

Short communication

Interferon-alpha treatment for severe atopic dermatitis

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Patients with both severe atopic dermatitis (AD) and chronic myeloid leukemia, chronic hepatitis B, or chronic hepatitis C were treated with interferon-alpha (IFN- α). IFN- α treatment improved AD. Moreover, there were also significant decreases in serum IgE and IgG4 levels and in *in vitro* spontaneous IgE and IgG4 production by patients' mononuclear cells.

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Atopic dermatitis (AD) is an inflammatory skin disease characterized by chronic pruritus and increased production of IgE *in vivo* and *in vitro*. In addition, we have previously reported that serum IgG4 and *in vitro* spontaneous IgG4 production by mononuclear cells were increased in AD (7). We and others have also reported that excessive production of interleukin-4 (IL-4) and/or defective production of interferon-gamma (IFN- γ) and IFN- α may play an etiologic role for AD (2, 8). Indeed, in children with AD, *in vivo* administration of IFN- γ improved eczema (2). In contrast, *in vivo* administration of IFN- α had no effect on AD in adults (9), although the addition of IFN- α to *in vitro* cultures decreased spontaneous production of IgE and IgG4 in patients with AD (8). On the other hand, *in vivo* administration of IFN- α was effective in the treatment of chronic myeloid leukemia (CML), chronic hepatitis B, and chronic hepatitis C (1, 3, 11). We treated children with both AD and CML, chronic hepatitis B, and chronic hepatitis C with IFN- α , and found that it improved AD remarkably. We also studied the effect of *in vivo* IFN- α administration on serum IgE and IgG4 levels, and *in vitro* spontaneous production of IgE and IgG4 in those patients with AD.

Material and methods

All patients had clinical features of severe AD by Hanfin & Rajika's grading (4) and by our skin scoring system (5), and were allergic to house-dust mite by scratch test and RAST. Moreover, all of the patients' parents had allergies, including allergic rhinitis, AD, or allergic conjunctivitis. The severity of AD was assessed by our scoring system, which assesses severity of inflammation, lichenification, and cracking on four areas of the body: face, trunk, arms, and legs. The maximum possible score is 24. Scores for itch were assessed as no itching (score 0), mild, only itching at times (score 1), moderate, frequent, annoying itching (score 2), and severe, constant, distressing itching (score 3). Scores for sleep were assessed as sound sleep, no disturbance (score 0), some difficulty in going to sleep, no disturbance during night (score 1), difficulty in going to sleep, disturbed once or twice during night (score 2), and great difficulty in going to sleep, disturbed many times during night (score 3) (5). For all the patients, treatment with steroid ointments, antihistamines, and antiallergic medication had failed. Patient characteristics are shown in Table 1. Patient 1 had persistent leuko-

Table 1. Effect of IFN- α on CML and chronic hepatitis

Patient (Age/sex) diseases	Treatment	Variables		
		Total leukocytes (/ μ l)	Metamyelocytes (/ μ l)	Eosinophils (/ μ l)
Patient 1 (9 years/F) CML	Baseline	23 600	5600	472
	4 weeks	13 900	1320	348
AD (8 years)*	8 weeks	5800	0	174
	22 weeks	5600	0	56
	1 year	5400	0	48
		GOT/GPT (IU/l)	HBe Ag/Ab/DNA-p	Eosinophils (/ μ l)
Patient 2 (13 years/M) Hepatitis B (CAH)	Baseline	136/125	+/-/+	819
	4 weeks	78/81	+/-/+	314
	8 weeks	31/34	+/-/+	125
AD (9 years)	22 weeks	23/21	-/+/-	83
	1 year	25/27	-/+/-	76
Patient 3 (10 years/F) Hepatitis B (CAH)	Baseline	95/122	+/-/+	1080
	4 weeks	62/57	+/-/+	821
	8 weeks	25/26	+/-/+	214
AD (7 years)	22 weeks	19/17	-/+/-	74
	1 year	24/21	-/+/-	56
		GOT/GPT (IU/l)	HCV-RNA/HCV Ab	Eosinophils (/ μ l)
Patient 4 (8 years/M) Hepatitis C (CAH)	Baseline	63/68	+/-	1498
	4 weeks	53/51	+/-	931
	8 weeks	34/29	+/-	484
AD (6 years)	22 weeks	27/23	-/+	78
	1 year	28/31	-/+	81
Patient 5 (11 years/F) Hepatitis C (CAH)	Baseline	127/178	+/-	1258
	4 weeks	109/98	+/-	821
	8 weeks	52/36	+/-	356
AD (10 years)	22 weeks	28/29	-/+	52
	1 year	27/24	-/+	61

DNA-p=HBV-DNA polymerase.

* In parenthesis, duration of AD is shown.

cytosis (24 600–14 800/ μ l) with 1–4% myelocytes. DNA blot analysis revealed rearrangement of *bcr* (by 3' end's probe) gene. The chromosomal analysis was 46, XX; thus, the patient was diagnosed as having Ph¹ (–) CML. She was treated with daily intramuscular administration of natural IFN- α (Sumiferon, Sumitomo Pharmaceuticals, Osaka, Japan) at a dose of 6×10^6 IU/day for 8 weeks, followed by administration of the same dose of IFN- α three times per week. Patients 2 and 3 had chronic hepatitis B associated with chronic active hepatitis (CAH) as diagnosed by liver biopsy. Both of the patients' mothers had HBe Ag. They were treated with daily intramuscular administration of natural IFN- α (Sumiferon) at a dose of 6×10^6 IU/day for 4

weeks followed by three times per week for 18 weeks. Patients 4 and 5 had chronic hepatitis C associated with CAH as diagnosed by liver biopsy. Patients 4 and 5 had a history of blood transfusions for operations for ventricular septal defect and fracture, respectively. They were treated with daily intramuscular administration of natural IFN- α (Sumiferon) at a dose of 3×10^6 IU/day for 4 weeks followed by three times per week for 18 weeks. During IFN- α treatment, no other drugs, including oral steroids, oral antihistamines, antiallergic medication, or steroid ointments, were given to the patients. The effect of IFN- α on AD was determined by comparison with before (baseline) and after 4, 8, and 22 weeks of treatment.

Serum IgE and IgG4 levels were determined by ELISA (5, 6). Mononuclear cells were separated from patients' peripheral blood by Ficoll-Hypaque, and they were cultured (2×10^5 cells/0.2 ml/well) in 96-well microplates with medium (RPMI-1640 supplemented with 10% FCS) alone for 7 days. Thereafter, spontaneous production of IgE and IgG4 was measured by ELISA (6). All results are reported as means. Statistical analysis was performed with two-tailed Student's *t*-test.

Results

As shown in Table 1, in patient 1, who had CML, IFN- α treatment decreased the numbers of total leukocytes, myelocytes, and eosinophils in her peripheral blood. After 8 weeks, no myelocytes were found, indicating effective treatment of the CML. After 1 years, she is still free of CML. Mild fever (37.2–37.8°C) and slight headache were observed on days 1–7 of IFN- α treatment as adverse effects, and they were easily managed by oral antipyretics (mefenamic acid). In patients 2 and 3, who had chronic hepatitis B, serum GOT/GPT levels decreased, and returned to normal levels after 22 weeks of IFN- α treatment. Moreover, in both patients, HBe Ag and HBV-DNA polymerase disappeared, while HBe Ab appeared. The numbers of eosinophils were also decreased by IFN- α treatment (Table 1). Slight headache was observed on days 1–4 of treatment in patient 2, while mild fever (37.1–37.7°C) was observed on days 1–5 of treatment in patient 3. Both of these adverse effects were easily managed by mefenamic acid. In patients 4 and 5, who had chronic hepatitis C, serum GOT/GPT levels decreased, and returned to normal levels after 22 weeks of IFN- α treatment. In both patients, HCV-RNA became undetectable, while HCV Ab appeared. The numbers of eosinophils were also decreased by IFN- α treatment (Table 1). Mild fever (37.2–37.9°C) and slight headache were observed on days 1–7 of treatment in patients 4 and 5, and they were easily managed by

mefenamic acid. All of these patients were free of hepatitis after 1 year without any medication.

As shown in Table 2, in all patients, after 4 weeks of IFN- α treatment, AD was significantly ($P < 0.01$) improved as demonstrated by a decrease in scores for skin, itch, and sleep. Each of these scores decreased further ($P < 0.01$) after 8 weeks of treatment compared with values after 4 weeks of treatment, and there was nearly complete resolution of AD after 22 weeks. In association with improvement of AD, there was significant decrease of serum IgE, but not serum IgG4, and *in vitro* spontaneous production of IgE and IgG4 at 4 weeks (Table 2). Serum IgE and *in vitro* spontaneous production of IgE and IgG4 were decreased further at 8 weeks compared with values at 4 weeks. Moreover, serum IgG4 was significantly decreased at 8 weeks of treatment compared to values at baseline. All of these values decreased further at 22 weeks, at which time these

values were almost normal compared with values for controls. In contrast, IFN- α treatment had no effect on serum and *in vitro* production of IgG1, IgG2, IgG3, IgM, IgA1, or IgA2 (data not shown). After 1 year, all of these patients were free of AD. Moreover, their serum IgE and IgG4 levels and *in vitro* production of IgE and IgG4 were not elevated (Table 2).

Discussion

We have demonstrated that IFN- α treatment for CML and chronic hepatitis also improved AD. In addition, IFN- α administration selectively decreased serum IgE and IgG4 levels and *in vitro* spontaneous production of IgE and IgG4. This is not surprising. We and others have reported that, in an *in vitro* culture system, the addition of IFN- α inhibited spontaneous production of IgE and IgG4 without affecting production of IgG1, IgG2, IgG3, IgM, or IgA (8, 10). Although serum IgG4 was not decreased at 4 weeks of treatment, this may be due to the difference in biologic half-life of IgE (2.3 days) compared with IgG4 (25 days). After 8 weeks, serum IgG4 levels were also decreased.

In contrast to our results, IFN- α treatment was ineffective for AD in adults (9). However, the difference of the IFN- α effect may be due to the doses used, since our patients received two- to fourfold dosages of the dosage of IFN- α used in that study. Alternatively, the difference of the effects may be due to the patients' age, as two adults (24 and 41 years old) were treated in that study (9) while children (8–13 years old) were treated in our study.

To our knowledge, this is the first report showing that *in vivo* administration of IFN- α improved AD and decreased serum IgE and IgG4 levels, as well as *in vitro* production of IgE and IgG4 in children. The exact mechanisms by which IFN- α improved AD and decreased *in vivo* and *in vitro* production of IgE and IgG4 remain to be elucidated. It is possible that there may be a strong placebo effect by injection of medication which could account for the clinical effects. However, this is unlikely for the following reasons. Patients 2 and 4 were previously treated by subcutaneous injection of house dust for 3 months as hyposensitization because they had asthma at that time. But hyposensitization neither improved AD or asthma nor decreased *in vivo* or *in vitro* production of IgE and IgG4, and the patients discontinued this treatment.

We and others have reported that in *in vitro* cultures IFN- α inhibited IgE and IgG4 production by mononuclear cells from patients with AD (6, 8, 10). We also found that 7 days' incubation was required to inhibit production of IgE ($69 \pm 13\%$ inhibition, $n = 4$) and IgG4 ($65 \pm 17\%$ inhibition, $n = 4$) by low

Table 2. Effect of IFN- α on atopic dermatitis and Ig production

Patients	Scores			Serum		Ig production <i>in vivo</i>	
	Skin	Itch	Sleep	IgE (IU/ml)	IgG4 (mg/dl)	IgE (ng/ml)	IgG4 (ng/ml)
Patient 1 (CML)							
Baseline	18	3	3	1512	81	5.8	30.9
4 weeks	10*	2#	2#	735*	71	2.7*	18.8*
8 weeks	4*	1*	0**	258*	35*	0.5*	2.1*
22 weeks	1*	0**	0**	121*	19*	<0.2**	<0.3**
1 year	1*	0**	0**	118*	18*	<0.2**	<0.3**
Patient 2 (hepatitis B)							
Baseline	19	3	3	2413	136	13.5	45.7
4 weeks	12*	2#	2#	1331*	126	9.3*	26.9*
8 weeks	2*	0**	0**	218*	78*	0.9*	2.6*
22 weeks	0**	0**	0**	103*	29*	0.4*	0.3*
1 year	0**	0**	0**	106*	30*	0.6*	0.5*
Patient 3 (hepatitis B)							
Baseline	17	3	3	3216	177	8.2	36.1
4 weeks	13*	2#	2#	2529*	191	3.1*	20.4*
8 weeks	3*	1*	0**	435*	95*	0.4*	7.2*
22 weeks	2*	1*	0**	213*	31*	<0.3**	1.4*
1 year	2*	1*	0**	234*	27*	<0.3**	0.8**
Patient 4 (hepatitis C)							
Baseline	18	3	3	3892	159	10.2	45.7
4 weeks	9*	2#	1*	2790*	142	5.4*	21.5*
8 weeks	2*	0**	0**	186*	82*	2.0*	4.3*
12 weeks	1*	0**	0**	78*	30*	<0.2**	<0.3**
1 year	1*	0**	0**	82*	25*	<0.2**	<0.3**
Patient 5 (hepatitis C)							
Baseline	19	3	3	4595	127	12.5	51.2
4 weeks	10*	2#	2#	2812*	109	7.2*	23.7*
8 weeks	3*	1*	0**	326*	62*	1.1*	9.2*
22 weeks	1*	0**	0**	121*	28*	0.5*	1.4*
1 year	0**	0**	0**	89*	21*	<0.2**	<0.3**
Controls	0	0	0	24–157	12–22	<0.2	<0.3

Controls: age-matched healthy children ($n = 10$). # $P < 0.05$; * $P < 0.01$; ** $P < 0.001$ compared to baseline (before treatment).

dose of IFN- α (250 U/ml) in *in vitro* cultures. In contrast, only 1-day incubation was necessary with a high dose of IFN- α (1500 U/ml) to inhibit production of IgE ($72 \pm 12\%$ inhibition, $n = 4$) and IgG4 ($75 \pm 10\%$ inhibition, $n = 4$). It is possible that *in vivo* administration of a high dose of IFN- α abrogated spontaneous IgE and IgG4 production. This possibility is currently under investigation in our laboratory. IFN- α can be considered to be safe and effective treatment for severe childhood AD. However, large-scale, placebo-controlled studies are needed.

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