

Level of osteopontin is increased after bee venom immunotherapy

To the Editor:

Venom immunotherapy (VIT)¹⁻³ proves to be the most effective in insect allergy. However, the regulatory mechanisms by which immunotherapy achieves its sustained clinical efficacy remain elusive, and the biomarkers associated with efficacious immunotherapy have not yet been identified. As a part of a genomics study to identify candidate biomarkers associated with successful VIT, we have previously identified a promising candidate,⁴ osteopontin, a postulated T_H1 cytokine,^{5,6} in patients who completed long-term VIT for insect sting-induced systemic allergic reactions and remained tolerant for 3 to 6 years, compared with the untreated patients.

To obtain longitudinal measurement of serum osteopontin levels after VIT, a total of 8 subjects with large local allergic reactions, but not systemic allergic reactions after sting, were recruited from our ongoing insect allergy research project. All had a history of allergic reactions to insect stings and had evidence of venom-specific IgE antibodies in the skin and/or serum. This group of patients received initial and maintenance VIT according to current practice parameters as previously reported,^{7,8} from which longitudinal data and specific outcome assessment (sting challenge) were available. All subjects gave informed consent under a protocol approved by the Institutional Review Board of the Johns Hopkins Medical Institutions.

This group of patients had demonstrable, but variable, levels of reduction in skin reactivity to bee sting challenge after VIT, and the majority of patients responded well to VIT as early as 2 months after VIT (Table I). Serum samples were collected at various time points before VIT (Pre) and at 2 (2 mo), 6 (6 mo), 12 (12 mo), and 24 (24 mo) months after starting VIT, and the levels of serum osteopontin were analyzed by the use of an ELISA (IBL Japan, Gunma, Japan) for all 8 subjects. As shown in Fig 1, a significant increase in the levels of osteopontin with time-dependent upward trend was found over the 2-year period of VIT compared with those detected before VIT ($P < .05$ vs untreated in all cases). The difference was particularly significant at the 12-month and 24-month time points, whereas no significant change was seen in the

levels of serum osteopontin at an earlier time point (2 months).

When the skin reactivity was evaluated, the majority of study subjects showed reduction in reactivity to sting challenge as early as 2 months after VIT (Table I), but the levels of serum osteopontin began to rise after more than 2 months of VIT. Two subjects (patients 3 and 5) showed significant change in the levels of serum osteopontin only at the 24-month time point, whereas reduction of the skin reactivity was seen throughout the study period. Of interest, 1 patient (1) showed an initial rise in osteopontin level at the 6-month time point, but the level decreased at the 1-year time point, followed by again a significant increase at the 24-month time point, corresponding with the change in skin reactivity to sting challenge (Table I).

It is often noted that the levels of serum IgE tend to increase shortly after VIT and gradually decline over the course of long-term VIT.¹ This trend was clearly evident for the majority of study subjects receiving VIT, except for patients 5 and 8, whose IgE levels either remained unchanged or decreased initially, but increased after 1 year of VIT (Fig 1). It is noted that although the patterns of kinetic change were variable among the study subjects, the levels of osteopontin showed an inverse trend compared with the levels of IgE over the course of VIT (Fig 1). Of interest, a significantly reduced level of osteopontin is associated with hyper-IgE syndrome.⁹ In contrast, the majority of the study subjects, with the exception of patient 8, showed no significant increase in the levels of serum specific IgG over the course of 1 year of VIT (Fig 1).

An overlapping, but distinct, allergic mechanism is expected in the large local reaction compared with that seen in systemic response, but the elevated level of IgE antibodies is a common feature. Further, conventional VIT is effective in both groups of patients, suggesting a common regulatory pathway. Interestingly, a similar increase in the level of osteopontin is seen in both groups of patients after VIT with various types of venom allergens, which suggests the existence of a common regulatory pathway associated with osteopontin independent of the types of venom allergens used. Although osteopontin's role in directly modulating the T_H2 response is unknown, accumulated evidence has suggested that osteopontin is involved in T_H1-mediated immunity.⁶ For

TABLE I. Sting challenge tests of patients with large local reactions

Patient #	Age (y)	Sex	Insect	% Reduction of peak size			% Reduction of peak time			% Reduction of duration		
				2 mo	12 mo	24 mo	2 mo	12 mo	24 mo	2 mo	12 mo	24 mo
1	61	M	MV	88	20	80	90	0	80	93	0	33
2	45	F	MV	39	55	73	0	50	95	43	43	97
3	42	M	MV	26	65	47	0	50	75	40	80	60
4	60	F	HB	0	78	0.1	50	95	50	50	88	66
5	45	M	MV	77	75	82	50	50	90	90	50	95
6	47	F	HB	9	83	70	50	75	0	0	98	60
7	44	M	HB	14	0	40	50	75	75	75	67	83
8	58	F	MV	79	68	79	93	93	93	93	80	90

HB, Honey bee; MV, mixed vespid.

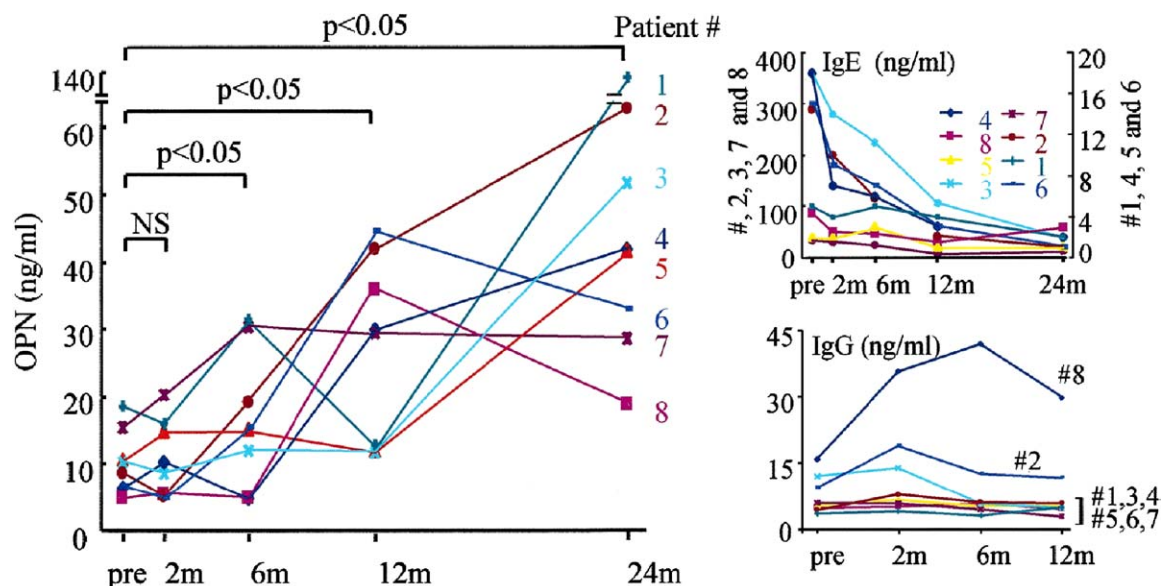


FIG 1. Kinetic changes of serum osteopontin (OPN), IgE, and IgG levels after VIT. The subject numbers correspond to those in Table I. The levels of IgG for each subject were available only up to the 12-month (12 mo) time point after VIT.

example, high levels of osteopontin have been observed in patients with rheumatoid arthritis, tuberculosis, and multiple sclerosis, featuring a strong T_H1 component.⁶ Thus, the known T_H1 -inducing activity of osteopontin may potentially play a role in modulating the allergic responses. Further studies are required to test this possibility, and a larger patient population is needed to evaluate the utility of serum osteopontin as a functional marker of VIT.

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Common variable immunodeficiency presenting with a large abdominal mass

To the Editor:

Common variable immunodeficiency (CVID) is often associated with recurrent sinopulmonary or gastrointestinal infections.¹ A history of recurrent infections usually raises the suspicion of CVID; however, associated conditions of granulomatous infiltration, autoimmunity, or malabsorption can be clues, leading to earlier diagnosis. The association between CVID and systemic caseating and noncaseating granulomas is well documented.² Here we discuss an unusual presentation of CVID in a young man with a large abdominal mass.

The patient was a 22-year-old autistic African American who presented to a local hospital with weight loss (>20 lbs) and daily fevers.

He had multiple episodes of otitis media in childhood, a dental abscess, and 2 presumed bacterial pneumonias (at 16 years and 21 years of age) requiring intravenous antibiotics. There was no history of sinusitis. There was no family history of immunodeficiency, and his mother has scleroderma.