

Clinical characteristics of patients with repeated systemic reactions during specific immunotherapy with hymenoptera venoms

A retrospective study

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In general, specific immunotherapy with hymenoptera venoms can be considered as safe, but occasionally there are patients who cannot reach the maintenance dose due to repeated systemic reactions (RSR) or who suffer from RSR during maintenance therapy. In a multicenter retrospective study comprising seven departments in Germany, Austria and Switzerland 23 patients with RSR were reported from approximately 3000 patients treated with hymenoptera venoms (bee and wasp venom to approximately equivalent frequency). From these, 22 were allergic to bee venom and only one to vespid venom. In general the clinical symptoms of RSR were milder than the initial reaction. But 4/23 (18%) exhibited cardiovascular reactions up to full shock. Neither anamnestic details, reactivity in skin tests or *in vitro* tests revealed a special pattern of patients with RSR. In some patients, however, an extremely high reactivity in the skin test was found and may indicate the possibility of further RSR.

Key words: hymenoptera venom allergy; specific immunotherapy; repeated systemic reactions.

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During specific immunotherapy with hymenoptera venoms systemic reactions are not uncommon, especially during the incremental phase (13). In a small number of patients, however, repeated systemic reactions (RSR) may necessitate profound alterations or even discontinuation of specific immunotherapy (1, 6, 7, 9, 15). In a retrospective multicenter study data of German, Austrian and Swiss patients with RSR were collected by questionnaire. The purpose of the study was to ascertain the existence of these

patients and to characterize them by anamnestic or *in vivo/in vitro* test data.

METHODS

The study was performed in a retrospective fashion comprising patients from seven centers over a period of 5 years. Clinical and immunological data were obtained by questionnaire. Most patients were treated according to rush schedules of specific immunotherapy. Mainte-

Table 1

Comparison of the initial systemic reactions (ISR) due to sting and repeated systemic reactions (RSR) during specific immunotherapy

Pat.	SG.	ISR	SG.	RSR
O.A.	II	U,A	II	GINT
A.E.	II	R,GINT	II	P,U,R
B.O.	II	U,R,GINT	II	GINT
G.I.	II	U,F,R,GINT	II	F,A
H.H.	II	U,F,R,GINT	II	P,U,GINT
K.H.	I	P,U	III	U,F,GINT,S
L.R.	III	U,F,S	I	P,U,F
S.H.	III	P,U,F,R,S	II	P,F,R
B.B.	II	P,A,R,GINT,CV	II	U,GINT,CV
F.I.	II	U,F,A,R,GINT,CV	II	U,F,A,R,GINT,CV
K.W.	III	P,R,GINT,S	II	P,F,GINT
W.L.K.	III	P,F,GINT,S	II	F,GINT
W.T.	III	R,S	II	U,R
M.H.	II	U,R	II	P,U
E.M.	III	U,F,R,S	II	U,F,R
H.F.	II	U,R	II	P,U,F,R
H.A.	II	GINT,N	I	N
S.C.	III	U,R,S	II	P,F,R,GINT
W.A.	II	P,U,A	II	U,F,R
Z.G.	III	S	I	P,F
E.H.	III	R,S	III	U,F,R,GINT,S
WÄ.K.	III	U,A,S	I	P,U
Z.F.	II	P,F,R	II	P,F,GINT

P = generalized pruritus, U,F,A = urticaria, flush, angioedema, R = respiratory symptoms, GINT = gastrointestinal symptoms, CV = cardiovascular reactions, S = shock, N = neurological symptoms. SG. = severity grade (I-IV according to Ring & Messmer) (11).

nance therapy was performed with 100 µg of hymenoptera venom. Patients with RSR were defined by the occurrence of more than two systemic reactions according to Ring & Meßmer grade I-IV (11) within 2 months of specific immunotherapy leading to profound alterations (repetition of the incremental phase, lower maintenance dose) or end of therapy. Skin testing was performed as prick and/or intradermal titration (the threshold doses eliciting a positive reaction are given in µg/ml). Specific IgE antibodies were determined by RAST (classes). Specific IgG antibodies were measured with a staphylococcus protein A sepharose test (10 ng Phos A/10 µl) (6), the Pharmacia IgG RAST (U/ml) or with an ELISA technique µg/ml) (14).

RESULTS

From an estimated number of approximately 3000 patients treated with hymenoptera venoms

(vespid and bee venom in approximately equal frequency (16)) in seven centers over a period of 5 years, 23 patients (9 males, 14 females, 9-60 years old, mean age 37 years) with RSR during hymenoptera venom immunotherapy were reported. Twenty-two of these 23 patients were treated with bee venom. One patient received vespid venom. Most of them (20/23) had RSR during the incremental phase and, if they were capable of reaching the maintenance therapy (12/23), also during maintenance therapy. In three patients (E.H., WÄ.K., Z.F.) RSR were only reported during maintenance therapy. Three of 15 patients (8 unknown) had a past history of hymenoptera venom allergy in their families and 6/13 (10 unknown) a past family history of bee-keeping. A past history of atopic diseases was mentioned in 5/21 (unknown) and in their families in 5/19 (4 unknown). Some patients with RSR showed an extremely high sensitivity in the skin test. *In vitro* tests for

specific IgE and IgG antibodies against hymenoptera venom during specific immunotherapy did not reveal a common pattern (Table 1).

Most patients with RSR experienced skin symptoms (pruritus, urticaria, flush, angioedema). Respiratory and gastrointestinal symptoms were also frequently noted. Four/23 (18%) patients exhibited cardiovascular reactions (tachycardia, drop in blood pressure) or full shock. In comparison with the initial systemic reaction RSR tended to be less severe (Table 2). Patients with RSR during the incremental phase as well as during maintenance therapy ($n = 12$) experienced RSR in 8/12 cases within the first 3 weeks after reaching the final dosage. In four cases RSR started after 4 to 12 weeks on maintenance therapy. The three patients with RSR only during maintenance therapy experienced RSR after 28 and 27 months. In eight patients specific immunotherapy had to be discontinued due to RSR. In four cases

treatment could be continued by reducing both the maintenance dose and the intervals between injections. In six patients specific immunotherapy could be successfully restarted after temporary discontinuation. Two patients received an increased maintenance dose up to 200 μg . In another three patients the application of a specific hyperimmunoglobulin against bee venom led to tolerance of specific immunotherapy. No follow-up data could be obtained in two cases.

DISCUSSION

There is definitely a subgroup of patients allergic to hymenoptera venoms who develop RSR during the course of specific immunotherapy leading to severe treatment problems. Fortunately, most RSR tend to be less severe than the initial reaction, but some patients experience shock. The vast majority of patients with

Table 2
Test results of patients with RSR, prior to therapy and after occurrence of RSR (*)

Patient	Skin test threshold		RAST (classes)	Specific IgG			
	Intradermal (µg/ml)	Prick (µg/ml)		Lev.	Met.	Int.	
O.A.	0.1	–	3	3*	20*	R	L
A.E.	0.000001	–	4	3*	14*	E	L
B.O.	–	100	4	3*	9*	E	L
G.I.	1	–	3	–	6*	S	L
H.H.	0.0001	–	4	3*	233*	R	L
K.H.	–	–	4	3*	16*	S	L
L.R.	–	–	3	3*	8*	S	L
S.H.	0.001	–	3	–	233*	R	L
B.B.	0.0001	–	3	–	–		
F.I.	–	100	3	–	200*	E	L
K.W.	0.0001	–	3	3*	178*	R	L
W.I.K.	–	10	4	3*	2*	E	L
W.T.	0.000001	–	3	3*	720*	R	H
M.H.	–	100	–	4*	–		
E.M.	–	1	4	–	36*	R	L
H.F.	–	1	–	3*	36*	R	L
H.A.	–	100	–	4*	74*	R	L
S.C.	–	10	4	–	–		
W.A.	–	10	4	4*	26*	R	L
Z.G.	–	100	–	4*	520*	R	H
E.H.	0.01	–	2	2*	–		
WÅ.K.	0.01	–	3	3*	60*	E	H
Z.F.	0.1	–	4	2*	3*	E	L

Lev. = level, Met. = method, Int. = interpretation, H = high, L = low levels of specific IgG antibodies; R: IgG RAST, U/ml; E: ELISA, $\mu\text{g/ml}$; S: staphylococcus protein A sepharose test, 10ng PhosA/10 μl .

RSR are allergic to bee venom. RSR during vespid venom immunotherapy appear to be rare, this difference is as yet unexplained. Most RSR occur during the incremental phase. Most patients with RSR during maintenance therapy have a past history of RSR during the incremental phase. In these patients RSR occurred when the amount of allergen administered per month was reduced by extending the intervals between injections. High sensitivity in the skin test may be an indicator of possible RSR, as it has been shown to be an indicator of fatalities with other allergens (5). However, the occurrence of RSR can only be assumed and can not be predicted by past history or any other diagnostic data. In some patients a decreased ability to produce specific IgG antibodies against allergens of hymenoptera venom may be responsible for RSR (3,15). However, the mechanisms underlying RSR are still by no means elucidated. An individual approach is necessary to continue treatment. Reduction of the maintenance dose as well as the intervals between injections or discontinuation of treatment for a certain period may be tried. Bee venom specific hyperimmunoglobulin (i.e. passive immunization) has been shown to increase tolerance, at least for some weeks (2,4,8,9). To prevent RSR, injection schedules for the incremental phase should be used with a decreased risk of systemic reactions. As a review of literature indicates, conventional injection schedules of more than 12 weeks or very short injection schedules (up to 3 days) may be appropriate (13). Further, antihistamines of the H1-type given as a premedication may reduce the frequency of RSR, although not prevent all of them (2). More work is necessary to elucidate the cause of RSR in patients on hymenoptera venom immunotherapy.

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