

Predictive value of venom-specific IgE, IgG and IgG subclass antibodies in patients on immunotherapy with honey bee venom

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Sixty-seven patients with a history of severe systemic reactions following honey bee stings were treated by immunotherapy (IT) with honey bee venom. During maintenance therapy all were submitted to a sting challenge under clinical conditions. 15 developed mostly minor symptoms of a systemic reaction while 52 showed only a local swelling at the sting site. Phospholipase A₂-specific IgE, IgG and IgG subclass serum antibodies were estimated in samples obtained before IT and immediately before the challenge. Specific IgE decreased in reactors and in non-reactors. There was no difference between the two groups at any time. Specific total IgG, IgG₁ and IgG₄ increased in both reactors and non-reactors during IT. An early increase of specific IgG₁ was observed while specific IgG₄ remained elevated throughout the treatment. Specific total IgG was higher in reactors than non-reactors before the challenge, specific IgG₁ higher in reactors before treatment and specific IgG₄ higher in reactors than non-reactors both before treatment and before challenge. In the individual patient, no single antibody estimation or combination of various antibodies was predictive of the outcome of a sting challenge.

Key words: honey bee venom; hymenoptera sting allergy; IgG-subclass antibodies; phospholipase A₂; sting challenge; venom immunotherapy.

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Venom immunotherapy (VIT) is highly effective treatment for patients with a history of systemic allergic reactions following Hymenoptera stings. According to a sting challenge (CH) during maintenance VIT with honey bee venom (HBV) approx. 80% of the patients are completely protected (8, 22, 25), the remaining usually develop only minor symptoms of a systemic reaction. VIT with yellow jacket (*Vespa* sp) venom is even more effective with 95-100% of patients being fully protected (4, 9, 20, 24).

Estimation of venom-specific serum antibodies before a CH in untreated patients has been showed to be of limited (5) or no predictive value (2, 15) regarding the outcome of the CH. This study was undertaken to investi-

gate the predictive value of serum antibody determinations, including venom-specific IgG subclass antibodies to the major allergen of honey bee venom, phospholipase A₂, in patients on maintenance VIT.

MATERIAL AND METHOD

Sixty-seven patients with a history of mostly severe systemic reactions (grades III and IV according to H. L. Mueller, modified (22)) and positive skin test (ST) and/or RAST were submitted to VIT with HBV (Pharmacia AB) up to a maintenance dose of 100 µg (in 49 patients) or 200 µg (in 18 beekeepers or family members of bee keepers). Patient data are given in Table 1.

Prior to sting challenge all patients had tolerated the maintenance dose of at least 100 µg

Table 1
Clinical and laboratory data of the 67 honey bee sting allergic patients before VIT

	Total	Challenge		Outcome of challenge	
		early	late	reactors	non-reactors
No. patients	67	29	38	15	52
Grade of systemic reaction					
II	5	3	2	1 (7)	4 (8)
III	40	16	24	9 (60)	31 (60)
IV	22	10	12	5 (33)	17 (33)
Skin test endpoint concentration in g/l					
10^{-3}	2	1	1	0	2 (4)
10^{-5} – 10^{-4}	23	10	12	4 (27)	19 (37)
10^{-7} – 10^{-6}	30	13	18	9 (60)	21 (40)
$\leq 10^{-8}$	12	5	7	2 (13)	10 (19)
RAST-class					
0	1	0	1	0	1 (2)
1	5	2	3	1 (7)	4 (8)
2	20	10	10	4 (27)	16 (31)
3	31	14	17	7 (47)	24 (46)
4	10	3	7	3 (19)	7 (13)

HBV without systemic side effects. None of the patients was on medication which could have influenced the outcome of the CH, such as antihistamines, beta-blocking agents or corticosteroids. The CH was performed on the intensive care unit, with an intravenous infusion of 5% glucose running and the patient connected to the monitor. Honey bees were supplied by the Swiss Institute of Agricultural Research, Liebefeld, Bern. They were applied to the forearm of the patient. The sting was removed exactly 1 min after the bee had stung and the patient observed for 2 h thereafter. Subjective systemic symptoms only (such as pruritus, paresthesias, headache, etc.) were recorded in five patients, objective systemic symptoms (such as flush, urticaria, angioedema, conjunctivitis, cough or hoarseness) in 10 patients. These 15 patients are called reactors (R), the 52 other patients, who developed only a local swelling at the sting site, non-reactors (NR).

The CH was performed during the first year of VIT in 29 patients after a mean of 4.41 ± 2.29 (SD) months of VIT (range 2 to 12 months). 38 other patients were challenged late during VIT after a mean of 60.6 ± 21.3 months of VIT (range 28–108).

Intracutaneous skin tests (ST) with HBV (Pharmacia AB) were performed as described previously (29). A wheal of 5 mm or more in diameter with erythema at a concentration of 10^{-4} g/l or less was regarded as a positive result.

For estimation of serum antibodies to HBV-phospholipase A_2 , serum samples were obtained before starting VIT and immediately before the CH and stored at -20°C until used. Phospholipase A_2 (PLA) was purchased from Sigma Chemical Company St. Louis Mo, USA.

HBV- and phospholipase A_2 specific IgE-antibodies (PLA-IgE). Reagents for Phadezym-RAST and HBV-discs were obtained from Pharmacia AB and tests performed in duplicate according to the recommendations of the manufacturer. For estimation of PLA-IgE, 500 bromcyanid-activated paper discs were coupled with 2 mg of PLA as described by Light et al. (18). Values are given in Phadebas-RAST-units (PRU). A value of ≥ 0.35 PRU ($\geq$ RAST class 1) was regarded positive.

Phospholipase A_2 -specific IgG (PLA-IgG) was estimated by an ELISA technique as described

previously (29). Briefly, polystyrol tubes activated with glutaraldehyde were coated with 0.15 µg of PLA per tube. Patient sera were diluted 1:50. The marker to detect IgG-antibodies was a conjugate of protein A (Pharmacia Fine Chemicals, Uppsala, Sweden) and alkaline phosphatase (Sigma Chemical Company, St. Louis, MO, USA). Results are given in arbitrary units in comparison with a standard curve obtained by serial twofold dilution of a bee keeper reference pool determined to contain 100 U of PLA-IgG per ml. The reference pool contains 20 µg of specific IgG against whole bee venom per ml, as kindly estimated by Dr. G. Hamilton, Baltimore, USA).

Phospholipase A₂-specific IgG subclass-antibodies.

IgG subclasses of antibodies to PLA were estimated by an ELISA technique on microtiter plates as described previously (21, 28). For coating, 200 µl of PLA at a concentration of 0.2 µg/ml were used per well. Patient sera were diluted 1:100. Monoclonal mouse antibodies to human IgG-subclasses were obtained from Unipath (Inotech AG, Wohlen, Switzerland) and were clones NL 16 (IgG₁), HP 6014 (IgG₂), ZG 4 (IgG₃) and RJ₄ (IgG₄). Rabbit antimouse IgG labelled with alkaline phosphatase was obtained

from Sigma Chemical Company, St. Louis, MO, USA. Results are given in arbitrary units in comparison with a standard curve obtained by serial twofold dilution of the same bee keeper reference pool as used for total IgG, determined to contain 100 units of each subclass antibody per ml.

Statistical evaluation

Geometric mean values of various antibody levels before treatment and before CH were compared by paired t-test, those between reactors and non-reactors by the t-test for independent variables.

RESULTS

As shown in Table 1, 15 patients developed systemic reactions following the sting challenge, 52 only a local swelling. Seven of the 29 (24%) early challenged and eight (21%) of the 38 late challenged patients were reactors. One (6%) of the 18 patients on a maintenance dose of 200 µg and 14 (29%) of the 49 on a maintenance dose of 100 µg were reactors. There was no significant difference between patients challenged early and late and between reactors and non-reactors regarding the grade of severity of the last reaction before VIT, the skin test endpoint concentration and the RAST-class distribution. During VIT, however, 12 of 15 reactors (80%) had developed at least one systemic reaction compared with only 18 of the 52 non-reactors (35%). This difference is statistically significant ($P < 0.01$) in the χ^2 -test.

Table 2 gives the symptoms and treatment of patients with systemic reactions. The 15 systemic reactions were minor and judged as much weaker than pretreatment reactions by all the patients. Five patients with urticaria, angioedema or flush had to be treated with antihistamines intravenously, two patients with additional cough and hoarseness received inhalations via an adrenaline Medihaler. No severe cardiovascular or respiratory symptoms were observed.

Table 2

Symptoms and treatment in 15 patients with systemic reactions to sting challenge

Symptom/Treatment	No. patients
Subjective symptoms only	5
paresthesias/pruritus:	5
palmoplantar	4
perioral, periorbital	3
anogenital	2
headache	1
Objective symptoms	10
flush, conjunctivitis	7
urticaria	4
angioedema	3
cough, hoarseness	3
tachycardia	2
Treatment necessary	5
adrenalin by inhalation	2
antihistamines	5

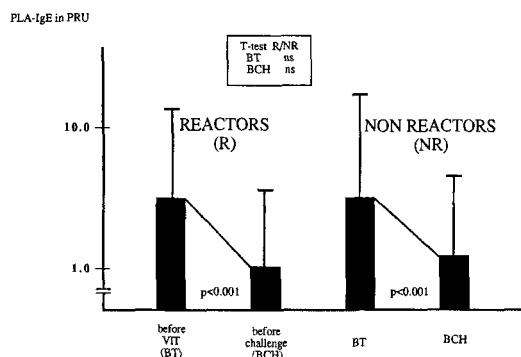


Fig. 1. PLA-IgE before treatment and before challenge in 67 bee venom-allergic patients on venom immunotherapy.

PLA₂-specific IgE-antibodies. As shown in Fig. 1 and Table 3 PLA-IgE decreased significantly in both reactors and non-reactors from pretreatment to prechallenge. This decrease was pronounced in late challenged patients and less prominent but still significant in early challenged patients. There was no difference between reactors and non-reactors regarding PLA-IgE both before treatment and before challenge.

Two (13.3%) of the reactors and nine (17.3%) of the non-reactors had no detectable PLA-IgE before the challenge.

PLA-IgG-antibodies (Fig. 2, Table 3). PLA-IgG increased in both reactors and non-reactors. This increase was clearly more pronounced in early challenged patients. Pretreatment and prechallenge PLA-IgG were higher in reactors than in non-reactors. The difference was only significant in the prechallenge sample.

IgG subclass antibodies to phospholipase A₂. Consistent elevations were only observed in PLA-IgG₁ and PLA-IgG₄. A minority of patients had also detectable levels of PLA-IgG₂ which were stimulated by VIT: 32 patients had measurable PLA-IgG₂ before VIT. In 28 patients treatment induced an increase of PLA-IgG₂. Because of the inconsistent elevations of PLA-IgG₂, only PLA-IgG₁ and PLA-IgG₄ will be reported in detail.

Table 3
Phospholipase A₂-specific IgE-, IgG-, IgG₁ and IgG₄-antibodies

Patient group	n	PLA ₂ -specific serum antibodies in units (geometric mean value) before VIT/before challenge					
		IgE	P*	IgG	P*	IgG ₁	P*
Reactors all	15	3.97/1.26	< 0.001	36.9/50.3	NS	47.2/25.1	17.5/38.0
early challenge	7	2.88/1.87	< 0.05	40.8/63.9	< 0.05	43.3/43.2	16.0/46.9
late challenge	8	5.05/0.87	< 0.001	34.3/40.9	NS	50.3/15.6	18.8/32.9
Non-reactors all	52	4.0 /1.52	< 0.001	17.1/33.4	< 0.01	18.8/22.7	7.9/18.4
early challenge	22	2.62/2.01	< 0.05	13.2/45.8	< 0.001	12.0/39.3	7.0/26.6
late challenge	30	5.51/1.24	< 0.001	19.3/24.5	NS	28.1/14.0	8.6/13.1
Early challenge all	29	2.71/1.99	< 0.01	17.5/49.6	< 0.001	15.1/39.9	8.4/29.0
Late challenge all	38	5.4 /1.17	< 0.001	21.9/27.3	NS	32.0/14.8	10.2/16.6
Maintenance dose	18	2.5 /1.23	< 0.05	16.0/48.2	< 0.001	15.7/49.4	7.7/28.4
200 µg	49	4.58/1.14	< 0.001	22.1/31.5	< 0.01	25.4/16.8	10.1/18.7
100 µg							

P* = values in paired t-test; NS = non significant

PLA-IgG₁ (Fig. 3, Table 3) increased significantly in early and decreased significantly in late challenged patients. They decreased in reactors and increased in non-reactors, although these alterations were not significant. Pretreatment *PLA-IgG₁* were significantly higher in reactors than in non-reactors.

PLA-IgG₄ (Fig. 4, Table 3) increased significantly in reactors and non-reactors and in early and late challenged patients. The increase was more pronounced in early challenged patients. Pretreatment and prechallenge *PLA-IgG₄* were significantly higher in reactors than in non-reactors.

PLA-IgG and *PLA-IgG* subclass antibodies were somewhat, but not significantly, higher before treatment in patients on 100 µg than those on 200 µg maintenance doses. The increase of all these antibodies during VIT was more pronounced in the patients on the higher maintenance dose.

Ratios of *IgG₄/IgE*, *IgG₄/IgG₁*, *IgG/IgE*, and *IgG₁/IgE* were higher in reactors than in non-reactors and in late than in early challenged patients. In the single individual none of these ratios was predictive of the outcome of the sting.

DISCUSSION

The sting challenge is the most reliable method for testing the efficacy of VIT in patients with Hymenoptera venom allergy (14, 22, 30). However, the challenge is not infallible. Thus the

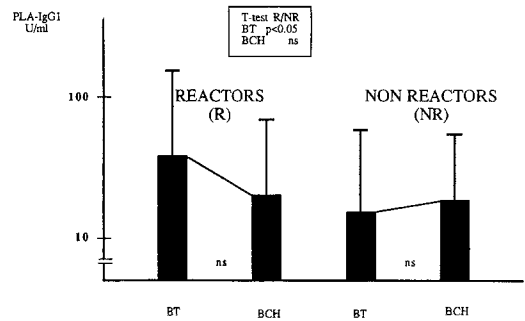


Fig. 3. *PLA-IgG₁* before treatment and before challenge in 67 bee venom-allergic patients on venom immunotherapy.

amount of venom applied with a sting may vary considerably according to the content of the venom sac and the age of the insect. In vespids, who may sting several times a day and even spray venom in the air when captured (13), this may be especially significant and explain why sting challenges in untreated patients are negative in 70–80%. During the challenge with honey bees the amount of venom applied is probably more constant, because honey bees usually lose their venom apparatus after a sting. Consequently, positive results of a sting challenge in untreated patients are observed more frequently in about 50% (2,15).

In this study the results of early and late challenges during VIT were similar. As would be expected, less reactors were found among the patients on a maintenance dose of 200 µg than

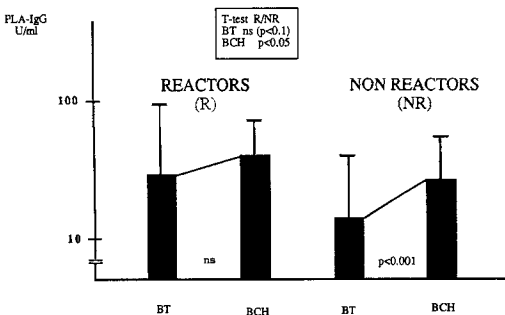


Fig. 2. *PLA-IgG* before treatment and before challenge in 67 bee venom-allergic patients on venom immunotherapy.

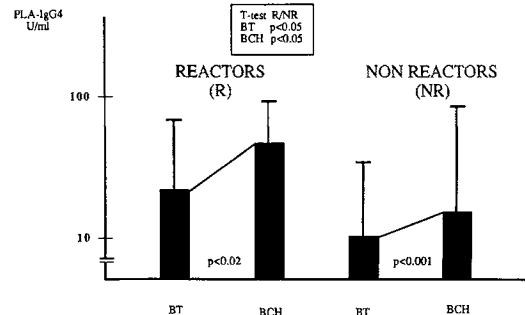


Fig. 4. *PLA-IgG₄* before treatment and before challenge in 67 bee venom-allergic patients on venom immunotherapy.

among those on 100 µg, and the IgG response was more pronounced under the higher dose.

We use sting challenges early during VIT to confirm protection, especially in heavily exposed patients, such as bee keepers and their family members, farmers and gardeners. The late challenge is performed before cessation of VIT. The challenge is expensive, time-consuming and not without risk for the patient. There is therefore a need for a simple and reliable *in vitro* test for estimating the efficacy of VIT.

Venom-specific serum IgE are obviously not suitable for this purpose in the early phase of VIT. They increase during the first few months (29), at a time when most patients are already fully protected. Some authors stop VIT, when venom-specific IgE have turned negative (26, 30). In this study, no significant difference of PLA-IgE between reactors and non-reactors was found, either before an early, or before a late challenge. Furthermore, two of the reactors had no detectable PLA-IgE in the pre-challenge serum. This suggests that a negative RAST may not be a reliable criterion for discontinuation of VIT.

Venom-specific IgG increase steeply during the initial phase of VIT, reach a maximum during the first half year of treatment and remain elevated after prolonged treatment (29). High levels are usually found in frequently stung bee keepers, and the protective effect of bee keeper gammaglobulin preparations has been demonstrated in several clinical studies (3, 17, 21). Attempts to define a protective level of venom-specific IgG (10, 11, 30) have, however, been disappointing (16, 22, 27). Although the majority of successfully treated patients have high venom-specific serum IgG-antibodies, some well-protected patients have low levels and in occasional treatment failures high levels are observed. In this study PLA-IgG increased in both reactors and non-reactors, most prominently in early challenged patients. Surprisingly, prechallenge PLA-IgG were significantly higher in reactors than in non-reactors.

It has been known for several years that HBV-IgG₄-antibodies are strongly elevated in heavily exposed bee keepers and patients on HBV-VIT (12). Aalberse (1) showed that early

during VIT and bee keeping there is a prominent IgG₁ response, while after prolonged VIT and bee keeping the IgG₄ response is more and more prevailing. These observations supported the concept that IgG₄ is the protective blocking antibody induced by immunotherapy. The finding of persistently elevated PLA-IgG₄ in successfully treated patients (7, 31), even 2 years after discontinuation of VIT (32) also favours this concept. However, to our knowledge no treatment failures have as yet been analysed with regard to venom-specific IgG subclass antibodies.

Kampelmacher et al. (15) estimated venom-specific IgG subclass antibodies in the serum of untreated Hymenoptera sting allergic patients taken immediately before challenge. They found no significant differences in venom-specific IgG₁ and IgG₄ or ratios of these antibodies in relation to IgE between reactors and non-reactors. In the present study dealing with patients on HBV-VIT, reactors had higher pretreatment PLA-IgG₁ and higher pretreatment and prechallenge PLA-IgG₄ than non-reactors.

Similar findings have been reported in patients on immunotherapy with grass pollen (6) and *Cladosporium herbarum* (19) for respiratory allergies. In these two studies a high IgG₄ level was associated with a poor clinical result. During immunotherapy with *Cladosporium* a strong increase of IgG₁ went together with frequent side effects and poor clinical efficacy.

These observations together with the results of our study indicate that the IgG response induced by immunotherapy is more an epiphenomenon and not the decisive protective mechanism. It is even possible that IgG₄ might sensitize mast cells or basophils under certain conditions (23) and thus actually be harmful. These findings show also that when evaluating an antibody for the follow up of immunotherapy, it must be studied in direct relation to treatment success.

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