

CORRESPONDENCE

Clinical and Experimental Allergy

Safety of immunotherapy revisited

F. Madsen

Allergy and Lung Clinic, Helsingør, Denmark (E-mail: flem-mad@dadlnet.dk)

A. J. Frew in his excellent update on safety aspects of immunotherapy (IT) focuses on the art of balancing pros and cons of treatments in general and summarizes data on risk of IT [1].

What makes immunotherapy so special that the discussion on safety seems to be never ending? For the last 25 years the treatment protocols have been unchanged, extracts are improved and data on serious adverse events (SAE) are accumulating in databases. Effectiveness of IT has been proved with the highest degree of evidence [2], but the discussion of safety goes on without quality improvement. Why has the relevant [3] data not been collected and analyzed? Nothing is unique about IT except of the academic handling of side effects, making the discussion go on.

A lesson can be learnt from the Bristol cardiac surgery incident [4]. We have to recognize substandard performance and handle it using the optimal quality control measures. We would have to run quality surveillance continuously for as long as IT will exist. Just like heart surgeons do. At present this is the only way to stay in control and respond fast to outliers. The problem and magnitude of substandard performance has not been adequately addressed by the academia in print or during official meetings. Therefore we must distinguish between safety of standardized IT and safety of physician performance. Every IT-related SAE has to be examined by an immediate root analyses and its cause determined and corrected.

Performance could better be judged substandard if we had a unifying standard. Unfortunately we do not and this may block the revitalizing of IT. One example of the resulting problems are the EAACI [5] demand for 30-min interval between injections of different allergens not claimed by AAACI and WHO [6, 7]. The evidence for this interval is non-existing and from a safety point it may seem as a harmless detail but the 30-min interval may increase risk because patients and extracts have to be identified twice.

The paper by Winther et al. [8] is another example of why we are not moving on. The Copenhagen group

constitutes leading voices of EAACI immunotherapy academy, and they have for year's co-authored "position papers" [5, 7] and driven interest groups on IT. Whether this is an advantage or not concerning the propagation of the safety issue is not clear? Are there barriers or maybe competing interest to be removed? A few examples from the Winther et al [8] paper will illustrate problems arising from lack of a single standard and stress the need for a unifying transatlantic IT standard like ATS and ERS have succeeded with in a joint standard for pulmonary function testing [9].

If the Winther et al. [8] paper is read carefully it becomes clear that absolutely nothing is mentioned about how IT was performed except for dosing regimens, extracts and pre-medication. "They all followed their own protocol"? Staff training, facilities, injection technique, pre-injection assessment, patient and extract identification and injection number pr. time and staff is not reported. In the Winther study some patients received injections with 30-min interval between different allergens and others not. Avoiding discussion of these details may add to the barrier for progress. From a safety point of view the essential part of the Winther paper is not the thousands of non-problematic injections but the eight SAE and what caused them?

Other examples of safety issues not mentioned in the paper and even not in the discussion are what constitutes too many patients and what constitutes too few? An academic discussion is strongly needed.

At present it seems safe to conclude that IT as a treatment is highly effective and safe if substandard performance is avoided [10]. In fact it may be much safer than assumed previously and it is time to realize that SAE has not been proven to be a part of the treatment but a severe potentially preventable complication [10].

The academia has to agree on a unifying standard for IT and peer reviewers have to be rough and scrutinize the methodological sections much, much harder. After more than 25 years of standardized IT it is disappointing to learn that lack of data [8] is considered to block unification of standards and I do not agree.

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Response by L. Winther, J. Arnved, H.-J. Malling and H. Mosbech

We completely agree with Madsen that safety aspects of allergen-specific immunotherapy are of paramount importance for widespread dissemination of this effective treatment of allergic diseases. In order to discuss safety aspects, knowledge of the frequency of side-effects and risk factors for side-effects are urgently needed. Side-effects are mostly reported in clinical trials and in a few studies evaluating the safety of daily practice.

The aim of the study was to evaluate the frequency of side-effects in four clinics performing immunotherapy according to daily practice. The study was initiated as a consequence of a seeming increase in severe side-effects in Denmark. We, therefore, wanted to use reports to a database to get a realistic depiction of the frequency.

Former reports on side-effects were based on data from the Danish Medicine Agency, and as the number of patients being treated was unknown, calculation of frequencies was not possible. Secondly, identifying risk factors was part of the objectives.

Serious side-effects are rare, and consequently risk factors must be based on the aggregation of information from multiple centres. We agree with Madsen that standards for performing the treatment are a prerequisite for identifying substandard performance. The European Academy for Allergology and Clinical Immunology has set down a Task Force for making standards for practical treatment. When these standards have been published, it will be possible to evaluate substandard treatment.

As the study did not attempt to make a core analysis, details of the practical treatment, experience of staff, pre-injection monitoring, etc. was not presented. There was, however, no difference in frequency of side-effects between centres, which would be expected if a difference in the standard of treatment played a major role.

We disagree with Madsen that only patients with serious side-effects are important. In contrast to the expression of Madsen, the essential part of the study actually is the thousands of unproblematic injections rather than the few severe side-effects. Only by comparing the serious side-effects with the thousands of unproblematic injections, possible risk factors could be made probable.

We disagree with Madsen that SAE are not an integrated component of the very treatment principle (injecting allergens into an IgE-sensitized patient), but do accept, that optimally performed pre-treatment monitoring and sticking to standard guidelines for dosing and dose modifications may reduce side-effects to a minimum.

Yours sincerely

Lone Winther
John Arnved
Hans-Jørgen Malling
Holger Mosbech

Copenhagen University Hospital Copenhagen Denmark
E-mail: Lone.Winther@dadlnet.dk

Response by A. J. Frew

I agree with Dr. Madsen that we should always try to learn from other areas of medicine. With SIT, the rate of adverse outcomes is so low that it will be difficult for individual centres to know when their performance is sub standard. In cardiac surgery, there is a significant fatality rate in every centre and so it does not take very long for

people to find out if they are performing badly. For SIT, fatalities occur once in perhaps 2 000 000 injections and that is (fortunately) too low a rate for different centres to make meaningful comparisons.

Comparisons between European and US practice are not as straightforward as Madsen suggests. The selection of patients and the preparation of extracts is quite different, with US allergists often treating with multiple allergens and adjusting the composition of the extract mixtures to reflect the degree of skin test sensitivity of the patient in ways that are simply not done in Europe. There are also several different schools of thought within the United States leading to quite wide variations in clinical practice. Within Europe we have made a start in trying to prepare standards for allergen immunotherapy and these have recently been updated (soon to be published in *Allergy*).

My personal conclusion is that if we believe in specific immunotherapy we should be able to standardize it so that different physicians approaching the same patient will come up with the same prescription and approach. When there are many different approaches and regimes the general conclusion must be that no single approach is optimal. I welcome any efforts to co-ordinate activity so that we can identify the key research questions to be answered in this area and try to move forward with what I believe to be an effective and worthwhile therapy for patients with allergic disease.

Yours sincerely

Anthony Frew

Brighton General Hospital East Sussex UK

E-mail: anthony.frew@bsuh.nhs.uk