DOI: 10.1111/all.14227

Good tolerability when switching from an aqueous ultra-rush Hymenoptera venom immunotherapy to a depot preparation

To the Editor,

Throughout Europe, aqueous preparations are generally used for the rapid up-dosing phase of Hymenoptera venom allergen immunotherapy (VIT) and are often substituted with an aluminum adsorbed (so-called "depot") preparation during maintenance treatment.[1] While VIT tolerability has been widely investigated,[2,3] only a few previous studies have included data on patients' tolerance of switching from an aqueous to a depot preparation.[4,5] The question of the interchangeability of venom preparations has been recently pointed out.[6] For the cohort of 90 patients, we studied previously that no systemic reactions occurred when an aqueous preparation was substituted with a depot preparation with vespid VIT.[7] In the current study, we evaluated the tolerability in over 200 more patients to both vespid and bee VIT when an aqueous preparation was substituted with a "purified" depot extract from a different manufacturer.

For inpatient up-dosing of VIT at the Division of Allergy and Immunology, subcutaneous injections of the aqueous venom extract Venomil™ (Bencard Allergie GmbH) are administered according to a 3-day ultra-rush protocol.[8] For maintenance, the preparation is switched to the ALK-depot SQ™ (ALK-Abelló Arzneimittel GmbH). Patient records were reviewed to locate those who underwent vespid (200 patients) or bee (20 patients) VIT between 2003 and 2018. Patient characteristics before VIT initiation are presented in Table 1. The mean duration of the vespid or bee VIT was 3 years. Systemic allergic reactions during the buildup phase, after the first injection of the depot preparation, and during the maintenance phase of vespid and bee VIT were classified according to the World Allergy Organization (WAO) grading system for allergen immunotherapy systemic allergic reactions (Figure 1).

Eight of the 200 patients (4%) receiving vespid VIT had systemic allergic reactions during the up-dosing phase, with WAO grade 1 reactions occurring in six patients (3%) and WAO grade 2 reactions occurring in 2 (1%). These reactions were mostly cutaneous and gastrointestinal, including pruritus, urticaria, flushing, angioedema, nausea, headache, and abdominal cramps. No respiratory or cardiovascular symptoms were observed. After the first injection of the depot preparation during the maintenance phase, three patients (1.5%) had allergic reactions, 2 of which were WAO grade 1 (1%) with generalized pruritus and 1 of which was WAO grade 2 (0.5%) with abdominal cramps. During subsequent injections of the maintenance dose using a depot preparation, nine patients (4.5%) had allergic reactions, with WAO grade 1 reactions occurring in five patients (2.5%) and WAO grade 2 reactions occurring in 4 (2%). The allergic reactions were pruritus, angioedema, rhinitis, cough, nausea, headache, abdominal cramps, and diarrhea. Three of the 20 patients (15%) undergoing bee VIT experienced allergic reactions during the up-dosing phase, with 2 who had WAO grade 1 (10%) and 1 who had WAO grade 2 reactions (5%). Symptoms included pruritus, urticaria, itchy throat, and cough. Switching from the aqueous to the depot preparation was well tolerated in all patients, and no systemic allergic reactions were documented with the first injection of the depot preparation. During the following injections of the maintenance dose, one patient (5%) had a WAO grade 1 allergic reaction with generalized pruritus. No systemic allergic reactions occurred in the four cohort patients who received both vespid and bee VIT in the up-dosing, when the switch occurred, nor during the maintenance phase. Moreover, in this cohort, systemic allergic reactions occurred only once during VIT and did not occur twice in the same patient.

The main risk factor for allergic reactions during VIT is treatment with bee venom. Significantly higher rates of systemic reactions after bee VIT compared to vespid VIT have been consistently reported.[2,3] Our data show similar findings, with a higher number of allergic reactions occurring during the up-dosing phase of bee VIT compared to vespid VIT. However, the large difference in the number of total patients undergoing bee and vespid VIT in our study (ie, 20 vs 200) must be taken into account. Other risk factors for allergic reactions during VIT are rush and ultra-rush buildup protocols, in which the maintenance dose is reached within a few days. Conventional protocols, which require weeks or months to reach the maintenance phase, seem to be better tolerated.[3,9] In a systematic literature review, a comparable rate of systemic allergic reactions was found during VIT in aqueous and depot venom allergen extracts in the overall patient population and among patients who underwent vespid VIT. However, a significantly lower frequency of allergic reactions was detected during bee VIT with a depot allergen extract.[2] Other authors have suggested that these results may be biased due to the slower buildup phase with depot preparations.[4] In our study, the number of patients with allergic reactions was comparable during both the up-dosing and maintenance phases of vespid VIT. In contrast, during bee VIT, we observed that a greater number of patients experienced allergic

TABLE 1 Patient characteristics before venom immunotherapy (VIT) initiation (mean ± SEM)

	Entire patient cohort		Patients with allergic reactions during VIT	
	Vespid VIT (n = 200)	Bee VIT (n = 20)	Vespid VIT (n = 20)	Bee VIT (n = 4)
Female	117 (59%)	11 (55%)	19 (95%)	2 (50%)
Age (years)	52 (±1)	49 (±2)	54 (±3)	46 (±5)
Total IgE (kU/L)	206.52 (±34.46)	204.26 (±54.77)	355.29 (±244.36)	397.97 (±126.26)
Vespid venom-specific IgE (kU/L)	11.85 (±1.25)	4.33 (±1.82)	10.62 (±3.26)	3.29 (±3.14)
Bee venom-specific IgE (kU/L)	2.14 (±0.66)	20.96 (±6.09)	0.20 (±0.06)	45.73 (±28.93)
Basal serum tryptase (µg/L)	6.33 (±0.49)	4.33 (±1.82)	5.02 (±0.91)	2.89 (±0.75)
Mueller grade II reaction	38 (19%)	4 (20%)	4 (20%)	0
Mueller grade III reaction	92 (46%)	9 (45%)	9 (45%)	3 (75%)
Mueller grade IV reaction	70 (35%)	7 (35%)	7 (35%)	1 (25%)
Mastocytosis	10 (5%)	1 (5%)	1 (5%)	0
Cardiovascular diseases	48 (24%)	1 (5%)	7 (35%)	0
Allergic asthma	11 (6%)	0	1 (5%)	1 (25%)

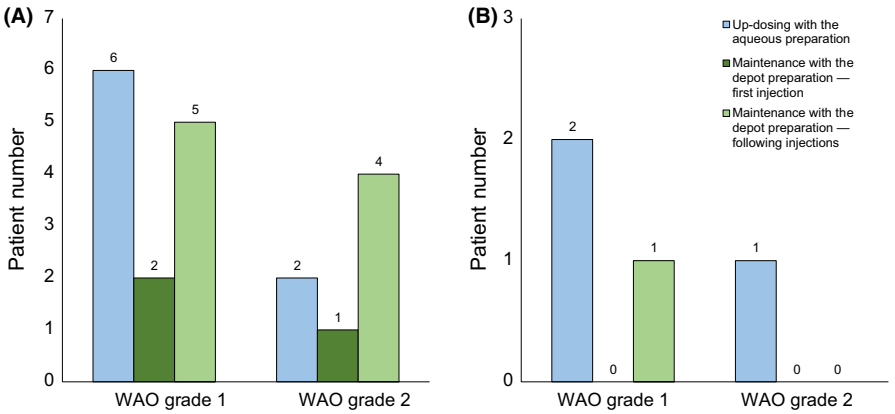

FIGURE 1 Systemic allergic reactions during the up-dosing phase of vespid (A, n = 200) and bee (B, n = 20) venom immunotherapy with an aqueous extract, after the first injection of the depot preparation, and during the maintenance phase, classified according to the World Allergy Organization (WAO) grading system for allergen immunotherapy systemic allergic reactions

reactions to the aqueous extract during the up-dosing phase compared to the maintenance phase (after injection of the depot preparation), during which only one patient had an allergic reaction. Similar results have been reported in bee VIT with preparations using a different purification grade.[5]

In conclusion, our data support and supplement previous results[4-7] by demonstrating that the likelihood of a systemic allergic reaction after switching from an aqueous to a depot preparation is very low. These data include results from two different preparation manufacturers and with a switch from a standard to a purified extract. Systemic symptoms were rare and led to mild outcomes with primarily cutaneous or gastrointestinal symptoms. Our findings are useful for clinical practice since they indicate that VIT can be continued safely and without complications in an outpatient setting.

KEYWORDS

allergen extract, switch, tolerability, venom immunotherapy

ACKNOWLEDGMENTS

We would like to thank the nursing team of the Division of Allergy and Immunology—Martina Lütticke, Michele Jäckel, and Claudia Tomaschewski—for their support.

CONFLICT OF INTEREST

RS has received a travel grant from ALK-Abelló Arzneimittel GmbH. EO has nothing to disclose. MK has nothing to disclose. MW has received speakers honoraria for advisory boards and lecture activities from Mylan Germany GmbH, ALK-Abelló Arzneimittel GmbH, Allergopharma GmbH & Co. KG, HAL Allergie GmbH, Stallergenes GmbH, Bencard Allergie GmbH, DBV Technologies S.A, Novartis AG, Aimmune Therapeutics UK Limited, Sanofi-Aventis Deutschland GmbH, and Regeneron Pharmaceuticals, Inc.

Roberta Scarpone
Elsbeth Oestmann
Magdalena Kraft
Margitta Worm

Division of Allergy and Immunology, Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany

Correspondence

Margitta Worm, Division of Allergy and Immunology,

Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany.
Email: margitta.worm@charite.de

ORCID
Roberta Scarpone https://orcid.org/0000-0001-9959-1944
Magdalena Kraft https://orcid.org/0000-0002-2770-9947
Margitta Worm https://orcid.org/0000-0002-3449-1245

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DOI: 10.1111/all.14228

Nasal specific IgE correlates to serum specific IgE: First steps towards nasal molecular allergy diagnostic

To the Editor,

Up to 40% of the European population suffer from respiratory type I hypersensitivity reactions induced by airborne allergens, such as plant pollen, fungal spores, or dust mite feces.[1] Guidelines for the treatment of AR in children recommend causative treatment, that is, allergen-specific immunotherapy (ASIT), as early as possible.[2] Allergy diagnostics is routinely performed by skin prick test (SPT) or blood test for the detection of allergen-specific immunoglobulin E (sIgE). If specific serum IgE is absent despite a positive history of allergic rhinitis, a nasal allergen provocation test is performed to assess local allergic rhinitis (LAR). Recent developments in microchip technology enabled the simultaneous detection of specific IgE levels against 112 individual allergens using only 30 µL of serum. However, SPTs are still often the method of choice when diagnosing young children, as children are typically afraid of needles. This can lead to improper diagnosis, since SPTs are prone to false-positive results due to the unspecified extracts used.[3] The aim of our study was therefore to adopt the Immuno Solid-phase Allergen Chip (ISAC) for nasal fluid as a noninvasive sampling method and to validate the technology as potential novel allergy test. Our analysis (see details in online supporting information) focused on the most relevant aeroallergens, that is, house dust mite (HDM), Betulaceae trees, including birch, hazel and alder, and grass pollen.[4]

Blood and nasal fluid samples as previously described [5] were obtained from 2 nonsensitized (NS) control subjects and 47 subjects sensitized (Figure S1and Table S2. online supporting information) to aeroallergens such as birch, hazel, alder, grass pollen, or house dust mite (HDM). Specific IgE levels were measured in sera and nasal fluid by the ImmunoCAP ISAC 112 (Table S1. online supporting information) according to the manufacturer's instruction (Thermo Fischer Scientific).

When correlating IgE against single allergen components, we observed a significant positive correlation (n = 49; $P < .001$) between serum and nasal tests (Figure 1, A), with a median of all Spearman correlation coefficients (r_s) across the whole panel of 0.77 (IQR 0.75, 0.85). The highest correlation coefficient was observed for Der p 2 and Aln g 1 ($r_s = .88$), followed by Cor a 1 ($r_s = .87$) and Bet v 1 ($r_s = .85$) (Figure 1, B).

We next determined the global sensitization profile of each subject's serum and nasal fluid and compared the profiles for all

FIGURE 1 Correlation between nasal and serum sIgE levels. A, Spearman correlation coefficients for all tested allergen components. B, Nasal sIgE levels (*y*-axis) plotted against serum sIgE levels (*x*-axis). Dots indicate study subjects. Fitted lines indicate positive linear correlations (Spearman). C, Spearman correlation coefficients per subject over the entire aeroallergen sensitization profile, as shown in panel A. D, Serum sIgE profile (*x*-axis) versus nasal sIgE profile (*y*-axis) shown for selected subjects. Blue dots indicate the 17 allergen-specific IgE tests included in the overall analysis. The red line represents the linear regression curve fit (positive Spearman correlation)