

EDITORIAL

Clinical and Experimental Allergy

Immunotherapy: how safe is safe?

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The principle of avoiding harm to patients while treating them has been at the heart of medical practice since the days of Hippocrates. The aphorism 'primum non nocere' or first do no harm, is enshrined in our consciousness even if its precise origins remain obscure [1]. However, if our medical forebears had subscribed fully to this doctrine, they would have made little progress. Virtually every surgical procedure involves some degree of harm to the patient and clearly the issue is more about acceptable levels of harm rather than absolute risks. Immediately, we move to the concept of acceptable or reasonable levels of risk, we bring personal and ethical judgements into play. A procedure with 40% mortality may be perfectly acceptable if the alternative is certain and immediate death but as the proximity and probability of death get less, there comes a point where the risks of the procedure outweigh the perceived gain.

In the context of allergen immunotherapy, the risk of serious side-effects has been recognized since the initial studies that defined anaphylaxis [2]. Indeed by its very nature, specific immunotherapy (SIT) is bound to cause some allergic side-effects. In this sense, allergic side-effects to SIT cannot be directly equated to allergic side-effects to antibiotics or anti-hypertensive agents. The fact that side-effects are predictable does not necessarily make them acceptable but it certainly allows us to understand the risks and discuss them with our patients. Non-fatal side-effects may be acceptable if the degree of benefit is large, the risk of side-effects is minimized and any side-effects that do occur are treated promptly and effectively. Local irritation and swelling are common after injections and have no particular significance. Large, delayed reactions are relatively unusual and are regarded as a reason for holding the dose of extract to the same level for subsequent injections until the degree of responsiveness reduces. Mild systemic reactions such as headache, tired-

ness and nasal congestion also occur commonly and may even occur in quite high frequencies during placebo treatment. More significant systemic side-effects such as bronchospasm, urticaria and angio-oedema are almost always treatment associated and require symptomatic treatment. When patients get significant systemic side-effects, the patient should be reviewed for possible risk factors that were overlooked and at the same time, the indication for giving immunotherapy should be carefully reviewed before deciding to continue with therapy.

In the UK, debates about the efficacy of immunotherapy have been overshadowed by concerns about safety. Twenty years ago, the Committee on the Safety of Medicines (CSM) noted that there had been 26 fatalities associated with immunotherapy between 1957 and 1986. There had also been a cluster of deaths in the early 1980s, which led them to impose stringent regulations on the performance of immunotherapy in the UK [3]. While these restrictions were well intentioned, they had unforeseen impacts on the practice of immunotherapy in the UK, where there were very few specialist centres able and willing to continue to deliver desensitization within the rules that had been imposed. The net result is that we now live in a world where most patients and doctors are not aware that desensitization is both available and effective. Indeed it is common for patients to tell us that they have been informed by their GP or their specialist that immunotherapy has been banned for years. In fact, immunotherapy never went away, it just became isolated within the relatively small number of specialist allergy centres that exist within the UK. With the concentration of services into these centres and increased attention to detail, there has been no further fatality over the last 20 years, although one has to admit that the total number of courses must be substantially less than were being administered in the early 1980s.

A key element of the discussion is the fact that the conditions treated by immunotherapy are not themselves generally fatal. A few patients probably die each year from wasp and bee sting anaphylaxis but these usually come out of the blue and it is impossible to know how

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many people are really prevented from dying by their desensitization. Hayfever and other forms of allergic rhinitis (AR) are never fatal and therefore the acceptable level of risk for treating AR has to be lower than would be the case for treating cancer or serious heart disease.

Accurate data on the side-effects of immunotherapy have been difficult to come by. In this month's issue of *Clinical and Experimental Allergy*, Winther et al. [4] have presented a 3-year prospective study of systemic side-effects associated with immunotherapy in a total of 1038 patients treated in Denmark. The patients were all treated with extracts from a single manufacturer and the data are thus relevant to this particular product line and do not necessarily tell us about the rates of side-effects that might be encountered with other manufacturers' extracts. Nevertheless, the data are useful in flagging up a number of clinical features that may help to inform future discussions on the safety of desensitization. During the build-up phase of treatment, three-quarters of the patients reached the maintenance dose without any systemic side-effects. The likelihood of having systemic side-effects was significantly greater in those patients treated with grass pollen, while the lowest likelihood of systemic side-effects during the build-up phase was seen in those receiving treatment for wasp venom hypersensitivity. In terms of severity, birch pollen was least likely to cause grade 3 reactions while grade 4 reactions were only seen in those treated with timothy grass. These results raise interesting questions about the mechanism and likelihood of side-effects. It may be that extracts vary in terms of their biological potency, thus increasing the risk of side-effects. Alternatively, there may be wider variation in terms of the spectrum of epitope recognition for certain allergens. So, if patients with timothy grass sensitivity show wide variation in the pattern of their IgE responses, this will tend to increase the likelihood of an accidental over-dosage of a particular allergenic component in somebody who has a high level of sensitivity to that particular component. Allergens that are less complex (in terms of their patterns of IgE recognition) may be easier to work with, as the range of biological responses may be more standardized.

Interestingly, this study did not find that asthma was a particular risk factor for side-effects. We do know that asthma is a risk factor for fatal outcome from side-effects as demonstrated in the original CSM report [3] and in the subsequent reviews by the American Academy of Allergy Asthma and Immunology (AAAAI) [4–7]. In other words, asthma may not be a risk factor for developing side-effects but it does have an adverse effect on the eventual outcome. In the latest survey by the AAAAI, 15 out of 17 immunotherapy deaths were in asthmatics [7]. The Americans calculate that the fatality rate is one per 2.5 million injections. We do not have precise data on how many asthmatics are treated compared with non-asthmatics but it is evident that even this fatality rate could

be substantially reduced by excluding patients with significant asthma from treatment. One of the difficulties we face in demonstrating that immunotherapy is safe is that even very large studies of safety [8] cannot get close to the number of safe injections that would be required to demonstrate that the risk is lower than one per 2.5 million. If one fatality per 2.5 million injections is unacceptable, how are we going to carry out the necessary studies to demonstrate to the regulators that we can in fact reduce this?

There is now convincing evidence that immunotherapy is effective in terms of reducing symptoms and medication requirements during the pollen season, after exposure to cats and to a lesser extent, in patients with house dust mite sensitivity [9]. There is also convincing evidence that immunotherapy can modify the course of disease by reducing new sensitizations, modifying the progression to asthma and reducing the likelihood of developing severe asthma. All of these properties would seem to be highly desirable and yet we in the UK have not been able to persuade our colleagues and the regulators of the benefits of immunotherapy. Three principal factors seem to be acting as barriers: direct costs, limited availability of trained personnel and concerns about safety. The paper by Winther is helpful in reassuring us about some aspects of safety. Clearly, even with 25 000 injections, it is under-powered to detect fatalities. Even a study 100 times larger would still only have one expected fatality if the American experience held true in the European theatre. Given that we are less likely to put patients with asthma onto immunotherapy, one might even have to look at a study 1000 times this scale before one would expect to see a single fatality. At the end of the day, nobody wants to be responsible for causing fatal systemic reactions but we do have to ask ourselves whether we are being over-cautious in restricting the availability of immunotherapy to patients who clearly can benefit from it when we will never be able to determine the true rate of fatal side-effects. Is it not time that we took a long cold look at the situation, accept that all treatments carry some risks and that when many patients stand to gain substantially from a treatment, we do have to accept the possibility of some adverse effects? Minimization and mitigation of risk seem a reasonable approach. Complete abolition of all risks may seem desirable but in its pursuit, doctors and regulators may be imposing an excessive burden of proof on themselves and their treatments. We need to be prepared to have open and robust discussions within the profession, with the regulators, with the public and with the media to achieve a better understanding of what constitutes a reasonable risk. Otherwise we will be left wringing our hands and saying 'well we could do things but it would be too dangerous to risk it' when in fact all we are doing is failing to take responsibility to explain the pros and cons and help our patients to make balanced judgements about

the options that they have for managing their allergic diseases.

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