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Practice of venom immunotherapy in the United Kingdom: a national audit and review of literature

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Summary

Background Venom immunotherapy (VIT) is the only effective treatment for prevention of serious allergic reactions to bee and wasp stings in sensitized individuals. However, controversies exist relating to diagnosis, indications for treatment and treatment schedules. We audited current practice of VIT in the United Kingdom to evaluate adherence to international guidelines.

Methods An online questionnaire was sent to all clinicians practising immunotherapy identified on the British Society of Allergy and Clinical Immunology website. Eighty-six questionnaires were sent and 53 responses (61.6%) were received. Of these, 48 (85%) carried out VIT at their centre.

Results Skin prick tests (SPT) and serum venom-specific IgE (SSiGE) were equally preferred as first-line investigation. Fifty percent of the respondents perform intradermal tests if both SPT and SSiGE are negative. While 8% of respondents commence VIT in patients with negative SSiGE and a history of severe reaction, 57% prefer to repeat the tests in 6–12 months if serum tryptase is elevated. If the insect responsible is uncertain and SSiGE is detected against bee and wasp venoms, 22% of the respondents will desensitize to both while 32% initiate treatment against the venom with the higher SSiGE. A protocol of weekly up-dosing for 12 weeks is preferred for induction and only 25% of respondents have ever used rush or ultra-rush protocols. Three years is thought to be optimum duration of VIT by most (56%). Eleven percent perform sting challenges at the end of treatment. Although 47% measure SSiGE at the end of treatment, only 3% use these results as a basis for discontinuing VIT.

Conclusion Currently there is considerable variation in the diagnosis and management of hymenoptera venom allergy in the United Kingdom. This audit has demonstrated that the current international guidelines for the diagnosis and management of hymenoptera venom allergy are not being followed by UK allergy practitioners.

Keywords current UK practice, hymenoptera allergy, national audit, RAST tests, skin tests, venom immunotherapy

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Introduction

It is estimated that life threatening reactions to insect stings occur in 0.4–0.8% of children and 3% of the adults in the United States [1]. Although similar estimates for the UK are lacking, a quarter of all fatal anaphylactic reactions in the United Kingdom are thought to be secondary to venom allergy [2]. Common insects from Hymenoptera family (order) seen in United Kingdom include honeybee, bumble bee, wasps and hornet [3]. Insects from genus

Polistes (paper wasp) are not encountered in United Kingdom.

Venom immunotherapy (VIT) is an effective and safe treatment for people with severe allergic reactions to hymenoptera venom [1, 4]. It is estimated to decrease the risk of venom-related anaphylaxis in these patients from a pre-treatment rate of more than 50% to <5% [1, 4]. However, many uncertainties exist regarding the optimal practice of VIT. This is partly because there is no objective method available to assess the efficacy of VIT – sting

challenge tests are high-risk procedures and are difficult to standardize.

UK has the highest prevalence of allergies in the western world [5]. Compared with the United States and other parts of Europe, the organization of allergy services in the United Kingdom is quite different. Although the number of centres offering allergy and immunotherapy services has increased recently, there are very few specialists trained exclusively in allergy in the United Kingdom [6]. Immunologists and specialists from various other fields (such as dermatology, respiratory medicine and paediatrics) with varied levels of specific allergy training contribute significantly towards meeting the needs of patients with allergic disorders.

Recent practice parameters have been published by the American Academy of Allergy, Asthma & Immunology (AAAAI) [1] and the European Academy of Allergology and Clinical Immunology (EAACI) [7, 8]. However, given the unique nature of allergy practice in the United Kingdom, there may be a case for UK-based guidance to optimize and coordinate the practice of VIT.

The aim of this audit was to understand the current practice of VIT across the United Kingdom, as a starting point for developing national guidelines and identifying relevant research questions.

Materials and methods

The British Society of Allergy and Clinical Immunology (BSACI) website carries information of all the centres and clinicians practising immunotherapy in the United Kingdom. An online questionnaire was sent to 86 clinicians identified from this website in December 2006. The initial responses were logged and further e-mails were sent in April and May 2007 if no response was received previously.

There were 24 questions, most of which were of the multiple-choice type and four questions had an additional option of answering in text (Table 1). Respondents who did not carry out VIT (answer 'no' to Q1) were taken to the end of the questionnaire.

Results: (Table 2)

A total of 53 clinicians responded (62%) of whom 85% (45) practise VIT. Around half of the respondents (55%) measure serum-specific IgE (SSiGE) as their first line of investigation. Of those performing skin prick tests (SPT) for diagnosis, almost all use venom extracts from ALK-Abelló (Hørsholm, Denmark). While the maximum strength of extract used by 43% of the respondents is 100 µg/mL, 55% use concentrations of up to 300 µg/mL.

Only half of our respondents proceed to carry out intradermal tests (IDT) if both SPT and SSiGE were negative. Of these, 45% use a maximum concentration of

1 µg/mL for the IDT and 40% use concentrations of up to 10 µg/mL.

When faced with patients sensitized to both bee and wasp venoms without clear history of the insect that caused the reaction, 36% will initiate immunotherapy with the venom for which the SPT reaction/SSiGE value are higher. Ten percent will discharge patients with an Epipen while 22% said they would initiate immunotherapy with both venoms (Fig. 1).

While 53% of our respondents check baseline serum tryptase (bT) levels in patients with systemic reactions (irrespective of severity), 20% check bT only in patients with history of anaphylaxis. Forty-seven percent do not check bT in any of their patients.

In patients with a history of systemic reactions and no detectable SSiGE, some clinicians (41%) feel that it is appropriate to discharge with an Epipen while 46% will repeat investigations in 6–12 months time. About 8% will initiate therapy with the relevant venom despite undetectable SSiGE. Fifty-six percent will review patients with elevated bT (Fig. 2).

Almost all the respondents use extracts from ALK-Abelló (Denmark) for immunotherapy and 92% employ the conventional 12-week up-dosing protocol. The others use a clustered (7–8 week up-dosing) regimen. Only a quarter of the respondents have ever used rush/ultra rush protocols.

Sixty-one percent use antihistamine pre-medication only in patients with troublesome local reactions while 42% use it on all patients undergoing VIT. Seventeen percent use antihistamines only in patients with history of grade 4 reactions to insect venom. When faced with patients who had grade 2–4 reactions during induction despite antihistamine premedication, 31% of respondents will discontinue immunotherapy while 11% will continue immunotherapy and a further 11% will use accelerated regimens.

Most respondents administer maintenance doses at a maximum of 8-week intervals (47%), while others prefer intervals of 4 weeks (11%), 6 weeks (31%) or 12 weeks (8%). Three percent give maintenance injections more than 12 weeks apart.

A maintenance dose of 100 µg is used by most (89%). Others use doses of up to 150 µg (3%) and 200 µg (8%) (Fig. 3). Most (55%) consider 3 years to be optimal duration for VIT. Five-year-therapy is preferred by 22% and some (6%) continue VIT for longer than 5 years (Fig. 4). None of our respondents estimate IgG4 blocking antibodies at the end of treatment. Although 47% check SSiGE at the end of treatment, only 3% will extend therapy if this were detectable.

Discussion

This is the first comprehensive audit of the diagnosis and management of patients with hymenoptera allergy in the

Table 1. The online questionnaire

1. Do you carry out VIT at your centre? ☐ Yes ☐ No If answered no, the respondent was directed to conclusion (Q 25) 2. What is your first line of investigation? ☐ SPT ☐ RAST 3. Which skin prick extract do you commonly use at your centre? ☐ ALK pharmlagen ☐ ALK commercial skin testing extract ☐ other 4. What is the highest concentration of extract for SPT at your centre? ☐ 10 mcg/mL ☐ 100 mcg/mL ☐ 200 mcg/mL 5. In case the skin prick test and RAST are both negative at 6 weeks and patient has a convincing history of a systemic reaction, would you proceed to do an intra dermal test (IDT)? ☐ Yes ☐ No 6. What is the highest concentration of extract you would use for an IDT? ☐ 0.01 mcg/mL ☐ 0.1 mcg/mL ☐ 1 mcg/mL ☐ 10 mcg/mL 7. In a patient who is not sure about the insect responsible for the reaction and has specific IgE against both bee and wasp, you would initiate treatment with ☐ Both wasp and bee venoms ☐ the venom to which the specific IgE titre (or SPT response) is higher ☐ Neither would discharge patient with Epipen/Anapen ☐ Other (please specify) 8. Do you check baseline plasma tryptase in patients referred with a history of systemic reactions? ☐ Yes ☐ No If the answer was yes – respondent answers Q9. If no, they were directed to Q10. 9. Do you check tryptase in ☐ Those patients who have had a severe anaphylactic reaction ☐ All patients with a history of systemic reaction irrespective of severity ☐ Other (please specify) 10. In a patient who has had a history of systemic reaction but no detectable IgE (in peripheral blood and by SPT), you would ☐ Discharge from clinic with advice to come back if any further episodes occur ☐ Discharge with Epipen ☐ Follow up in 6 months/1 year to repeat investigations ☐ Commence immunotherapy with the relevant venom 11. In a patient with history of systemic reactions who has no detectable specific IgE (in peripheral blood/by SPT) but has elevated baseline serum tryptase (done 6 weeks after the reaction) ☐ Discharge with advice ☐ Discharge with Epipen/Anapen ☐ Follow up in 6–12 months with a view to repeat investigations ☐ Commence immunotherapy with the relevant venom 12. What immunotherapy extract do you use? ☐ ALK pharmlagen ☐ Other	13. What induction protocol do you normally employ? ☐ Conventional (12 week, weekly up dosing) ☐ Clustered protocol (7–8 weeks, weekly injection) ☐ Rush (1 week) ☐ Ultra rush (24 h) ☐ Other (please specify) 14. Have you ever employed rush/ ultra rush protocols? ☐ Yes ☐ No (Q15 only if the answer to Q14 was yes) 15. If yes, please comment on your indication for use of the accelerated regimen (open text) 16. Use of Antihistamines (you can choose more than one answer) ☐ I use it in patients with troublesome local reactions ☐ I use them only in patients who have had systemic reactions ☐ I use them only in patients with asthma or cardio respiratory problems ☐ I use them in all patient undergoing venom immunotherapy ☐ Other (please specify) 17. If a patient is having recurrent grade 2–4 reactions during induction phase (dose < 20 mcg) despite adequate antihistamine premedication, would you ☐ Discontinue treatment and recommend that the patient carries an Epipen/Anapen ☐ Consider accelerated induction regimens ☐ Persist with the immunotherapy as usual ☐ Other (please specify) 18. What is your maximum interval between injections during the maintenance phase? ☐ 4 weeks ☐ 6 weeks ☐ 8 weeks ☐ 12 weeks ☐ > 12 weeks 19. What is your target maintenance dose? ☐ 20 mcg ☐ 50 mcg ☐ 100 mcg ☐ 150 mcg ☐ 200 mcg 20. Do you check IgG4 (blocking) antibodies during or at the end of treatment? ☐ Yes ☐ No 21. What do you believe is the optimal duration for VIT? ☐ 2 yrs ☐ 3 yrs ☐ 5 yrs ☐ more than 5 yrs ☐ other 22. Would you consider performing 'sting challenges' at the end of the treatment programme? ☐ Yes ☐ No 23. Do you look for specific IgE in peripheral blood at the end of the desensitisation programme? ☐ Yes ☐ No 24. Would you extend the duration of VIT in a patient if the specific IgE was detectable at the end of 3–5 years? ☐ Yes ☐ Only if the patient had a grade 4 reaction prior to VIT ☐ No Thank you for taking part in the survey. We expect the results of this audit to be presented at the BSACI conference in July 2007
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United Kingdom. The data obtained reveals inconsistencies in practice across the various centres performing VIT. Differences in practice were also noted compared with Europe and United States which could, at least in part, be attributed to entomological differences and differences in health systems between the United Kingdom and these regions.

Diagnosis of insect venom allergy

Our audit has shown that in the United Kingdom 55% of specialists use SSiGE as the first investigation for insect venom allergy. The remaining use SPT rather than IDT while 50% of specialists use IDT in patients with a history

Table 2. Results

(1) Carry out VIT? Yes: 45 (85%) No: 8 (15%)	(15) Comment on indication for use of accelerated regimes ✖ See below
(2) First line of investigation SPT: 45% SSiGE: 55%	(16) Use of antihistamines (can choose more than one response) Troublesome local reactions: 61% Systemic reactions: 17% asthma or cardio-respiratory problems: 6% All patients: 42% **Other: 8%
(3) SPT extract used: ALK pharmlagen: 62% ALK SPT extract: 33% *Other: 5%	(17) If grade 2–4 reaction despite antihistamine Discontinue treatment: 31% Accelerated regime: 11% Persist with treatment as usual: 11% Other: 47%
(4) Highest conc. of SPT extract: 10 µg/mL: 2% 100 µg/mL: 43% 300 µg/mL: 55%	(18) Maximum interval during maintenance 4 weeks: 11% 6 weeks: 31% 8 weeks: 47% 12 weeks: 8% > 12 weeks: 3%
(5) Intradermal testing carried out? Yes: 50% No: 50%	(19) Target maintenance dose 20 µg/mL: 0% 50 µg/mL: 0% 100 µg/mL: 89% 150 µg/mL: 3% 200 µg/mL: 8%
(6) Highest conc. of intradermal test 0.01 µg/mL: 0% 0.1 µg/mL: 15% 1 µg/mL: 45% 10 µg/mL: 40%	(20) Check IgG4 antibodies at end of treatment? Yes: 0% No: 100%
(7) Bee and Wasp venom positive patients; treatment initiated with Both venoms: 22% Venom to which more IgE is detected: 36% Neither-discharge with epipen: 10% * Other: 32%	(21) What is the optimal duration for VIT? 2 yrs: 3% 3 yrs: 55% 5 yrs: 22% > 5 yrs: 6% Other: 14%
(8) Baseline tryptase checked in systemic reaction? Yes: 53% No: 47%	(22) Sting challenges at the end of VIT Yes: 11% No: 89%
(9) If yes to Q8, do you check it in patients with Severe systemic reactions: 20% All systemic reactions: 80%	(23) Check specific IgE at the end of desensitisation? Yes: 47% No: 53%
(10) In systemic reaction but no detectable IgE Discharge with advice: 5% Discharge with Epipen: 41% Follow up in 6–12 months: 46% Commence immunotherapy: 8%	(24) Would you extend VIT if specific IgE was detectable Yes: 3% Only if grade 4 reaction: 11% No: 78% Other: 8%
(11) In systemic reaction, no detectable IgE but elevated baseline tryptase Discharge with advice: 3% Discharge with Epipen: 30% Follow up in 6–12 months: 56% Commence immunotherapy: 11%	* Other reagent used was not specified * Other responses included: venom to which IgE is higher, wasp unless bee keeper, will carry out blocking studies, titrate down SPT solution concentration ✖ Responses included: Patients live far away from hospital, high risk patients, Carried out previously but stopped now due to lack of inpatient facilities ** Other responses included only until maintenance reached, if minor reactions continue despite changes to schedule
(12) Immunotherapy agent used ALK pharmlagen: 97% *Other: 3%	
(13) Immunotherapy protocol employed Conventional: 92% Clustered: 8% Rush: 0%	
(14) Ultra Rush: 0% Other: 0% Ever employed rush or ultra rush protocols? Yes: 25% No: 75%	

of serious systemic reaction if the SPT and SSiGE are negative. Severity of systemic reactions (SR) may be graded as per the Mueller's classification (Table 3) [9].

The AAAAI and EAACI guidelines [1, 7] recommend that IDT (0.001–1 µg/mL) performed at least 2 weeks after the sting reaction should be used as first-line investigation for diagnosis of venom allergy. SPT is a diagnostic option [7] (concentration 0.01–100 µg/mL), but IDT is up to 90% more sensitive than SPT at a concentration of 1 µg/mL and

must be used as a confirmatory test when SPT is negative [7, 10, 11]. When skin tests are negative despite a positive clinical history of SR, they must be repeated along with SSiGE after an interval of 1–2 months [7]. In our audit only 46% of the clinicians followed the latter recommendation.

Using ultra-sensitive SSiGE kits, it has been reported that 10–20% of patients with a positive history of SR to insect sting will have detectable SSiGE in the absence of a positive IDT [12, 13].

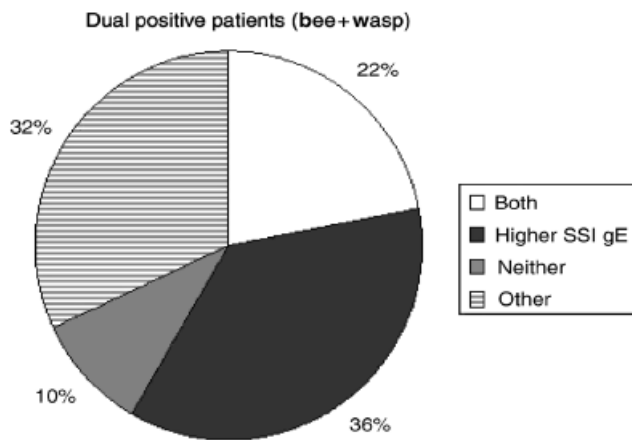


Fig. 1. (Question 7) In a patient with specific IgE against both bee and wasp, a significant proportion of respondents chose to initiate venom immunotherapy (VIT) based on grade of specific IgE and some also chose to start VIT against both venoms. Few of the 'other' responses included-treat as wasp venom allergy unless bee keeper or other risk for bee stings, ask whether stinger was left behind and diagnosing with help of challenge tests.

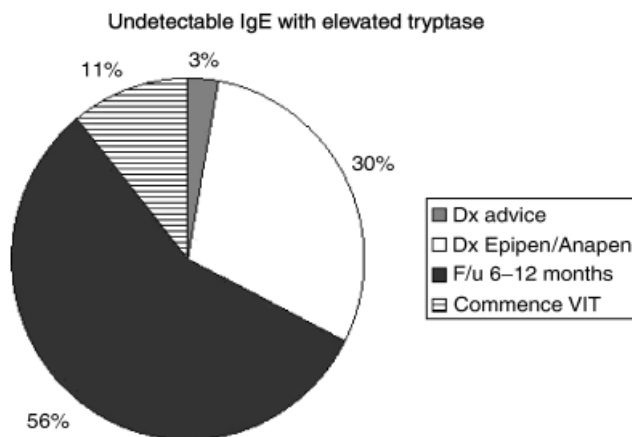


Fig. 2. (Question 11) In patients with no detectable serum-specific IgE (SSi gE) at the end of 6 weeks (by skin/ blood tests) and elevated baseline serum tryptase (bT), most clinicians prefer to follow up in 6-12 months. This is in keeping with the current international recommendations.

Skin tests and SSi gE have limitations. While they are important to assess presence of sensitization before commencement of VIT, the level of positivity does not predict severity of a future sting reactions. A majority of patients continue to have detectable specific IgE at the end of 3-5 year course of VIT despite being protected from sting reactions [14]. Also the true specificity of venom-specific IgE is difficult to define. Recent studies have shown that the sensitivity of basophil activation test (BAT) (markers CD63/CD203c) is comparable to while its specificity is greater than that of skin tests and SSi gE. Further, it has been reported that BAT can be particularly useful when skin tests and SSi gE are inconclusive or equivocal [15-17].

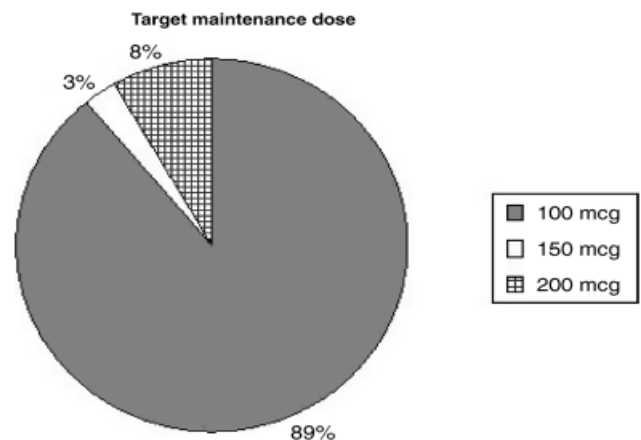


Fig. 3. (Question 19) Most physicians favoured a target dose of 100 mcg/mL while a few used higher doses (150 or 200 mcg/mL).

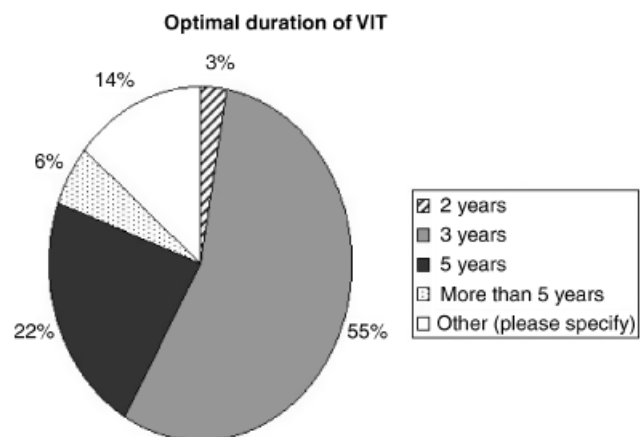


Fig. 4. (Question 21) Most UK physicians felt that 3 years was optimal duration of venom immunotherapy (VIT). A few continued treatment for 5 years (5%) while 14% treated patients for >5 years. 'Other' responses included unsure but will continue for 3 years, will tailor to individual patient depending upon tryptase, initial severity etc.

Dual sensitization to bee and wasp venom may occur in patients with hymenoptera venom allergy. This may be due to true double sensitization or because of cross-reactive antibodies which recognize common carbohydrate epitopes in these venoms [8, 18-20]. Although it may be difficult to identify the insect responsible for the sting reaction, skin testing is thought to be more specific than SSi gE in such situations [21]. Fluorescent enzyme immunoassay (FEIA) inhibition tests may be necessary in a few patients [8, 18]. Our audit suggests that UK clinicians may be relying unduly on the SSi gE tests, and there is wide variation in practice.

Mast cells and venom allergy

Mastocytosis is a clonal disorder of mast cell lineage characterized by abnormal proliferation/maturation of

Table 3. Grade of systemic reaction (Mueller's classification)

Grade 1	Generalized urticaria, itching, malaise, and anxiety
Grade 2	Any of the above plus two or more of: angioedema, chest constriction, nausea, vomiting, diarrhea, abdominal pain, dizziness
Grade 3	Any of the above plus two or more of: dyspnea, wheezing, stridor, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster
Grade 4	Any of the above plus two or more of: fall in blood pressure, collapse, loss of consciousness, incontinence, cyanosis

this cell type and is regarded as 'continuum of a disease' because various subtypes have been described with a potential of progression.

While there is little doubt that systemic mastocytosis (SM) *per se* is a 'risk factor' for anaphylaxis in hymenoptera venom allergy [22], relatively minor forms of mastocytosis including Telangectasia Macularis Eruptiva Perstans (TMEP) associated with only a modest increase in baseline serum tryptase can also predispose to severe systemic sting reactions [23, 24]. Hence, it has been suggested that bT is checked at least in those patients presenting with severe (grade 4) systemic reactions to insect stings.

Although patients with SM are considered to be 'high risk' for VIT, a recent report [25] on a relatively small group of patients with indolent SM suggests that treatment is well tolerated and effective. Another recent study, while confirming the efficacy of VIT, reported a higher incidence of SRs and treatment failures in these patients [26].

SM is a condition, therefore, with important implications on counselling and treatment of patients with Hymenoptera allergy. Our audit suggests that significant proportion of respondents do not check bT in patients who have experienced severe systemic sting reactions.

Immunotherapy protocols

The time required to reach maintenance dose varies according to the induction protocol employed. Conventional (a minimum of 12 weeks with weekly up-dosing) [27–29], rush (few days) and ultra rush (few hours) [30–33] have all been tried and proven successful.

Published data on safety of various induction VIT regimens are difficult to compare due to differences in patient selection, protocols employed and various classification systems used to grade SRs. However, several studies have shown comparable safety profiles for conventional and other rapid induction protocols including 'rush' and 'ultra rush' [30–33]. In contrast, a recent multi-centre European study involving 19 centres in 10 countries has shown increased rate of SRs with rapid dosage regimens [34]. It is worth pointing out that the treatment protocols that were employed at the different centres in this study were not standardized. Treatment protocols must be tailored to the individual patient based on co-morbid factors, social circumstances, resources, expertise and facilities available in respective centres.

Most UK centres offer an out-patient-based service and use a conventional up-dosing regime. 'Rush' and 'ultra-rush' methods require in-patient management and this probably explains their unpopularity in the United Kingdom.

Pre-medication with H1 receptor antagonists reduces the incidence of large local reactions as well as mild (but not severe) systemic adverse reactions after VIT [35, 36]. Some researchers have suggested that pre-medication with antihistamines may also enhance the efficacy of bee VIT [37] perhaps by down regulating the T helper type 2 (Th2) response in peripheral T cells [38]. UK practice clearly varies with some centres using antihistamines in all VIT patients, and others only when troublesome reactions occur.

Current official guidance is that the interval between injections should be 4 weeks for the first year and 6–8 weeks during subsequent years [1, 8, 39]. In one report, an interval of 12 weeks was found to be effective and safe in most patients [40]. There is much variation between UK centres with regards to induction and maintenance injections and hence there may be scope for standardization, and perhaps some cost-savings.

Current EAACI and AAAAI [1, 8] guidelines recommend a maintenance dose of 100 µg, but in patients who continue to have injection related reactions or have a severe reaction to a field sting, this can be increased up to 200 µg to confer protection [41]. In general, a maintenance dose of 100 µg only provides complete protection from SRs in 75% of honeybee-allergic and 85% of Yellow jacket/Polistes-venom-allergic patients [42]. Overall, UK practice appears to be in line with current dosing recommendations.

Treatment duration

The AAAAI guidelines [1] recommend that VIT may be discontinued after 3–5 years of treatment. The decision to discontinue VIT has to be based on the initial clinical presentation and risk of repeat venom exposure of individual patients. VIT can be discontinued after 3 years if venom-specific IgE becomes undetectable by skin tests and *in vitro* tests (SSiGE) [1]. However, more than 75% of the patients continue to have detectable SSiGE even after 5 or more years of treatment [43, 44].

Long-term observations suggest that, regardless of SPT and SSiGE at the end of 5 years of treatment, the incidence of systemic reactions to stings in these patients remains 10–15% even after 10–15 years of stopping treatment and

the cumulative risk with subsequent stings is higher at about 17% [14, 45, 46]. The risk is considerably lower in children (3%) even 10–20 years after stopping treatment [47].

Our audit shows that the duration of VIT varies between centres, and UK specialists do not rely on the value of SSiGE when deciding whether or not to continue VIT beyond 3 years. The decision about discontinuation of VIT is individualized after taking into account severity of SR before commencement of VIT, whether there were any SRs to field stings or to injections while undergoing VIT, presence of mast cell disease, occupation, hobbies and patient preferences [1, 8].

Conclusion

This audit demonstrates that there is considerable variation in the diagnosis and management of hymenoptera allergy and that currently the AAAAI and EAACI guidelines are not being implemented in United Kingdom clinical practice. This study makes a strong case for developing better educational programmes for specialists and trainees in the United Kingdom involved in the management of patients with hymenoptera venom allergy.

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