

Editorial

Sublingual Immunotherapy: Validated!

The impact of allergic disease on both developing and developed nations is considerable (1, 2). Economically important because of lost productivity and the constant demands of chronic health care, immunoglobulin-E (IgE)-mediated diseases are a growing problem. The next generation is likely to be a more atopic population according to increasing evidence in recent birth cohorts and epidemiological studies (3). Many atopic patients can fear, even with quite minor symptoms, a reduced quality of life, whilst in other patients, their disease may progress to allergic asthma and become potentially life threatening (4).

Allergen-specific immunotherapy has been shown to reduce the symptoms and suffering in allergic rhinitis patients since its introduction almost a century ago (5). Nevertheless, when immunotherapy is administered subcutaneously, it is not an ideal choice for all patients. Injections require repeated visits to a healthcare centre over periods of weeks at a time, and often at personal inconvenience. The procedure itself can be at best uncomfortable and, at worst, dangerous (6). Sublingual immunotherapy (SLIT), self-administered at home, has been widely proposed as an alternative to subcutaneous injections or continued medication (7).

It is interesting to assess the acceptability of SLIT in guidelines. In 1993, the EAACI Position Paper on Specific Immunotherapy (SIT) proposed that SLIT might be used as an investigational therapy to prove its efficacy and safety (8). SLIT was not even mentioned in the BSACI Position Paper (9). In 1998, the WHO Position Paper on SIT found four double-blind, placebo-controlled (DB-PC) studies on SLIT and proposed that SLIT may be used in adults with allergic rhinitis, but there was insufficient evidence to use it in children (5). Serious concerns were even published in an EAACI paper on local immunotherapy (8). In 2001, the Allergic Rhinitis and its Impact on Asthma (ARIA) document retrieved over 10 DB-PC studies and indicated that the efficacy of high allergen dose sublingual-swallow specific immunotherapy (at least 100 times the cumulative dose of subcutaneous immunotherapy) has been documented in DB-PC studies carried out on allergic rhinitis induced by certain pollens and mites (4). In this document, the safety of SLIT in children and adults was confirmed. A major paper produced was Wilson's Cochrane meta-analysis on the efficacy and safety of SLIT in rhinitis (10). The conclusions of this paper were of interest: 'SLIT is a safe treatment which

significantly reduces symptoms and medication requirements in allergic rhinitis. The size of this benefit compared to that of other available therapies, particularly injection immunotherapy, is not clear, having been assessed directly in very few studies. Further research is required concentrating on optimising allergen dosage and patient selection'. New papers on SLIT published over the past year and presented at meetings (11–19) convincingly show that SLIT is one of the treatments of allergic rhinitis. Some studies on the relationship between SLIT and subcutaneous SIT have been published but more data are required (20). Two new unpublished studies using appropriate methodology (21) have recently been presented and confirm the efficacy and safety of SLIT. Thus, in around 13 years, there has been a complete new thinking about a treatment which will soon be over a century old. Today, we can say with certainty that SLIT is safe and effective, although it is clear that we need more data to assess its mechanisms and indications (22).

In this supplement, some of Europe's most experienced investigators and researchers in immunotherapy provide a unique collection of articles that give the reader a comprehensive and up-to-date review of SLIT in the 21st century. Based on the authors' experiences, these articles provide an overview of SLIT from the latest of laboratory developments and recombinant DNA technology, through pharmaceutical and clinical studies to every day patient care.

The remarkable safety profile of SLIT is well recognized and, in his article on SLIT in children, Professor Scheinmann and his colleagues describe how even in a vulnerable patient group, children under 5 years, this treatment is well tolerated and compliance is high. Although young children are probably the most likely group of patients to benefit from SLIT, they are particularly difficult to treat, especially with procedures that require long-term intervention. One reason for this is the need for parents to observe a benefit of treatment without risk before agreeing to continued treatment.

The mechanisms of SLIT are still unclear and this aspect is reviewed by Professor Akdis' team, who discuss the immune mechanisms underlying SLIT and explain how a new understanding of the role of the oral mucosa in the immune response can be harnessed to achieve a better and more rapid build-up of allergen tolerance.

The presentation and formulation of the allergen is also critical to the success of the treatment. Indeed, the

heterogeneity of dosage and poor quality of allergens are commonly cited reasons for not using SLIT. Dr Moingeon describes how scientific innovation is enabling an improvement in SLIT formulations and the characterization of allergens by replacing traditional allergen extracts with well-characterized molecules of known structure.

Adult patients also benefit from SLIT, as shown in the article by Professors Canonica and Passalacqua. Positive efficacy is considered as relief from symptoms, less need for medication and less incidence of asthma. However, in his provoking paper on clinical trials, Professor Malling suggests that there have been lost opportunities in many studies performed to date. He speculates that, by following stricter guidelines with well-designed studies, the evidence base for SLIT efficacy could become robust and, therefore, have greater acceptability as a treatment for type I, IgE-mediated allergies.

The final paper in this series, from Professor Didier, reviews the changes in SLIT taking place today based on the innovations in protein technology (described by

Dr Moingeon) as well as the increased understanding of the specific mechanisms of oral immunity (described by Professor Akdis). New formulations, such as tablets that dissolve under the tongue and adjuvants that specifically target the oral mucosa, are likely to increase both the efficacy and compliance of SLIT. These advances also give us a tantalizing glimpse of a future where patients' treatment could be tailored to suit their particular allergy and personal response to a specific allergen.

I hope that the reader will be as enthusiastic about this series of papers and I thank the authors for their valuable contributions to the progress of SLIT. I also hope that 'pro' and 'con' sessions will cease on SLIT as it has now been validated!

Professor Jean Bousquet

Clinique des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, Centre Hospitalier Universitaire, Montpellier Cedex, France

References

1. Law M, Morris JK, Wald N, Luczynska C, Burney P. Changes in atopy over a quarter of a century, based on cross sectional data at three time periods. *BMJ* 2005; **330**: 1187–1188.
2. Von Hertzen LC, Haahtela T. Asthma and atopy – the price of affluence? *Allergy* 2004; **59**: 124–137.
3. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004; **59**: 469–478.
4. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; **108**: S147–S334.
5. Bousquet J, Lockey R, Malling HJ. WHO Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998; **53** (Suppl.): 1–42.
6. Passalacqua G, Guerra L, Pasquali M, Lombardi C, Canonica GW. Efficacy and safety of sublingual immunotherapy. *Ann Allergy Asthma Immunol* 2004; **93**: 3–12.
7. Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. *J Allergy Clin Immunol* 2003; **111**: 437–448.
8. Malling H, Weeke B. Position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 1993; **48**: 9–35.
9. Position paper on allergen immunotherapy. Report of a BSACI working party. January–October 1992. *Clin Exp Allergy* 1993; **23** (Suppl.): 1–44.
10. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005; **60**: 4–12.
11. Ciprandi G, Fenoglio D, Cirillo I, Milanese M, Minuti P. Sublingual immunotherapy and regulatory T cells. *Allergy* 2006; **61**: 511–513.
12. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. *Allergy* 2006; **61**: 185–190.
13. Kleine-Tebbe J, Ribell M, Herold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. *Allergy* 2006; **61**: 181–184.
14. Moingeon P, Batard T, Fadel R, Frati F, Sieber J, Van Overtvelt L. Immune mechanisms of allergen-specific sublingual immunotherapy. *Allergy* 2006; **61**: 151–165.
15. Bieber T. Allergen-specific sublingual immunotherapy: less mystic, more scientific. *Allergy* 2006; **61**: 149–150.
16. Marcucci F, Sensi L, Di Cara G, Incorvaia C, Frati F. Dose dependence of immunological response to sublingual immunotherapy. *Allergy* 2005; **60**: 952–956.
17. 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.
18. Rolinck-Werninghaus C, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV, et al. 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.
19. Bufe A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004; **59**: 498–504.
20. Khinchi MS, Poulsen LK, Carat F, Andre 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.
21. Malling HJ. Methodology and quality of immunotherapy trials. *Allergy* 2004; **59**: 482–484.
22. Bousquet J. Sublingual immunotherapy: from proven prevention to putative rapid relief of allergic symptoms. *Allergy* 2005; **60**: 1–3.