



Efficacy of birch-pollen immunotherapy on cross-reactive food allergy confirmed by skin tests and double-blind food challenges. Bolhaar STHP, Tiemsen MM, Zuidmeer L et al. *Clinical and Experimental Allergy* 2004; 34: 761-769



Birch pollen SIT reduces allergy to apples

Biologically remote species may be quite closely related allergenically. Researchers from the University Medical Center in Utrecht in Holland have been exploring the controversial relationship between birch pollen and apples. They set out to investigate the effect of birch-pollen immunotherapy in patients who had a food allergy to apples and evaluate the allergenic relationship. Twenty-five adults who were allergic both to birch-pollen and apples were randomly assigned to receive birch-pollen SIT or symptomatic medication. They monitored IgE and IgG4 antibodies for birch-pollen, apple, natural Bet v 1 and Mal d 1 as well as carrying out skin prick-tests using recombinant extracts rBet v 1 and rMal d 1. Double-blind, placebo-controlled food challenges were used to assess outcome. After three months of SIT, there was a significant decrease in

skin prick-test reactivity; thirty-fold for rBet v 1 and ten-fold for rMal d 1. In addition, there was potent induction of IgG4 Bet v 1 antibodies with cross-reactivity to Mal d 1. Nine out of the thirteen treated patients had a greater than ten-fold reduction in reactivity, three of whom were no longer reactive. Levels and functioning of the regulatory T cells, CD4⁺ and CD25⁺ were unaffected. Patients using symptomatic medication experienced no change in allergic status. This study shows that immunotherapy for an airborne allergy can have beneficial effects on related food allergy. In this instance, birch-pollen SIT reduced allergy to apple because it contains Bet v 1-homologous allergens. The study also shows how the use of recombinant allergens in combination with food challenge can be used to monitor the effect of immunotherapy for airborne allergens on related food allergies.

Specific immunotherapy in honeybee venom allergy: a comparative study using aqueous and aluminium hydroxide adsorbed preparations. Ruëff F, Wolf H, Schinkter J et al. *Allergy* 2004; 59: 589-595.



Aluminium hydroxide takes the «sting» out of SCIT

Until recently, subcutaneous immunotherapy has been the only treatment – safer, but perhaps only slightly less painful, than the bee sting itself. Now, a German team has developed a less painful version of SCIT for the treatment of bee venom allergy. They took 65 patients who were allergic to honeybee venom and had a history of systemic anaphylactic reactions to honeybee stings. The patients were assigned to three different treatment groups. Groups A and B received a conventional aqueous SCIT preparation starting with a rush protocol. Group C was treated with an aluminium hydroxide adsorbed depot preparation but with a conventional "slow" titration protocol. A maintenance dose of 100 micrograms of venom was used in all groups but group A was given an aqueous preparation, administered every 4 weeks, and groups B and C were given the depot preparation, administered every 8 weeks in group B and every 4 weeks in group C.

The treatments were assessed six to twelve months after the maintenance dose had been reached, using a live honeybee. Forty-nine patients were tested this way but another seven patients received honeybee stings whilst going about their daily lives. There were no statistically significant differences between groups in the efficacy of treatments but there was a trend towards less frequent large local reactions to treatment with the aluminium hydroxide formulation 3.9% vs. 7.6% ($p=0.059$) and a significant reduction in local reactions during maintenance 12.1% vs. 49.4% ($p<0.001$). There was also a difference in the incidence of systemic side effects occurring during rush (31.0%) compared with slow (13.0%) titration, although this did not reach statistical significance. The researchers favour initial rush aqueous immunotherapy, to provide rapid protection against future stings and maximise compliance, followed by the depot preparation for maintenance because it caused fewer adverse reactions over the period of the study.

Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. Bernstein DI, Wanner M, Borish L, Liss GM. J Allergy Clin Immunol 2004; 113: 1129-1136.



The importance of guidelines

An American survey has revealed some common factors leading to fatal and near-fatal allergic reactions in clinical practice. Stating that no survey had been conducted since 1989, the research team sent out a short survey to member practices of the American Academy of Allergy, Asthma and Immunology. Those reporting fatalities received an 87-item questionnaire. There was a 25% response to the short survey, revealing 20 direct reports of fatal immunotherapy reactions and 21 indirect reports for the years 1990 to 2001.

The survey results suggested that there was one fatal reaction for every 2.5 million injections – an average of 3.4 deaths per year. One fatality was confirmed after skin-prick testing with multiple food allergens. Among the 17 deaths described in the detailed questionnaires, 15 were asthmatic patients of whom the majority did not have their symptoms optimally controlled. The rate of fatal reactions to immunotherapy was similar to those in previous surveys although there had been some improvement in clinical

practice, for example the exclusion of patients on beta-blockers. However, the main reasons for fatalities were conducting immunotherapy in an inappropriate setting and failure to adhere strictly to practice guidelines. The researchers made the following recommendations.

- Administer immunotherapy in a fully equipped clinic with staff trained in establishing and maintaining the airway.
- Assess asthma and check PEFr before injecting.
- Avoid skin-prick testing and withhold immunotherapy for patients with uncontrolled asthma.
- Minimise the number of test antigens in severe asthmatics and reconsider the risk/benefit ratio of immunotherapy.
- Observe high-risk patients for more than 30 minutes following injection.
- Provide self-injectable epinephrine for high-risk patients.
- Be prepared to administer high dose epinephrine using 1:10,000 IV infusion if intramuscular injections prove inadequate.

Mechanisms of immunotherapy. Till SJ, Francis JN, Nouri-Aria K, Durham SR. J Allergy Clin Immunol 2004; 113: 1025-1034



Immunotherapy in a nutshell recommended reading

Although there is always more to learn about the complex processes that drive the immune system, there is a comprehensive account of present day knowledge in this article, which originates from Imperial College, London. The authors, first of all point out that SCIT is highly effective in IgE-mediated disease such as allergic rhinitis or venom anaphylaxis and that immunotherapy inhibits both early and late responses to allergen exposure.

Immunotherapy boosts allergen-specific IgG, particularly IgG4, which inhibits not only IgE-mediated histamine release but also the activity of antigen presenting cells. Immunotherapy not only reduces exposure of T cells to antigen but it also modifies their response from T_H2 to the T_H1 response. Also within the mucosal tissues, there is an increase in production of the interleukin, IL-10 following immunotherapy. This substance has many anti-allergic properties, suppressing the acti-

city of cells involved in the allergic response and, in particular, switching B cells to IgG4. The regulatory T cells, CD4⁺ and CD25⁺ are the important producers of IL-10 but it is the dendritic cells that seem to be essential in regulatory T cells activation.

The article ends with an account of recent developments in immunotherapy, including the use of adjuvants, such as monophosphoryl lipid A or bacterial nucleotides to potentiate T_H1 responses, and the use of allergen-derived peptides or recombinant allergen extracts to minimise the allergic response that is triggered by natural whole protein.

The article is accompanied by excellent diagrams of the key players in the switch from allergy to immunity and should be read by all doctors – British doctors can obtain a Continuing Medical Education credit for doing so!