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# Economic evaluation of sublingual vs subcutaneous allergen immunotherapy

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**Background:** Sublingual allergen immunotherapy (SLIT) is a commonly used alternative route of administration to standard subcutaneous immunotherapy (SCIT) in Europe. Despite its wide use, the cost-effectiveness of SLIT vs SCIT has not been well established.

**Objective:** To evaluate the cost and effectiveness of SLIT compared with SCIT in patients with allergic rhinoconjunctivitis during a 3-year specific allergen immunotherapy (SIT) from a third-party payer's, a patient's, and society's perspectives.

**Methods:** We performed an open-label randomized clinical trial of patients receiving SLIT (n = 19), patients receiving SCIT (n = 23), and a control group (n = 22). The outcome measures were Rhinoconjunctivitis Quality of Life Questionnaire score, visual analog scale score, symptomatic medication reduction, and direct and indirect costs.

**Results:** SLIT offered clinical benefits to patients comparable to those provided by SCIT. From the perspective of a third-party payer, the total average direct medical cost per patient of 3-year SIT was estimated at €416 vs €482 in the SLIT and SCIT groups, respectively. A patient who received SLIT paid less than a patient who received SCIT for all out-of-pocket costs (€176 for SLIT vs €255 for SCIT) but more for sole allergen extracts (€72 for SLIT vs €55 for SCIT). When both direct and indirect costs were considered, the 3-year SIT expenditures per patient reached €684 vs €1,004 in the SLIT and SCIT groups, respectively.

**Conclusions:** SLIT represents a less expensive alternative relative to subcutaneous administration from all perspectives. However, from a patient's perspective, SCIT offers a less expensive alternative for patients who do not experience loss of income and travel costs associated with treatment.

*Ann Allergy Asthma Immunol.* 2008;100:482–489.

## INTRODUCTION

Allergic rhinitis is a chronic condition with high prevalence in most highly developed countries.<sup>1</sup> The overall costs associated with allergic rhinitis and certain adverse effects of pharmacologic treatment, such as discomfort, somnolence, and cognitive impairment (impaired learning, memory, and performance), are substantial and create a significant economic burden to the society.<sup>2</sup>

From both an economic and a patient well-being perspective, allergen immunotherapy offers a real alternative because of its ability to reduce symptom-medication scores in the long term and improve the quality of life.<sup>3</sup> Today, specific allergen immunotherapy (SIT) is the only treatment that addresses the cause of IgE-mediated immunopathology and modulates the natural course of the disease.<sup>4</sup> Furthermore, SIT has been shown to prevent further progress of the disease and the onset of new sensitizations and asthma long after it was discontinued.<sup>5–7</sup> Subcutaneous allergen immunotherapy (SCIT) is a

well-established standard of care in patients with allergic rhinitis, rhinoconjunctivitis, atopic asthma, and Hymenoptera anaphylaxis for whom symptomatic treatment and allergen avoidance are not a sufficient way to control the disease.<sup>4</sup> Sublingual allergen immunotherapy (SLIT) is an alternative administration route recently proven to be effective and safe, with less serious systemic adverse effects than SCIT.<sup>8</sup>

The cost-savings potential of SCIT and SLIT compared with standard pharmacologic therapy has only been described in a few studies.<sup>9–13</sup> Our comparative study is, to the best of our knowledge, the first economic evaluation that directly compares SLIT to SCIT. The purpose of this study was to evaluate the effectiveness and costs of SCIT and SLIT in patients with seasonal allergic rhinoconjunctivitis (SARC) after 3 years of SIT administration from 3 perspectives: third-party payer, patient, and society.

## METHODS

The design was an open-label randomized clinical trial (January 1, 2002, to January 1, 2006). Sixty-four patients were randomly assigned to 3 study groups: SLIT, SCIT, and control. The SCIT patients were treated with a standardized grass pollen extract (Phostal; Stallergènes SA, Antony, France) administered at a clinic. Standardized grass pollen extracts (Staloral; Stallergènes SA) for SLIT patients were self-administered at home. Patients were treated continuously from January 2003 according to the manufacturer's instructions. All patients, including the control group, followed a standard symptomatic treatment according to World Health Organiza-

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**Disclosures:** Authors have nothing to disclose.

**Financial Support:** The study received public funding in the form of a 3-year grant from the Ministry of Health of the Czech Republic (MZ CR NI/7470–3).

Received for publication May 21, 2007; Received in revised form October 23, 2007; Accepted for publication October 23, 2007.

tion and Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines.<sup>1</sup> The study was conducted according to the guidelines of good clinical practice and was approved by an independent ethics committee. Informed written consent was obtained from all patients.

#### Patients

All patients were 18 years or older, had a history of SARC for at least 2 years uncontrolled by symptomatic treatment, and had moderate persistent rhinitis (according to the classification of seasonal allergic rhinitis severity based on ARIA recommendations, 2001).<sup>1</sup> The diagnosis of the SARC was based on medical history and clinical symptoms and was verified by positive skin prick test results and the presence of grass pollen specific IgE. Patients with a concomitant diagnosis of intermittent or mild persistent seasonal grass pollen-induced asthma were allowed to participate. Exclusion criteria were concomitant perennial allergic rhinitis and standard contraindication for immunotherapy.<sup>4</sup>

#### Effectiveness

The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was used to measure health outcomes in our study.<sup>14</sup> We compared the proportion of clinically improved patients in the third year compared with the first year of SIT. A change in the score of greater than 0.5 point for each of the domains and overall scores is interpreted as the minimal important difference that is considered clinically significant.<sup>15</sup> This evaluation was supplemented by a visual analog scale, a 100-mm scale with 0 mm indicating no impairment and 100 mm indicating maximal impairment, which was used to estimate the health improvements both before and during SIT. Each year patients were asked to evaluate severity of rhinoconjunctivitis symptoms during the high peak pollen season before and after SIT treatment. Decrease in the consumption of symptomatic medication related to SARC was expressed as a mean defined daily dose (DDD) per anatomical therapeutic class (ATC) using the ATC/DDD methodology.<sup>16</sup>

#### Cost Evaluation

Direct medical costs included costs of medication and health care services. Costs arising from adverse effects of treatment (medication, emergency department visit, hospitalization) were also considered. Health care service costs included specialist visits (consultations, laboratory tests, diagnostic tests, nurse services), emergency department visits, and hospitalizations. The economic analysis excluded services that were provided strictly for the purposes of the study. Patients' costs covered medication copayment, over-the-counter drugs, travel costs, loss of income due to allergy symptoms, and treatment. From a society's perspective, costs also included productivity loss as an indirect cost. Costs that resulted from productivity reduction as a consequence of allergy symptoms, such as fatigue and concentration loss, were neglected.

Fixed costs included the costs for medication and health care services. The cost of health care services was calculated by multiplying the number of units per service and the unit

price. The cost of medication was calculated from the number of DDDs and cost per DDD.<sup>16</sup> Patient travel costs were computed by multiplying the number of specialist visits and travel costs per specialist visit. A human capital approach was used to calculate indirect cost (productivity loss).<sup>17,18</sup> Direct and indirect costs were discounted at a rate of 3% per year. The unit costs are given in Table 1.

#### Resource Use

Data such as medication use, physician time, and health care service costs (specialist visits, emergency department visits, and hospitalizations), demographics, and comorbid conditions were retrieved from the central database of patient medication records managed by the Department of Economy at the University Hospital. The number of units for health care services and the cost per unit were set by the Czech Republic's Health Care Directive of 2002.<sup>19</sup> The reimbursement costs of drugs were retrieved from the Czech National Drug Price List of 2002.<sup>20</sup> There is no central information source on retail sale prices of drugs in the Czech Republic. Prices of prescribed medication and over-the-counter drugs were represented by an average price calculated from the actual 2002 retail prices obtained from a sample of retail and hospital pharmacies in the study location. The following data were collected by using a patient questionnaire: over-the-counter medication use, hospitalizations and emergency department visits, sick leaves, work and school absenteeism, and time associated with specialist visits. Travel costs were based on the distance between the patient's place of residency and the allergist office and a price estimate of €0.01 per kilometer.<sup>21</sup>

The monetary value of productivity loss was expressed in terms of lost workdays per employee. Each workday loss was valued at a 2002 gross salary average for employees in the Czech Republic and divided by the number of working days

Table 1. Unit Cost

| Unit   | Cost, € <sup>a</sup> |
|--|----------------------|
| Medication <sup>b</sup>  |                      |
| Allergen extracts (sublingual administration), package (reimbursement/copayment)   |                      |
| Initiation phase   | 41.57/9.42           |
| Maintenance phase  | 41.25/10.12          |
| Allergen extracts (subcutaneous administration), package (reimbursement/copayment) |                      |
| Initiation phase   | 40.04/11.30          |
| Maintenance phase  | 33.88/9.08           |
| Health care service, unit  | 0.03                 |
| Productivity or income loss, working day   | 24.52                |
| Travels, km  | 0.11                 |

<sup>a</sup> 1 Euro = 31.80 Czech koruna.

<sup>b</sup> Prescription and over-the-counter drugs were reimbursed based on the Czech National Drug Price List of 2002 and priced at the average price calculated from actual retail prices obtained from a sample of retail and hospital pharmacies in the study location in 2002.

per year, published in the 2002 Statistical Yearbook by the Czech Statistical Office of the Czech Republic.<sup>22</sup> Costs were expressed in Euros using the purchasing power parity value in the Czech Republic in 2002.<sup>23</sup>

### Statistical Analysis

Categorical data among the groups were analyzed using the  $\chi^2$  test or Fisher exact test (2-tailed). Kruskal-Wallis, Wilcoxon tests, analysis of variance, and paired *t* test were used for continuous variables, depending on normal distribution.  $P < .05$  was considered statistically significant. Costs were analyzed using a nonparametric bootstrap-*t* method (1,000 iterations). This technique is recommended for making inferences about arithmetic means for moderately sized samples of highly skewed data such as cost.<sup>24</sup> The patients' annual drug consumption and a reduction of medication were expressed as the mean DDD using the ATC/DDD methodology or the mean number of packages in the case of allergen extracts.<sup>16</sup> Health care service costs and resources were expressed as the average cost or use per patient per year or total cost or resource use per 3 years of SIT per patient. Sensitivity analysis was performed varying costs by  $\pm 50\%$  of the base case key parameters at a 0% discount rate (cost of allergen extracts and health care services). All analyses were performed using SPSS statistical software, version 12.0 (SPSS Inc, Chicago, Illinois).

## RESULTS

### Patients

A total number of 64 patients were assigned to receive allergen immunotherapy sublingually (SLIT group,  $n = 19$ ), allergen immunotherapy subcutaneously (SCIT group,  $n = 23$ ), or symptomatic treatment alone (control group,  $n = 22$ ). Four patients from the SLIT and control group were withdrawn from the study within the first 3 years because of

inconvenience (change of residency). There were no statistically significant differences between groups in the baseline characteristics. The patient characteristics are given in Table 2.

### Effectiveness

After 3 years of SIT the number of clinically improved patients as measured by the RQLQ and the visual analog score did not significantly differ between the SIT groups (median visual analog score for the SLIT vs SCIT group:  $\Delta 38$  mm vs  $\Delta 49$  mm,  $P \geq .07$ ; RQLQ for the SLIT vs SCIT group: 41% vs 48%,  $P \geq .75$ ) (Table 3). Each year there was a noticeable decrease in the need for symptomatic medication of SIT in all 3 groups except for the control group (SLIT group [R06]:  $\Delta -56$  DDD; SCIT group [R06]:  $\Delta -70$  DDD; control group [R06]:  $\Delta 6$  DDD;  $P = .002$ ) (Table 3). A significant decrease in symptomatic medication consumption was reached as early as the first or second year of treatment. SCIT patients showed slightly better improvements in all clinical outcomes.

### Health Care Utilization

Average annual physician office visits of SCIT patients were substantially higher than those of SLIT patients, with the highest frequency of visits in the first year because of the SIT initiation phase. On average, SCIT patients visited their allergist 6 times more frequently than before the SIT treatment (Table 4). No hospitalizations and emergency department visits related to rhinitis were reported during the study. No systemic adverse effects developed within 30 minutes of the subcutaneous administration.

### Costs

The overall mean cost per patient from all the perspectives is given in Table 5 and Figure 1.

Table 2. Characteristics of Patients Completing Specific Allergen Immunotherapy

| Characteristics                              | SLIT group (n = 17) | SCIT group (n = 23) | Control group (n = 20) |
|--|---------------------|---------------------|------------------------|
| Age, y                                       |                     |                     |                        |
| Mean (SD)                                    | 27.4 (6.5)          | 31.3 (7.6)          | 28.4 (8.7)             |
| Median                                       | 26                  | 30                  | 26                     |
| Female, No. (%)                              | 8 (47)              | 10 (43)             | 14 (70)                |
| History of asthma, No. (%)                   | 5 (29)              | 8 (35)              | 5 (25)                 |
| Positive family history of allergy, No. (%)  | 13 (77)             | 20 (87)             | 14 (70)                |
| Duration of SARC, y                          |                     |                     |                        |
| Mean (SD)                                    | 10.5 (4.8)          | 8.8 (6.6)           | 10.1 (8.5)             |
| Median                                       | 9                   | 7                   | 7.5                    |
| Smokers, No. (%)                             | 2 (12)              | 3 (13)              | 2 (10)                 |
| Visual analogue score, median, mm            | 64                  | 75                  | 62                     |
| Drug consumption (ATC/DDD)                   |                     |                     |                        |
| Oral antihistamines (ATC = R06)              | 105                 | 124                 | 96                     |
| Employees, No. (%)                           | 15 (88)             | 22 (96)             | 17 (85)                |
| Employees (unpaid hours), No. (%)            | 3 (18)              | 3 (13)              | 2 (10)                 |
| Place of residency (local patients), No. (%) | 8 (47)              | 12 (52)             | 15 (75)                |

Abbreviations: ATC/DDD, anatomical therapeutic classification/defined daily dose; SARC, seasonal allergic rhinoconjunctivitis; SCIT, subcutaneous allergen immunotherapy; SLIT, sublingual allergen immunotherapy.

Table 3. Change in Clinical Outcome From Baseline Years to the Annual 3-Year Specific Allergen Immunotherapy

| Outcome  | SLIT group<br>(n = 17)      | SCIT group<br>(n = 23)      | Control group<br>(n = 20)    | SLIT vs SCIT<br>(95% CI), Δ |
|--|-----------------------------|-----------------------------|------------------------------|-----------------------------|
| RQLQ, No. (%)  |                             |                             |                              |                             |
| Patients improved  | 7 (41)                      | 11 (48)                     | 8 (40)                       | -4                          |
| Patients stabilized                                      | 8 (47)                      | 10 (43)                     | 8 (40)                       | -2                          |
| Patients impaired  | 2 (12)                      | 2 (9)                       | 4 (20)                       | 0                           |
| RQLQ total score, mean (SD)                              |                             |                             |                              |                             |
| Second year of SIT                                       | -0.41 <sup>b</sup> (0.67)   | -0.59 <sup>b</sup> (1.07)   | -0.38 <sup>b</sup> (0.58)    | 0.18 (-0.38 to 0.74)        |
| Third year of SIT  | -0.30 (0.73)                | -0.74 <sup>b</sup> (0.95)   | -0.30 (1.42)                 | 0.44 (-0.12 to 1.00)        |
| Visual analog score, mm <sup>a</sup>                     |                             |                             |                              |                             |
| First year of SIT  | -18 <sup>c</sup> (-25, -8)  | -21 <sup>c</sup> (-29, -11) | -21 <sup>b</sup> (-30, 0)    | -1 (-10 to 8)               |
| Second year of SIT                                       | -30 <sup>c</sup> (-40, -18) | -31 <sup>c</sup> (-38, -25) | -18 <sup>b,d</sup> (-38, 0)  | 2 (-7 to 11)                |
| Third year of SIT  | -38 <sup>c</sup> (-48, -22) | -49 <sup>c</sup> (-58, -35) | -20 <sup>b,e</sup> (-34, -2) | 10 (-1 to 21)               |
| Symptomatic medication reduction<br>(R06/DDD), mean (SD) |                             |                             |                              |                             |
| First year of SIT  | -14 <sup>b</sup> (44)       | -11 <sup>b</sup> (78)       | -3 (35)                      | -3 (-42 to 37)              |
| Second year of SIT                                       | -42 <sup>b</sup> (56)       | -49 <sup>b</sup> (66)       | -24 (62)                     | 7 (-34 to 47)               |
| Third year of SIT  | -56 <sup>c</sup> (48)       | -70 <sup>c</sup> (78)       | 6 <sup>1</sup> (59)          | 14 (-30 to 57)              |

Abbreviations: CI, confidence interval; DDD, defined daily dose; SCIT, subcutaneous allergen immunotherapy; SIT, specific allergen immunotherapy; SLIT, sublingual allergen immunotherapy; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

<sup>a</sup> Median (25th, 75th percentile).

<sup>b</sup> *P* = .05 (within-group comparison).

<sup>c</sup> *P* = .001 (within-group comparison).

<sup>d</sup> *P* = .05 (among-group comparison).

<sup>e</sup> *P* = .001 (among-group comparison).

Table 4. Mean Use of Resources During 3-Year Sublingual and Subcutaneous Allergen Immunotherapy

| Resource                                   | SLIT group<br>(n = 17) | SCIT group<br>(n = 23) | Control group<br>(n = 20) |
|--|------------------------|------------------------|---------------------------|
| Baseline year                              |                        |                        |                           |
| Medication (ATC/DDD)                       |                        |                        |                           |
| Oral antihistamines (ATC = R06), DDD       | 105.3                  | 123.5                  | 96.3                      |
| Outpatient visits, No.                     | 3.4                    | 3.1                    | 3.0                       |
| Productivity loss, No. of working days     | 1.55                   | 0.84                   | 0.95                      |
| Loss of income, No. of unpaid working days | 0.56                   | 0.96                   | 0.57                      |
| Three-year SIT                             |                        |                        |                           |
| Medication (ATC/DDD)                       |                        |                        |                           |
| Allergen immunotherapy, No. <sup>a</sup>   | 1/6.38                 | 1/4.96                 |                           |
| Oral antihistamines (ATC = R06), DDD       | 204.0                  | 241.0                  | 259.0                     |
| Outpatient visits, No.                     | 10.8                   | 55.6                   | 7.1                       |
| SCIT-related visits, No.                   |                        | 52.0                   |                           |
| Productivity loss, No. of working days     | 5.75                   | 14.03                  | 2.72                      |
| Loss of income, No. of unpaid working days | 7.77                   | 16.25                  | 3.52                      |

Abbreviations: ATC, anatomical therapeutic class; DDD, defined daily dose; SCIT, subcutaneous allergen immunotherapy; SIT, specific allergen immunotherapy; SLIT, sublingual allergen immunotherapy.

<sup>a</sup> Number of packages of allergen extracts: initiation/maintenance phase.

*Third-party payer perspective.* The total direct medical costs after 3 years of SIT were higher in the SCIT compared with the SLIT group (€416 for SLIT vs €482 for SCIT, *P* < .001). Overall, SIT-related expenses accounted for €318 (77%) and €398 (82%) of the total direct costs in the SLIT and SCIT groups, respectively. Although the cost of allergen extracts during the 3-year period was €94 less in the SCIT group than in the SLIT group (€297 vs €204, *P* < .001), the higher frequency in specialist visits related to subcutaneous admin-

istration accounted for a higher health care service costs in the SCIT group by €173 (€21 for SLIT vs €194 for SCIT, *P* < .001). The initial cost for SIT assignment was the same for both groups (€21).

In patients treated subcutaneously, most of the overall direct medical costs were attributable to outpatient visits (€214; 44%), allergen extracts (€204; 42%), and symptomatic medication (€64; 13%). On the other hand, the composition of direct medical costs of patients treated sublingually was

Table 5. Comparison of Mean Baseline and Overall Costs of 3-Year Sublingual and Subcutaneous Allergen Immunotherapy

|                                 | Mean cost per patient (95% CI), € <sup>a</sup> |                          | Bootstrap-t P value |
|---------------------------------|--|--------------------------|---------------------|
|                                 | SLIT group (n = 17)                            | SCIT group (n = 23)      |                     |
| Baseline year                   |  |                          |                     |
| Medication                      |  |                          |                     |
| Medication reimbursement        | 30.30 (26.04–34.19)                            | 32.91 (26.37–40.83)      | .54                 |
| Medication copayment            | 2.60 (1.76–3.59)                               | 1.99 (1.21–2.94)         | .4                  |
| Over-the-counter medication     | 0.11 (0.00–0.33)                               | 0.18 (0.00–0.44)         | .74                 |
| Outpatient visits               | 16.67 (14.12–19.47)                            | 16.41 (14.58–18.25)      | .88                 |
| Travel costs                    | 23.62 (6.61–54.06)                             | 7.75 (3.90–12.35)        | .38                 |
| Loss of income                  | 12.62 (5.61–28.05)                             | 21.5 (8.42–44.88)        | .52                 |
| Productivity loss               | 34.88 (23.75–47.13)                            | 18.87 (14.73–23.27)      | .04                 |
| Three-year SIT                  |  |                          |                     |
| Medication                      |  |                          |                     |
| Allergen extracts reimbursement | 297.41 (285.58–308.93)                         | 203.72 (197.09–211.08)   | <.001               |
| Allergen extracts copayment     | 72.23 (69.48–74.99)                            | 55.13 (53.35–56.90)      | <.001               |
| Medication reimbursement        | 51.79 (42.59–61.50)                            | 64.16 (53.92–74.57)      | .12                 |
| Medication copayment            | 3.74 (2.08–5.66)                               | 5.35 (3.48–7.57)         | .13                 |
| Over-the-counter medication     | 0.23 (0.00–0.69)                               | 0.25 (0.00–0.54)         | .92                 |
| Outpatient visits               | 66.58 (62.27–70.86)                            | 213.96 (204.30–223.44)   | <.001               |
| SIT-related visits              | 20.78 (20.78–20.78)                            | 193.77 (184.67–203.49)   | <.001               |
| Travel costs                    | 71.48 (22.95–144.84)                           | 144.30 (68.07–229.18)    | .18                 |
| Loss of income <sup>b</sup>     | 121.80 (77.96–205.38)                          | 383.43 (172.36–695.48)   | .30                 |
| Productivity loss <sup>b</sup>  | 136.15 (85.99–211.78)                          | 331.92 (268.78–401.15)   | <.001               |
| Direct medical costs            | 491.91 (476.27–510.27)                         | 542.35 (525.85–559.24)   | <.001               |
| Total costs <sup>c</sup>        | 683.52 (584.88–824.92)                         | 1004.14 (866.10–1158.96) | <.001               |

Abbreviations: CI, confidence interval; SCIT, subcutaneous allergen immunotherapy; SIT, specific allergen immunotherapy; SLIT, sublingual allergen immunotherapy.

<sup>a</sup> The CI was computed with a bootstrap-t procedure; costs are expressed in 2002 euro and are discounted at 3% per year.

<sup>b</sup> Average loss of income or productivity loss based on number of employed persons.

<sup>c</sup> Direct (medication, health care service, and travel costs) and indirect costs (productivity loss).

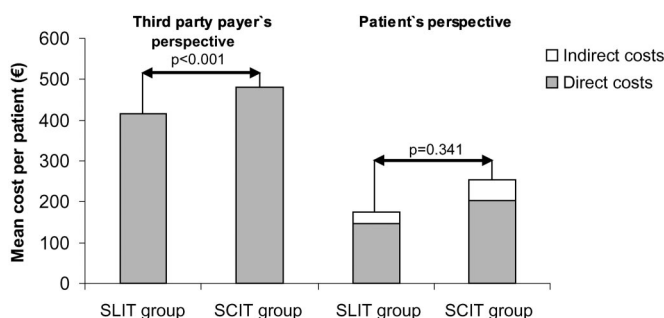


Figure 1. Mean cost of a 3-year specific allergen immunotherapy from a third-party payer's and a patient's perspectives. SCIT indicates subcutaneous allergen immunotherapy; SLIT, sublingual allergen immunotherapy.

more skewed toward allergen extracts (€297; 72%) rather than outpatient visits (€67; 16%) and symptomatic medication (€52; 12%).

Savings associated with the decreased use of medications for SARC during SIT therapy reached €39 and €35 ( $P = .67$ ) in the SLIT and SCIT group, respectively. A significant reduction of medication cost was observed starting the first year in the SLIT group only (SLIT:  $\Delta 23\%$ ,  $P = .001$ ; SCIT:  $\Delta 9\%$ ,  $P = .10$ ), reaching significant reduction for both

groups during the second and the third year of treatment (third year of SIT:  $\Delta 60\%$  for SLIT vs  $\Delta 55\%$  for SCIT;  $P = .99$ ).

**Patient perspective.** To a patient, SLIT was less expensive than the SCIT therapy (€176 vs €255,  $P = .34$ ). Medication copayments for allergen extracts (€72 for SLIT vs €55 for SCIT;  $P < .001$ ) and loss of income were the main contributors to the overall costs. When considering fixed costs alone, SCIT was less expensive than the SLIT therapy, by almost one third ( $\Delta 27\%$ , €76 vs €60;  $P < .001$ ) (Table 5).

**Society perspective.** From a societal perspective, SLIT was 32% less expensive than the alternative SCIT treatment (€684 vs €1,004;  $P < .001$ ). Approximately 82% vs 68% of the total expenditures were attributed to direct costs in the SLIT and SCIT groups, respectively (€492 vs €542;  $P < .001$ ). The higher cost associated with productivity loss in the SCIT group accounted for most of the increase in the total cost throughout the SIT administration period (€136 [6 workdays] vs €332 [14 workdays],  $P < .001$ ) (Table 5).

#### Sensitivity Analysis

The sensitivity analysis results confirmed the advantage of SLIT vs SCIT from the third-party payer's perspective (Table 6).

Table 6. Sensitivity Analysis From a Third-Party Payer's Perspective

|                                | Mean 3-year SIT cost per patient (95% CI), € <sup>a</sup> |                        | Bootstrap-t P value |
|--------------------------------|---|------------------------|---------------------|
|                                | SLIT group (n = 17)                                       | SCIT group (n = 23)    |                     |
| Total cost (-50%) <sup>b</sup> | 212.81 (205.82–219.54)                                    | 246.98 (240.09–254.21) | <.001               |
| Total cost (+50%) <sup>b</sup> | 638.44 (618.15–659.12)                                    | 740.95 (719.41–762.97) | <.001               |

Abbreviations: CI, confidence interval; SCIT, subcutaneous allergen immunotherapy; SIT, specific allergen immunotherapy; SLIT, sublingual allergen immunotherapy.

<sup>a</sup> The CI was computed with a bootstrap-t procedure.

<sup>b</sup> Costs are expressed in 2002 euro and are varying by  $\pm 50\%$  of the base case key parameters (cost of allergen extracts, health care service) at 0% discount rate.

## DISCUSSION

This study was a 3-year, open-label randomized clinical trial that evaluated the clinical benefits and overall costs of SCIT vs SLIT treatment of SARC in adults from 3 perspectives (third-party payer, patient, and society) using a cost-minimization model. The study demonstrates that both SLIT and SCIT were comparable in their clinical outcomes, each producing a statistically significant reduction of symptoms and symptomatic drug intake. Nevertheless, the SCIT group exhibited slightly better improvement in visual analog score and a greater reduction of systemic antihistamines vs SLIT in the third year compared with the baseline year. We can expect this improvement to become statistically significant in a study with larger study arms.

SLIT proved a less expensive alternative relative to SCIT from all 3 perspectives. However, from a patient perspective, SCIT was financially preferable to SLIT for those patients who had no loss of income or travel expenses. From a societal perspective, a greater productivity loss in the SCIT group accounted for most of the increase in the total cost during the administration period. Since allergologists can administer injection immunotherapy outside the working hours in some countries such as the United States, costs associated with workday loss due to SCIT administration could eliminate the advantage of SLIT. Nevertheless, in our study, a hypothetical elimination of productivity loss and travel expenses would not make enough of a difference to shift the benefits from SLIT to SCIT.

Although SLIT has been recently validated as a viable alternative to SCIT, the benefits of SLIT compared with standard SCIT have not yet been established on a large scale. In a study of 20 patients with grass allergy by Ongari et al,<sup>25</sup> SLIT and SCIT were similar in efficacy when compared with pharmacologic treatment. SLIT and SCIT were found equally effective after 12 months in 2 other small studies by Quirino et al<sup>26</sup> and Mungan et al.<sup>27</sup> Yet another study by Bernardis et al<sup>28</sup> showed clinical improvement with *Alternaria tenuis* extract in 23 patients in both the SLIT and SCIT groups after 1 year. Although these studies add compelling data to the discussion, the data lack significance because of multiple methodologic flaws, including small study sizes, the absence of randomization before study group allocation, the lack of placebo control, and the failure of the studies to encompass the recommended treatment duration.

The most methodologically valid study was performed by Khinchy et al.<sup>29</sup> Khinchy et al conducted a double-blind, double-dummy, placebo-controlled study of 58 patients with birch allergy who were randomized into SLIT, SCIT, and placebo groups. In the first year of treatment (the only year evaluated), Khinchy et al did not find any significant difference in either symptoms or drug intake reduction between the SLIT and SCIT groups. As in our study, both SCIT and SLIT showed clinical efficacy, with SCIT being slightly better in terms of reduced disease severity. In contrast to our findings, Khinchy et al did not see any improvement in quality of life within the 2 groups. The difference in our findings could have been caused by the fact that Khinchy et al used a general health-related quality-of-life questionnaire but the questionnaire used in our study was disease specific. Additional studies of either SLIT or SCIT confirm improvement of quality of life.<sup>30,31</sup> It is not clear whether the improvement can be attributed to a greater effect of SCIT on mediators of inflammation in contrast to SLIT.<sup>32</sup> More data are needed.

Additional aspects of SIT outside the scope of our study need to be considered, namely, durability, preventive character of SIT, and compliance. A 3-year study of SCIT was found to exert a durable effect after its discontinuation.<sup>6</sup> On the other hand, the durability of SLIT is still uncertain. Several studies have demonstrated a long-lasting efficacy of SLIT after treatment, but the evidence is limited and the preventive effect on asthma onset of both SLIT and SCIT was so far demonstrated only in children.<sup>33,34</sup> A few studies capture the long-term cost-effectiveness of either SLIT or SCIT as a result of durability.<sup>12,35,36</sup> A long-term comparative study is needed to properly determine the magnitude of the long-term cost-savings potential for each administrative route.

Our study suggests additional cost factors that we did not measure, such as increased productivity due to improved symptoms. On the other hand, costs would have increased had we encountered serious systemic adverse effects, which rarely occur with SCIT.<sup>4</sup>

A cost increase related to severe adverse effects may arise in a larger study in which those rare adverse effects can manifest. Despite recently reported anaphylaxis in specific cases of multiple extract SLIT treatment, we do not expect to see the same increased cost in SLIT, since SLIT has been established as a safer administration route compared with SCIT.<sup>37,38</sup>

It is not clear which type of SIT administration has a better compliance rate. Although SCIT compliance is expected to be higher than SLIT (which is home administered), published studies report SCIT noncompliance rates of up to 50%, citing inconvenience and adverse effects as the primary reasons for SCIT discontinuation.<sup>39,40</sup> In contrast, SLIT compliance rates were shown to be relatively high.<sup>41–43</sup>

The limitations of our study include absence of a placebo arm, absence of a double-blind method, small size, and limited possibilities for valid statistical analysis between the arms based on these considerations. The study's advantage is its randomized prospective character, with its collection of both cost and efficacy data, including quality of life, during the entire recommended treatment period.

In conclusion, our study showed that SLIT and SCIT reduced clinical symptoms and the need for symptomatic medication in adults with grass pollen-induced rhinoconjunctivitis compared with standard pharmacologic treatment. The clinical efficacy of SLIT and SCIT was not significantly different in the third year of SIT. Overall, SLIT showed a better cost profile from all 3 perspectives. SCIT was financially favorable from a patient perspective, where no loss of income or travel costs were present. Larger studies that examined the cost-effectiveness of the sublingual and subcutaneous routes of administration, including the durability and preventive effect of immunotherapy, as well as safety and compliance, must be conducted to evaluate the weighted benefits of each administration route and its cost-saving potential in different populations.

## ACKNOWLEDGMENTS

We thank Iva Selke-Krulichova, PhD, at the Department of Medical Biophysics at Faculty of Medicine of Charles University in Prague, for her statistics advice.

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