

Editorial

Specific immunotherapy – an optimistic future

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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 been performed since the 1960s and standardized allergen vaccines have only been available for the past 25 years (1).

It is now a recognized fact that subcutaneous SIT using appropriate doses, high-quality allergen vaccines and an appropriate indication is effective in pollen- and mite-induced rhinitis and asthma (2).

New important information on SLIT

Although sublingual immunotherapy (SLIT) using high-dose vaccines is widely used in many European countries (3), it was controversial for many years and this form of therapy has gained little acceptance in the USA. It was thought to be ineffective (4, 5), causing great concern (6, 7), or possibly effective but with many unanswered questions (8, 9). In France and Italy, SLIT is administered to more than 50% of the patients suffering from pollen and mite allergy. In all European countries, the percentage of patients receiving SLIT is increasing steadily.

‘Evidence-based medicine’ (EBM) is an increasingly important concept which has become a new paradigm in medicine (10). The increasing influence of EBM, due partly to the work achieved by the Cochrane Collaboration, has led the way in setting new standards for preparing clinical recommendations (11). Wilson et al. (12) have published the Cochrane Collaboration meta-analysis of SLIT in rhinitis. 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); $P = 0.00003$] after immunotherapy. The Cochrane meta-analysis (12) was followed by several studies which accorded with the results of the review (13–25). Moreover, two pivotal trials have been carried out this year and the results were disclosed recently. These two registration trials included over 600 patients each and showed convincingly that in grass pollen allergy, SLIT is safe and effective (23). A recent meta-analysis in children showed that the sublingual delivery of an allergen vaccination constitutes a safe and effective alternative to the injectable route, reducing allergy respiratory symptoms and drug intake (26). However, more data are required to fully confirm the efficacy of SLIT in asthma.

Our journal has always been at the forefront of the science on SLIT (23, 27, 28) and many European authors have been quite enthusiastic about this form of treatment (3, 29–32). This issue of *Allergy* contains important papers complementing our knowledge.

Abbreviations: EBM, evidence-based-medicine; SIT, specific immunotherapy; SLIT, sublingual immunotherapy.

A Cochrane meta-analysis on the efficacy of SLIT in asthma shows that this form of treatment is effective. This is the third key paper published since meta-analyses have shown that SLIT was effective in rhinitis (12) and in children (26). Twenty-five studies on 1706 patients were included in a meta-analysis on SLIT in asthma (33). According to the Jadad quality method, 64% of the studies were assigned scores of 4 or 5. Immunotherapy was seen to significantly reduce asthma severity when parameter compositions were all analyzed by categorical outcomes.

In children, although the Olaguibel et al. meta-analysis found that SLIT was effective (26), it is important to confirm these results by a middle-scale study. In a double-blind, placebo-controlled study, 88 children (5–15 years) with a history of birch pollen-induced allergic rhinoconjunctivitis were studied (34). SLIT with tree pollen extract resulted in significantly reduced symptoms and medication use. The treatment was well tolerated.

These two papers convincingly complete the missing parts of the puzzle. There is no more debate concerning the efficacy of SLIT in rhinitis, asthma, adults and children (30).

The safety of SLIT in all patients including asthmatics and children is now ascertained (24, 35–38). A phase I study with grass pollen showed that SLIT is safe at doses 10 times greater than the selected dose for clinical trials (39). In this issue of the journal, another phase I study has confirmed the safety of SLIT in grass pollen allergy (40). However, two clinical cases found systemic adverse events with SLIT. The first dealt with latex SLIT which may not be well tolerated because of the aggressivity of the allergen (41). The second is more intriguing as it reports a patient receiving SLIT with inhalant allergens (42). However, the allergen vaccine used in this study is different to those used in Europe. The patient received a mixture of more than six allergens, of which only two were standardized. These two cases indicate that SLIT should be performed with standardized extracts of known potency and that mixtures are not to be recommended. It is however clear that SLIT is far better tolerated than the injectable form with standardized extracts (43, 44) or recombinant allergens (45).

The mechanisms of SLIT are poorly understood. In this issue of the Journal, Savolainen et al. (46) showed that, in the placebo group, during a 2-year follow-up trial, the allergen-induced expression of IL-5 was increased and that the expression of IL-10 mRNA was decreased when compared with the allergen vaccine.

It is clear that there are still many unanswered questions concerning SLIT and that we need more data to find the relative indications of SLIT and subcutaneous SIT (3, 47, 48). We also need to improve our knowledge on the mechanisms and pharmacokinetics of SLIT (49) as well as on compliance to the treatment (50). It is also possible to administer SLIT with a rapid schedule for a rapid onset efficacy (29).

Although further studies are still required to fully understand the role of SLIT, there is no doubt that this form of therapy is safe and effective, is rapidly gaining wide acceptance in Europe and that confirmatory trials will be performed in the USA (7).

EAACI Immunotherapy Practice Parameters

One article published as a supplement of the Journal has attempted to establish a common European Standard for Practical Allergen-Specific Immunotherapy. This paper could serve as an overall 'gold standard' to ensure optimum quality for this form of treatment (51). WHO defines quality of health care as a 'high professional standard', an 'effective use of resources', a 'minimal patient risk', a 'high patient satisfaction' and a 'continuity in patient care'. These Standards are minimum requirements for Best Clinical Practice and form the basis for a Quality Assurance Programme. The Clinical Guidelines should be available, known and understood by all staff dealing with allergen-specific immunotherapy. The greatest problem encountered in trying to provide standards related to practical immunotherapy is the lack of evidence-based information. Consequently, the present standards are based on scientific information and complement the WHO Position Paper on Immunotherapy as well as the ARIA document (1, 2).

National practice parameters have already been published (52, 53) but this is the first truly international document which puts evidence into practice (51). This paper has been written by the EAACI interest group on specific immunotherapy and should be the basis for the establishment of national Clinical Guidelines (more comprehensive local guidelines for immunotherapy) that are adapted to national regulations, local conditions and related to the service and the patients.

The future of immunotherapy

On November 14, 2005, the National Institute of Allergy and Infectious Disease (NIAID) and the Division of Allergy, Immunology and Transplantation (DAIT) sponsored a workshop entitled 'Immunologic Basis of Antigen-Specific Asthma/Allergy Therapeutic Strategies Meeting.' Important aspects on immunotherapy were presented: Basic Immunology Relevant to Allergen Immunotherapy, Allergens Relevant to Allergen Immunotherapy and Clinical Aspects of Allergen Immunotherapy. In order to advance clinical trials using chemically well-defined allergens and reagents, support is needed for core facilities that will use innovative techniques to isolate, purify and identify novel allergens from various sources. The panel identified the need for future clinical trials to examine and compare the clinical effectiveness of subcutaneous allergen immunotherapy

(SCIT) and sublingual allergen immunotherapy (SLIT) particularly with respect to clinical effectiveness, the short- and long-term therapeutic benefits and the under-

lying mechanisms associated with these benefits. We are proud to announce that the report of this very important workshop is published in this issue of the Journal (54).

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