

Response of six patients with idiopathic hypereosinophilic syndrome to interferon alfa*

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Effective long-term management of the hypereosinophilic syndrome (HES) has remained elusive. Hardy and Anderson¹ initially recognized that HES was likely part of a continuum with other eosinophilic disorders. Patients with HES who have favorable prognoses may require no therapy,^{2, 3} whereas development of significant eosinopenia after an oral prednisone challenge is a sign of anticipated favorable therapeutic response to glucocorticoids alone.⁴ Unfortunately a "good" response to prednisone alone was achieved in less than 40% of patients with HES in a National Institutes of Health series. Patients with unfavorable prognostic signs such as high leukocyte counts, overt congestive heart failure, nervous system involvement, or splenomegaly^{3, 4} generally have required additional therapy with cytotoxic agents. Use of cytotoxic agents, however, is often associated with unacceptable side effects. Because of this, and because for many patients the sequelae of HES may develop over an extended period of time, there has been continued interest in identifying more effective agents that are better tolerated to treat this disorder. The potential benefit of the biologic response modifier interferon alfa (IFN- α) to patients with HES was suggested by the initial reports of Zielinski and Lawrence,⁵ Murphy et al.,⁶ and Busch et al.⁷ These authors found that IFN- α was effective for HES patients unresponsive to therapy with gluco-

Abbreviations used

HES: Hypereosinophilic syndrome
IFN- α : Interferon α
MBP: Eosinophil major basic protein
MRI: Magnetic resonance imaging
WBC: White blood cell

corticoids and hydroxyurea. Here we report our experience with IFN- α in six patients with HES, five of whom were intolerant of or unresponsive to conventional therapy.⁸

METHODS

Men and nonpregnant women 18 years of age and older meeting the criteria for HES^{4, 9, 10} were candidates for inclusion in this phase I study. This study was approved by the institutional review board of the Mayo Clinic. After giving informed consent, patients were carefully screened to exclude secondary causes of eosinophilia. This entailed a general medical history and examination, a bone marrow biopsy (if not previously done), and a thorough review of previous laboratory reports, x-ray films, clinical studies, and records of prior or current therapy.

IFN- α was administered daily as a single subcutaneous injection. The initial dosage of IFN- α ranged from 1.0 to 6.25×10^6 U/day (MU/day) and was individualized for each patient, depending on clinical status, tolerance, and our clinical judgment. As the eosinophil count decreased, concurrent medications were tapered and, if possible, discontinued. Peripheral blood counts including hemoglobin, platelet count, leukocyte count, and white blood cell (WBC) differential were followed daily during initial dose escalation and every 3 to 4 weeks thereafter. The goal was to reduce the total eosinophil count by 90% or to less than 1000 cells/mm³. Each patient received IFN- α for at least 9 months (Fig. 1). A bone marrow biopsy was repeated after each patient received IFN- α for a minimum of 9 months. Serum levels of eosinophil major basic protein (MBP) were determined in each patient with a specific double-antibody radioimmunoassay.¹¹

CASE REPORTS

Patient 1

A 42-year-old white man with a 2-year history of HES, had echocardiographic evidence of cardiac in-

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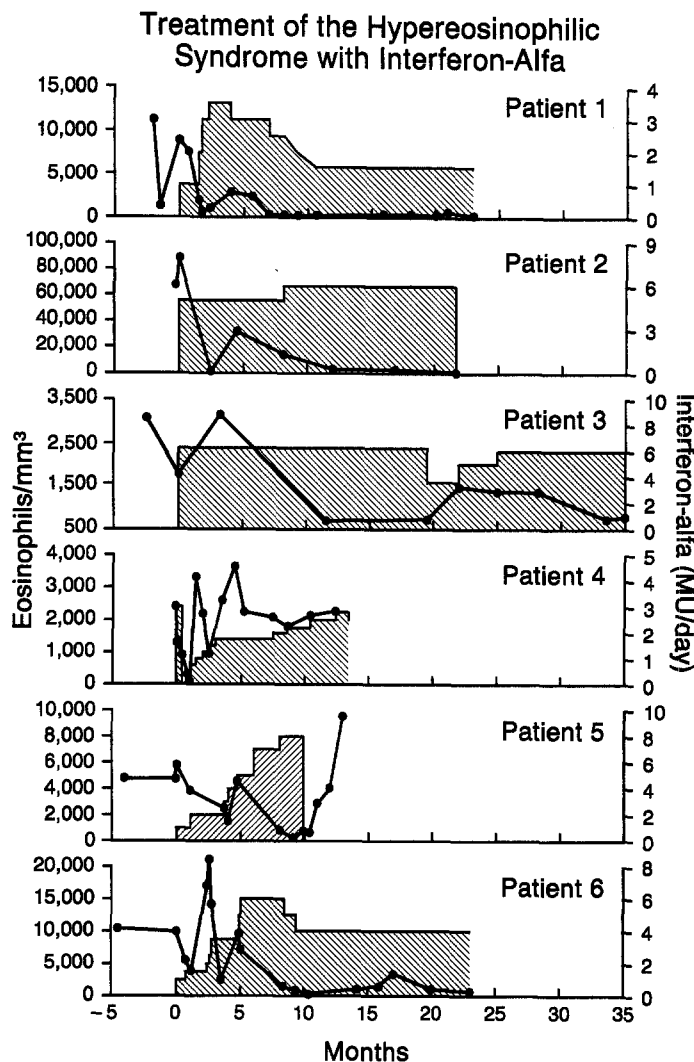


FIG. 1. Summary of blood eosinophil levels and interferon- α dosages for all six patients. Time 0 is normalized to the beginning of interferon- α treatment for each patient. *Solid line* shows eosinophils/mm³; *hatched area* shows interferon- α (MU/day) dosages, and *vertical line* at right of hatched area shows end of treatment (death in patient 2). (Reproduced with permission from Butterfield JH, Gleich GJ. *Ann Intern Med* 1994;121:648-53.)

involvement, cognitive dysfunction, visual loss, and probable central nervous system demyelination (by magnetic resonance imaging (MRI)). He had had no prior response to or had been intolerant of prednisone, hydroxyurea, etoposide, or a combination of cyclosporine and prednisone. When he came to us he had weakness and visual blurring associated temporally with high eosinophil counts. His medications were prednisone, 20 mg/day, and one aspirin daily. Physical examination was remarkable for a 1-2/6 systolic murmur, auscultated at the lower left sternal border and radiating to the cardiac apex, and hypertension of 160 to 170/100 to 110 mm Hg.

Bone marrow examination revealed approximately 30% eosinophilia. Echocardiogram revealed an additional tissue layer laterally and inferiorly from the tip of the posterior mitral leaflet to the apex, metallic brightness of the anterior mitral leaflet, and mitral regurgitation. Electrocardiogram revealed left ventricular hypertrophy with QRS widening. Response to methacholine inhalation challenge was positive. The leukocyte count was 17,500 cells/mm³ with 52% eosinophils, 25.5% segmented neutrophils, 1.5% bands, 2% basophils, and 16.5% lymphocytes. Hemoglobin level was 13.5 mg/dl, and the platelet count was 133,000 cells/mm³. Serum IgE levels and vitamin B₁₂ were also normal.

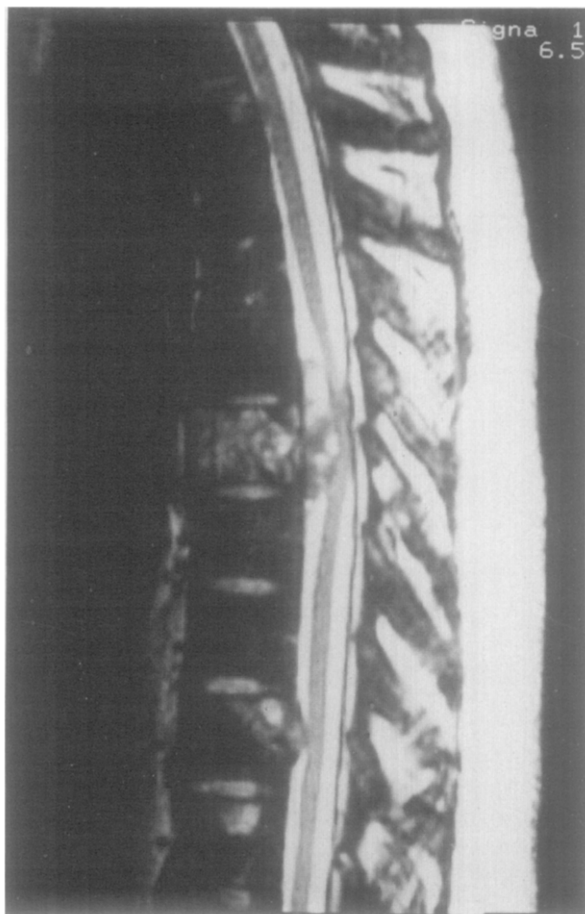


FIG. 2. Patient 2. MRI scan of spine shows diffusely abnormal marrow signal within all imaged vertebrae, consistent with diffuse marrow replacement. Abnormal T-2 signal is throughout T-7 vertebral body, with large epidural soft tissue mass centrally and to right of midline, which effaces the thecal sac and compresses the thoracic cord. Less extensive area of epidural disease is at T-10 without significant central canal narrowing.

The patient started IFN- α , 1 MU/day subcutaneously, and the dosage was increased as tolerated. After 14 weeks the dosage of IFN- α reached 3.5 MU/day, the total WBC count and percentage of eosinophil decreased to 5800 cells/mm³ and 10%, respectively; however, because of thrombocytopenia (63,000 cells/mm³), the dosage of IFN- α was subsequently decreased. At an IFN- α dosage of 1.5 to 2.0 MU/day, his total WBC stabilized at 3700 cells/mm³ with 9% eosinophils. He discontinued prednisone. Since then his clinical course has been marked by paroxysmal cough and dyspnea that is unresponsive to glucocorticoids, pansinusitis demonstrated by computed tomographic scan, and recurrent abdominal discomfort, vomiting, and diarrhea.

He has fixed visual and neurologic deficits, particularly of the fine motor movements, which have not progressed since he started IFN- α .

Patient 2

A 23-year-old white man, had chest and abdominal pain with gastric erosions necessitating treatment with a H₂-receptor antagonist and transfusion of 4 U of packed red blood cells. Physical examination revealed splenomegaly, and the echocardiogram showed an immobile posterior leaflet of the mitral valve and low cardiac ejection fraction. The serum vitamin B₁₂ was greater than 2000 ng/L (normal, 190 to 900 ng/L). Peripheral blood (leukocyte count, 31,300 cells/mm³, 68% eosinophils) and bone marrow eosinophilia (40% eosinophils) were present. Cytogenetic studies showed no apparent abnormal clone on this or numerous subsequent bone marrow aspirates.

Initial therapy with varying dosages of prednisone and hydroxyurea was ineffective. Splenectomy was performed to relieve thrombocytopenia. The patient was hospitalized for progressive leukocytosis and eosinophilia, with a WBC count of 216,000 cells/mm³ with 41% eosinophils. At this time he was given intravenous methylprednisolone, 2 gm/day for 4 days; IFN- α , 5 MU/day subcutaneously; vincristine, 2 mg/wk intravenously; therapeutic leukapheresis; platelet transfusions; and packed erythrocyte transfusions. He remained platelet and transfusion dependent for 3 months. Subsequently he required IFN- α , 5 to 6 MU/day 5 days per week, and aspirin, one tablet daily; prednisone, 10 to 20 mg every other day, was tapered and discontinued. Of interest, his wife became pregnant while the patient was taking IFN- α and gave birth to a healthy baby boy. During the subsequent 15 months of treatment with IFN- α , his total eosinophil count slowly decreased to 2800/mm³. The patient suddenly had midthoracic myelopathic symptoms. MRI scan revealed spinal cord compression at T-7, T-10 and L-3 by extradural masses (Fig. 2). Open biopsy showed that the masses were granulocyte sarcomas (chloromas) and radiation therapy was administered. After radiation therapy the dosage of IFN- α was increased to 6.5 MU/day for 5 days a week. He continued to have joint and muscle pain in the lower extremities. An area of hypesthesia developed in the right cheek. Six months later he had documented recurrence of chloromas at several spinal cord levels and intracranially. His total WBC count decreased to 6600 cells/mm³ with 12% eosinophils. A second course of radiation therapy was begun; however, the patient became septic and died.

Patient 3

A 32-year-old white man had chronic fatigue, dysphonia, episcleritis, fever, prostration, and coryza several

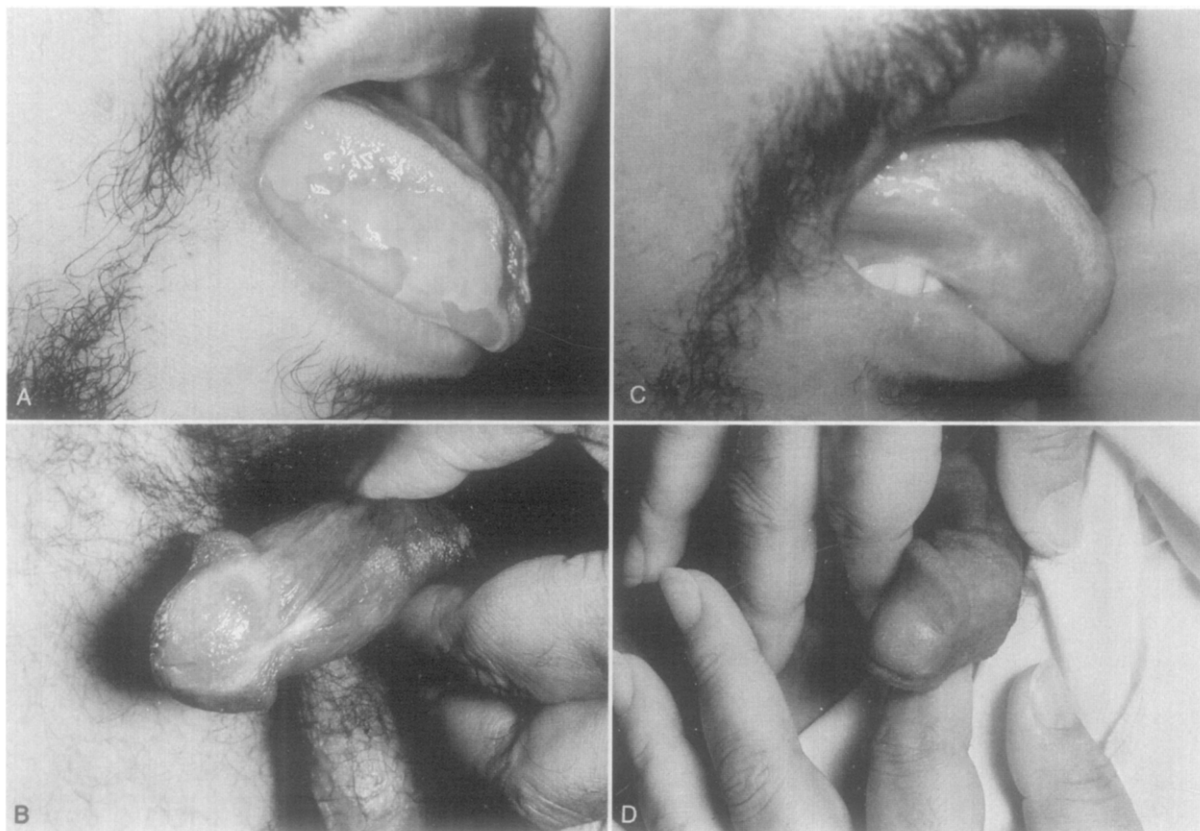


FIG. 3. Patient 4. Tongue lesions (A) and penile lesion (B) before IFN- α therapy. Sharply margined ulcers are present, which were painful and unresponsive to therapy with prednisone and hydroxyurea. During therapy with IFN- α , 1.5 to 2.5 MU/day, complete healing of tongue (C) and penis (D) is evident. (Reproduced with permission from Butterfield JH, Gleich GJ. *Ann Intern Med* 1994;121:648-53.)

months after a flulike illness. Early on, waxing and waning of mouth ulcers, a penile ulcer, and a fine erythematous rash on the thighs subsequently developed. Furuncles of the legs and arms, which grew *Staphylococcus aureus*, subsequently developed. His skin lesions were partially responsive to prednisone and colchicine. Physical examination revealed splenomegaly; no cardiac findings were evident. The glans penis was occupied by a yellow dried exudate from a chronic ulceration. Bone marrow biopsy showed 60% eosinophils; peripheral blood eosinophil count was 6000 to 12,000 cells/mm³. Treatment with IFN- α , 6.25 MU/day, improved his penile and mucosal ulcers. These resolved after 8 weeks and have not recurred, fatigue has improved, and he has been able to return to work while he has continued a stable dose of IFN- α . Since beginning IFN- α treatment he has had three episodes of cellulitis involving the left groin with associated high fever and adenopathy. These responded to intravenous cefazolin. His eosinophil count has averaged less than 1000 cells/mm³. Repeat

bone marrow biopsy after 9 months of treatment with IFN- α showed 10% eosinophils.

Patient 4

A 35-year-old black man had multiple aphthous-type oral ulcers and fevers. Biopsy specimens revealed a nonspecific inflammatory reaction. His WBC count was 8800 cells/mm³ with 30% eosinophils. Initially he was treated with acyclovir and subsequently with high-dose prednisone. Erosive duodenitis and esophagitis with ulcerations and a sedimentation rate of 38 mm/hr (normal, up to 22 mm/hr) subsequently developed. Treatment with hydroxyurea was begun, the oral ulcers partially responded, and he was able to taper the prednisone dosage; however, his oral ulcers returned. He was subsequently admitted to the hospital on two occasions for fever, mucositis, and a penile ulcer. Because of this, hydroxyurea and prednisone were again given. Subsequently, he had weight loss, a worsening penile ulcer, fever, chills, night sweats, right medial

TABLE I. Echocardiographic findings

Patient No.	Findings
1	Increased left ventricular wall thickness consistent with mild concentric left ventricular hypertrophy. Left ventricular cavity size increased. Hyperdynamic systolic function with EF of 69%. Additional tissue layer in lateral and inferior distribution extending from tip of posterior leaflet to apex (presumed to be product of HES but atypical in its distribution), causing decreased mobility of posterior leaflet. Echodense and reflective mitral valve suggests endocardial change. Mild to moderate mitral regurgitation.
2	Left ventricle enlargement, with low-normal systolic function (EF, 53%). Immobile posterior leaflet of mitral valve with moderate to severe mitral regurgitation. During IFN- α treatment, normal left ventricular systolic function with EF of 62%. Echodense endocardial layer of inferolateral wall segments. Immobile posterior leaflet of mitral valve. Mild mitral regurgitation. No apical thrombus.
3	Normal left ventricular cavity size with hyperdynamic systolic function with EF of 68%. During IFN- α treatment, normal left ventricular size and systolic function with EF of 64%.
4	Trivial mitral and aortic regurgitation; normal left ventricular cavity size and systolic function with EF of 65%.
5	Mitral leaflet somewhat thickened at base as opposed to tip of leaflet. No limitation in mobility.
6	Tricuspid valve location slightly displaced toward right ventricular apex suggesting Ebstein's anomaly, 3+ tricuspid regurgitation. Coarse systolic fluttering of pulmonic valve, 1+ pulmonic insufficiency, left atrial enlargement, marked right atrial enlargement, left ventricle normal

EF, Ejection function.

TABLE II. Changes in serum eosinophil MBP levels during therapy with IFN- α

Patient No.	MBP level (ng/ml)*	
	Before IFN- α	During IFN- α †
1	9020	3174
2	25,687	10,320
3	5173	4780
4	3466	3958
5	20,971	4392
6	13,088	2548

*Serum MBP levels: before IFN- α , mean $\pm$ SD, 12,900 $\pm$ 8859 ng/ml; during IFN- α , 4862 $\pm$ 2794 ng/ml; normal from blood bank control, 538 $\pm$ 144 ng/ml. By paired *t* test MBP levels before IFN- α are different from MBP levels during IFN- α at *p* < 0.05.

†Minimum of 9 month of therapy.

thigh and axillary abscesses, and oral mucositis despite therapy with prednisone and hydroxyurea. His echocardiogram was normal, and results of an HIV serologic test were negative.

He was treated with IFN- α , 3 MU/day, to control his oral ulcers; however, this dosage worsened ulcer pain and mucositis and interfered with oral intake and ability to handle secretions. He was hospitalized, hy-

droxyurea was discontinued, prednisone was increased to 50 mg twice daily, and IFN- α was discontinued for 3 days. Esophagogastroduodenoscopy revealed a granular and erythematous esophagus with no frank ulcers. Nasal mucosal biopsy revealed no evidence of vasculitis. IFN- α was restarted at 0.5 MU/day. This dosage was increased by 0.25 MU/day every 2 weeks as tolerated, and prednisone was tapered and eventually discontinued. With this protocol the penile lesions cleared and oral lesions slowly resolved after 20 weeks. The patient's most recent dosage of IFN- α was 2.5 MU/day, and he has remained free of mucosal and penile ulcers. The eosinophil count has fluctuated since he discontinued prednisone and hydroxyurea, but it has generally remained less than 2500 cells/mm³. Fig. 3, *A* and *B*, show the appearance of oral and penile ulcers before treatment with IFN- α . Fig. 3, *C* and *D*, show healing of the tongue and penis after treatment with IFN- α .

Patient 5

A 41-year-old white man had memory loss, dizziness, and chest pains. His WBC count was 33,000 cells/mm³ with 50% eosinophils. His initial treatment with prednisone was of no benefit, and he started hydroxyurea, 500 mg twice daily. He required transfusions on two occasions for anemia. His echocardiogram was normal. When he was first seen at our institution, examination showed a 1/6 systolic murmur at the lower left sternal

TABLE III. Bone marrow and blood responses to IFN- α

Patient No.	Bone marrow cytology		Peripheral blood eosinophilia				
	Before IFN- α therapy	During IFN- α therapy	Before IFN- α		During IFN- α *		IFN- α (MU/day)
			WBC/mm ³	Eosinophils (%)	WBC/mm ³	Eosinophils (%)	
1	30% eosinophils	6% eosinophils	17,500	52	3200	7.0	1.5-2.0
2	40% eosinophils	10% eosinophils	216,000	41	6600	12	6.5 (5/7 days)
3	50%-60% eosinophils	10% eosinophils	8200	28	4330	22	6.0
4	"Significant" increased number of eosinophils (no % available)	25% eosinophils	8800	30	5700	40	2.5
5	25% eosinophils	25% eosinophils	33,000	50	3300	24	8.0
6	60% eosinophils, 100% cellularity	50% eosinophils, 70% cellularity	19,600	75	3200	30	6.0

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*Minimum of 9 months of therapy.

border and splenomegaly. The WBC count was 12,800 cells/mm³ with 44% eosinophils, 31.5% segmented neutrophils, 10% bands, 9.5% lymphocytes, 4.5% monocytes, and 0.5% basophils. The serum vitamin B₁₂ level was greater than 2000 ng/L, but results of other routine studies, including serum IgE, were normal.

He was treated with IFN- α , 1 MU/day, and the dosage was increased as tolerated to 8 MU/day with a decrease in the total eosinophil count to 792/mm³. After 9 months this patient discontinued IFN- α , and during the subsequent 4 months his total WBC count and percentage of eosinophils rebounded and exceeded pretreatment levels. He continued to have episodic chest pains of undetermined cause and lost approximately 10 pounds, but was lost to follow-up in April 1994.

Patient 6

A 36-year-old white man had had eosinophilia since age 30 years (1986), when he first went to an emergency room for abdominal pain. Subsequently he had a 40-pound weight loss, night sweats, and malaise. A bone marrow evaluation in 1987 revealed 100% cellularity with 60% eosinophils. His echocardiogram was reportedly normal in 1987; however, his blood pressure was elevated and his creatinine value was 1.7 mg/dl. His treatment with high-dose prednisone caused fluid retention, weight gain, and hypertension. His medical care was irregular until June 1990, when he was seen for hypertension, hepatosplenomegaly, and renal failure. He underwent balloon angioplasty of a congenital right renal artery stenosis, and in November 1990 he started treatment with hydroxyurea for eosinophilia.

Because of blurred vision and right arm weakness, he began warfarin therapy in March 1991. In April 1991 he was treated with ciprofloxacin for salmonellosis. In August 1991 an echocardiogram was consistent with an atypical Ebstein's malformation causing pulmonary hypertension. In March 1992 diplopia and gait ataxia developed. Physical examination was remarkable for splenomegaly, 4 cm below the right costal margin. His serum vitamin B₁₂ and IgE levels were normal. In May 1992 he began taking IFN- α , 1 MU/day. At this time he was also taking prednisone, 20 mg/day; hydroxyurea, 1000 mg/day; aspirin and erythropoietin (Epo-gen), 4000 U three times weekly. While taking IFN- α , he has been able to discontinue prednisone, hydroxyurea, aspirin, and erythropoietin. His only side effect to date has been an episode of watery stools and minor nausea and vomiting. As the dosage of IFN- α was advanced to 6.0 MU/day and then tapered to 4 MU/day, a decrease in the percentage of eosinophils from as high as 88% to 14% to 23% has been observed despite cessation of cytotoxic and glucocorticoid medications.

RESULTS

Clinical characteristics and course of eosinophilia

Four patients (Nos. 1, 2, 5, and 6) had echocardiographic abnormalities (Table I) and evidence of neurologic involvement. Splenomegaly was detected in four patients (Nos. 2, 3, 5, and 6) and two patients (Nos. 3 and 4) had recurrent mucosal ulcers. After a minimum of 9 months of

treatment with IFN- α , five of six patients showed decreased serum levels of MBP (Table II). Peripheral eosinophil counts decreased to less than 1000 cells/mm³ in these same five patients (Table III); in four of five patients in whom bone marrow WBC differentials were done, the percentage of eosinophils decreased during treatment with IFN- α (Table III). Patient 2, who had the highest eosinophil levels at the start of therapy, required prolonged treatment with IFN- α to normalize his total eosinophil count. He initially required chemotherapy with IFN- α , pulse-dose methylprednisolone and vincristine to control his eosinophil count ($>80,000$ cells/mm³). One year later, while he was receiving IFN- α , 6 MU for 5 days a week, and prednisone, 20 mg every other day, his eosinophil count had fallen to 3000 cells/mm³. After an increase of IFN- α to 6.5 MU for 5 of 7 days, his final eosinophil counts were 1349 and 792 cells/mm³. Despite control of eosinophilia, recurrent granulocytic sarcomas involving the spinal cord and central nervous system developed. Both patients (Nos. 3 and 4) with mucosal ulcers had healing of lesions while they were receiving treatment with IFN- α . Patient 4 was able to discontinue prednisone and hydroxyurea while he was receiving IFN- α , but his eosinophil count remained relatively stable, as did the serum MBP value. In neither patient with mucosal ulcers have other stigmata of HES developed during IFN- α therapy.

Dosage and side effects

IFN- α was generally well tolerated and safe. The effective dosage of IFN- α varied widely among our patients. Two patients were started at high-dosage IFN- α : patient 2 had uncontrollable eosinophilia, anemia, and thrombocytopenia, and began IFN- α therapy at 5.0 MU/day, whereas patient 3 had incapacitating mucosal ulcers and started therapy at 6.25 MU/day. These higher initial dosages were well tolerated. Patient 3 has had three episodes of cellulitis, high fevers, and inguinal adenopathy while receiving a stable dosage of IFN- α , 6 MU/day; he has not altered the dosage of IFN- α . A second patient with mucosal ulcers (patient 4) had worsening of mucositis, fever, and chills when started with IFN- α at 3 MU/day; however, after dosage reduction to 0.5 MU/day and stepwise increments of 0.25 MU, he subsequently tolerated IFN- α , 2.5 MU/day, and his ulcers resolved. Thrombocytopenia developed in patient 1 at an IFN- α dosage of 3.5 MU/day,

necessitating dosage reduction. In contrast, patient 5 tolerated IFN- α , 8 MU/day; patient 6 tolerated IFN- α , 6 MU/day.

DISCUSSION

Patients with untreated HES have a poor prognosis.¹⁰ Approaches to the treatment of HES have remained fragmented, perhaps reflecting the heterogeneity of this disorder. Recent studies suggest that HES may be due to clonal proliferation of abnormal cells,¹² which have a prolonged half-life in the peripheral blood.¹³ Corticosteroids have remained a major therapeutic modality, especially in patients with HES who have elevated IgE levels^{9, 14} or angioedema.⁴ This group of cases appears to represent a subset of HES with a benign overall prognosis. Unresponsiveness to glucocorticoids in HES may potentially be due to loss of glucocorticoid binding sites on eosinophils.¹⁵ The addition of hydroxyurea, a DNA inhibitor,^{16, 17} has been valuable in some corticosteroid-resistant cases.¹⁸ Scattered reports of successful treatment of HES have included programs of prednisone, hydroxyurea, and vincristine¹⁹ (vincristine is also favored as an inducing agent² for cases of HES with leukocyte counts greater than 100,000 cells/mm³); vincristine and mercaptopurine,²⁰ prednisone and cyclosporine,²¹ etoposide,²² psoralen-ultraviolet A therapy,²³ and long-term plasmapheresis and leukapheresis.²⁴ The use of platelet-inhibiting agents and warfarin have been of unsubstantiated benefit for the prevention of thromboembolic complications of HES.²⁵ For patients with ventricular disease and valvular involvement (especially mitral valve disease), an aggressive surgical approach can be beneficial.^{26, 27} Bone marrow transplantation has proved unsuccessful in one patient previously unresponsive to therapy with corticosteroids and hydroxyurea.²⁸

Initially, three case reports⁵⁻⁷ suggested that IFN- α may prove successful in otherwise treatment-resistant HES. Additional reports of success with IFN- α have continued to appear.²⁹⁻³¹ IFN- α has previously been used successfully in the treatment of chronic myelogenous leukemia³² and of hairy cell leukemia.³³ Successful IFN- α treatment of malignant HES with or without associated T-cell lymphoma is associated with a dramatic decrease in elevated serum levels of soluble interleukin-2 receptor.³⁴ In vitro studies suggest that IFN- α inhibits colony formation by human bone marrow multipotential, erythroid, granu-

locyte-macrophage, and eosinophil progenitor cells.³⁵ IFN- α causes a dose-dependent inhibition of day-7 (late progenitor) granulocyte-macrophage colonies with little effect on day-14 colony growth.³⁶ These effects are due to a direct effect on the progenitor cells and are not mediated through accessory cells.^{35, 36} The present study suggests that the reduction in eosinophil numbers in HES by IFN- α is due to both a reduction in the total WBC count and in the percentage of eosinophils.

IFN- α has been beneficial in several respects. IFN- α proved useful as part of the induction protocol in patient 2, who had a rapidly deteriorating clinical condition, uncontrolled eosinophilia, and a WBC count of 216,000 cells/mm³. The poor prognosis of patients with HES having a WBC count greater than 100,000/mm³ has previously been recognized.⁹ Patient 2 also had improvement in cardiac function and decrease in mitral regurgitation (by echocardiogram) after control of eosinophilia with IFN- α . However, in the same patient, IFN- α did not prevent development of granulocytic sarcomas and a midthoracic myelopathy from spinal cord compression. Two patients with recurrent mucosal ulcers had healing of these previously intractable lesions after institution of IFN- α . In our experience these lesions have generally been refractory to therapy, interfere with adequate hygiene and nutrition, and indicate a subset of HES patients having a poor prognosis with death caused by vascular events or infection.³⁷ In neither of the two patients with mucosal ulcers has vascular disease developed since treatment with IFN- α .

A clinical grading system for HES has been devised by Schooley et al.³ This has been used to predict which patients with HES require no specific antieosinophilic therapy and which patients require progressively more intensive therapy with glucocorticoid and/or cytotoxic medications. On the basis of the clinical cohorts of Schooley et al., our patients are included in those groups with incomplete responses to glucocorticoids and cytotoxic therapy, that is, the most severely affected patients. Four of our six patients had detectable splenomegaly, a predictor of a more aggressive clinical course.³ IFN- α has been of benefit in our patients, five of whom are still alive. Whether therapy with IFN- α in less severely ill HES patients could forestall or prevent disease progression is an important but unanswered question.

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