

Arbeiten aus dem Paul-Ehrlich-Institut
11th International Paul-Ehrlich-Seminar, Bad Homburg 2005
Verlag Chmielorz

A Bright Future for Sublingual Immunotherapy? – Pro

Jean Bousquet

Allergen specific immunotherapy (SIT) for the treatment of allergic rhinitis and asthma was first introduced in 1911. Although millions of patients have received this form of treatment, it has remained a controversial therapy since its inception. The vast majority of randomized double-blind, placebo-controlled trials have only been performed since the 1960s and standardized allergen vaccines have only been available for the past 25 years [1].

It is now recognized that subcutaneous SIT using appropriate doses, high quality allergen vaccines and an appropriate indication is effective in rhinitis and asthma due to pollens and mites [2]. However, although sublingual immunotherapy (SLIT) using high dose vaccines is widely used in many European countries [3], it was still controversial for many years [4] and this form of therapy has gained little acceptance in the US. In Europe, SLIT is administered to more than 50% of the patients suffering from pollen and mite allergy, in France and Italy. In all countries, including Germany and Spain, the percentage of patients receiving SLIT is increasing.

“Evidence-based medicine” (EBM) is an increasingly important concept which has become a new paradigm in medicine. It is the ability to track down, critically appraise (for its validity and usefulness) and incorporate the information obtained from randomized trials to establish the clinical bases for diagnosis, prognosis and therapeutics [5]. The increasing influence of EBM is due partly to the work of the Cochrane Collaboration which has led the way in setting new standards for preparation [6]. Cochrane reviews are, on average, more systematic and less biased than systematic reviews published in paper journals. However, they have not yet all been perfected, as errors and biases also occur in Cochrane reviews [7]. For SLIT, there was, however, no pivotal controlled trial nor has a meta-analysis yet been published. An evidence-based evaluation was therefore impossible.

Wilson *et al.* [8] have published the Cochrane Collaboration meta-analysis of SLIT in rhinitis. The objective of the study was to evaluate the efficacy of SLIT, com-

pared with placebo, for reductions in symptoms and medication requirements. The Cochrane Controlled Clinical Trials Register, MEDLINE (1966-2002), EMBASE (1974-2002) and Scisearch were searched, up to September 2002, using the terms (Rhin* OR hay fever) AND (immunotherap* OR desensiti*ation) AND (sublingual). All studies identified by the searches were assessed by the reviewers to identify Randomized Controlled Trials involving participants with symptoms of allergic rhinitis and proven allergen sensitivity, treated with SLIT or corresponding placebo. Data from identified studies was abstracted onto a standard extraction sheet and subsequently entered into RevMan 4.1. Analysis was performed by the method of standardized mean differences (SMD) using a random effects model. P-values < 0.05 were considered statistically significant. Subgroup analyses were performed according to the type of allergen administered, the age of participants and the duration of treatment. Twenty-two trials involving 979 patients were included. There were six trials of SLIT for house dust mite allergy, five for grass pollen, five for *Parietaria*, two for olive and one each for ragweed, cat, tree and *Cupressus*. Five studies enrolled exclusively children. Seventeen studies administered the allergen by sublingual drops subsequently swallowed, three by drops subsequently spat out and two by sublingual tablets. Eight studies involved treatment for less than 6 months, 10 studies for 6–12 months and four studies for greater than 12 months. All included studies were double-blind placebo-controlled trials of parallel group design. Concealment of treatment allocation was considered adequate in all studies and the use of identical placebo preparations was almost universal. There was significant heterogeneity, most likely due to widely differing scoring systems between studies, for most comparisons. Overall there was a significant reduction in both symptoms (SMD –0.42, 95% confidence interval –0.69 to –0.15; P = 0.002) and medication requirements [SMD –0.43 (–0.63, –0.23); P = 0.00003] following immunotherapy. Subgroup analyses failed to identify a disproportionate benefit of treatment according to the allergen administered. There was no significant reduction in symptoms and medication scores in those studies involving only children but total numbers of participants were too small to make this a reliable conclusion. Increasing duration of treatment does not clearly increase efficacy. The total dose of allergen administered may be important but insufficient data was available to analyze this factor.

A recent meta-analysis in children showed that sublingual delivery of allergen vaccination constitutes a safe and effective alternative to the injectable route to reduce allergy respiratory symptoms and drug intake [9]. However, more data are needed to fully confirm the efficacy of SLIT in asthma and in children.

The Cochrane meta-analysis [8] was followed by several studies which accord with the results of the review [10-22]. Moreover, two pivotal trials have been carried out this year, and the results were disclosed within the past month. These two registration trials on over 600 patients each showed convincingly that in grass pollen allergy SLIT is safe and effective. An extremely interesting study has been recently published. SLIT with hazelnut is effective [23]. This appears to be the first convincing trial in food allergy immunotherapy. Although no definite answer can be given, it appears that SLIT has a prolonged effect when stopped [19,24].

The safety of SLIT in all patients including asthmatics and in children is now ascertained [25–28]. A phase I study with grass pollen showed that SLIT is safe at doses 10 times greater than the selected one for clinical trials [29]. In the study of André *et al.* [25], 690 subjects, 472 adults and 218 children, took part in trials of specific immunotherapy (SIT) for the treatment of rhinoconjunctivitis and/or asthma. 347 patients received SIT and 343 patients received placebo. The daily dose taken during maintenance therapy ranged from 100 to 300 IR (index of reactivity) and cumulative doses ranged from 4,500 to 104,000 IR. Treatment duration ranged from 4 months to 2 years. Adverse events, reported either spontaneously by the patient or on direct questioning by the investigator, were analyzed. 145 unusual events were reported in the subjects receiving active SIT and 79 in those receiving placebo ($p < 0.001$). Unusual events involving the buccal cavity (61 SIT, 13 placebos) and the gastro-intestinal tract (47 SIT, 15 placebos) were significantly more frequent in the SIT-treated patients ($p < 0.001$). Wheezing (9 SIT, 21 placebos) was more frequent in the placebo-treated patients ($p < 0.05$). No event was reported as serious. Post-marketing surveillance has also widely shown that SLIT is safe [30,31].

It is clear that there are still many unanswered questions concerning SLIT and we need more data to find the relative indications of SLIT and subcutaneous SIT [3,32,33]. We also need to improve our knowledge on the mechanisms and pharmacokinetics of SLIT [34] as well as on compliance to the treatment [35]. It is also possible that SLIT may be given with a rapid schedule for a rapid onset efficacy [36].

So, although many studies still need to be done to fully understand the role of SLIT, there is no doubt that this form of therapy is safe and effective rapidly gaining acceptance in Europe, and that confirmatory trials will be done in the USA [37]. In this country, trials will have to be carried out with vaccines standardized using the US methods.

References

1. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: Therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998; 102 : 558–562.
2. Bousquet J, van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108: S147–S334.
3. Passalacqua G, Canonica GW. Sublingual or injection immunotherapy: The final answer? *Allergy* 2004; 59: 37–38.
4. Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. *J Allergy Clin Immunol* 2003; 111: 437–448; quiz 449.
5. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: What it is and what it isn't. *BMJ* 1996; 312: 71–72.
6. Bousquet J, van Cauwenberge P. A critical appraisal of 'evidence-based medicine' in allergy and asthma. *Allergy* 2004; 59 (Suppl 78): 12–20.
7. Olsen O, Middleton P, Ezzo J, Gotzsche PC, Hadhazy V, Herxheimer A, Kleijnen J, McIntosh H. Quality of Cochrane reviews: Assessment of sample from 1998. *BMJ* 2001; 323: 829–832.
8. Wilson DR, Torres LI, Durham SR. Sublingual immunotherapy for allergic rhinitis. *Allergy* 2005; 60: 4–12.
9. Olaguibel JM, Alvarez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. *J Investig Allergol Clin Immunol* 2005; 15: 9–16.
10. André C, Perrin-Fayolle M, Grosclaude M, Couturier P, Basset D, Cornillon J, Piperno D, Girodet B, Sanchez R, Vallon C, Bellier P, Nasr M. A double-blind placebo-controlled evaluation of sublingual

- immunotherapy with a standardized ragweed extract in patients with seasonal rhinitis. Evidence for a dose-response relationship. *Int Arch Allergy Immunol* 2003; 131: 111-118.
11. Wessner D, Rakoski J, Ring J. Efficacy of sublingual immunotherapy in grass pollen allergy. *Chem Immunol Allergy* 2003; 82: 53-61.
 12. Guez S. Efficacy of desensitization via the sublingual route in mite allergy. *Chem Immunol Allergy* 2003; 82: 62-76.
 13. Wüthrich B, Bucher C, Jorg W, Bircher A, Eng P, Schneider Y, Schnyder F, Eigenmann P, Senti G. Double-blind, placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. *J Investig Allergol Clin Immunol* 2003; 13: 145-148.
 14. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Clinical, functional, and immunologic effects of sublingual immunotherapy in birch pollinosis: A 3-year randomized controlled study. *J Allergy Clin Immunol* 2005; 115: 1184-1188.
 15. Tonnel AB, Scherpereel A, Douay B, Mellin B, Leprince D, Goldstein N, Delecluse P, André C. Allergic rhinitis due to house dust mites: Evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004; 59: 491-497.
 16. Bufer A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, Braun W. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: A double-blind placebo-controlled study. *Allergy* 2004; 59: 498-504.
 17. Sopo SM, Macchiaiolo M, Zorzi G, Tripodi S. Sublingual immunotherapy in asthma and rhinoconjunctivitis: Systematic review of paediatric literature. *Arch Dis Child* 2004; 89: 620-624.
 18. Pajno GB, Passalacqua G, Vita D, Caminiti L, Parmiani S, Barberio G. Sublingual immunotherapy abrogates seasonal bronchial hyperresponsiveness in children with *Parietaria*-induced respiratory allergy: A randomized controlled trial. *Allergy* 2004; 59: 883-887.
 19. Smith H, White P, Annala I, Poole J, André C, Frew A. Randomized controlled trial of high-dose sublingual immunotherapy to treat seasonal allergic rhinitis. *J Allergy Clin Immunol* 2004; 114: 831-837.
 20. Rolinck-Werninghaus C, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV, Hammermann J, Leupold W, Bartels P, Gruebl A, Bauer CP, Schnitker J, Wahn U, Niggemann B. A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Allergy* 2004; 59: 1285-1293.
 21. Bowen T, Greenbaum J, Charbonneau Y, Hebert J, Filderman R, Sussman G, del Carpio J, Gold M, Keith P, Moote W, Cecchetto S, Cecchetto O, Sharp D, Broutin O, André C. Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2004; 93: 425-430.
 22. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006; 61: 185-190.
 23. Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, Castello JV, Alonso R, de Mateo JA, Cerda-Trias T, San Miguel-Moncin MM, Monzon S, Garcia M, Palacios R, Cistero-Bahima A. Sublingual immunotherapy for hazelnut food allergy: A randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005; 116: 1073-1079.
 24. di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, Canonica GW, Passalacqua G. 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: 206-210.
 25. André C, Vatrinet C, Galvain S, Carat F, Sicard H. Safety of sublingual-swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000; 121: 229-234.
 26. Canonica GW, Compalati E, Fumagalli F, Passalacqua G. Sublingual and oral immunotherapy. *Immunol Allergy Clin North Am* 2004; 24: 685-704, vii.
 27. Baena-Cagnani CE, Passalacqua G, Baena-Cagnani RC, Croce VH, Canonica WG. Sublingual immunotherapy in pediatric patients: Beyond clinical efficacy. *Curr Opin Allergy Clin Immunol* 2005; 5: 173-177.
 28. Agostinis F, Tellarini L, Canonica GW, Falagiani P, Passalacqua G. Safety of sublingual immunotherapy with a monomeric allergoid in very young children. *Allergy* 2005; 60: 133.
 29. Kleine-Tebbe J, Ribel M, Herold D. Safety of a standardized grass allergen tablet for sublingual immunotherapy: A randomized, placebo-controlled trial. *Allergy* 2006; 61: 181-184.
 30. Passalacqua G, Fumagalli F, Guerra L, Canonica GW. Safety of allergen-specific sublingual immunotherapy and nasal immunotherapy. *Chem Immunol Allergy* 2003; 82: 109-118.

31. di Rienzo V, Minelli M, Musarra A, Sambugaro R, Pecora S, Canonica WG, Passalacqua G. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. *Clin Exp Allergy* 2005; 35: 560–564.
32. Khinchi MS, Poulsen LK, Carat F, André C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: A randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004; 59: 45–53.
33. Malling HJ. Comparison of the clinical efficacy and safety of subcutaneous and sublingual immunotherapy: Methodological approaches and experimental results. *Curr Opin Allergy Clin Immunol* 2004; 4: 539–542.
34. Bagnasco M, Altrineti V, Pesce G, Caputo M, Mistrello G, Falagiani P, Canonica GW, Passalacqua G. Pharmacokinetics of Der p 2 allergen and derived monomeric allergoid in allergic volunteers. *Int Arch Allergy Immunol* 2005; 138: 197–202.
35. Lombardi C, Gani F, Landi M, Falagiani P, Bruno M, Canonica GW, Passalacqua G. Quantitative assessment of the adherence to sublingual immunotherapy. *J Allergy Clin Immunol* 2004; 113: 1219–1220.
36. Bousquet J. Sublingual immunotherapy: From proven prevention to putative rapid relief of allergic symptoms. *Allergy* 2005; 60: 1–3.
37. Nelson HS. Advances in upper airway diseases and allergen immunotherapy. *J Allergy Clin Immunol* 2005; 115: 676–684.