the opposite of the well-known priming effect, and it can be measured by sequential nasal challenge. LNIT was demonstrated effective with all the major pollens (birch, ragweed, grasses, parietaria) in adults, whereas there are only 2 studies performed with a mite extract; three studies were carried out in children. Therefore its use in mite-induced rhinitis in adult patients is not sufficiently evidence-based so far. The only follow-up study available suggested that LNIT does not maintain its clinical efficacy once discontinued and that a preseasonal course is needed every year.

LNIT is usually prepared as aqueous solution or as powder in capsules to be broken and sprayed into the nose through a proper device. The administration requires therefore a good training and some precautions to avoid inhalation into the deep airways. Premedication with nasal cromolyn before each dose has been recommended by some authors, but there is no strict scientific support in favor of this. Usually, LNIT consists of a buildup phase, followed by a maintenance phase, but very recently a simplified schedule with a single and steady dosage has been shown equally effective.

The clinical use of LNIT in Europe is progressively declining, although new studies have been recently published. This is mainly due to the fact that SLIT is easier to manage and it can be used also in patients with concomitant asthma. LNIT remains, in principle, a viable alternative to SCIT; the optimal patients would be adult and well-trained patients with pollen-induced rhinitis and with a diameter of 40 to 50 µm allow a uniform deposition on the nasal mucosa and do not provoke clinical symptoms. In fact, in all the studies with dry powders, no or negligible side effects were reported. In one study, three patients withdrew because of bronchospasm after administration, but this was ascribed to incorrect technique. LNIT was demonstrated effective with all the major pollens (birch, ragweed, grasses, parietaria) in adults, whereas there are only 2 studies performed with a mite extract; three studies were carried out in children. Therefore its use in mite-induced rhinitis in pediatric age is not sufficiently evidence-based so far. The only follow-up study available suggested that LNIT does not maintain its clinical efficacy once discontinued and that a preseasonal course is needed every year.

LOCAL NASAL IMMUNOTHERAPY

**Table III. Summary of the DBPC studies of SLIT**

<table>
<thead>
<tr>
<th>First author, year (reference)</th>
<th>Age range (y)</th>
<th>Patients (A/P)</th>
<th>Allergen</th>
<th>Duration</th>
<th>Cumulative dose</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tari, 1990 (60)</td>
<td>5-12</td>
<td>30/28</td>
<td>Mites</td>
<td>18 mo</td>
<td>365 STU</td>
<td>R/A</td>
</tr>
<tr>
<td>Sabbah, 1994 (61)</td>
<td>13-51</td>
<td>19/29</td>
<td>Grasses</td>
<td>17 wk</td>
<td>4,500 IR</td>
<td>R</td>
</tr>
<tr>
<td>Feliziani, 1995 (62)</td>
<td>14-48</td>
<td>18/16</td>
<td>Grasses</td>
<td>3.5 mo</td>
<td>25 BU</td>
<td>R</td>
</tr>
<tr>
<td>Troise, 1995 (63)</td>
<td>17-60</td>
<td>15/16</td>
<td>Parietaria</td>
<td>10 mo</td>
<td>105 BU</td>
<td>R</td>
</tr>
<tr>
<td>Hirsch, 1997 (64)</td>
<td>6-16</td>
<td>15/15</td>
<td>Mites</td>
<td>1 y</td>
<td>570 µg Der p 1</td>
<td>R/A</td>
</tr>
<tr>
<td>Passalacqua, 1998 (69)</td>
<td>15-46</td>
<td>10/9</td>
<td>Mites (monoid)</td>
<td>2 y</td>
<td>10,000 AU</td>
<td>R</td>
</tr>
<tr>
<td>Vourdas, 1998 (67)</td>
<td>7-17</td>
<td>33/31</td>
<td>Olive</td>
<td>2 y</td>
<td>4 mg Ole e 1</td>
<td>R/A</td>
</tr>
<tr>
<td>Clavel, 1998 (65)</td>
<td>8-55</td>
<td>62/28</td>
<td>Grasses</td>
<td>6 mo</td>
<td>28 µg Phl p 5</td>
<td>R/A</td>
</tr>
<tr>
<td>Horak, 1998 (66)</td>
<td>16-48</td>
<td>18/16</td>
<td>Birch</td>
<td>4 mo</td>
<td>250 STU</td>
<td>R</td>
</tr>
<tr>
<td>Hordijk, 1998 (68)</td>
<td>18-45</td>
<td>30/27</td>
<td>Grasses</td>
<td>6 mo</td>
<td>100,000 BU</td>
<td>R/A</td>
</tr>
<tr>
<td>Bouquet, 1999 (71)</td>
<td>15-37</td>
<td>15/15</td>
<td>Mites</td>
<td>2 y</td>
<td>25 mg Der p 1</td>
<td>A</td>
</tr>
<tr>
<td>Passalacqua, 1999 (70)</td>
<td>15-42</td>
<td>15/15</td>
<td>Parietaria</td>
<td>8 mo</td>
<td>16 µg Par j 1</td>
<td>R/A</td>
</tr>
<tr>
<td>Pradalier, 1999 (73)</td>
<td>6-25</td>
<td>59/61</td>
<td>Grasses</td>
<td>4 mo</td>
<td>5,000 STU</td>
<td>R/A</td>
</tr>
<tr>
<td>La Rosa, 1999 (74)</td>
<td>6-14</td>
<td>20/21</td>
<td>Parietaria</td>
<td>6 mo</td>
<td>4,000 STU</td>
<td>R/A</td>
</tr>
<tr>
<td>Purello, 1999 (72)</td>
<td>14-50</td>
<td>14/16</td>
<td>Parietaria</td>
<td>8 mo</td>
<td>12 µg Par j 1</td>
<td>R/A</td>
</tr>
<tr>
<td>Pajno, 2000 (76)</td>
<td>8-15</td>
<td>12/12</td>
<td>Mites</td>
<td>2 y</td>
<td>2.4 mg Der p 1</td>
<td>A</td>
</tr>
<tr>
<td>Guez, 2000 (75)</td>
<td>6-51</td>
<td>24/18</td>
<td>Mites</td>
<td>2 y</td>
<td>2.2 mg Der p 1</td>
<td>R</td>
</tr>
<tr>
<td>Caffarelli, 2000 (77)</td>
<td>4-14</td>
<td>24/20</td>
<td>Grasses</td>
<td>3 mo</td>
<td>32,000 AU</td>
<td>R/A</td>
</tr>
<tr>
<td>Arian, 2001 (78)</td>
<td>19-50</td>
<td>10/10</td>
<td>Cypress</td>
<td>8 mo</td>
<td>250,000 RU</td>
<td>R/A</td>
</tr>
<tr>
<td>Bahciciler, 2001 (79)</td>
<td>7-15</td>
<td>8/7</td>
<td>Mites</td>
<td>6 mo</td>
<td>2,000 IR</td>
<td>R/A</td>
</tr>
<tr>
<td>Volottilini, 2001 (80)</td>
<td>15-52</td>
<td>24/13</td>
<td>Trees</td>
<td>24 mo</td>
<td>4,000 IR</td>
<td>R</td>
</tr>
<tr>
<td>Lima, 2002 (81)</td>
<td>16-48</td>
<td>24/22</td>
<td>Grasses</td>
<td>18 mo</td>
<td>16 mg Phl p 5</td>
<td>R</td>
</tr>
</tbody>
</table>

A/P, Active/placebo; STU, standard units; R, rhinitis; A, asthma; IR, index of reactivity; BU, biological units; AU, allergenic units; RU, RAST units.
those patients refusing injections or who do not tolerate the subcutaneous regimen.

**SUBLINGUAL IMMUNOTHERAPY**

The original rationale for administering immunotherapy sublingually was that of achieving a prompt and rapid absorption of the vaccine to avoid possible gastrointestinal degradation. Although it was recently demonstrated that no relevant direct absorption through the sublingual mucosa occurs, SLIT proved effective in a great number of trials; therefore, it is presently the most widely used noninjection route for immunotherapy in Europe. Usually a SLIT course involves a buildup phase (extract administered at increasing doses) and a maintenance phase, in which the maximum dose is administered 2 or 3 times a week. Furthermore, SLIT can be administered preseasonally, pre-coseasonally, or continuously; pre-coseasonal schedules are the choice for pollen allergy, whereas continuous treatments are preferred for perennial allergens.

**Efficacy**

SLIT was first investigated in a DBPC rigorous trial in 1986; after 12 years, in 1998, the WHO position paper mentioned 4 studies, and the EAACI/ESPACI document published in the same year considered 6 studies. To date, 22 DBPC trials conducted with adequate methods and analysis have been published in peer-reviewed journals (Table III), thus testifying to the rapid development of the clinical interest in this route of administration.

All the studies but three confirmed the clinical efficacy of SLIT in rhinitis induced by common allergens such as grass, mites, birch, and parietaria. There are also single positive studies with olive, cypress, and mixed-trees extracts. The magnitude of the clinical efficacy ranged between about 20% and 50% reduction of symptom or medication scores, thus quite superior to the placebo effect and close to the effect of SCIT.

A very recent controlled study failed to demonstrate a significant clinical effect (symptom score and medication intake) of SLIT in rhinitis due to grass, although the self-evaluation made by the patients was largely positive and a systemic immunologic effect was also apparent. Also in 2 studies conducted with mite extracts SLIT performed poorly; a trend toward clinical improvement was seen in the active groups, but it did not reach statistical significance. This fact is well known also for SCIT, which is usually less effective in patients with mite allergy than in patients with pollen sensitivity. In patients with mite allergy, the duration of the treatment seems to be crucial; in fact, those treatments lasting at least 2 years gave positive results.

It is important to notice that SLIT exerts its effect not only on rhinitis but also on asthma symptoms. The results from some recent studies showed a reduction of the days with asthma symptoms, of the use of β2-agonists, of the intake of systemic steroids, and of clinical symptoms. One single study also demonstrated a measurable effect of SLIT on the quality of life of patients. More conclusive data on this topic will be provided by the randomized controlled 3-year trial, named QOLIT, that is presently underway in a large population of patients. Finally, in an open controlled study with a grass extract it was shown that SLIT significantly reduced the nonspecific bronchial hyperresponsiveness to methacholine measured out of the pollen season.

**Comparison with SCIT**

When comparing 2 different routes of administration, the gold standard methodology is the double-blinded double-dummy one. At present we have available a single double-dummy study published as a full paper. This trial, conducted in patients with grass pollen allergy, showed that the clinical efficacy of SLIT (symptoms and need for drugs) was equivalent to that of SCIT. A well-designed rigorous double-dummy trial with birch pollen extract has been recently published as an abstract, showing that SLIT and SCIT were equally effective, although the safety and tolerability were quite superior to the noninjection route. Some other comparative studies have been published, but they were all conducted in an open fashion and therefore the results cannot be assumed as conclusive. Ongari et al demonstrated that SLIT and SCIT had similar efficacy in 20 patients with grass allergy and that both treatments were significantly more effective than pharmacologic treatment alone. Bernardis et al performed an open comparative 12-month study in patients with Alternaria tenuis allergy and found a significant clinical improvement in both groups (even greater with SLIT). In another study, the clinical efficacy of SLIT, SCIT, and LNIT was assessed in 43 patients with rhinitis due to mites; in this study only the immunologic changes were emphasized. The authors evidenced the good tolerability of SLIT, although SCIT was more effective and able to induce immunologic changes. The most recent open comparison, again in patients with mite allergy, showed that clinical improvement was more prompt with the subcutaneous route, especially for asthma symptoms, although SLIT controlled rhinitis symptoms well.

**Safety**

The main rationale of SLIT is of minimizing the risks for adverse events; therefore, particular attention has been paid to safety in all the studies. The most frequently reported side effect was the onset of oral/sublingual itching after taking the dose. This phenomenon was always described as mild and self-resolving. In the recent pediatric studies, the occurrence of side effects was negligible and they were not troublesome. In a single study, a significant rate of gastrointestinal complaints was reported, but in this study the amount of allergen was as high as 375 times the amount usually administered in a standard SCIT course. Headache, rhinorrhea, constipation, and urticaria were reported only sporadically, and their incidence did not differ from the placebo groups. Noticeably, no severe
systemic adverse event was ever reported in the literature during a period of 15 years. André et al89 recently reviewed the safety aspects of the controlled trials performed with the vaccines of a single manufacturer. Six hundred ninety subjects were enrolled (347 active + 343 placebo), with 218 children (103 active + 115 placebo). The large majority of events were mild. All events had a superimposable incidence in active and placebo groups, with the exception of the oral and gastrointestinal side effects, which were more frequent in SLIT patients, although mild. The occurrence of side effects and dropouts was similar in adults and children.

The information on safety provided by the controlled trials are valuable, but the populations are highly selected and the administration of SLIT is usually supervised. This situation is profoundly different from that occurring in the clinical reality. Therefore, more consistent information on safety should be obtained when SLIT is prescribed and administered in everyday clinical practice, ie, in postmarketing surveillance studies. An early study of pharmacosurveillance90 reported that the incidence of side effects was indeed low; oral itching represented about 50% of the untoward effects, followed by rhinorrhea and constipation. Urticaria and asthma were very rare. More than 90% of the effects were mild and did not require any kind of medical treatment. Di Rienzo et al91 performed a postmarketing study in 268 children aged between 2 and 15 years and receiving SLIT for up to 3 years; it showed that the overall incidence of systemic side effects was 3% of the patients and 1/12,000 doses. Of 8 side effects, only 1 (urticaria) was moderate and required treatment with a single dose of oral antihistamine. Overall, in none of the patients was the discontinuation of the treatment required. Another pharmacosurveillance study in adult patients was recently published,92 with 198 patients observed while receiving SLIT either preseasonally or continuously during a 3-year period. Side effects occurred in 7.5% of patients and 0.52/1000 doses administered. Four urticarias and 2 gastrointestinal complaints were judged as moderate. Also in this study, side effects were controlled by a temporary dose adjustment and in no case was the treatment discontinued. It has been claimed that SLIT could be at particular risk in patients with oral allergy syndrome by possibly eliciting severe edema. Indeed, a controlled study performed in 30 patients with oral allergy syndrome did not confirm this hypothesis.93 Finally, the possible effects of the sublingual administration of allergens were investigated by measuring the mucosal level of tryptase and eosinophil cationic protein; no change in the levels of these mediators could be detected at all, even in 1 patient reporting oral itching after SLIT intake.94

It is important to remember that the rate of occurrence of severe systemic (near-fatal) adverse events with SCIT ranges between 0.5% and 6%,15.95,96 Concerning the occurrence of systemic reactions in general, a comprehensive review by Stewart and Lockey97 on SCIT reported a range between 0.8% and 46.7%, depending on the schedule of administration. These figures are, on average, quite higher than those reported with SLIT. Surprisingly, in about 20% of the published studies with SCIT there is no information at all concerning side effects, and in the remaining studies side effects are reported only in an incomplete manner,98 with an average occurrence of systemic effects in 24% of patients. Collecting together the data from the randomized controlled trials and the pharmacosurveillance studies, the safety of SLIT is well documented. In fact, in the ARIA document it was suggested that SLIT can be administered safely in both adults and children.20

IMMUNOLOGY AND PHARMACOKINETICS

Much is known about the possible mechanisms of action of SCIT,99,100 including the downregulation of cytokine and mediator release, the inhibition of activation and recruitment of effector cells,101,102 and the modulation of T_{H1}/T_{H2} balance.103,104 This latter aspect, in particular, seems to be of primary relevance for the immunomodulatory effect exerted by immunotherapy, ie, the long-lasting efficacy after discontinuation.105-107 On the other hand, because local immunotherapy has been studied mainly from a clinical point of view, few observations concerning its mechanisms of action have been made. A relevant effect of OIT and SLIT on serum immunoglobulins was observed only in a minority of studies.27,31,60,63,71,74,81 It seemed that, in general, local routes do not induce a decrease of IgE and an increase of IgG1 and IgG4, or that these changes are not constant and reproducible.

In humans SLIT has been demonstrated to be capable of reducing the proliferative response of T lymphocytes from atopic subjects,108 and the same effect has been seen also with LNIT.57 When the inflammatory phenomena (cellular infiltration and adhesion molecule expression on epithelia) were studied in the target organs (nose and conjunctiva) by means of the allergen challenge, a superimposable incidence in active and placebo groups, with the exception of the oral and gastrointestinal side effects, which were more frequent in SLIT patients, although mild. The occurrence of side effects and dropouts was similar in adults and children.

The local administration of immunotherapy relies on a number of experimental observations in animal models, in which it is well known that the oral route is “tolerogenic” and can redirect the T_{H1}/T_{H2} differentiation.110-113 In addition, the dendritic cells of oral mucosa behave as efficient antigen-presenting cells and produce IL-12.114-116 In an animal model it was seen that the mucosal administration of the antigen could select a functionally disabled population of CD4+ cells.117

After one century of clinical use, no data are available on the pharmacokinetics (absorption and fate) of
the subcutaneous allergenic extracts in humans. Indeed, this aspect would be of particular relevance in the case of antigens administered to the mucosae; in fact, the clinical studies invariably showed that the allergen immediately swallowed (oral route) performs poorly, whereas the sublingual administration works. On the basis of the few available data, it seems that an almost complete degradation of the allergen occurs in the duodenum in humans. In rats and rabbits a significant absorption of the allergen through sublingual and nasal mucosae has been shown. This latter fact is in agreement with the increased permeability of nasal epithelium to macromolecules observed in subjects with allergy. Actually, as reviewed by Falagiani et al, the pharmacokinetics of allergens is, in general, still controversial.

Very recently, the pharmacokinetics of local routes was assessed in humans by using a radiolabeled purified allergen (Par j 1) and a special procedure. After the administration (oral, sublingual, or intranasal) of the radiolabeled 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; plasma radioactivity increased only after the allergen was swallowed. Moreover, the allergen was retained for long times (up to 40 hours) at mucosal level, in both the nose and the mouth. Finally, a gastrointestinal absorption was present, but no trace of the native allergen could be detected in the bloodstream. If a modified allergen (monomeric allergoid) was administered, it could be detected unmodified in traces in plasma (Fig 2). No significant difference in terms of pharmacokinetics existed between the sublingual-swallow and the sublingual-spit modes, but with this latter modality about 30% of the extract is lost. These data suggest that (1) the contact of the allergen with the oral mucosa is critical and (2) the allergen is not absorbed in the mouth. A drainage of the allergen into regional lymph nodes can be hypothesized, but this hypothesis is difficult to test because it would require the administration of a long half-life beta-emitter.

THE OPEN QUESTIONS

The results from the clinical trials led to the official approval of SLIT (and LNIT) for routine clinical use. Nevertheless, because the studies are a matter of 15 years only, several points still need to be better addressed.

Optimal dose of allergen

On the basis of the available literature, the effective doses of allergen for SLIT range between approximately 3-5 and 375 times the doses of SCIT. Of course, this interval is quite wide, and there is no proof that one particular dosage performs better than others. Moreover, there is no clear evidence that the efficacy is dose-dependent within the mentioned range; in particular, we do not know the dose-response behavior at dosages higher than 375 times the SCIT (Fig 3). On the other hand, it is known that high amounts of allergen are associated with troublesome gastrointestinal symptoms, whereas too low doses are quite ineffective. In summary, dose-ranging studies are lacking, and the methods of standardization used do not allow an exact comparison among the different extracts. The use of vaccines with known content of major allergen will probably allow better defining of this point in the future.
Similarly to SCIT, accelerated buildup schedules have been studied for SLIT on the basis of the good safety profile. A rush buildup (20 days) with Parietaria extract proved effective and safe. More recently, a 1-day ultra-rush buildup with a cypress extract was also used without side effects.

Adherence and costs

It is difficult to assess the adherence to treatment, which is self-administered, and SCIT has been claimed to be superior in this sense, because it is given by the physician. Nevertheless, looking at the studies assessing compliance, we observe that the rate of discontinuation with SCIT ranges between 10% and 34% and that up to 50% of the patients are noncompliant because of the occurrence of side effects. Thus, the safety of SLIT would imply also a better compliance, although this aspect needs specific studies.

Concerning the costs, it is true that the cumulative dose of allergen given via sublingual route is 20 to 300 times the usual dose of SCIT; therefore the cost of the vaccine is expected to be higher. This higher cost is effectively balanced by the reduced need for medical and nursing time, so that the global cost of SLIT is even less than that of SCIT as summarized in Table IV. Nevertheless, a formal cost-benefit analysis is still lacking.

Preventive effect and long-lasting efficacy

SCIT has been shown capable of modifying the natural history of the disease (ie, the onset of asthma in patients with rhinitis) and of preventing the onset of new sensitizations. Moreover, a long-lasting effect of SCIT after discontinuation has been seen in several clinical trials. At present, such demonstrations still lack for local routes, because SLIT has been used routinely only in the last 10 years. We can now report the results of a prospective, parallel groups, controlled study carried out in 60 children (mean age, 8.5 years) with allergic asthma/rhinitis due to mite. Thirty-five children underwent a 4- to 5-year course of SLIT with a standardized extract, and 25 (control group) received only drug therapy. The patients were evaluated at baseline, at the end of SLIT, and 4 to 5 years later. We found in the SLIT group a significant difference versus baseline for the presence of asthma (P < .001) and the use of asthma medications (P < .01) even 5 years after discontinuation, whereas no difference was observed in the control group (Fig 4).

TABLE IV. Estimated costs of immunotherapy per 1 year of continuous treatment

<table>
<thead>
<tr>
<th>SLIT</th>
<th>Cost</th>
<th>Comment</th>
<th>SCIT</th>
<th>Cost</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of the extract</td>
<td>$360</td>
<td>3 refills</td>
<td>$150</td>
<td>1.5 vials</td>
<td></td>
</tr>
<tr>
<td>Specialist visit</td>
<td>$100</td>
<td>2 interim visits</td>
<td>—</td>
<td>Patient seen at each injection</td>
<td></td>
</tr>
<tr>
<td>Injections</td>
<td>—</td>
<td>No injection</td>
<td>$144</td>
<td>$12 per injection × 12</td>
<td></td>
</tr>
<tr>
<td>Time lost</td>
<td>—</td>
<td>Self-administered</td>
<td>$240</td>
<td>$10 per h, 2 h per injection × 12</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>$460</td>
<td></td>
<td>$534</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSIONS

The treatment of respiratory allergy is based on allergen avoidance, pharmacologic treatment, and immunotherapy. Immunotherapy is an allergen-oriented immunomodulator that affects the immune response to allergens and whose action develops over a long time (months). The local routes, SLIT in particular, represent a significant advance because of safety and good acceptance. Nonetheless, the self-administration itself requires careful instruction and detailed follow-up of the patients. Its prescription must be made only by a specialist, after a detailed diagnosis has been established and the expected benefit/cost ratio has been carefully evaluated. The clinical efficacy of SLIT in both asthma and rhinitis is now supported by a large number of controlled trials, and it appears particularly suitable also in pediatric patients, in whom an optimal safety profile is required. After a period of justified skepticism because of the few studies available, in very recent years there was a gradual change in the general opinion, and SLIT became more and more accepted.

SLIT is, in general, suggested in patients showing low compliance with SCIT or with previous severe adverse reactions to SCIT, but it should not be considered as a last choice treatment. It is important to remember that SLIT must not be regarded as a substitute for SCIT, but rather as an additional choice or therapeutic tool. Similarly to SCIT, SLIT is not an alternative to drugs for controlling symptoms, but it must be used in combination with them.

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