

High-dose intravenous γ -globulin treatment for hyperimmunoglobulinemia E syndrome

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Background: Hyperimmunoglobulinemia syndrome (HIES) is an inflammatory skin disease, and management of it is not satisfactory. However, high-dose intravenous γ -globulin (IVGG) is a safe and effective treatment for Kawasaki disease.

Methods: I initially treated two patients with Kawasaki disease, both of whom also had HIES, with IVGG. Subsequently, I treated patients with HIES alone, atopic dermatitis, Kawasaki disease, or idiopathic thrombocytopenic purpura with IVGG and measured serum IgE levels and in vitro spontaneous IgE production by peripheral blood mononuclear cells from patients. Direct effects of IgG on in vitro IgE production were also studied.

Results: IVGG treatment remarkably improved severe eczema in patients with HIES with or without Kawasaki disease and in patients with atopic dermatitis. Moreover, serum IgE levels and in vitro spontaneous IgE production were decreased in these patients but not in patients with Kawasaki disease or idiopathic thrombocytopenic purpura. The addition of high concentrations of IgG to cultures of peripheral blood mononuclear cells from patients with HIES or atopic dermatitis decreased in vitro spontaneous IgE production. Moreover, IgG also decreased IgE production by normal B cells stimulated with interleukin-4 plus anti-CD40 monoclonal antibody.

Conclusion: IVGG is effective in the treatment of severe eczema in patients with HIES and atopic dermatitis. IVGG also decreased enhanced IgE production both in vivo and in vitro. (J ALLERGY CLIN IMMUNOL 1995;95:771-4.)

Key words: Hyperimmunoglobulinemia E syndrome, IgE production, intravenous γ -globulin, eczema, atopic dermatitis, interleukin-4, Kawasaki disease

Hyperimmunoglobulinemia E syndrome (HIES) is an inflammatory skin disease characterized by (1) severe eczema, (2) recurrent staphylococcal infections of the skin and sinopulmonary tract, (3) cold subcutaneous abscesses, and (4) high serum IgE levels.¹ Management of HIES is not satisfactory.^{2,3}

High-dose intravenous γ -globulin (IVGG) is a safe and effective treatment for Kawasaki disease. Moreover, IVGG also reversed lymphocyte activation in vivo.⁴ I treated two patients who had Kawasaki disease and HIES with high-dose IVGG, which resulted in improvement of severe eczema associated with HIES. Subsequently, patients with HIES alone or with atopic dermatitis were treated

Abbreviations used

AU:	Arbitrary units
HIES:	Hyperimmunoglobulinemia E syndrome
IL:	Interleukin
ITP:	Idiopathic thrombocytopenic purpura
IVGG:	Intravenous γ -globulin
PBMCs:	Peripheral blood mononuclear cells

with IVGG, and skin symptoms improved in all patients. Only a single course of IVGG was given; that is, no maintenance therapy was required.

METHODS

Patients

Patient 1 is a 3-year-old boy who has had HIES since the age of 1 year. He had frequent scalp abscesses caused by *Staphylococcus aureus*, chronic otitis media, and severe eczema. He had been admitted to hospitals several times for treatment of pneumonia, including pyothorax caused by *S. aureus*. Topical steroids and

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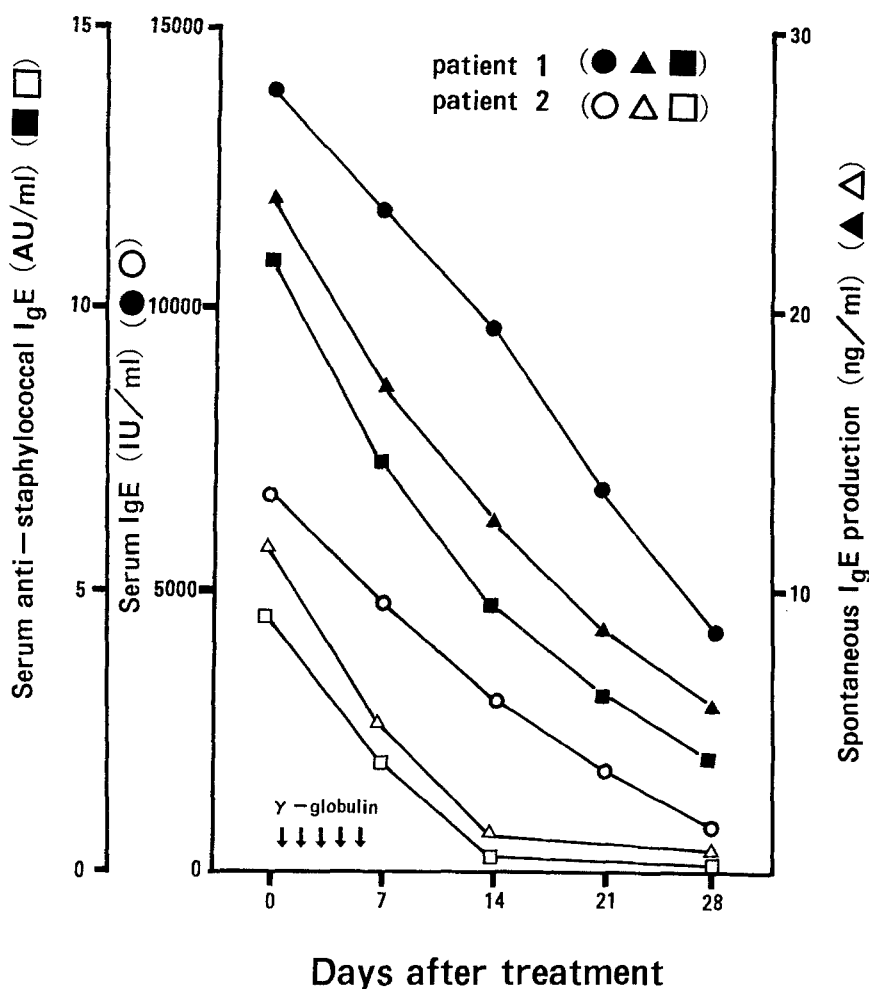


FIG. 1. Serum total IgE levels, serum anti-staphylococcal IgE levels, and in vitro spontaneous IgE production after high-dose IVGG treatment.

TABLE I. Effects of high-dose IVGG treatment of serum IgE levels and in vitro spontaneous IgE production in various patients

Patient No.	Diagnosis	Age (yr)	Serum IgE (IU/ml)*			IgE production (ng/ml)†		
			Day 0	Day 14	Day 28	Day 0	Day 14	Day 28
3	HIES	2.5	4120	2112	612	9.4	6.1	2.0
4	AD	3.2	3213	1051	314	3.4	1.2	0.5
5	AD	5.0	6238	4627	821	8.2	5.1	1.2
6	KD	1.6	56	42	58	<0.2	<0.2	<0.2
7	KD	2.0	31	25	28	<0.2	<0.2	<0.2
8	ITP	6.5	121	135	109	<0.2	<0.2	<0.2
9	ITP	2.4	103	112	101	<0.2	<0.2	<0.2

AD, Atopic dermatitis; KD, Kawasaki disease.

*Mean serum IgE (IU/L) after day 0 (before treatment) and after 14 and 28 days of treatment.

†Mean spontaneous IgE production in vitro after day 0 (before treatment) and after 14 and 28 days of treatment.

antibiotics had been unhelpful in treating eczema. He also had Kawasaki disease and received IVGG (Venilon; Teijin, Ltd., Tokyo, Japan) at 400 mg/day for 5 days, after which his fever subsided. Eczema and skin infec-

tions also improved remarkably after 5 days of treatment and disappeared altogether after 28 days.

Patient 2 is a 2½-year-old girl who has had HIES since the age of 7 months. She had severe eczema, cold skin

TABLE II. Effects of IgG on immunoglobulin production in vitro

Patient No.	Diagnosis	IgE (ng/ml)		IgM (ng/ml)		IgA (ng/ml)	
		IgG–	IgG+	IgG–	IgG+	IgG–	IgG+
1	HIES and KD	24.2	3.8	230	223	82	71
2	HIES and KD	11.5	1.2	101	99	45	42
3	HIES	9.8	2.4	82	89	23	26
4	AD	3.6	0.5	103	112	32	29
5	AD	2.7	0.3	298	286	68	71
6	KD	<0.2	<0.2	112	109	51	48
7	KD	<0.2	<0.2	78	76	23	26
8	ITP	<0.2	<0.2	248	231	89	78
9	ITP	<0.2	<0.2	67	71	24	21
10	Normal PBMCs	<0.2	<0.2	157	161	67	71
11	Normal PBMCs	<0.2	<0.2	67	69	32	30
12	Normal PBMCs + IL-4	6.1	1.2	211	201	99	92
13	Normal PBMCs + IL-4	4.4	0.5	121	128	56	59
14	Normal B + IL-4/anti-CD40	8.3	2.1	58	49	22	31
15	Normal B + IL-4/anti-CD40	9.6	1.7	36	41	25	29

AD, Atopic dermatitis; KD, Kawasaki disease. PBMCs from various patients were cultured with medium, and PBMCs (10-13) or B cells (14 and 15) from normal donors were cultured with medium (10 and 11) or stimulated with IL-4 (800 U/ml) (12 and 13) or with IL-4 plus B anti-CD40 monoclonal antibody (0.1 μ g/ml) (14 and 15), and IgG (2 mg/ml) was added. After 14 days of culture, immunoglobulin production was determined. Results were the means from triplicate cultures.

abscesses, chronic sinusitis, and lung abscesses caused by *S. aureus*. Topical steroids and antibiotics and oral antiallergic medication were without effect in treating eczema. She received IVGG at 400 mg/day for 5 days for treatment of Kawasaki disease, after which her fever subsided. Eczema and skin infection were significantly improved after 5 days and disappeared after 21 days.

Several other patients were also treated with IVGG at 400 mg/kg/day for 5 days after informed consent was obtained (Table I). Only a single course of IVGG was given. Patient 3 is a 2½-year-old boy who has had HIES since the age of 1 year. He had severe eczema, cold skin abscesses, chronic bilateral otitis media, and frequent episodes of pneumonia caused by *S. aureus*. Patients 4 and 5 are girls who had atopic dermatitis with severe eczema. Topical steroids and oral antiallergic medication were unhelpful. After 5 days of treatment with IVGG, severe eczema in these patients (patients 3, 4, and 5) improved significantly and almost disappeared after 28 days. Patients 6 and 7 are boys who have Kawasaki disease, and patients 8 and 9 are girls who have idiopathic thrombocytopenic purpura (ITP). Patients 6, 7, 8, and 9 had no allergy or eczema, and their serum IgE levels were within the normal range (Table I).

Cell culture

Peripheral blood mononuclear cells (PBMCs) were obtained from patients on day 0 (before IVGG treatment) and after 7, 14, 21, and 28 days of IVGG treatment. PBMCs were also obtained from normal control subjects of the same age. PBMCs were cultured ($2 \times 10^5/0.2$ ml/well) with medium alone. PBMCs obtained on day 0 were also cultured in either the absence

or presence of human IgG (2 mg/ml). Alternatively, PBMCs and B cells from normal control subjects were cultured with interleukin (IL)-4 (800 U/ml) and IL-4 plus anti-CD40 monoclonal antibody (0.1 μ g/ml), respectively, as described above. Immunoglobulin production was measured by ELISA after 14 days of treatment.⁵ The specificity of the assay was confirmed, as reported previously.^{5,6} Levels of IgE as low as 0.2 ng/ml could be detected in the presence of 2 mg/ml IgG. Serum IgE, IgM, IgA, and anti-staphylococcal IgE antibody levels were measured by ELISA.^{6,7} Serum anti-staphylococcal IgE levels were expressed as arbitrary units (AU) per milliliter, where 1 AU/ml represents the amount present in a 1:10 dilution of the HIES pooled serum. In normal control subjects and in patients with atopic dermatitis, Kawasaki disease, or ITP, serum anti-staphylococcal IgE levels were less than 0.1 AU/ml.⁷

RESULTS

In patients 1 and 2, serum IgE levels, anti-staphylococcal IgE levels, and in vitro IgE production decreased gradually and returned to almost normal after 28 days of IVGG treatment (Fig. 1). In contrast, serum IgM or IgA levels or in vitro spontaneous IgG, IgM, or IgA production by PBMCs did not decrease in either patient (data not shown). No side effects were observed. After 6 months, both patients were free of coronary aneurysms, eczema, and staphylococcal infections; and no maintenance therapy was required.

IVGG treatment also decreased serum IgE levels and spontaneous IgE production in vitro in the

patient with HIES alone (patient 3) and in the patients with atopic dermatitis (Table I). IVGG also decreased serum anti-staphylococcal IgE levels from 5.2 AU/ml at baseline to 0.3 AU/ml after 28 days of treatment. In contrast, IVGG treatment did not decrease serum IgE levels in patients with Kawasaki disease or ITP (Table I). After IVGG treatment, eczema improved remarkably in patients with HIES or atopic dermatitis; fever subsided in patients with Kawasaki disease, and platelet count increased from 10 and $31 \times 10^9/L$ at baseline to 156 and $218 \times 10^9/L$ in patients with ITP (patients 8 and 9, respectively). Therefore the failure of serum IgE levels to decrease was not due to the differences in the effects of IVGG.

The effects of IgG on IgE production were also studied in vitro. As shown in Table II, addition of IgG decreased spontaneous IgE production in patients with HIES or atopic dermatitis without affecting spontaneous production of IgM or IgA. In contrast, no spontaneous IgE production was observed in patients with Kawasaki disease or ITP or in normal control subjects. In these cases the addition of IgG had no effect on production of IgE, IgM, or IgA. Then the effects of IgG on IL-4-induced IgE production were studied. IgG inhibited IgE production by normal PBMCs stimulated with IL-4 without affecting production of IgM or IgA. Moreover, IgG also selectively inhibited IgE production by normal B cells stimulated with IL-4 plus anti-CD40 monoclonal antibody (Table II).

DISCUSSION

I have demonstrated that high-dose IVGG treatment improved severe eczema and decreased IgE production both in vivo and in vitro in patients with HIES. IVGG also improved eczema and decreased IgE production in patients with atopic dermatitis, whereas it had no effect on serum IgE levels in

patients with Kawasaki disease or ITP. Subsequent study revealed that IgG selectively inhibited IgE production induced by IL-4. It is possible that enhanced IgE production in patients with HIES or atopic dermatitis may be due to in vivo activation of B cells by IL-4, as I and others have previously reported.^{5,6,8} IVGG may attenuate this activation. Detailed mechanisms of the selective inhibition of IgE production by IVGG are currently under investigation. High-dose IVGG may be a safe and effective treatment for HIES and atopic dermatitis. Moreover, the finding that IgG inhibits IL-4-induced IgE production in T cell-dependent and T cell-independent cultures may be useful for the study of IgE regulation.

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