

EDITORIAL

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Venom immunotherapy: worth the time and trouble!

This editorial discusses the findings of the paper in this issue by Oude Elberink et al. [12].

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Of all forms of specific allergen immunotherapy, the most spectacularly successful appears to be venom immunotherapy (VIT). Placebo-controlled studies using deliberate prospectively observed stings as the primary outcome attest to the value of VIT for protecting subjects with a history of immediate generalized allergic reactions (IGR) [1, 2]. Why then are there so many questions regarding application of this potent immunomodulatory therapy?

In contrast to the situation with aeroallergens where exposure is ongoing and thus clinical sensitivity is relatively easy to assess, insect venom exposure is intermittent and erratic. Our major problem relates to assessment of risk of a systemic reaction and death with future stings. A combination of diagnostic laboratory and intradermal venom skin tests for venom-specific IgE (sIgE) and clinical criteria have reasonable sensitivity but very limited positive predictive value [3, 4]. The development of sIgE is common after stings but only a small proportion of these subjects will have clinical reactivity to stings [3]. Even with a history of IGR and a positive test for sIgE the risk of a reaction on future sting by the same insect ranges from approximately 25% to just over 70% depending on severity of previous reaction and the insect involved [2, 3, 5]. These risks are lower if there is a history of less severe reactions but we and others have clearly demonstrated the potential for life-threatening reactions even if previous reactions have been of only moderate severity [2].

So far the available laboratory diagnostic methods including sIgE, sIgG, basophil activation tests and whole blood or leucocyte mediator release studies have not been

shown to add any clear value in terms of predicting the result of a future sting other than confirming the insect species or species group to which a patient has reacted to in the past [5, 6]. Sting challenges are the gold standard in comparing groups in clinical trials, but are problematic in routine practice [2, 4] with subjects giving inconsistent responses, significant risks of anaphylaxis and the possibility of further sensitization arising from the test.

Deaths are likely to be undiagnosed in many or even most instances [7]. In recent UK and Australian data, sting allergy lies second only to allergy to drugs as a cause of lethal anaphylaxis, accounting for two to three times as many deaths as food anaphylaxis [7, 8]. However, from viewpoint of justifying VIT, recognized death from anaphylaxis to a sting is rare to an extent that prevents us using it as an end-point in any reasonably sized clinical study and, frustratingly, around half occur in subjects with no prior history of sting allergy [3, 4].

Therefore, on first appraisal because of the limited specificity of diagnostic testing, we seem to be offering VIT with the significant morbidity, economic and time costs that it carries [2, 9, 10] to far more people than require it and without preventing more than the occasional death.

However, an important part of the equation so often overlooked is that of effect of VIT on quality of life (QOL). For example, in Australia a simple visit to the letter box at the front gate through the territory of a jack jumper ant (*Myrmecia pilosula*), genetically programmed to leap from ground or vegetation towards whatever moves in its territory, can be terrifying to a person with a history of allergic reactions to these ants. Our highly venomous and aggressive elapid snakes show more discriminating behaviour!

The series of articles by Oude Elberink et al., including the one in this issue of the journal [11, 12], using a

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validated Vespid allergy Quality of Life Questionnaire (VQLQ) [13] demonstrate unequivocal benefit in subjects with allergy to vespula stings from VIT that surpasses the problematic 'reassurance' provided by an automated adrenaline syringe. This extends previous observations on subjects with a history of moderate-severe IGR [11] to subjects who have a history of mild IGR limited to the skin [12]. In these patients with milder allergy the number needed to treat (NNT) to achieve meaningful VQLQ improvement in one patient was 1.7. This was only slightly higher than the NNT of 1.4 in their previous study. They also propose that the VQLQ instrument may be useful in defining a subgroup of patients with a favourable prognosis, whose QOL is sufficiently unimpaired by their sting allergy that they are unlikely to benefit from VIT.

Caution is required in extrapolating the results of these studies. The VQLQ instrument has been designed and validated only for vespid sting allergy; epidemiology and efficacy/morbidity of VIT is to a degree insect specific [2, 3, 10]. The observations need to be repeated in the contexts of other hymenoptera but it would be surprising if the observations lacked some generality. Another qualification is that subjects with comorbidities were excluded, including systemic mastocytosis and/or β -blocker treatment in whom the benefit/risk equation might be more favourable for VIT [14].

While arguments for VIT relating to prevention of death may be difficult to promote at a general population level, the high susceptibility of those with a past history of anaphylaxis [3] and particularly hypotensive anaphylaxis [15] to further life-threatening reactions continues to impress those in daily contact with such patients. This subgroup appears to be too small to demonstrate protection from death in even the largest of population surveys yet that aim appears a most reasonable rationale for VIT in at least those subjects.

QOL improvement and prevention of death are not the only reasonable justifications for VIT. Often overlooked are the personal and health care costs of non-lethal anaphylactic events and the contribution of sting allergy to the same. In a recent study in an Australian city, sting allergy caused 30% of 1149 consecutive presentations to an Emergency Department with IGR [16]. Many of these also required pre-hospital care by ambulance paramedics and overnight admission. Preventing such events, at least in regions with a high prevalence of sting allergy, appears likely a worthwhile endeavour. Given that sting reactions require doses of adrenaline above those provided by automated adrenaline syringes [17], that compliance with the same is documented to be poor in many subjects [18] and that it is extremely difficult to care for adrenaline in warm temperate climates, such devices can hardly be regarded as more than first aid measures, leaving VIT as the definitive measure.

The strength of the series of papers by Oude Elberink et al. [11–13] is that they account for the effect of sting allergy on 'real people' living life with extra fears and inconveniences and provide a method for examining such effects. If we are to justify VIT as a treatment for subjects with sIgE to the relevant venom and a history of IGR of mild to moderate severity in an increasingly cost-sensitive environment, we need similar studies to be performed in situations involving allergy to other hymenoptera, subjects living in other environments and subjects with co-morbidities.

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