

EDITORIAL

The safety of immunotherapy

A. P. Williams, M. T. Krishna and A. J. Frew

Allergen immunotherapy is the only recognized treatment of allergic disease that can both ameliorate symptoms and alter the natural course of the allergic disease [1, 2]. The efficacy of allergen immunotherapy has been proven through well-conducted double-blind placebo-controlled trials involving patients with rhinitis, asthma and anaphylaxis. Although the exact mechanism of action of immunotherapy is not known, its allergen specificity and clinical effectiveness within different allergic diseases make it an attractive (and possibly unique) therapy. The drawbacks of allergen immunotherapy relate to its safety profile, compliance and possibly cost. It was noted by Noon [3] in 1911 that in the early stages of 'immunization', some individuals may manifest a severe attack of hayfever. Although adverse reactions to allergen immunotherapy and allergen skin prick testing were recognized in the latter half of the last century, it was not until the mid-1980s that retrospective safety data were collected and the safety issues of allergen immunotherapy addressed. In the United Kingdom, the Committee on Safety of Medicines (CSM) reported on 26 deaths associated with immunotherapy in the preceding 29 years [4]. A similar study by Lockey et al. [5] in the United States reported on 46 deaths over a 40-year period. The responses of the respective country's advisory bodies to these retrospective data collection series differed considerably. The UK CSM suggested that immunotherapy should only be carried out where full cardiopulmonary resuscitation facilities were immediately available and that patients should be kept under observation for a minimum of 2 h. The practice in the United States also altered following these observations with greater consideration of the risk factors identified through these reports and a minimum waiting time of 20 min requested [6]. The European Academy of Allergology and Clinical Immunology reviewed the available evidence and reached a consensus for a 30-min waiting period after injections [7]. A paper by Moreno et al. [8] in this issue extends these observations and recommendations of the safety of immunotherapy through a prospective multi-centre study of subcutaneous allergen immunotherapy of adults and children with rhinitis and/or asthma.

This paper examined the prevalence of systemic side-effects, graded according to the EAACI immunotherapy position paper criteria, in 488 patients over 2 years. This study reports on over 17 000 injections through up-dosing and maintenance phases. The key figures from this extensive review are the number of individuals who experienced a systemic reaction (SR) (3.7%) and the number of SR per administered dose (0.3% ~ 1 in 333 injections). Interestingly, of the 18 individuals who experienced an SR, 11 experienced only a single SR throughout their course of therapy, with seven of these occurring in the up-dosing period. Two individuals

experienced two or three SRs, with the remaining five patients experiencing 40% of all SRs. No grade IV SRs were noted and adrenaline was given on only seven occasions, each time for a grade 3 reaction.

A number of other interesting observations are made within the paper. Firstly, the rate of SRs was not greater during the up-dosing phase compared with maintenance. It would be interesting to know the details of the maintenance phase reactions, in particular their time relationship to the end of up-dosing, and whether any alterations in medication had occurred (i.e. antihistamines/inhaled steroid usage). Previous studies have suggested that the use of prophylactic antihistamines before immunotherapy injections can reduce adverse reactions without impairing the effectiveness of immunotherapy [9, 10]. Previous studies have commented upon the higher SR frequency in those individuals with asthma and in those receiving mite immunotherapy compared with other allergy [11]. The inherent bias within such an association is the confounder that asthmatics more frequently receive mite immunotherapy. It would be interesting to sub-analyse the rhinitic and rhinitic +/- asthmatic cohorts for mite sensitivity to see if the SRs are significantly higher in the mite patients with rhinitis alone compared with the rhinitic pollen patients.

Of those who experienced more than three SR, all were aged 15 years or less, male and had both rhinitis and asthma. Indeed, within this study, SRs are strongly associated with male sex ($P = 0.0001 \times 10^{-3}$). Previous studies published in this journal have also found a lower risk of SR in those with only rhinitis and observed a risk of SR in those under the age of 20 compared with those >40 years of age [12].

There are currently no strict guidelines addressing the withdrawal of allergen immunotherapy after adverse reactions. Generally speaking, this is a clinical decision, which has to be based upon the type and severity of the SR, the context of the indication for immunotherapy, and the wishes of the patient. Of the six individuals with >three SRs within Moreno's study, half withdrew and half continued on a reduced dose. As the optimum dose for successful immunotherapy is not clearly established (although for most allergens it is thought to be >5 µg of allergen), the aims should be to use the minimum effective dose in all individuals who experience SRs. Alternatively, one could argue that exclusion of 1.2% (6/488) of individuals (of which half would withdraw anyway) from immunotherapy would reduce the SR from approximately 1 in 300 to 1 in 500 per injection. Finally, to set this all in perspective, we should note that a side-effect risk of 0.2% without any episodes of anaphylaxis (Grade IV) in over 17 000 injections compares favourably with the risk of anaphylaxis secondary to the administration

of other medical treatments such as antibiotics and analgesics (1 in 10 000 exposed patients) [13].

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A. P. Williams, M. T. Krishna and A. J. Frew
Medical Specialties Clinical Group
Southampton General Hospital
Southampton SO16 6YD
 UK
 E-mail: ajf1@soton.ac.uk