

Health economics of allergen-specific immunotherapy in the United States

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Although 19 published studies report that allergen-specific immunotherapy (SIT) may decrease health care costs,¹⁻¹⁹ a scant 4 pertain to the health economics of SIT in the United States (US).^{5,8,9,12} This editorial presents an overview of these published US studies and an appeal for additional US health economics research regarding SIT. We specifically focus on subcutaneously administered SIT (SCIT), the predominant and only US Food and Drug Administration–approved route of administration in the US.

The first US health economics study of SCIT was published in 1999 (Table I).⁵ This was a 4-year (1988-1992) retrospective claims analysis of health maintenance organization enrollees with allergic rhinitis (AR). The study compared costs between patients who completed a course of SCIT (at least 61 injections over 3.5 years) and those who received less than a complete course during a mean 7-month follow-up period. Costs included all procedures associated with the administration and testing of SCIT and prescription medications, inpatient services, emergency department services, and outpatient services for the treatment of asthma, rhinitis, sinusitis, and nasal polyps. Average per-patient annual health care costs were higher for patients who completed SCIT than for those who did not (\$508 vs \$421; statistical significance not provided), with differences primarily attributable to medication costs. There are several limitations to this study. First, patients who completed SCIT had 30% higher costs for asthma and AR treatment in the year before SCIT initiation, which may reflect greater disease severity among SIT completers, and these pre-SCIT costs were not accounted for when examining cost differences after SCIT. Second, the follow-up period after SCIT completion may have been too brief to detect cost savings. Third, by virtue of their greater persistence to SCIT, completers also may have been more adherent

to other treatments, including pharmacotherapy and routine office visits, thereby incurring higher costs.

A later US study applied data from a 1996 American College of Allergy Asthma and Immunology report²⁰ to provide the basis for estimating the 5-year average cost of SCIT (including costs for allergen extract plus physician office visits) at \$5000 versus symptomatic pharmacologic treatment of AR (consisting of the daily use of an antihistamine decongestant and intranasal corticosteroid spray) at \$10,200. This back-of-the-envelope cost comparison has several shortcomings. First, rough estimates of the use and cost of pharmacologic treatment were not further substantiated or validated. Second, the analysis assumed that patients who received SCIT refrained from concomitant use of symptomatic drug therapy. Third, the analysis excluded medical costs (eg, physician office visits and hospital admissions) aside from those directly associated with the administration of SCIT or symptomatic drug therapy. Finally, the analysis did not account for the long-term benefits of SCIT, such as sustained clinical effectiveness after treatment discontinuation.

In another US economic study of SCIT, Hankin et al⁸ conducted a 7-year (1997-2004) retrospective claims analysis of children newly diagnosed with AR (with or without asthma) and naive to SIT who were enrolled in Florida Medicaid. Among 354 identified patients, medical costs incurred during the 6 months before SCIT initiation were compared with costs incurred during the 6 months after SCIT discontinuation. Although only 16% of patients completed 3 or more years of SCIT, and more than half of patients received 1 year or less of SCIT, pharmacy, outpatient, and inpatient costs were significantly reduced in the 6 months after compared with the 6 months preceding SCIT. The mean, weighted, per-patient, 6-month cost reduction for health services use (pharmacy, outpatient visits, and inpatient admissions) was \$401, which offset the total mean cost for SCIT (\$424 per patient). The main limitations of this study were its short-term follow-up and the unique characteristics of the sample (Medicaid-eligible patients).

In subsequent research analyzing 10 years of Florida Medicaid claims (1997-2007), Hankin et al⁹ used a retrospective matched cohort study design to compare the median, 18-month, per-patient direct costs (pharmacy, outpatient visits, inpatient admissions) of newly diagnosed children (age <18 years) with AR (with or without asthma) to the median, 18-month, per-patient direct costs of a matched cohort who did not receive SCIT. Patients were matched by age at AR diagnosis, sex, race/ethnicity, comorbid illness burden, and the presence of asthma, conjunctivitis, or dermatitis. Compared with matched controls who did not receive SCIT, children who received SCIT had significantly lower 18-month, median, per-patient, total health care costs (\$3247 vs \$4872), outpatient costs exclusive of SCIT

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TABLE I. Summary of US SCIT economic studies

| Study/country | Design | Sample characteristics | Results |
|-------------------------------|--|---|--|
| Bernstein, 2004 ¹² | Economic modeling study SCIT + ST vs ST | Hypothetical model, 3 allergy treatment centers | 5-y direct costs SCIT: \$4560-\$4773 5-y direct costs ST: \$10,200 |
| Donahue, 1999 ⁵ | Retrospective administrative claims analysis (HMO) SCIT vs no SCIT | 603 adults and children with AR with or without asthma 33% (N = 128) completed 3.5 y IT | Mean cost difference = completed SCIT – discontinued SCIT Annual cost difference (SCIT): \$698 – \$508 = \$190 Annual cost difference (no SCIT): \$421 – \$247 = \$174 |
| Hankin, 2008 ⁸ | Retrospective administrative claims analysis 6 mo pre-SCIT initiation vs 6 mo post-SCIT discontinuation | 354 children with AR with or without asthma | Costs reported in 1997-2004 USD Mean cost difference = 6 mo pre-SCIT – 6 mo post-SCIT Pharmacy costs: -\$54 Outpatient costs: -\$233 Inpatient costs: -\$2316 Total costs: -\$215 Mean weighted 6-mo savings: \$401 |
| Hankin, 2010 ⁹ | Retrospective administrative claims analysis (SCIT) vs (matched controls without SCIT) | 2771 children with AR who received SCIT vs 11,010 matched controls with AR who did not receive SCIT | Costs reported in 1997-2007 USD 18-mo median per-patient health care costs: AR with SCIT vs AR without SCIT Inpatient costs: \$3901 vs \$4414 (<i>P</i> = .06) Outpatient costs: \$1829 vs \$ 2594 (<i>P</i> < .001) Outpatient costs excluding visits related to SCIT or the cost of SCIT: \$1107 vs \$ 2626 (<i>P</i> < .001) Cost of SCIT: \$463 vs not applicable Pharmacy costs: \$1108 vs \$1316 (<i>P</i> < .001) Total health care costs: \$3247 vs \$4872 (<i>P</i> < .001) |

HDM, House dust mite; *HMO*, health maintenance organization; *SLIT*, sublingual immunotherapy; *ST*, symptomatic treatment.

(\$1107 vs \$2626) or inclusive of SCIT (\$1829 vs \$2594), and pharmacy costs (\$1108 vs \$1316; *P* < .001 for all). A significant difference in total health care costs was evident as early as 3 months after SCIT initiation and increased through the study end (total median per-patient cost savings associated with SCIT were \$248, \$527, \$1061, and \$1625, respectively, at 3, 6, 12, and 18 months of follow-up; *P* < .001 at all time points). Among the study drawbacks was the nature of retrospective claims data, which limits the types of variables that can be analyzed and used to interpret outcomes. In addition, findings were based on Medicaid enrollees and may not generalize to patients receiving care through private health care systems. Furthermore, the 18-month duration of follow-up is likely insufficient to reveal the full impact of SCIT on health outcomes and costs.

Given the current environment, which calls for health care cost reform on the basis of comparative clinical and cost-effectiveness research, it is unfortunate that few US cost-effectiveness studies of SCIT have been conducted. Health economics studies of SCIT conducted outside the United States include findings from prospective clinical trials of AR-diagnosed adults with or without asthma conducted in Italy and the Czech Republic^{1,3}; patient and physician questionnaires obtained from allergy clinics in Denmark and France^{4,7}; and decision-tree and Markov cost-effectiveness models developed in France and Germany based on data derived from systematic literature reviews, Delphi panels, and retrospective claims analyses (Table II).^{14,16-18} SCIT has

been consistently shown to be cost saving and cost effective,^{1,3,7,14,16-18} with the exception of 1 study.⁴ This anomalous study had significant disadvantages: (1) data were based on patient recall of health care use for up to 7 previous years; (2) drug use was restricted to allergy or asthma medications and did not include antibiotics or other medications that may serve as clinically meaningful signals of treatment effect; and (3) annual medication use, which was projected from 7 months of actual data that included the peak grass pollen season, may have overestimated actual use of medications.⁴

In concert, despite wide variation in design, patient samples, and analytic methods, studies conducted outside and within the US suggest that SCIT is associated with substantial health care cost savings. The magnitude of these savings has varied, with up to an 80% reduction in costs seen 3 years after completion of treatment.¹

As more sophisticated and higher cost drugs, biologics, medical devices, and breakthrough health care technologies proliferate, it becomes increasingly tempting to assume their superiority over traditional treatment. Currently, SIT is used by only a minority (2% to 6%) of appropriate US patient candidates.^{5,8,21} In this centennial year for allergen immunotherapy, it is especially important to note that the health economic attributes of SCIT remain largely unexplored in the US. As the only disease-modifying treatment available to patients with allergies, this standard of care must be promptly and carefully benchmarked.

TABLE II. Summary of non-US SCIT economic studies

| Study/country | Design | Sample characteristics | Results |
|---|--|---|---|
| Prospective clinical trials | | | |
| Ariano, 2006 ¹ Italy | Prospective, randomized, open-label, parallel-group trial SCIT + ST vs ST | 30 adults with AR and/or asthma caused by <i>Parietaria</i> pollen SCIT + ST (N = 20) ST (N = 10) | <ul style="list-style-type: none"> ■ Costs reported in unspecified year (assume 2006) in USD ■ Mean annual per-patient cost difference between ST vs SCIT + ST = ST – SCIT + ST <ul style="list-style-type: none"> ● Year 1: \$104 (not significant) ● Year 2: –\$172 (not significant) ● Year 3: –\$581 (P < .0001) ● Year 4: –\$947 (P < .0001) ● Year 5: –\$952 (P < .0001) ● Year 6: –\$958 (P < .0001) <p>Negative results denote cost savings, and positive results denote cost outlay</p> |
| Pokladnikova, 2008 ³ Czech Republic | Economic Modeling Study SCIT vs SLIT vs ST | 64 patients with allergic rhinoconjunctivitis who received SLIT (n = 19), SCIT (n = 23), or standard symptomatic treatment (control; n = 22) over 3 y | <ul style="list-style-type: none"> ■ Costs reported in 2002 Euros* ■ There was a noticeable decrease in the need for symptomatic medication in the immunotherapy groups vs control (P = .002) ■ A significant reduction of medication cost was observed during the second and third years of SCIT (third year of IT: Δ 60% for SLIT vs Δ 55% for SCIT; P = .99) |
| Patient and physician surveys | | | |
| Petersen, 2005 ⁴ Denmark | Retrospective administrative claims analysis 1 y pre-SCIT initiation vs 1 y post-SCIT discontinuation 4-y course of SCIT vs 4-y course of ST | Retrospective analysis of patient survey data 253 adults with AR with or without asthma caused by mite or pollen allergy who received SCIT during 1996-2002 | <ul style="list-style-type: none"> ■ Costs reported in 2002 Danish Krone† ■ Mean annual per-patient direct costs: <ul style="list-style-type: none"> ● Year preceding SCIT: \$445 ● Year following SCIT: \$230 ■ Mean 4-y per-patient direct costs <ul style="list-style-type: none"> ● SCIT: \$4751 ● ST: \$1616 ● 4-y SCIT costs do not confer overall cost savings |
| Le Pen, 1997 ⁷ France | Physician questionnaires: SCIT duration, diagnosis, allergy type; past 15 d symptoms, treatments administered, other physicians seen, work missed (by SCIT duration) | 851 patients with allergy who received SCIT of varying duration Costs = past 15 d: number of SCIT treatments, other allergy treatments, physician visits, allergy-related hospitalizations, work days missed | <ul style="list-style-type: none"> ■ Costs reported in 1996 French Franc ■ 15-d costs by duration of SCIT: <ul style="list-style-type: none"> ● <1 y SCIT ~\$38 vs 1-2 y SCIT ~\$24 (P value unspecified, but reportedly “significant”) |
| Cost-effectiveness models | | | |
| Omnes, 2007 ¹⁶ France | Economic modeling study—decision-tree analysis based on literature survey and expert opinion SCIT + ST vs SLIT + ST vs ST | 1000 hypothetical adult and child patients with AR who received either SCIT/SLIT (3-4 y) or ST over 7-8 y Model cast in terms of incremental cost per improved patient and incremental cost per asthma case avoided Direct costs: clinic visits, diagnosis, follow-up tests, drugs, SCIT; indirect costs included for adult model (productivity loss); hospitalizations were not included because considered rare | <ul style="list-style-type: none"> ■ Costs reported in 2003 Euros ■ Incremental cost-effectiveness ratio per additional improved patient (SCIT vs ST) <ul style="list-style-type: none"> ● \$362 (children-HDM); \$435 (children-pollen) ● \$232 (adults-HDM); \$748 (adults-pollen) ■ Incremental cost-effectiveness ratio per additional asthma case avoided for SCIT vs ST: <ul style="list-style-type: none"> ● \$604 (children-HDM); \$619 (children-pollen) ● \$407 (adults-HDM); \$1282 (adults-pollen) |

(Continued)

TABLE II. (Continued)

| Study/country | Design | Sample characteristics | Results |
|--|--|--|--|
| Buchner, 1995 ¹⁸ Germany | Economic modeling study—decision-tree analysis based on literature SCIT vs ST | Estimated mean 10-y per-patient total cost of patients with AR and asthma receiving SCIT vs ST | <ul style="list-style-type: none"> ■ Costs reported in 1990 Deutsche Mark ■ Break-even point reached after 6 y of treatment in patients with AR and 4 y of treatment in patients with asthma ■ Mean cost difference = 10 y ST – 10 y SCIT <ul style="list-style-type: none"> ● Per patient with AR: \$16,343 – \$8992 = \$7351 ● Per patient with asthma: \$24,296 – \$10,126 = \$14,170 |
| Schadlich, 2000 ¹⁷ Germany | Economic modeling study SCIT vs ST | 1000 hypothetical adults with AR receiving SCIT vs ST for 3 y and followed for 10 y | <ul style="list-style-type: none"> ■ Costs reported in 1997 Deutsche Mark ■ Break-even point (cumulative costs) reached between years 6 and 8 ■ Net savings of \$623 (payer) to \$1141 (societal) per patient over 10 y ■ 10-y incremental cost-effectiveness ratio (ICER) (payer) for SCIT vs ST per additional asthma case avoided: –\$3490 to –\$3904 |
| Brüggenjürgen, 2008 ¹³ Germany | Economic modeling study SCIT vs ST | 1000 hypothetical patients with AR or allergic asthma who received either SCIT (for 3 y) or ST over a time horizon of 15 y | <ul style="list-style-type: none"> ■ Costs reported in unspecified year (assume 2008) in Euros ■ Total costs/patient @ 15 y: SCIT = \$16,392; ST = \$17,826 (annual cost savings ~ \$143 per SCIT-treated patient) ■ After 10 y of disease duration, SCIT and ST treatment reach the break-even point ■ If SCIT costs excluded, SCIT associated with cost savings from treatment outset ■ SCIT ICER = –\$9710 per additional quality-adjusted life year (QALY), indicating that SCIT + ST more effective and less costly compared with ST ■ From a third-party payer's perspective, a patient treated with SCIT + ST incurred annual costs of approximately \$368 compared with \$339 of those receiving only ST ■ The resulting ICER was positive for all patients (\$4077 per QALY) and demonstrated that SCIT was a cost-effective treatment |

*Costs reported in foreign currency in articles are shown in USD. Values were converted to USD using the average exchange rate for the year reported.

†For all studies reporting costs in foreign currency, values were converted to USD for the year reported.

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ALLERGY ARCHIVES

TOXIC IDIOPATHIES



Otto Prausnitz

Dr A. W. Frankland explains the preferred terminology of John Freeman.

Freeman published his book on his life's work in 1950.¹ In the book he explains that *toxic idiopathies* was a name he invented in 1919. He writes that a normally harmless protein substance becomes a specific poison—which he called an *idiotoxin*—for the patient, such as grass pollen in a hay fever patient. Freeman also writes that Prausnitz had shown that the serum from a subject suffering from a toxic idiopathy contained the specific idioceptor which was transferable to the skin of a normal recipient.

Because the word *allergic* “covered nearly all medicine,” he stated at a meeting in Oxford in 1949, “I have replaced the equivocal word ‘allergic’ by ‘idiotoxic.’” Freeman stated that the word *allergy* had so many meanings that “we might particularise as Allergy I, Allergy II, Allergy III etc.”

I was shown Freeman's book in galley-proof form a few years before publication. I advised him that he must use modern nomenclature. He would not take my advice: “I invented the words with advice from Almoth Wright. I am not going to change them. The book has taken 25 years to write and re-write.” Yet in the foreword of the book, I am thanked for the help (which he did not accept) that I had given him.

Freeman also would never use the word *immunotherapy*. The laboratory made all the extracts used for diagnostic skin testing and immunotherapy. If injection treatment was advised, he always wrote “PTD.” After attending his outpatient clinics for 2 years, I finally asked him what the letters PTD stood for—“Too long to write but it is Prophylactic Thoroughgoing Desensitisation.” I did not ask him what the word “Thoroughgoing” meant.

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