Tolerance of an immunotherapy switch between two aqueous hymenoptera venoms

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To the Editor

Immunotherapy with Hymenoptera venom is an effective treatment for patients with Hymenoptera venom allergy. At the end of 2019, the production of the aqueous, partly purified honey bee (HBV) and wasp venom (WV) Pharmalgen® (ALK-Abello, Horsholm, Denmark) was discontinued. The switch from the aqueous HBV and WV Venomil® (Bencard Allergie GmbH, Munich, Germany) to the depot preparation Alutard® (ALK-Abello Horsholm, Denmark) is mostly well tolerated [1; 2]. However, a change to an aluminium precipitated depot preparation is not suitable for all patients [3]. High dose venom immunotherapy has not been evaluated specifically for aluminium toxicity [4]. The amount of aluminium is actually restricted to 1.25mg per human dose in Europe [5]. Treatments with doses over 100µg (e.g. in beekeepers or therapy-refractory cases) with Alutard® are off-label (this corresponds to a dose of more than 100,000 SQ-U Alutard® with 1.13 mg of the adjuvant aluminium according to the manufacturer information) and clearly exceed this threshold. Furthermore, aqueous venoms would be preferable in younger children or subjects with long-term immunotherapy (e.g. cases with mastocytosis) as an aluminium free alternative [3] or patients with primary sensitization to Api m 10 [6].

We describe a cohort of HBV and WV allergy patients under maintenance therapy with Pharmalgen® or Alutard® who were switched to Venomil®. Immunotherapy switch protocols are summarized in table 1. We have retrospectively investigated all cases with a treatment change between October 2019 and June 2020 from either Pharmalgen® to Venomil® or Alutard® to Venomil®. All data were investigated as a quality assurance project. All patients gave informed consent to the evaluation and publication of their allergy history.

26 patients were examined (69% female). Intradermal tests (venom concentrations used: 0.00001 µg/mL, 0.001 µg/mL, 0.1 µg/mL, and 1.0 µg/mL), specific IgE (HBV, WV, Api m 1, Api m 10, Ves v 1, Ves v 5) and tryptase measurements were performed before initiation of immunotherapy (S1 table). 19 (73.1%) had HBV allergy, 6 (23.1%) WV allergy, and one patient both. Three patients had high tryptase levels (range 14.5-50.5 µg/L). Reasons for the switch to Venomil® are shown in table 2: the most frequent reason was high dose Hymenoptera venom treatment due to beekeeping (16/26, 61.5%). The maintenance dose before switching to Venomil® was 100 µg HBV in 3 patients (15.0%), 200 µg in 16 subjects (80.0%) an 300 µg in one person (5.0%). WV dose before was 100 µg in 6 persons (85.8%) and 200 µg in one subject (14.3%).

In patients with HBV allergy, 17 out of 20 persons tolerated the initial changeover. There were 6 systemic reactions in 4 persons: 5 out of 6 were mild. Three reactions occurred at the change, three during the updosing (two persons with reactions at change and updosing). In two cases

the maintenance dose was not reached, of whom 1 was later successfully treated with an ultra-rush procedure with Venomil®. Especially a reduction to 10 µg Venomil® HBV was always tolerated.

We found similar data in WV allergy patients: Systemic reactions occurred in 2 persons with two events each. All systemic reactions were mild and the maintenance dose was achieved in all 7 subjects with WV allergy. The first administration with 20 µg Venomil® was well tolerated in 4 out of 5 subjects.

Over half of all patients with systemic reactions after venom change to Venomil® had risk factors (2x mastocytosis, 1x sting challenge not tolerated, 1x monosensitization to Api m 10).

Our data show that the switch from one to another aquaeous venom of different companies is mostly well tolerated when decreasing the dose. However, systemic reactions may occur. Caution is advisable when treating at-risk patients [7]. Patients with elevated tryptase or poor tolerance of Hymenoptera stings under immunotherapy seem to bear a risk of reaction upon venom change. New therapy induction with ultra rush procedure or an accelerated ambulant schedule [8] might be necessary in such cases. This study has the following limitations: our cohort was only small and it is unclear if our data can be transferred to aqueous HBV and WV of other companies.

In summary, a reduction of the maintenance dose of HBV and WV to 10-20 µg is promising and was mostly well tolerated when changing to another aqueous venom (Venomil®). Risk factors must be taken into account.

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Authors contributions

LJ designed and planned the project, acquired, analyzed and interpreted the data and wrote the manuscript. AG, MF and AH participated in data analysis, interpretation, writing the manuscript and critically reviewed. All authors read and approved the final manuscript.

Tables

Table 1 Two protocols for immunotherapy switch from Pharmalgen®/Alutard® to Venomil®

	A		B	
Week	**Dose (µg)**	**Volume (ml)**	**Dose (µg)**	**Volume (ml)**
1	10	0.1	20	0.2
	20	0.2	30	0.3
	40	0.4	50	0.5
2	50	0.5	100	1.0
	50	0.5	50	0.5
3	100	1.0	100	1.0
	50	0.5	100	1.0
4	100	1.0	200	2.0 (or 1.0 with 200 µg/ml)
	100	1.0		
5	200	2.0 (or 1.0 with 200 µg/ml)		

The switch from Pharmalgen® to Venomil® was largely based on the two protocols A and B. Patients with reactions when switched to Venomil® were treated conventionally (without cluster up-dosing). The protocols were slightly modified in some patients, e.g. with skipping a cluster step, change from protocol B to A at week 2 or directly start at a higher dose etc. Higher starting doses (with 50 µg, 70 µg or even 100 µg) were used initially in some patients because a good tolerance was assumed based on unpublished data from patients who switched from Alutard® to Pharmalgen®. All cluster steps were performed with 30min intervals.

Table 2 Patient characteristics

	Bee venom allergy N=20	Wasp venom allergy N=7
Demographics		
Age	46.1 ± 11.0	53.9 ± 10.9
Gender (female)	14 (70.0%)	4 (57.1%)
Clinical		
Grade of index reaction (H.L. Mueller):		
Grade I	3 (15.0%)	0 (0%)
Grade II	3 (15.0%)	1 (14.3%)
Grade III	3 (15.0%)	1 (14.3%)
Grade IV	11 (55.0%)	5 (71.4%)
Duration of immunotherapy (months)	10.5 (3.0; 41.8)	17.0 (11.0; 47.0)
Maintenance dose before change:		
100 µg	3 (15.0%)	6 (85.7%)
200 µg	16 (80.0%)	1 (14.3%)
300 µg	1 (5.0%)	0 (0%)
Tolerance of maintenance	18 (90.0%)	6 (85.7%)

Therapy (yes)		
Venom preparation before change		
Pharmalgen	18 (90.0%)	7 (100.0%)
Alutard	2 (10.0%)	0 (0%)
Cause of change		
Bee keeper	16 (80.0%)	-
Bee/Wasp sting not tolerated under maintenance treatment	1 (5.0%)	1 (14.3%)
Refusal of Alutard	0 (0%)	4 (57.1%)
Sensitization to Api m 10	1 (5.0%)	-
Mastocytosis / high tryptase	2 (10.0%)	2 (28.6%)
other	1 (5.0%)	0 (0%)
Change to Venomil		
Initial dose:		
10 µg	8 (40.0%)	0 (0%)
20 µg	8 (40.0%)	5 (71.4%)
50 µg	2 (10.0%)	2 (28.6%)
70 µg	1 (5.0%)	0 (0%)
100 µg	1 (5.0%)	0 (0%)
Tolerance of initial dose:		
10 µg	8/8 (100%)	-
20 µg	6/8 (75.0%)	4/5 (80.0%)
50 µg	2/2 (100%)	1/2 (50.0%)
70 µg	1/1 (100%)	-
100 µg	0/1 (0%)	-
Tolerance of subsequent updosing	17/20 (85.0%)	5/7 (71.4%)
Total number of change related systemic reactions:	6	4
Grade of reaction (H.L. Mueller):		
Grade I	2/6	2/4
Grade II	3/6	2/4
Grade III	1/6	0
Grade IV	0	0
Maintenance dose reached (yes)	18/20 (90.0%)	7/7 (100%)

Values are mean ± standard deviation for continuous variables, or median and interquartile ranges (IQR) for non-normally distributed variables. Categorical variables reported as n (%).