

A Double Blind Study on Immunotherapy with Chemically Modified Honey Bee Venom: Monomethoxy Polyethylene Glycol-Coupled versus Crude Honey Bee Venom

U. Müller^a, A. Lanner^b, P. Schmid^a, M. Bischof^a, S. Dreborg^b, R. Hoigné^a

^a Medical Division, Zieglerspital, Bern, Switzerland

^b Medical Department, Allergy and Diagnostic Division, Pharmacia AB, Uppsala, Sweden

Abstract. 24 patients with honey bee sting allergy were treated with either honey bee venom (HBV) or monomethoxy polyethylene glycol-coupled HBV (PEG-HBV) in a double blind trial. Both treatments induced a strong increase in HBV-specific IgG antibodies in most patients. Immunotherapy with PEG-HBV was much better tolerated than that with HBV. Conversely, patients on HBV did considerably better during a sting challenge with a living honey bee. Only 4 developed a large local and one a mild systemic reaction compared to 7 large local and 3 moderate to severe systemic reactions in the PEG-HBV-group. A higher maintenance dose of PEG-HBV may still be well tolerated but prove more effective at reexposure.

Venom immunotherapy (VIT) is a highly effective treatment for patients with systemic reactions (SR) following Hymenoptera stings [2, 4]. Allergic side effects are, however, frequently observed and sometimes require discontinuation of VIT. A chemically modified preparation of honey bee venom (HBV), monomethoxy polyethylene glycol-coupled HBV (PEG-HBV) has been studied in experimental animals and human volunteers [1, 5]. It is of a low toxicity, has a significantly reduced allergenicity compared to HBV in skin test endpoint titration but is still able to induce a strong blocking antibody response [5]. In the present study, 24 patients with SR following honey bee stings were treated in a double blind trial with either HBV or PEG-HBV in order to compare their efficacy and tolerance in immunotherapy (IT).

Methods

All patients had a positive RAST [>0.35 Phadebas RAST units (PRU)] and a positive skin test at $\leq 10^{-3}$ g/l with HBV. The interval between the last SR and start of IT was less than 3 years in all. None had received previous VIT. Patients were randomly assigned to the two treatment groups. Table I gives demographic data and results of diagnostic tests which show that the two groups are comparable.

IT was administered as a cluster regimen with weekly sessions up to a maintenance dose of 100 μ g of HBV and 200 μ g of PEG-HBV. Patients were challenged with a honey bee sting under clinical

conditions 2 weeks after the 4th application of the maintenance dose, in the absence of allergic side effects usually in week 14 after starting VIT. Because of two treatment failures in the first series of 14 patients it was afterwards decided to double the maintenance dose in case of an insufficient increase in IgG (to less than 120 units) before the challenge in the remaining 10 patients. This was necessary in 2 of 5 patients on PEG-HBV and 1 of 5 on HBV.

Serum samples were obtained before VIT, after 1 and 3 months of treatment, immediately before and 2 weeks after the sting chal-

Table I. Demographic data and results of diagnostic tests

	Treatment	
	HBV	PEG-HBV
Number of patients	12	12
Male/female	10/2	9/3
Mean age	34.8 (22–52)	35.2 (23–50)
Type of reaction		
Urticaria-angioedema	2	3
Respiratory	7	6
Shock	3	3
HBV-specific IgE, PRU ¹	6.18 (0.72–16)	4.35 (0.7–18.2)
HBV-specific IgG, U/ml ¹	45.8 (20–320)	34.5 (20–460)
Skin test sensitivity ²	6.42 $\pm$ 0.99	5.83 $\pm$ 0.83

Figures in parentheses indicate range.

¹ Geometric mean.

² Given as the negative logarithm of the end point concentration in g/l $\pm$ SD.

Table II. Treatment tolerance

Reaction	Treatment	
	HBV	PEG-HBV
Large local	7	6
Systemic	6	1
Mild	4	1
Moderate	2	0
Severe	0	0
Drop-outs because of side effects	2	0

Table III. Results of reexposure by sting challenge

Reaction	Treatment	
	HBV	PEG-HBV
None	5	2
Large local	4	7
Systemic	1	3
Urticaria-angioedema	1	0
Respiratory	0	1
Shock	0	2

lenge. HBV-specific IgE-antibodies were estimated by Phadebas-RAST. Results are given in PRU. HBV-specific IgG-antibodies were estimated by Phadebas G-RAST. Results are given in arbitrary units. 125 units correspond to approximately 5 µg/ml of HBV-specific IgG.

Results and Discussion

Table II shows the treatment tolerance. Large local reactions exceeding 10 cm in diameter and lasting sometimes for several days were observed frequently in both groups. SR were, however, by far more often seen under HBV and caused two drop outs in this group. Table III gives the results of the sting challenge. 3 SR and 7 large local reactions were observed on PEG-HBV, 1 mild SR and 4 large local reactions on HBV. Serologic studies (fig. 1) revealed a mild initial increase of mean HBV-specific IgE in the HBV-group which was absent in the PEG-HBV-group. A definite increase of HBV-specific IgG-antibodies was observed in all patients. In 2 of the first 14 (1 on PEG-HBV, 1 on HBV) and 3 of the additional 10 patients (2 on PEG-HBV, 1 on HBV) the level of 125 units was however not reached. Only 1 of the treatment failures,

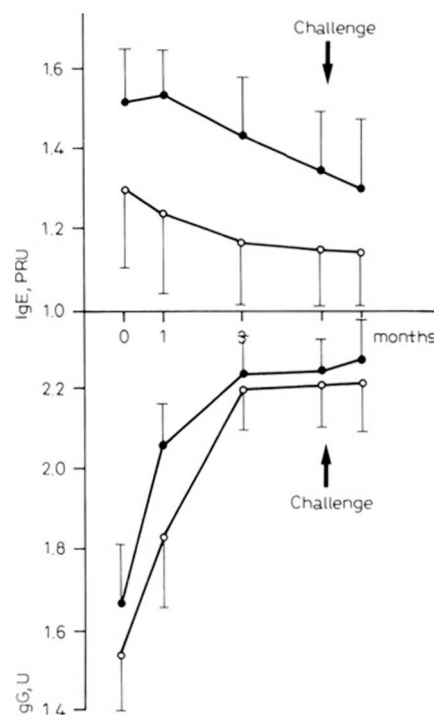


Fig. 1. HBV-specific IgE- and IgG-antibodies during treatment with HBV (●) or PEG-HBV (○). Geometric means of antibody levels ± SEM are logarithmically transformed.

a patient on PEG-HBV had an IgG level below 125 units. Possible reasons for treatment failures, which were observed more often in the PEG-HBV-group, are quantitatively or qualitatively inadequate stimulation of blocking-antibody production. With respect of the high IgG-levels in 3 of 4 treatment failures it must be assumed, that qualitative inadequacy is more important. Alternatively other mechanisms of protection like the induction of T suppressor cells specific for reaginic antibody producing B cells may be insufficiently triggered by PEG-HBV in the dose studied in this trial [3].

Considering the excellent tolerance of IT with PEG-HBV and the 75% treatment success a further controlled trial with a higher maintenance dose seems justified.

References

- Ahlstedt, S.; Björkstén, B.; Åkerblom, E.: Antibody responses to honey bee venom and monomethoxy polyethylene glycol modified honey bee venom in mice. *Int. Archs Allergy appl. Immun.* 71: 228-232 (1983).

- 2 Hunt, K.J.; Valentine, M.D.; Sobotka, A.K.; Benton, A.W.; Amodio, F.J.; Lichtenstein, L.M.: A controlled trial of immunotherapy in insect hypersensitivity. *New Engl. J. Med.* 299: 157-161 (1978).
- 3 Lee, W.J.; Schon, A.H.; Akerblom, E.: Suppression of reaginic antibodies with allergens. IV. Induction of suppressor T cells by conjugates of polyethylene glycol and monomethoxy polyethylene glycol with ovalbumin. *Int. Archs Allergy appl. Immun.* 64: 100-114 (1981).
- 4 Müller, U.; Thurnheer, U.; Patrizzi, R.; Spiess, J.; Hoigné, R.: Immunotherapy in bee sting hypersensitivity. *Allergy* 34: 369-378 (1979).
- 5 Ohman, S.; Bjorkander, J.; Malling, H.J.; Weeke, B.; Dreborg, S. and Lanner, A.: Immunotherapy with a monomethoxy polyethylene glycol modified honey bee venom preparation. *Folia allergol. immunol. clin.* 30: suppl., pp. 142 (1983).

Correspondence to: Dr. U. Müller,
Medical Division,
Zieglerspital,
CH-3000 Bern (Switzerland)