

Editorial

Long-lasting clinical efficacy of allergen specific immunotherapy

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Despite ongoing criticisms, specific immunotherapy (SIT) or specific allergy vaccination is now officially recognized as an effective approach for treating respiratory allergy (1), to be used in combination with drug therapy. This view has been made official first in the 1998 WHO document (2) and very recently in the international document entitled Allergic Rhinitis and its Impact on Asthma (3). Of note, this latter document has been prepared using the Evidence Based Medicine criteria for evaluating strategies and treatments.

There is an important difference between the 1998 and the 2001 documents: in the first it was stated that SIT is indicated when drug treatment is ineffective or not tolerated, whereas the latter (3) states that SIT “does not take the position of being an ultimate treatment principle, but represents a supplement to drug treatment used in the early phase of the disease.”

This important statement is the result of emerging experimental evidence that SIT clinically modifies the natural course of the disease, in addition to symptom improvement. In an early report from 1968, Johnstone (4) observed that young rhinitic patients receiving SIT were less likely over a long time to develop asthma subsequently. This article received important criticisms due to its intrinsic methodological biases, and it was therefore not considered strong enough to support the prophylactic effect of SIT. In the very recent past we have had a unique opportunity to clarify, at least in part, the mechanisms underlying the clinical effects of SIT, i.e. the redirection of CD4+ T lymphocytes towards the Th1 phenotype (5, 6). This fact implies that SIT acts at a very early stage of the allergic reaction, even before the development of the clinical early- and late-phase. These mechanisms of action make SIT unique, and different from any other pharmacological treatment in many senses. First, at variance with drugs,

SIT can modify the natural history of allergic disease, as recently confirmed in rigorously conducted trials such as the PAT (7), whose results are to be published soon. Second, SIT can prevent the onset of new sensitizations, as demonstrated clearly in children in several studies (8–10). Third, SIT even maintains its clinical efficacy years after discontinuation. This latter fact is now supported by different studies using subcutaneous SIT for a variety of allergens (11–16), including mites, grasses cat dander, and *Parietaria*.

In the present issue of *Allergy*, Eng and colleagues (17) describe the result of a long-term follow-up of children who, in 1989–1991, underwent a three-year course of preseasonal SIT with grass pollen extract, in a double-blind placebo controlled study. Of the original 28 patients (14 active treatment and 14 placebo) the authors reassessed 23 patients in the 1997 pollen season: 13 from the former SIT group and 10 from the former placebo group. Rhinitis and asthma symptoms, medication use, skin prick test and conjunctival challenge were evaluated. There was a significant difference in symptom score, thus confirming that a clinical effectiveness of SIT was still persisting, but the most intriguing results were those related to the natural course of the disease. In fact, Eng et al. Found that all the patients of the control group had developed new sensitizations, compared to 61% of the former SIT patients. Moreover, only 23% of the SIT patients still had asthma symptoms, whereas in the control group the prevalence of asthma remained as high as 70%.

The findings of Eng and colleagues are in agreement with those previously described by Hedlin (13), Durham (16), Des-Roches (8) and Pajno (9) concerning both the type of results and the percentages obtained. The present work has certain limitations, such as the low number of patients observed and the open design, however performing such a long-term study in a

double-blind fashion is not feasible in practice. Moreover, the use of objective measurements, such as skin reactivity, adds scientific value to clinical assessment, which can be subjective and somewhat questionable. Again in accordance with existing literature, a three-year course of SIT seems to be optimal to achieve a long-lasting effectiveness. In this regard, positive results have also been obtained with shorter courses (15), and it has been suggested that the duration of the clinical effect of SIT after cessation is related to the duration of the treatment itself (14).

The results provided herein are quite encouraging, especially when considered alongside increasing experimental evidence that favours the long-lasting and prophylactic effects of SIT. It would probably be advisable to conduct more studies on large numbers of patients to better define the extent of this prophylactic effect. Moreover, some important questions remain unanswered: can we predict the long-term response? What is the duration of the effect of SIT? Is the effect dose-dependant?

Long-term questions for a long-lasting effect.

References

1. JOHANSSON SGO, O'B HOUIRHANE J et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–824.
2. BOUSQUET J, LOCKEY RF, MALLING HJ. WHO Position Paper. Allergen immunotherapy. *Allergy* 1998;**54**.
3. BOUSQUET J, VAN CAUWENBERGE P. WHO Position Paper. Allergic Rhinitis and its Impact on Asthma (ARIA). *J Allergy Clin Immunol* 2001;**108**:S147–S334.
4. JOHNSTONE R. A study of the natural history of bronchial asthma in children. *Am J Dis Child* 1968;**115**:213.
5. HAMID Q, SCHOTMAN E, JACOBSON M, WALKER S, DURHAM S. Increases in interleukin-12 (IL-12) messenger RNA + (mRNA⁺) cells accompany inhibition of allergen induced late skin responses following successful grass pollen immunotherapy. *J Allergy Clin Immunol* 1997;**99**:254–260.
6. EBNER C, SIEMANN U, BOHLE B, et al., Immunological changes during specific immunotherapy of grass pollen allergy: reduced lymphoproliferative responses to allergen and shift from TH2 to TH1 in T-cell clones specific for Phl p 1, a major grass pollen allergen. *Clin Exp Allergy* 1997;**27**:1007–1015.
7. JACOBSEN L, DREBORG S, MØLLER C et al. Immunotherapy ad a preventive treatment. *J Allergy Clin Immunol* 1996;**97**:232(abstr).
8. DES-ROCHES A, PARADIS L, MÈNARDO J-L, BOUGES S, DAURÈS J-P, BOUSQUET J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitisations in children. *J Allergy Clin Immunol* 1997;**99**:450–453.
9. PAJNO G, BARBERIO G, DE LUCA F, MORABITO L, PARMIANI S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001;**31**:1392–1397.
10. PURELLO D'AMBROSIO F, GANGEMI S, MERENDINO RA et al. Prevention of new sensitizations in monosensitized subjects, submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy* 2001;**31**:1295–1302.
11. MOSBECH H, ØSTERBALLE O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. *Allergy* 1988;**43**:523–529.
12. GRAMMER LC, SHAUGHNESSY MA, SUSZKO IM, SHAUGHNESSY JJ, PATTERSON R. Persistence of efficacy after a brief course of polymerized ragweed allergen: a controlled study. *J Allergy Clin Immunol* 1984;**73**:484–489.
13. HEDLIN G, HEILBORN H, LILJA G et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. *J Allergy Clin Immunol* 1995;**96**:879–885.
14. DES-ROCHES A, PARADIS L, KNANI J et al. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. V. Duration of efficacy of immunotherapy after its cessation. *Allergy* 1996;**51**:430–434.
15. ARIANO R, AUGERI M, KROON L, PASSALACQUA G, CANONICA GW. Long term allergoid immunotherapy to *Parietaria*: clinical and immunological effects in a double blind trial. *Allergy* 1999;**54**:313–319.
16. DURHAM SR, WALKER SM, VARGA EM et al. Long term clinical efficacy of grass pollen immunotherapy. *N Eng J Med* 1999;**341**:468–475.
17. ENG PA, REINHOLD M, GNEHM HPE. Long-term efficacy of preseasonal grass pollen immunotherapy in children. *Allergy* 2002;**57**:306–312.