Switch-over from Pharmalgen to Alutard Bee and Wasp venom in the UK

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To the editor,

Hymenoptera venom immunotherapy (VIT) extracts can be non-purified aqueous, purified aqueous, or purified aluminium hydroxide adsorbed ("depot") preparations. All of these are efficacious, but the choice of preparation will influence the updosing protocol and dose interval. Pharmalgen Bee Venom and Wasp Venom (ALK) are partially-purified aqueous products, and until now have been the only licensed products available in the UK. However, ALK has advised that the Pharmalgen product-line will be discontinued, with a plan to substitute with Alutard SQ Bee and Wasp Venom products. Supplies of Pharmalgen are expected to last until the end of 2019. Alutard SQ has been widely used internationally for many years, and its introduction into the UK is part of a long-term corporate strategy to streamline products and improve efficiency.

Alutard SQ is a depot preparation, and received a UK licence on 13th September 2019. There are no plans to take the new product through the National Institute for Health and Care Excellence (NICE) technology appraisal process, and the NICE recommendation regarding Pharmalgen (1) will not be valid for Alutard SQ. However, the British Society for Allergy and Clinical Immunology (BSACI) guidance on the management of Hymenoptera venom allergy (2) will continue to apply to the new product, as the basic principles underpinning VIT remain unchanged. Some important differences between the two products that impact on current UK clinical practice are summarised below.

In contrast to Pharmalgen which was supplied in a single vial that required manual dilution during updosing, Alutard SQ Bee and Wasp Venoms are supplied in two product kits. The initial updosing kit consists of 4 vials, containing 100 SQ-U/mL, 1000 SQ-U/mL, 10,000 SQ-U/mL, and 100,000 SQ-U/mL. The maintenance kit contains a single 100,000 SQ-U/mL vial containing 5mL of product, and once established on maintenance therapy a dose of 1mL is administered every 6-8 weeks. The NHS acquisition cost of Alutard SQ is 16.5% greater than Pharmalgen over three years of VIT, but the associated indirect costs may be reduced, as

fewer visits would be required for doses every 6-8 weeks rather than every 4-6 weeks. Importantly, in contrast to the aqueous extracts, Alutard SQ cannot be used for "accelerated", "rush"or "ultra-rush" updosing but the Summary of Product Characteristics allows for a choice of weekly updosing over 7, 15, or 25 weeks depending on baseline patient characteristics.

Both Pharmalgen and Alutard SQ Bee Venom contain venom obtained from a single species of honey bee (*Apis mellifera*). In contrast, both Pharmalgen and Alutard SQ Wasp Venom comprise the venom from six *Vespula* species using the same purified mixed allergen source. The manufacturer has provided assurance that the products are interchangeable in practice, and that although the venom concentration is given in different units (100,000 SQ-U/mL of Alutard SQ = 100mcg/mL of Pharmalgen), the millilitre dosing is equivalent; with either product 1mL constitutes the usual maintenance dose (3).

Treatment with bee and vespid VIT is effective in preventing systemic reactions to subsequent stings in 95-100% of vespid venom and approximately 80% of bee venom anaphylaxis, and this benefit appears to be similar with both aqueous and depot products (2). However, safety and efficacy of bee and vespid venom VIT (including long-term) is not well established in the context of clonal mast cell disorders. Depot preparations seem to be associated with fewer local reactions than aqueous preparations, but such comparisons may be biased by slower updosing phases with depot preparations (4). A systematic review comparing aqueous and depot extracts for hymenoptera VIT showed a similar rate of systemic reactions although rates between vespid non-purified (eg Pharmalgen) and purified aqueous extracts were not distinguished (5). Muller (6) in an editorial speculated that systemic reactions may be relatively more delayed due to the depot nature of the product. Such delayed reactions with alum-based vaccines are uncommon and generally mild, although should be borne in mind when switching a patient from Pharmalgen to Alutard SQ. Overall however, the available safety data on transitioning from aqueous to depot venom preparations is reassuring (7,8)

The depot Alutard SQ product cannot be used for intradermal testing, due to the inclusion of aluminium hydroxide. Sensitisation should therefore be confirmed using skin prick testing using an available commercial kit, and serum specific IgE testing. Ideally these should both be positive, but in cases of negative and borderline responses, or in subjects with dual sensitisation, specific IgE to venom components should be requested.

Every patient will need to transition to Alutard SQ in view of the discontinuation of Pharmalgen, unless they are due to finish their maintenance treatment in the next few months. In order to facilitate transition to the new product, we suggest the following:

1. There is sufficient existing Pharmalgen product to allow all patients currently being updosed to reach maintenance therapy, but once on maintenance they should all be switched over to Alutard SQ.
2. No new patients should be commenced on Pharmalgen, in view of the potential unavailability of the product during the updosing period.

3. Allergy Departments should consult with their local Drug and Therapeutics Committee (DTC) as a formal application may be required to allow use of the product.
4. Once local DTC approval has been obtained, all new patients should be started on Alutard SQ using one of the updosing protocols included in the Summary of Product Characteristics and package insert. The choice of protocol will depend on the history and level of allergen sensitivity of the patient. The majority of patients will receive the 'conventional' 15 week updosing protocol whereas a 25 week regimen is recommended for very sensitive patients. If there is urgency then a shortened 7 week cluster regimen may occasionally be appropriate.
5. Once the maintenance dose has been achieved the patient should receive doses at intervals of 2, 4, and then every 6-8 weeks during maintenance.
6. Venom Alutard SQ products are *not* suitable for "ultra-rush" or "accelerated" rush protocols, due to the depot nature of the product.
7. Although the maintenance dose of both bee and vespid venom products are likely equivalent to their Pharmalgen equivalents, (i.e., 100,000SQ-U Alutard SQ = 100mcg Pharmalgen), specialists may consider a split-dose (50% in each arm with a 30 minute interval) for the first administration of Alutard SQ, particularly in patients who have: (a) experienced large local reactions or previous systemic reactions to Pharmalgen; (b) a history of severe index sting reactions or reactions to field stings whilst on maintenance VIT with Pharmalgen; (c) raised baseline serum tryptase or clonal mast cell disorders; (d) those with associated cardiorespiratory comorbidities; or any other factors which may complicate VIT on an individual basis.
8. As with all forms of allergen immunotherapy the patient must be advised to consult a doctor or emergency department immediately in the extremely unlikely event of systemic delayed reactions.

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