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Use of pegylated interferon in hypereosinophilic syndrome

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ABSTRACT

Scant information exists about pegylated interferons (PEG-IFNs) use for treating hypereosinophilic syndrome (HES). We describe 6 patients with HES—1 patient with a newly identified chromosomal abnormality—who received PEG-IFNs. PEG-IFN alpha-2b replaced interferon (IFN) alpha-2b for 4 patients and was initial treatment of 2 patients. PEG-IFN alpha-2a was substituted when PEG-IFN alpha-2b became unavailable. PEG-IFNs were well tolerated and controlled eosinophilia. The dose of PEG-IFNs often could be tapered and the interval between doses lengthened beyond 7 days. Adverse effects included dose-related increases in liver enzyme levels, hair loss, mild lymphopenia, and neutropenia. PEG-IFNs are effective treatment of HES.

1. Introduction

The first reports that the biologic response modifier interferon (IFN) alpha-2b could be a useful agent for the treatment of hypereosinophilic syndrome (HES) appeared more than 20 years ago [1,2]. Since then, evidence has appeared in the medical literature regarding the ability of IFN alpha to control hypereosinophilia that is resistant to prednisone [3–5], hydroxyurea [6,7], and the combination of prednisone and hydroxyurea [1–3,8,9], as well as various other agents singly and in combination [3,4,10–12]. The clinical spectrum of IFN alpha's effectiveness has been well documented. These findings include clinical and cytogenetic remission of HES in patients with diverse chromosomal abnormalities [6,13–15] and resolution or improvement of organ system dysfunction, such as hepatomegaly [1], splenomegaly [2,14,16], hepatosplenomegaly [3], congestive heart failure [3,6], pulmonary infiltrates [5], and dermatologic manifestations, including incapacitating mucosal ulcers [11,16] and pruritic papules, nodules, and plaques [5,17].

In vitro studies suggest that the action of IFN alpha in hypereosinophilic disorders is multifaceted. A functional receptor for IFN alpha is present on the eosinophils of patients with various eosinophilic disorders, although the percentage of receptor-positive eosinophils can range widely (from 20% to 86%) [18]. Hypereosinophilic patients receiving IFN alpha treatment have significant reductions in serum levels of eosinophil major basic protein [11], a clinical finding supported by in vitro studies in which preincubation of eosinophils with IFN alpha inhibited release of other secondary granule proteins, eosinophil-derived neurotoxin, and eosinophil cationic protein by eosinophils activated by immunoglobulin (Ig) A or IgE immune complexes [18]. IFN alpha also inhibits eosinophil colony growth by nonadherent, non-T bone marrow cells stimulated with either interleukin (IL)-5 or granulocyte-macrophage colony-stimulating factor [19]. Reduction of eosinophil numbers in this manner also serves to interrupt the autocrine loop through which the eosinophil's own production of IL-5 continuously increases terminal differentiation of eosinophil precursor cells [20]. In several in vitro systems, IFN alpha has been shown to inhibit production of eosinophil-active cytokines [21–23]. IFN also promotes development of T_H1 cells, 1 product of which (IFN gamma) has diverse inhibitory effects on eosinophil differentiation and migration [24,25], as well as promotion of apoptosis [26].

Pegylated interferon (PEG-IFN) is prepared by either chemical covalent conjugation of 1 molecule of branched methoxy polyethylene glycol (PEG) to lysine residues in the IFN molecule via urethane bonds (PEG-IFN alpha-2a) or covalent attachment of monomethoxy PEG to the secondary amine of the histidine-34 residue (PEG-IFN alpha-2b) [27]. In vitro PEG-IFN alpha-2a retains properties of IFN alpha, including receptor binding, signal transduction [28], and antiproliferative activity against human tumor cells [29]. The attachment of the 12,000-D monomethoxy PEG polymer to native IFN alpha-2b greatly increases serum half-life, enabling weekly administration [30]. PEG-IFN alpha-2b has been effective in

Abbreviations: CML, chronic myelogenous leukemia; HES, hypereosinophilic syndrome; IFN, interferon; IL, interleukin; Ig, immunoglobulin; MU, million units; PEG, polyethylene glycol; PEG-IFN, pegylated interferon.

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controlling disease in a significant proportion of BCR-ABL-negative myeloproliferative disorders [31].

For IFN alpha-2b, the effective dose for HES ranges from 0.5 to 3.0 million units (MU) every other day to 6.25 MU daily [32]. Dosing guidelines for PEG-IFN use in HES are not well established. Treatment of patients having chronic myelocytic leukemia (CML) and patients having solid tumors with PEG-IFN alpha-2b at a dose of 6 μg/kg per week gave a safety profile comparable to a nonpegylated IFN alpha-2b dose of 3–5 MU/m^2 per day [33]. For patients with hepatitis C, exposure to PEG-IFN at 0.25 μg/kg per week gave a similar exposure as non-PEG-IFN alpha-2b at a dose of 3 MU 3 times per week, based on observed area under the curve [33]. In another study of patients with hepatitis C, the incidence and severity of adverse events were similar among patients treated with PEG-IFN alpha-2b at 0.5 μg/kg per week and with non-PEG-IFN alpha-2b at 3 MU 3 times per week [34]. Treatment of 4 HES patients with PEG-IFN alpha-2b (exact dose not specified) (median dose, 1.5 μg/kg per week) resulted in 1 complete and 1 partial response [31]. Because the effectiveness of PEG-IFN in hypereosinophilic disorders has not been widely reported, we reviewed our experience with use of PEG-IFNs in 6 patients with HES.

2. Materials and methods

We evaluated 6 patients who met the current criteria for HES [35] who had received PEG-IFN in the course of therapy. After documenting an initial patient's successful response to PEG-IFN from 2004 to 2007 (patient 3 in the present series), we considered PEG-IFN to be of possible therapeutic benefit to our HES patients and we began to gradually introduce it into our practice for treating HES. The present report includes a retrospective review of our initial patient and 5 additional patients seen with HES (out of approximately 40 new HES patients) between 2007 and 2010 who received PEG-IFN treatment of HES for at least 1 year. The starting date of PEG-IFN therapy for each patient is given in Table 1, which provides specific details concerning patient laboratory findings. All patients continue to receive PEG-IFN. A brief clinical vignette for each patient is provided herein. This study was approved by the Mayo Clinic Institutional Review Board.

Patient 1 was a 46-year-old woman with hypereosinophilia (3550 cells/mm^3) that had gone unevaluated and untreated for more than 1 year. Ongoing medical issues included difficult-to-control asthma, bronchiectasis, and eosinophilic dermatitis. At our clinic, skin biopsy showed a superficial dermal, perivascular mixed inflammation with numerous eosinophils; however, further blood, urine, and stool studies confirmed a diagnosis of porphyria cutanea tarda. Her initial treatment of eosinophilia was prednisone (40 mg/day) and, subsequently, IFN alpha-2b (3 MU) 3 times per week and resulted in normalization of the eosinophil count. IFN alpha then was discontinued and treatment with PEG-IFN alpha-2b (50 μg/week) was started. Phlebotomies were begun for porphyria cutanea tarda 5 months after our evaluation. Seven months after starting PEG-IFN therapy, the patient received a diagnosis of Graves' disease and was given radioactive iodine therapy. After 17 months, the treatment was changed to PEG-IFN alpha-2a (90 μg/week) because of unavailability of the former medication. Although the patient continued to take prednisone intermittently for respiratory symptoms, she had marked improvement in the control of her respiratory symptoms and in her clinical pulmonary examination. Her eosinophilia was well controlled with the PEG-IFNs and her dermatitis resolved.

Patient 2 was a 68-year-old man with hypereosinophilia (30,960 cells/mm^3) and associated eosinophilic bronchitis. An abnormal chromosome 20 that had a rearrangement involving the p-arm and q-arm of chromosome 20 was found on 2 of 30 metaphases from the bone marrow biopsy specimen (46, XY, der (20) add (20) (p13) add (20) (q13.1)[2]/46, XY[28]). Although it is of uncertain significance, this arrangement was believed to be consistent with a neoplastic process. His initial therapy consisted of prednisone (20 mg 3 times daily). Treatment with IFN alpha (3 MU on 3–7 days per week), subsequently increased to 5 MU/day plus hydroxyurea (500 mg/day), allowed gradual tapering of prednisone therapy. After reduction of the IFN alpha dosage to 3 MU on 5 days per week, IFN alpha was replaced with PEG-IFN alpha-2b (64 μg/week) and hydroxyurea was continued. Subsequently, his dose of PEG-IFN ranged between 64 and 80 μg/week and the dose of hydroxyurea ranged from 500 mg on 3–7 days per week. PEG-IFN use was associated with modest elevation in the levels of aspartate aminotransferase and alanine aminotransferase, as well as mild neutropenia (Table 1). Eight months after starting PEG-IFN therapy, the patient had a myocardial infarction that was treated with percutaneous placement of a drug-eluting stent. Coronary artery atherosclerosis involving several vessels was found in the course of his cardiac evaluation. Treatment with PEG-IFN alpha-2b and hydroxyurea was continued, with control of eosinophilia. Bronchitis symptoms have been well controlled with use of fluticasone/salmeterol diskus inhaler. A repeated bone marrow examination has not been performed.

Patient 3 was a 65-year-old woman with a past history of chronic obstructive pulmonary disease that was treated intermittently with prednisone. Hypereosinophilia (7000–8000 cells/mm^3) was discovered in 2003 after episodes of aphasia, anxiety, and confusion. It was noted in hospital that treatment with intravenous hydrocortisone sodium succinate resulted in near-immediate improvement in the patient's aphasia. Initial treatment consisted of prednisone plus azathioprine and, subsequently, of prednisone alone, which rapidly normalized her total eosinophil count. Because reduction of prednisone dose to below 20 mg/day resulted in flare-ups of her neurologic symptoms, IFN alpha therapy was begun at a dose of 3 MU 3 times per week, and subsequently the patient was able to discontinue the prednisone treatment completely. IFN alpha treatment then was discontinued, and PEG-IFN alpha-2b treatment was instituted at a dose of 80 μg/week. During the next 3 years, the dose was reduced gradually to 30 μg and the interval between doses increased to 10 days, with continued control of her eosinophilia. A graphic summary of this patient's course is given in Fig. 1.

Patient 4 was a 26-year-old man with a history of asthma, multiple allergies, angioedema, and urticaria in whom hypereosinophilia (35,518 cells/mm^3) was discovered. Evaluation for secondary causes of eosinophilia was unrevealing, and his initial treatment consisted of repeated tapering courses of prednisone beginning at 60–100 mg/day. Cyclosporin (200–300 mg/day) was given to treat the angioedema and urticaria. PEG-IFN alpha-2b (80 μg/week) was added to his prednisone program and was increased briefly to 120 μg/week. Because of neutropenia, the dose of PEG-IFN was tapered subsequently to 50 μg every 9–12 days. Because of unavailability of PEG-IFN alpha-2b, the patient's treatment was transitioned to PEG-IFN alpha-2a (50 μg every 15 days). Prednisone therapy was discontinued. Eosinophilia has been well controlled, and his symptoms of asthma, urticaria, and angioedema completely resolved.

Patient 5 was a 57-year-old woman with hypereosinophilia (8700 cells/mm^3), asthma, and sinusitis, and a computed tomographic scan of the chest that revealed bilateral central bronchiectasis. She required multiple courses of systemic corticosteroids for control of eosinophilia and sinus symptoms. Treatment with PEG-IFN alpha-2b (50 μg/week) was begun, with return of the eosinophil count to normal, dramatic improvement in asthma and sinus symptoms, and the ability to taper prednisone therapy to 5 mg/day. The interval between doses of PEG-IFN was increased gradually to every 9 days because of hair loss, lymphocytopenia, and an increase in levels of liver function enzymes. Subsequently, her eosinophil count and clinical symptoms have continued to be under good control despite a further increase in the interval to every 12 days.

Patient 6 was a 51-year-old woman who presented with splenomegaly, fatigue, dyspnea, shortness of breath, low-grade fevers, a 30-pound weight loss, and anemia requiring several transfusions. Dehydration, severe odynophagia, and severe bilateral pain in the upper extremities developed. A positron emission tomographic scan showed diffuse, increased metabolic activity throughout the axial and proximal appendicular skeleton, with focal sites of fluorodeoxyglucose uptake in several skeletal areas, a diffusely enlarged spleen, and fluorodeoxyglucose-avid infiltrates in both lungs.

The patient's eosinophil count increased steadily during her evaluation, to a maximum of 38,900 cells/mm^3, despite prednisone therapy (100 mg/day). She had visual changes and proximal weakness and magnetic resonance imaging abnormalities of multiple subacute infarcts, consistent with a watershed stroke despite daily methylprednisolone sodium succinate treatment (1 g intravenously). She then was treated with prednisone (200 mg/day) and hydroxyurea (1 g/day). Despite a decrease in the total eosinophil count to 9700 cells/mm^3, pain developed in the left upper shoulder, chest, and back and she was found to have troponin levels of 0.76 ng/mL and 0.62 ng/mL (reference range <0.01 ng/mL) with no acute changes on electrocardiography. IFN alpha (5 MU on 5 days per week) was added to her scheduled treatments and prednisone therapy was tapered and discontinued. The IFN alpha dose was reduced to 5 MU and then to 3 MU for 3 days per week and hydroxyurea treatment was reduced and discontinued. Then, treatment with IFN alpha was discontinued and treatment with PEG-IFN alpha-2b (80 μg/week) was started. PEG-IFN use was associated with increased levels of liver function enzymes, which responded to gradual dose tapering. Although the dose of PEG-IFN gradually was tapered to 20 μg every 10 days, the eosinophil count continued to be at reference level and her clinical symptoms resolved. A graphic summary of this patient's clinical course is given in Fig. 2.

3. Results

Abnormal findings on bone marrow examination of these 6 patients included slight to moderate hypercellularity ($n = 5$); increased eosinophil numbers ($n = 6$), including left-shifted eosinophil maturation ($n = 3$); and reduced granulopoiesis ($n = 2$). In no case was there evidence of a chronic myeloproliferative disorder, increased numbers of blasts, plasma cells, or findings of lymphoma. Features of systemic mastocytosis were not present in any specimen.

Table 1 summarizes the clinical and laboratory findings for each patient. Tryptase was at reference level for 5 patients tested, all 6 patients tested negative for the CHIC2 deletion, and in the 2 patients

Table 1
Laboratory results of 6 patients with a diagnosis of hypereosinophilic syndrome.

Patient no.	Sex	Associated disorders and leading clinical findings	Medications used before PEG-IFN	PEG-IFN therapy started, mo/year	Highest eosinophil count, cells/mm^3 (ref. range, 50–500 cells/mm^3)	IL-5, pg/mL (ref. range, <7.8 pg/mL)	Serum B_{12}, ng/L (ref. range, 180–914 ng/L)	IgE, kU/L (mean, 13.2 kU/L) (ref. range, kU/L: +1SD 41.0, +2SD 127.0)	T-cell receptor gene rearrangement[a] (ref. range, neg)	Cytogenetics	Other findings	PEG-IFN complications
1	F	Asthma; bronchiectasis; eosinophilic dermatitis	PDN; IFN alpha	5/2008	3550	13.1	953	775	Neg (PCR)	46 XX	TEL-PDGFRB fusion neg	Graves' disease (possible)
2	M	Eosinophilic bronchitis	PDN; IFN alpha; HU	10/2007	30,960	58	909	1319	Neg (PCR)	46, XY, der (20) add (20) (p13) add (20) (q13.1)[2]/46, XY[28]	BCR-ABL fusion neg	Increased liver function enzymes[b,c] (ALT, 1.1; AST, 1.7); neutropenia
3	F	COPD; neurologic (aphasia, visual, tremor); anxiety; confusion	IFN alpha	8/2004	8000	<7.8	1030	51.7	Neg (PCR)	ND	BCR-ABL fusion neg	None
4	M	Asthma; urticaria; angioedema; food allergy; anaphylaxis	PDN; cyclosporin	10/2008	35,518	<7.8	49.5	654	Equivocal (PCR); neg (Southern)[d]	ND	BCR-ABL fusion neg	Neutropenia
5	F	Sinusitis; asthma; bronchiectasis	PDN	6/2010	8700	13.5[e]	1385	32.7	Neg (PCR)	46, XX	TEL-PDGFRB fusion neg	Hair loss; lymphopenia; increased liver function enzymes[b,c] (ALT, 4.0; AST, 2.9)
6	F	Oral ulcer; anemia; constitutional symptoms (weight loss, fevers); dehydration; watershed stroke; myalgias; splenomegaly	PDN; HU; methylprednisolone sodium succinate; IFN alpha	4/2010	38,900	<7.8	298	2.7	Neg (PCR)	46, XX	BCR-ABL fusion neg; kitD816V neg	Increased liver function enzymes[b,c] (alkaline phosphatase, 1.7; ALT, 3.6; AST, 2.5)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; HES, hypereosinophilic syndrome; HU, hydroxyurea; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; ND, not done; PCR, polymerase chain reaction; PDN, prednisone; PEG-IFN, pegylated interferon; ref., reference.

[a] The T-cell receptor gene rearrangement method is a PCR-based assay performed with primers that bind the gamma chain gene.

[b] Representative values.

[c] Fold change above normal.

[d] Southern blot assay is performed on extracted DNA using EcoR1 restriction enzyme digestion and 2 separate probes for the beta gene: one to the first and one to the second joining regions.

[e] Reference range, <3.5 pg/mL.

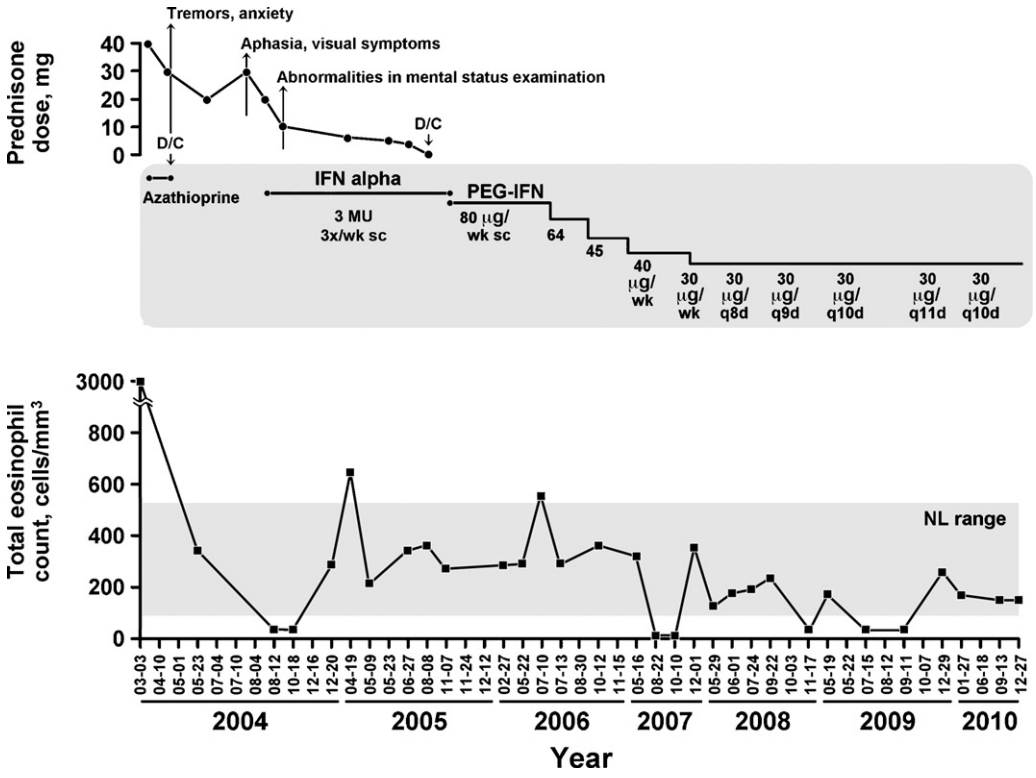

Fig. 1. Clinical response to therapy for patient 3. Tremors and anxiety occurred on 07-04-2004; aphasia and visual symptoms occurred on 07-10-2004; and abnormalities in mental status examination occurred on 08-12-2004. D/C indicates discontinued; IFN, interferon; MU, million units; NL, normal; PEG-IFN, pegylated interferon; sc, subcutaneous. (Portions presented in a poster at the annual meeting of the American Academy of Allergy, Asthma, and Immunology, San Diego, CA, February 23–27, 2007.)

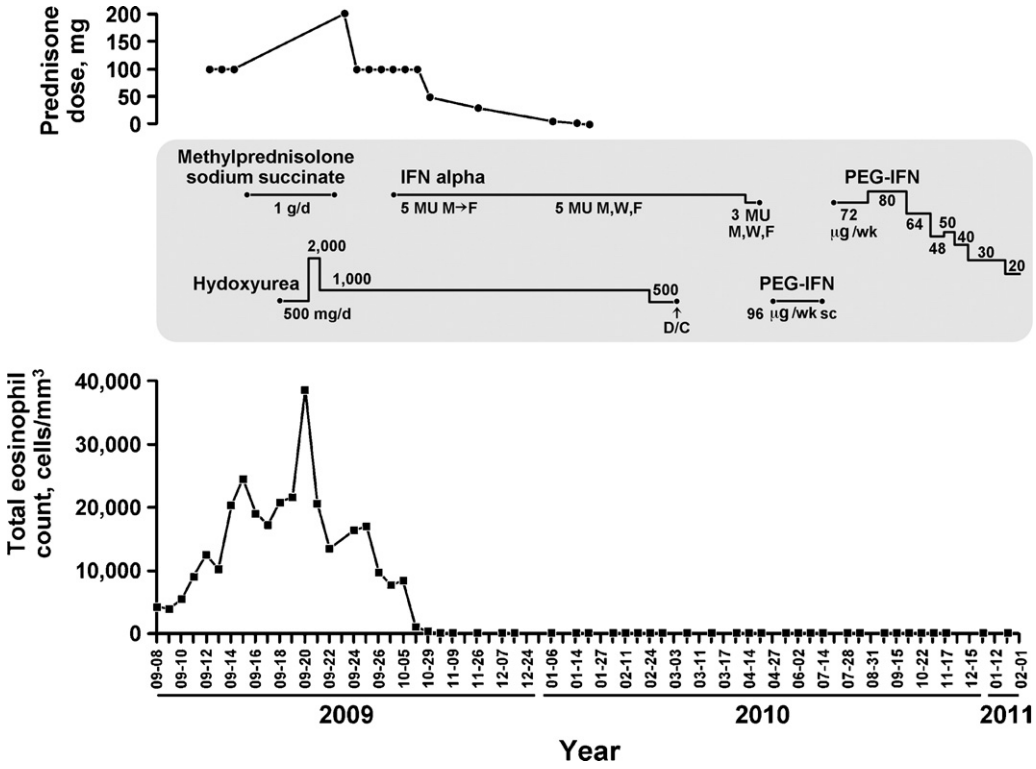

Fig. 2. Clinical response to therapy for patient 6. D/C indicates discontinued; F, Friday; IFN, interferon; M, Monday; MU, million units; PEG-IFN, pegylated interferon; sc, subcutaneous; W, Wednesday.

tested for the JAK2V617F mutation, the result was negative. Cytogenetics testing of bone marrow cells from patient 2 showed that 2 of 30 metaphases were abnormal, having a rearrangement involving the p-arm and q-arm of chromosome 20 (Table 1). Flow cytometry for detection of abnormal T-cell phenotypes was performed with the following antibodies: (1) CD3, CD10, CD16, CD19, CD45, and kappa and lambda surface immunoglobulin light chains (triage panel) and (2) CD2, CD3, CD4, CD5, CD7, CD8, and gamma/delta T-cell receptor (T-cell panel). Testing showed normal results for all patients.

Generally, the patients tolerated the PEG-IFN treatment well. As in our prior experience with IFN alpha, the PEG-IFN dose often could be tapered with unchanged efficacy. Additionally, for some patients the interval between doses could be extended to beyond the standard 7-day interval, with continued control of eosinophilia. In 4 of the 6 patients, PEG-IFN treatment was begun after an initial course of treatment for hypereosinophilia that included IFN alpha-2b. For 2 patients, PEG-IFN treatment was started as a corticosteroid-sparing agent, after an initial use of prednisone alone, to control eosinophilia. Adverse effects from PEG-IFN use occurred in 4 patients and responded to dose reduction; Graves' disease developed in a fifth patient 7 months after PEG-IFN treatment was started (Table 1).

4. Discussion and conclusions

The observations reported in the current series show that PEG-IFN alpha can be used to control eosinophilia in patients with HES. In the report of Jabbour et al. [31], 2 of 4 patients treated with PEG-IFN had complete or partial responses. Although the majority of reported series have used IFN alpha-2b to control eosinophilia, IFN alpha-2a, which differs from IFN alpha-2b by a single amino acid [36], also can induce complete hematologic and cytogenetic responses in HES [15]. We found that when PEG-IFN alpha-2a was substituted for PEG-IFN alpha-2b (because of unavailability of the latter medication), no change occurred in eosinophilia control. Furthermore, we often were able to taper the dose of PEG-IFN alpha. In several patients, the interval between doses of PEG-IFN could be increased beyond 7 days as well.

The safety and pharmacodynamic profiles of PEG-IFN and non-PEG-IFN alpha-2b, studied in patients with chronic hepatitis C, have been comparable [37]. Both PEG-IFN and non-PEG-IFN alpha-2b are absorbed rapidly, with maximal concentrations occurring approximately 8–12 h after administration. In contrast, PEG-IFN alpha-2b has a sustained maximal serum concentration lasting up to 72 h after administration while levels of non-PEG-IFN alpha-2b decline rapidly. The elimination half-life of PEG-IFN alpha-2b is 10-fold greater and the mean apparent clearance is one-tenth that of non-PEG-IFN alpha-2b [37].

The ease of weekly PEG-IFN administration and the reduced frequency of injections were welcomed by the patients, who previously had received multiple weekly injections of IFN alpha. Whether PEG-IFN was substituted for shorter-acting IFN or was used first, each patient was already receiving prednisone when given PEG-IFN. This fact, as well as the prolonged half-life of PEG-IFN, may explain in part the lack of dose-limiting symptoms witnessed in our patients. Our experience with PEG-IFN suggests that this agent can be used in the treatment of HES either (1) to replace IFN alpha after eosinophilia has been controlled (4 of our patients) or (2) as an add-on medication in prednisone-intolerant or resistant cases, although our clinical experience in this regard is more limited (2 patients). With no specific guidelines to follow for initial PEG-IFN dosing for HES, we based the initial PEG-IFN alpha-2b dose on the patient's mass [38]. This approach proved to be a reasonable initial-dose approach and, as outlined, with time the dose could be tapered. Adverse effects, including elevated levels of liver function enzymes, leukopenia, and neutropenia, responded to dose reduction during taper. Additional adverse effects included hair loss and, possibly, Graves' disease. Clinical features of HES that resolved during PEG-IFN therapy included asthma, bronchitis, neurologic symptoms (e.g., aphasia, anxiety, confusion, watershed stroke symptoms), angioedema, urticaria, sinusitis, myalgias, and constitutional symptoms (e.g., fever, weight loss).

Patient 2 was found to have an abnormal karyotype 46, XY, der (20) add (20) (p13) add (20) (q13.1)[2]/46, XY[28]. Although deletion of chromosome 20q has been reported in 2 cases of HES [39], we were unable to find another report of the rearrangement of the p-arm and q-arm of chromosome 20 found in 2 of 30 metaphases from this patient's bone marrow aspirate and biopsy. We cannot be certain that this chromosomal abnormality is "within" the eosinophils; however, 20q abnormalities are common in myeloid cancers [40]. This case therefore possibly represents a novel cytogenetic abnormality for HES. Of note, this patient required 80–120 μg of PEG-IFN alpha-2b, as well as hydroxyurea, to control eosinophilia, with no tapering of either medication or increased interval between doses possible to date.

In summary, PEG-IFN is a useful medication that can be substituted for shorter-acting IFN alpha to maintain eosinophil control in patients with HES who previously have received prednisone, hydroxyurea, IFN alpha, and other agents. In our experience, use of PEG-IFN as an initial medication added to prednisone alone was successful also, though the number of patients treated in this manner is limited. Higher doses of PEG-IFN alpha, along with hydroxyurea, were required for a patient with HES who had a newly identified cytogenetic abnormality. Our experience suggests that PEG-IFN can be useful in disorders of excessive eosinophil proliferation.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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References

[1] Murphy PT, Fennelly DF, Stuart M, O'Donnell JR. Alfa-interferon in a case of hypereosinophilic syndrome. Br J Haematol 1990;75(August (4)):619–20.
[2] Zielinski RM, Lawrence WD. Interferon-alpha for the hypereosinophilic syndrome. Ann Intern Med 1990;113(November (9)):716–8.
[3] Fruehauf S, Fiehn C, Haas R, Doehner H, Hunstein W. Sustained remission of idiopathic hypereosinophilic syndrome following alpha-interferon therapy. Acta Haematol 1993;89(2):91–3.
[4] Ceretelli S, Capochiani E, Petrini M. Interferon-alpha in the idiopathic hypereosinophilic syndrome: consideration of five cases. Ann Hematol 1998;77(October (4)):161–4.
[5] Yoon TY, Ahn GB, Chang SH. Complete remission of hypereosinophilic syndrome after interferon-alpha therapy: report of a case and literature review. J Dermatol 2000;27(February (2)):110–5.
[6] Yamada O, Kitahara K, Imamura K, Ozasa H, Okada M, Mizoguchi H. Clinical and cytogenetic remission induced by interferon-alpha in a patient with chronic eosinophilic leukemia associated with a unique t(3;9;5) translocation. Am J Hematol 1998;58(June (2)):137–41.

[7] Kobayashi M, Katayama T, Ochiai S, Yoshida M, Kaito K, Masuoka H, et al. Interferon-alpha therapy in the myeloproliferative variants of hypereosinophilic syndrome. Rinsho Ketsueki 1993;34(March (3)):367–72 [in Japanese].
[8] Bockenstedt PL, Santinga JT, Bolling SF. Alpha-interferon treatment for idiopathic hypereosinophilic syndrome. Am J Hematol 1994;45(March (3)):248–51.
[9] Baratta L, Afeltra A, Delfino M, De Castro S, Giorgino F, Rossi-Fanelli F. Favorable response to high-dose interferon-alpha in idiopathic hypereosinophilic syndrome with restrictive cardiomyopathy: case report and literature review. Angiology 2002;53(July–August (4)):465–70.
[10] Hansen PB, Johnsen HE, Hippe E. Hypereosinophilic syndrome treated with alpha-interferon and granulocyte colony-stimulating factor but complicated by nephrotoxicity. Am J Hematol 1993;43(May (1)):66–8.
[11] Butterfield JH, Gleich GJ. Interferon-alpha treatment of six patients with the idiopathic hypereosinophilic syndrome. Ann Intern Med 1994;121(November (9)):648–53.
[12] Busch FW, Schmidt H, Steinke B. Alpha-interferon for the hypereosinophilic syndrome. Ann Intern Med 1991;114(February (4)):338–9.
[13] Quiquandon I, Claisse JF, Capiod JC, Delobel J, Prin L. Alpha-interferon and hypereosinophilic syndrome with trisomy 8: karyotypic remission. Blood 1995;85(April (8)):2284–5.
[14] Luciano L, Catalano L, Sarrantonio C, Guerriero A, Califano C, Rotoli B. AlphaIFN-induced hematologic and cytogenetic remission in chronic eosinophilic leukemia with t(1;5). Haematologica 1999;84(July (7)):651–3.
[15] Schoffski P, Ganser A, Pascheberg U, Busche G, Gaede B, Hertenstein B. Complete haematological and cytogenetic response to interferon alpha-2a of a myeloproliferative disorder with eosinophilia associated with a unique t(4;7) aberration. Ann Hematol 2000;79(February (2)):95–8.
[16] Acaba L, Mangual A, Velez Garcia E. Excellent response to interferon therapy in a patient with hypereosinophilic syndrome and elevated serum immunoglobulin E levels. Bol Asoc Med P R 2000;92(April–August (4–8)):59–62.
[17] DeYampert NM, Beck LA. Eosinophilia and multiple erythematous indurated plaques: idiopathic hypereosinophilic syndrome (IHS). Arch Dermatol 1997;133(December (12)):1581–4.
[18] Aldebert D, Lamkhioued B, Desaint C, Gounni AS, Goldman M, Capron A, et al. Eosinophils express a functional receptor for interferon alpha: inhibitory role of interferon alpha on the release of mediators. Blood 1996;87(March (6)):2354–60.
[19] Kioke T, Nakamura Y, Enokihara H. Interferon-α inhibits interleukin-5 and granulocyte-macrophage colony formation from bone marrow progenitor cells. Dokkyo J Med Sci 1998;25:45–52.
[20] Desreumaux P, Janin A, Dubucquoi S, Copin MC, Torpier G, Capron A, et al. Synthesis of interleukin-5 by activated eosinophils in patients with eosinophilic heart diseases. Blood 1993;82(October (5)):1553–60.
[21] Krishnaswamy G, Smith JK, Srikanth S, Chi DS, Kalbfleisch JH, Huang SK. Lymphoblastoid interferon-alpha inhibits T cell proliferation and expression of eosinophil-activating cytokines. J Interferon Cytokine Res 1996;16(October (10)):819–27.
[22] Enokihara H, Nakamura Y, Nagashima S, Furusawa S, Shishido H. Regulation of interleukin-5 production by interleukin-4, interferon-alpha, transforming growth factor-beta and interleukin-6. Int Arch Allergy Immunol 1994;104(Suppl 1(1)):44–5.
[23] Krishnaswamy G, Hall K, Youngberg G, Hossler F, Johnson D, Block WA, et al. Regulation of eosinophil-active cytokine production from human cord blood-derived mast cells. J Interferon Cytokine Res 2002;22(March (3)): 379–88.
[24] Ochiai K, Iwamoto I, Takahashi H, Yoshida S, Tomioka H, Yoshida S. Effect of IL-4 and interferon-gamma (IFN-gamma) on IL-3- and IL-5-induced eosinophil differentiation from human cord blood mononuclear cells. Clin Exp Immunol 1995;99(January (1)):124–8.
[25] Nakajima T, Yamashita N, Matsui H, Suzuki N, Kaneoka H, Mizushima Y, et al. Induction of differentiation into monocyte/macrophage cell lineage of a human eosinophilic leukaemia cell line EoL-1 by simultaneous stimulation with tumour necrosis factor-alpha and interferon-gamma. Br J Haematol 1995;89(February (2)):258–65.
[26] Morita M, Lamkhioued B, Soussi Gounni A, Aldebert D, Delaporte E, Capron A, et al. Induction by interferons of human eosinophil apoptosis and regulation by interleukin-3, granulocyte/macrophage-colony stimulating factor and interleukin-5. Eur Cytokine Netw 1996;7(December (4)):725–32.
[27] Quintas-Cardama A, Kantarjian HM, Giles F, Verstovsek S. Pegylated interferon therapy for patients with Philadelphia chromosome-negative myeloproliferative disorders. Semin Thromb Hemost 2006;32(June (4 Pt 2)):409–16.
[28] Husa P, Slesinger P, Stroblova H, Svobodník A, Husova L. Efficacy of pegylated interferon alpha-2a and ribavirin treatment in chronic hepatitis C patients depends on various baseline parameters and early viral kinetics. Klin Mikrobiol Infekc Lek 2008;14(April (2)):67–73 [in Czech].
[29] Kiladjian JJ, Cassinat B, Chevret S, Turlure P, Cambier N, Roussel M, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood 2008;112(October (8)):3065–72. Epub 2008 July 23.
[30] Grace M, Youngster S, Gitlin G, Sydor W, Xie L, Westreich L, et al. Structural and biologic characterization of pegylated recombinant IFN-alpha2b. J Interferon Cytokine Res 2001;21(December (12)):1103–15.
[31] Jabbour E, Kantarjian H, Cortes J, Thomas D, Garcia-Manero G, Ferrajoli A, et al. PEG-IFN-alpha-2b therapy in BCR-ABL-negative myeloproliferative disorders: final result of a phase 2 study. Cancer 2007;110(November (9)):2012–8.
[32] Butterfield JH. Treatment of hypereosinophilic syndromes with prednisone, hydroxyurea, and interferon. Immunol Allergy Clin North Am 2007;27(August (3)):493–518.
[33] Bukowski RM, Tendler C, Cutler D, Rose E, Laughlin MM, Statkevich P. Treating cancer with PEG Intron: pharmacokinetic profile and dosing guidelines for an improved interferon-alpha-2b formulation. Cancer 2002;95(July (2)):389–96.
[34] Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, et al. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. Hepatology 2001;34(August (2)):395–403.
[35] Simon HU, Rothenberg ME, Bochner BS, Weller PF, Wardlaw AJ, Wechsler ME, et al. Refining the definition of hypereosinophilic syndrome. J Allergy Clin Immunol 2010;126(July (1)):45–9.
[36] Vilcek J, Feldmann M. Historical review: cytokines as therapeutics and targets of therapeutics. Trends Pharmacol Sci 2004;25(April (4)):201–9.
[37] Glue P, Fang JW, Rouzier-Panis R, Raffanel C, Sabo R, Gupta SK, et al. Pegylated interferon-alpha2b: pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data. Clin Pharmacol Ther 2000;68(November (5)):556–67.
[38] Physicians' desk reference 2008. 62nd ed. Montvale (NY): Thomson PDR; 2007. p. 2994–3001.
[39] Brigaudeau C, Liozon E, Bernard P, Trimoreau F, Bordessoule D, Praloran V. Deletion of chromosome 20q associated with hypereosinophilic syndrome: a report of two cases. Cancer Genet Cytogenet 1996;87(March (1)):82–4.
[40] Huh J, Tiu RV, Gondek LP, O'Keefe CL, Jasek M, Makishima H, et al. Characterization of chromosome arm 20q abnormalities in myeloid malignancies using genome-wide single nucleotide polymorphism array analysis. Genes Chromosomes Cancer 2010;49(April (4)):390–9.