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Subcutaneous venom immunotherapy in children

Efficacy and safety

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ABSTRACT

Background: Venom immunotherapy (VIT) is safe in children, although adverse effects can occur.
Objective: To document adverse effects and to determine re-sting reactions and the efficacy of VIT in childhood.
Methods: We retrospectively analyzed data from children who had taken VIT from 2002 through 2015. These patients were queried by telephone to determine reactions after re-stings during or after VIT.
Results: In total 107 children with a systemic reaction after Hymenoptera sting and with proved immunoglobulin E-mediated sensitization were enrolled. Participants had a median age of 10.0 years (7.2–12.4 years) at the beginning of immunotherapy. Fifty-two participants had allergic reactions during VIT; 40 of these reactions were local (37.4%), 5 were large local (4.7%), and 7 were systemic (6.5%). Of the 52 patients with adverse reactions, most reactions were local (n = 40, 89%) and were observed mainly in dose-increase periods (n = 25, 60%; $P < .001$). Although local reactions were more frequently seen with *Vespula* treatment ($P = .047$), systemic reactions were common with *Apis* treatment ($P = .031$). Sixty-eight patients (63.5%) were queried for re-sting, 33 (48.5%) had a re-sting and 24 (72.7%) of these 33 patients developed allergic reactions. The reactions were local (n = 19), large local (n = 1), and systemic (n = 4). Risk analysis for local and systemic reactions during VIT showed pre-existing asthma as an independent risk factor (odds ratio 4.1, 95% confidence interval 1.3–12.7, $P = .016$).
Conclusion: In children, VIT appears to be safe and protective against severe reactions after re-sting. However, pre-existing asthma was identified as a risk factor for systemic and large local reactions during VIT in children.

Introduction

Hymenoptera stings can cause allergic reactions ranging from insignificant local effects to severe anaphylaxis. The systemic reaction risk has been reported to be approximately 1% in children, 5% to 7.5% in adults, and as high as 32% in beekeepers.[1]

Because of the possibility of allergic reactions and even fatal outcomes, insect venom induces high anxiety in many patients.[2] To date, venom immunotherapy (VIT) is the only treatment for venom allergies, and it is used in patients with previous systemic allergic reactions caused by venom stings and in those who have had positive venom diagnostic test reactions.[3] Allergic reactions during VIT are mostly local,[4] although intimidating systemic reactions are seen at the relatively low rate of 0.1% to 0.2%.[3–5] Although adverse effect profiles of immunotherapy have been well documented in adults, data from children are limited. Moreover, risk factors that can be used to predict systemic adverse reactions during VIT have not been fully defined. Adverse symptoms occurring during immunotherapy cause difficulties in treatment compliance and can lead to anxiety for the affected children and their parents.

The present study assessed the frequency and severity of adverse reactions during VIT in children and determined predictive factors for the development of adverse reactions. We present observations from children who received VIT in our outpatient clinic and their experiences with re-sting in the field.

Methods

Study Population

In this retrospective cross-sectional study, we analyzed data from children who received subcutaneous conventional VIT (SCIT) in our department from January 2002 through December 2015. All patients undergoing VIT had a history of at least 1 systemic reaction after *Apis mellifera* and/or *Vespula* stings[6] and positive diagnostic test reactions (skin prick test [SPT] or specific immunoglobulin E [IgE]) for culprit insect venom.[7] The data used in this study were collected from medical files filled out by physicians at each visit.

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These files were unique for each patient and consisted of immunotherapy schedules, adverse effects during SCIT, and treatments administered after adverse reactions. Diagnostic test results (ie, SPT, intradermal tests [IDTs], *Vespula*-specific IgE, and honeybee-specific IgE), total IgE, and eosinophil numbers were recorded. We asked patients to describe their personal and family histories of aeroallergen and/or food atopy, allergic rhinitis (AR), asthma, and venom allergy. AR and asthma were defined according to international guidelines.[8,9] Patients were administered VIT if they were at least 5 years old, had no severe uncontrolled asthma, and had no other systemic or autoimmune disorders. This study was approved by the ethics committee of the university, and written informed consent was obtained from the participating children and their parents.

Diagnosis of Venom Allergy

Diagnosis of venom allergy was made based on European Academy of Allergy and Clinical Immunology guidelines.[7] All participants had positive SPT and IDT reactions for *Vespula* species and honeybee and/or positive specific IgE (>0.35 kU/L) levels measured using the Pharmacia CAP (Pharmacia & Upjohn, Uppsala, Sweden) system for the 2 venom types. SPTs and IDTs were applied at least 4 to 6 weeks after systemic reactions.[7] Saline solution and histamine were used as negative and positive controls, respectively, and venom extracts (100% *A mellifera* or *Vespula* species; Alutard SQ, ALK, Hørsholm, Denmark) were given at 15- to 20-minute intervals in incremental doses of 1, 10, 100, and 1000 ng/mL epidermally and intradermally.[10] SPT and IDT reactions were considered positive when the mean wheal diameters were at least 3 and 5 mm, respectively, compared with the negative control, and the test reactions were accepted as positive at the lowest concentration of venom extract that produced a positive result.[7]

When assessing the culprit venom, we took into account venom-specific IgE levels, patient history, and social environment (eg, living in a wooded area, beekeeper in the family or neighbors).

Serum basal tryptase (sBT) levels were measured at the start of SCIT by the UniCAP method (System ImmunoCAP Tryptase, Pharmacia & Upjohn).

Venom Immunotherapy

All patients underwent conventional SCIT; 103 patients were given Alutard SQ 100% *A mellifera* or *Vespula* species and 4 patients were given Alyostal (Stallergenes, Antony Cedex, France). Doses were administered in 1-week intervals starting with 3 to 8 μg/dose and were gradually increased to the maintenance dose of 100 μg over 6 months.[11] After this "build-up" period, maintenance doses were administered every 4 to 6 weeks for up to 5 years.[12] The maintenance doses were decreased by 10% with each new bottle. All injections were administered to the lateral parts of the upper arm.

Adverse Reactions

Local, large local, and systemic reactions during the course of treatment were noted on each patient's immunotherapy card. Large local reactions were defined as those reactions having a diameter of induration larger than 10 cm. Reactions smaller than 10 cm were accepted as local reactions. Systemic adverse effects included widespread skin lesions, such as generalized urticaria, angioedema, and other system involvements.[13] In addition, patients were queried by telephone to evaluate re-sting reactions during or after VIT. We verified sting reactions in the field first by phone calls and second by asking during routine visits and during VIT.

Statistics

The data were not normally distributed; therefore, results were expressed as median (interquartile range). Correlations were evaluated with Spearman correlation analysis. Statistical analyses included univariate and multivariate analyses. Odds ratios with relevant 95% confidence intervals were calculated to evaluate potential associations. *P* values less than .05 were accepted as significant.

Results

In total 107 patients (77 boys and 30 girls) with a median age of 10.0 years (interquartile range 7.2–12.4 years) at the start of VIT were enrolled in this study. The demographic and clinical features of patients are presented in Table 1. Immunotherapy was given to

Table 1
Characteristic Features of Study Group

	Vespula species (n = 81)	*Apis* species (n = 25)	*P* value
Age at first dose of VIT (y), median (IQR)	10.46 (7.75–12.46)	9.07 (7.18–11.92)	.49
Boys/girls (% boys)	58/23 (71.6)	18/7 (72.0)	.97
Total IgE (kU/L), median (IQR)	175 (84–484)	250 (132–660)	.16
Eosinophil number (mm^3/mL), median (IQR)	200 (100–400)	300 (125–550)	.17
Eosinophils (%), median (IQR)	3.2 (1.8–4.5)	3.25 (1.87–5.94)	.61
Specific IgE, median (IQR)	8.54 (3.36–29.90)	19.2 (10.70–82.30)	.042
During IT, %			
Local reaction	42	20.0	.047
LLR	6.2	0	.20
SR	3.7	16.0	.03
Re-sting with responsible Hymenoptera during VIT (n = 68), %	42.3	50	
Reaction after exposure to Hymenoptera during IT, %	42.3	40	
No reaction or local reaction	81.8	80	.29
LLR	4.5	0	.76
SR	13.6	20	.19
Asthma, %	23.3	28.6	.68
Allergic rhinitis, %	23.0	30.8	.55
Allergy to foods, aeroallergen sensitization, asthma and allergic rhinitis, %	34.4	30.8	.80
Aeroallergen sensitization in family, %	42.4	27.3	.35
Family history of venom allergy (LLR + SR), %	37.3	36.4	.95

Abbreviations: IgE, immunoglobulin E; IQR, interquartile range; IT, immunotherapy; LLR, large local reaction; SR, systemic reaction; VIT, venom immunotherapy.