

Disease-modifying effect and economic implications of sublingual immunotherapy

Giorgio Walter Canonica, MD, and Giovanni Passalacqua, MD *Genoa, Italy*

Key words: Sublingual immunotherapy, respiratory allergy, preventive effect, pharmacoeconomy

Specific immunotherapy (SIT) approaches such as subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) have many important socioeconomic, as well as clinical, effects. The first randomized controlled trials of SITs were performed in the 1960s, but efficacy was assessed only by symptom and medication intake scores. This is reasonable because the main goal of any medical intervention is to reduce the clinical manifestations of the disease. However, SIT has additional effects that are not induced by pharmacologic therapies, including long-lasting persistence of benefit after discontinuation of therapy (a “carry-over” effect), prevention of onset of new sensitizations, and reduction of risk of asthma onset in patients with allergic rhinitis. These effects probably result from the complex mechanisms of action of SIT, which induce profound changes in the allergen-specific immune response.¹

The effects of SCIT for allergies were described more than 40 years ago in an observational study by Johnstone and Dutton,² who reported that a significantly smaller proportion of children who received SCIT developed asthma compared with children given only medication. Subsequently, the Preventive Allergy Treatment study confirmed the preventive effects of SCIT on the development of asthma in children, which persisted 7 years after discontinuation of SIT.³ In parallel, SCIT was found to reduce the onset of new sensitizations as assessed by skin prick tests (see review⁴).

After the introduction SLIT to clinical practice, it was hypothesized that this form of immunotherapy could also have disease-modifying effects. During the last 10 years, confirmatory data have begun to appear. Di Rienzo et al⁵ performed a prospective, nonrandomized open-label study of 60 children with asthma/rhinitis caused by mites who were followed for 10 years. Thirty-five subjects received SLIT for 4 to 5 years, and 25 received therapy with drugs only. The SLIT group had a significant reduction in asthma from baseline levels compared with the medication treatment group; the difference between groups persisted for 5 years

after discontinuation of SLIT. Another prospective controlled study, with a 15-year follow-up period,⁶ found that the effects of a 4-year course of SLIT persisted for more than 5 years. In a 6-year randomized, prospective trial, Tahamiler et al⁷ showed that the improvements in allergy symptoms achieved with SLIT were maintained for 3 years after treatment discontinuation. More recently, a carry-over effect of SLIT was reported in a follow-up study of a large, methodologically rigorous trial conducted with grass allergen tablets.⁸

In addition to reducing allergy symptoms, SLIT prevents the onset of asthma. The first study to investigate this effect was published in 2004⁹ and involved 113 children, 5 to 14 years old, with seasonal rhinitis from grass pollen. They received either SLIT or only pharmacotherapy (controls). After 3 years, 8 of 45 of the subjects who received SLIT and 18 of 44 controls had developed asthma, with a relative risk of 3.8 for untreated patients versus those receiving SLIT. Another randomized, open-label, controlled trial¹⁰ involved 216 children (5-17 years old) with allergic rhinitis, with or without intermittent asthma, who were given SLIT or only pharmacotherapy (controls); after 3 years, 1.5% of children in the SLIT group and 30% in the control group had an occurrence of persistent asthma (odds ratio, 0.04), with a number to treat of 4. The onset of new sensitizations was 3% in the SLIT group and 34% in the control group (odds ratio, 0.06).

It is clear that the preventive and long-term effects of SLIT may have relevant socioeconomic implications, because many resources are allocated to treat patients with asthma. The cost-effectiveness of an intervention is a fundamental part of the evaluation process for preparing evidence-based guidelines.¹¹ Economic studies can be performed with a variety of models and outcomes, for instance comparing only the costs of the treatments, or the costs in association with outcomes. In the case of SLIT, it is expected that the reduction of symptoms of allergies and asthma (and therefore of drug intake) would result in a reduction of direct medical costs (eg, drugs, clinic visits, hospitalizations) and indirect costs (eg, loss of work and school days, patients' quality of life).

Several studies have assessed, by various approaches, the economic aspects of SLIT (see review¹²). Although none have specifically addressed prevention, they have considered the economic impact of the reduced symptoms and the need for medications secondary to SLIT. The first economic study of SLIT was a cost-to-cost analysis, conducted in 135 children with respiratory allergies¹³; it found a substantial reduction in direct and indirect costs for patients receiving SLIT compared with before they received SLIT. The average annual medical cost per patient was €2672/y before SLIT and €629/y while patients received SLIT. These results were confirmed in a larger study,¹⁴ in which data from adult patients were collected from clinical databases and then patients were followed prospectively. Among patients who received SLIT, costs of drugs for rhinitis were reduced by 22%

From Allergy and Respiratory Diseases, Department of Internal Medicine, University of Genoa.

Disclosure of potential conflict of interest: Both Authors have received speaker and consultant fees during the last year from Alk-Abelló, Allergy Therapeutics, Anallergo, Lofarma, and Stallergenes.

Received for publication August 11, 2010; revised September 14, 2010; accepted for publication September 16, 2010.

Reprint requests: Giorgio Walter Canonica, MD, Allergy and Respiratory Diseases,
Department of Internal Medicine, Padiglione Maragliano, L.go R. Benzi 10, 16132
Genoa, Italy. E-mail: canonica@unige.it.

J Allergy Clin Immunol 2010;■■■:■■■-■■■.

0091-6749/\$36.00

© 2010 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2010.09.037

and costs of drugs for rhinitis with asthma were reduced by 34% compared with patients who received drugs only and did not receive SLIT. The difference between the patients treated with SLIT and those receiving drugs became significant only at the end of the first year of treatment.

A cost-effectiveness analysis, based on an epidemiologic model, took into account not only direct and indirect costs but also the cost of patients who became free of asthma after taking SLIT.¹⁵ SLIT became more advantageous than only drug therapy in the fourth year in the perspective of the National Healthcare System (direct costs), and in the second year in the societal perspective (direct plus indirect costs). In this study, which was performed in Italy, the monthly costs were about €50 for SLIT, €30 for antihistamines and topical steroids, and €60 for anti-asthma therapy. Two additional studies evaluated the cost and utility of SLIT with grass allergen tablets in northern¹⁶ and southern¹⁷ Europe. Each study calculated quality-adjusted life-years for 9 consecutive years. At a price of €6/tablet in northern Europe and €5.5/tablet in southern Europe, SLIT produced a significant and economically relevant advantage as calculated by quality-adjusted life-years.

In conclusion, SLIT, as well as SCIT, has an enormous therapeutic potential, represented by its clinical efficacy and, more importantly, by its preventative and long-term effects.¹⁸ Many studies have demonstrated the economic impact of these SITs compared with pharmacotherapies for allergy and asthma, which has been confirmed by using different pharmacoeconomic models. A formal evaluation, with adequate methods and sample size calculation, of the economic impact of the preventative effects of SLIT and SCIT is needed, especially in children, for whom modifying the natural history of allergies and asthma would significantly reduce indirect and direct medical costs. Also, quality of life should be part of the assessment of the effects of SLIT on socioeconomic parameters.

One problem in evaluating the economic aspects of SIT is the large proportion of polysensitized subjects who might need multiallergen SIT. Most clinical trials are performed using a single allergen. A cost-benefit comparison of multiple versus single allergens has not been performed. In addition, to extrapolate the economic benefits of SLIT properly, rigorous standardized trials should be performed with appropriate methodologies.^{19,20} More independent (not performed by pharmaceutical companies) pharmacoeconomic studies of SLIT in adults and children are needed.

REFERENCES

1. James LK, Durham SR. Update on mechanisms of allergen injection immunotherapy. *Clin Exp Allergy* 2008;38:1074-88.

2. Johnstone DE, Dutton A. The value of hyposensitization therapy for bronchial asthma in children—a 14-year study. *Pediatrics* 1968;42:793-802.
3. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007;62:943-8.
4. Passalacqua G, Durham SR. ARIA update: allergen immunotherapy. *J Allergy Clin Immunol* 2007;119:881-91.
5. Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003;33:206-10.
6. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long lasting effect according to the duration of SLIT: a 15-year prospective study. *J Allergy Clin Immunol* 2010;126:969-75.
7. Tahamiler R, Saritzali G, Canakcioglu S. Long-term efficacy of sublingual immunotherapy in patients with perennial rhinitis. *Laryngoscope* 2007;117:965-9.
8. Durham SR, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, et al. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010;125:131-8.
9. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2004;114:851-7.
10. Marogna M, Tomassetti D, Bernasconi A, Colombo F, Massolo A, Businco AD, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008;101:206-11.
11. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines, part 1 of 3: an overview of the GRADE approach and grading quality of evidence about interventions. *Allergy* 2009;64:669-77.
12. Berto P, Frati F, Incorvaia C. Economic studies of immunotherapy: a review. *Curr Opin Allergy Clin Immunol* 2008;8:585-9.
13. Berto P, Bassi M, Incorvaia C, Frati F, Puccinelli P, Giaquinto C, et al. Cost effectiveness of sublingual immunotherapy in children with allergic rhinitis and asthma. *Eur Ann Allergy Clin Immunol* 2005;37:303-8.
14. Berto P, Frati F, Incorvaia C, Cadario G, Contiguglia R, Di Gioacchino M, et al. Comparison of costs of sublingual immunotherapy and drug treatment in grass-pollen induced allergy: results from the SIMAP database study. *Curr Med Res Opin* 2008;24:261-6.
15. Berto P, Passalacqua G, Crimi N, Frati F, Ortolani C, Senna G, et al. Economic evaluation of sublingual immunotherapy versus symptomatic treatment in adults with pollen-induced respiratory allergy: the Sublingual Immunotherapy Pollen Allergy Italy (SPAI) study. *Ann Allergy Asthma Immunol* 2006;97:615-21.
16. Bachert C, Vestenbaek U, Christensen J, Griffiths UK, Poulsen PB. Cost-effectiveness of grass allergen tablet (GRAZAX) for the prevention of seasonal grass pollen induced rhinoconjunctivitis—a Northern European perspective. *Clin Exp Allergy* 2007;37:772-9.
17. Canonica GW, Poulsen PB, Vestenbaek U. Cost-effectiveness of GRAZAX for prevention of grass pollen induced rhinoconjunctivitis in Southern Europe. *Respir Med* 2007;101:1885-94.
18. Canonica GW, Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009;64(suppl 91):1-59.
19. Bousquet PJ, Demoly P, Passalacqua G, Canonica GW, Bousquet J. Immunotherapy: clinical trials—optimal trial and clinical outcomes. *Curr Opin Allergy Clin Immunol* 2007;7:561-6.
20. Casale TB, Canonica GW, Bousquet J, Cox L, Lockey RF, Nelson H, et al. Recommendations for appropriate sublingual immunotherapy clinical trials. *J Allergy Clin Immunol* 2009;124:665-70.