

RESEARCH LETTER

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Factors associated with venom immunotherapy side-effects, re-sting reactions, and adherence in real-life

To the Editor,

A single Hymenoptera sting can potentially be fatal. Venom immunotherapy (VIT) is an effective and disease-modifying treatment for IgE-mediated venom allergy and the only approved treatment to prevent severe sting reactions.¹ VIT is recommended for 3–5 years, with 5 years being superior.¹ In patients with a severe initial sting reaction, systemic side effects

during VIT, mastocytosis, or a high risk of re-sting, lifelong VIT is recommended.¹

Systemic side effects during VIT are reported in up to 20%,² and relapse has been described in up to 10%, 1–5 years after completing VIT³ and in up to 15%, 5–10 years after completing VIT.⁴

This study aimed to evaluate potential risk factors for side effects during VIT, reaction at field re-sting, and adherence in a patient

TABLE 1 Multivariate logistic regression analyses for factors related to side effects during VIT and relapse after completed VIT besides injection/sting site reactions.

	Side effects during VIT ^a			Moderate-severe side effects during VIT ^b			Relapse after VIT ^c		
	Odds ratio	95% CI	p Value	Odds ratio	95% CI	p Value	Odds ratio	95% CI	p Value
VIT venom									
Vespid	Ref	–	–	Ref	–	–	Ref	–	–
Honeybee	2.21	1.22–4.00	.009	2.33	0.88–6.17	.088	0.76	0.14–4.14	.76
Sex									
Male	Ref	–	–	Ref	–	–	Ref	–	–
Female	2.91	1.75–4.87	.001	3.50	1.49–8.20	.004	0.46	0.11–1.98	.29
Age									
<60 years	Ref	–	–	Ref	–	–	Ref	–	–
≥60 years	0.71	0.37–1.05	.078	0.68	0.27–1.68	.403	1.33	0.33–5.28	.69
Comorbidities									
Asthma	0.54	0.13–2.23	.40	0.67	0.08–5.42	.70	–	–	–
Cardiovascular disease	2.62	0.37–18.74	.95	0.93	0.11–8.04	.95	–	–	–
Mastocytosis	1.18	0.46–3.03	.34	1.99	0.52–7.53	.31	–	–	–
Antihypertensive treatment*									
No	Ref	–	–	–	–	–	–	–	–
Yes	0.36	0.03–4.08	.41	–	–	–	–	–	–
Moderate-severe initial reaction (Sampson 3–5)									
No	Ref	–	–	Ref	–	–	Ref	–	–
Yes	1.94	0.95–3.94	.068	8.29	1.00–68.33	.049	1.06	0.19–6.03	.95
Side effects during VIT (Sampson 1–5)									
No	–	–	–	–	–	–	Ref	–	–
Yes	–	–	–	–	–	–	6.25	1.40–27.92	.016

Abbreviations: CI, Confidence interval; Sampson, Sampsons severity score; VIT, Venom immunotherapy.

*Treatment with angiotensin-converting-enzyme inhibitors and/or β adrenergic blocking agents.

^aSampson score 1–5.

^bSampson score 3–5.

^cAllergic reactions (Sampson's severity score 3–5), in patients exposed to field re-sting after completed VIT.

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population who initiated VIT at a highly specialized allergy centre. In addition, self-reported adherence was compared with registered information on retrieval rates.

This is a combined questionnaire and register study among patients who received VIT at the Allergy Centre, Odense University Hospital, Denmark, from 1 January 2010 to 31 December 2019. For patients who completed the questionnaire, self-reported adherence was compared with retrieval rates for VIT and adrenaline autoinjector (AAI) at the pharmacy using the Danish National Health Service Prescription Database (DNHSPD). Reactions were scored according to Sampson's severity score. Data were analysed both using a univariate logistic regression model and a multivariable logistic regression analysis with a clustered sandwich estimator, as some patients reported two courses of VIT, one with vespid venom and one with honeybee venom. p -Value < .05 was considered statistically significant. Data analyses were conducted by using STATA (version 17.0) software.

A total of 671 patients received an electronic questionnaire, which was completed by 66% (443/671). Of these 443 patients, 372 had received vespid VIT, 62 honeybee VIT, and nine had received both vespid and honeybee VIT. VIT injection site reaction was reported in 15% (66/452) and systemic side effects in 19% (88/452). Patients self-reported systemic side effects, graded according to Sampson's severity score: grade 1 ($n=44$), grade 2 ($n=16$), grade 3 ($n=8$), grade 4 ($n=20$) and no patients reached grade 5.

Table 1 illustrates factors related to side effects (Sampson score 1–5), where honeybee venom and female sex were significant risk factors. When considering only moderate-to-severe side effects (Sampson score 3–5), female sex and moderate-to-severe initial sting reactions were significant risk factors.

Re-sting during VIT was reported in 35% (157/452) of the courses with an allergic reaction (Sampson score 1–5) in 15% (24/157) of the cases, and re-sting after a premature termination of VIT (<5 years) was reported in 40% (20/50) with an allergic reaction in 30% (6/20). After completing VIT, re-sting was reported in 33% (75/224), with an allergic reaction in 17% (13/75). The median time between completed immunotherapy and an allergic reaction was 2 years; most had a severity score of 1–2 (62%). Side effects during VIT were a risk factor for allergic reaction at re-sting (Table 1).

The self-reported adherence to VIT was overall 84% (254/304) compared to 79% (239/304) based on the retrieval rate from the pharmacy. In patients with mastocytosis, 92% (11/12) was adherent. No significant risk factors for non-adherence were identified. Self-reported adherence to AAI before VIT was 78%, compared to adherence based on retrieval rates of 79%. In patients with mastocytosis, 85% (23/27) collected their AAI. Adherence to AAI before VIT was significantly associated with the severity of the initial systemic sting reaction (SSR) (moderate-to-severe, $p=.018$, data not shown).

Systemic side effects during VIT were seen in 19% (88/452), with honeybee venom and female sex identified as risk factors, in line with a previous large multicenter study.² Studies on field stings during VIT have reported SSR in 12%,⁵ and in studies performing sting challenges 1–3 years after termination of VIT, SSR was

Summary box

- VIT side effects are associated with female sex, honeybee venom, and severity of initial sting reaction.
- Re-sting reactions after completed VIT are associated with side effects during VIT.

observed in 0%–17%.^{3,6} This is in line with our result of SSR after completing VIT in 17% after a field sting. In accordance with the literature,⁷ we found that after completing VIT, allergic reactions after re-sting were associated with systemic side effects during VIT, while we could not verify honeybee venom nor severe initial sting reaction as risk factors.

The self-reported adherence to VIT in this study (84%) corresponded to the upper level of the previously reported adherence.⁸ Adherence to AAI before VIT was 78% and associated with moderate-to-severe initial sting reaction in line with previous results from our group.⁹

The strength of this study was that 66% of VIT patients answered the electronic questionnaire. However, the data were self-reported. Thus, recall and social desirability bias may affect the answers. Another limitation is that re-sting in the field is a non-standardized procedure and might lead to misidentification of which insect.

To conclude, side effects during VIT were associated with honeybee venom, female sex, and severe initial sting reactions. After completion of VIT, allergic reactions in patients exposed to field stings were associated with side effects during VIT. High adherence to VIT and AAI were found, both self-reported and by redeemed prescriptions, however, when VIT was prematurely terminated, adherence to AAI was low.

AUTHOR CONTRIBUTIONS

CGM, CBJ, and LP designed the study. LP and CGM are accountable for the database. LP, HFK, CBJ, OSG, and CGM analysed the data. LP wrote the first draft of the manuscript. HFK, CBJ, SH, SBO, OSG, and CGM corrected the manuscript. All authors contributed to the data explanation and accepted the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data that support the results are accessible on request from the corresponding author. Data for this study are not publicly accessible due to ethical restrictions or privacy.

ETHICS STATEMENT

The study protocol was reviewed and approved by the Executive Secretariat at the Region of Southern Denmark (13/04/2021J. no. 21/20074 and 12/05/2020J. no. 20/21389) and DNHSPD (16/03/2021J. no. 2012-54-0016). The study was reported to the Regional Committees on Health Research Ethics for Southern Denmark (03/27/2020J. no. 20202000-72).

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