A Phase II Trial of Pegylated Interferon α-2b Therapy for Polycythemia Vera and Essential Thrombocythemia

Feasibility, Clinical and Biologic Effects, and Impact on Quality of Life

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BACKGROUND. Conventional interferon-α (IFN) is an effective treatment for patients with myeloproliferative disorders. However, many patients discontinue therapy because of side effects.

METHODS. In this 24-month, Phase II feasibility study of pegylated interferon α-2b (PEG-IFN) treatment, a starting dose of 0.5 μg/kg per week was received by 21 patients with polycythemia vera (PV) and 21 patients with essential thrombocythemia (ET). The treatment objective, a complete platelet response (CR), was a platelet count $<400 \times 10^9$/L in symptomatic patients and <600 in asymptomatic patients. Neutrophil polycythemia rubra vera-1 (PRV-1) messenger RNA expression was analyzed prior to and during therapy. Quality of life (QoL) was investigated by using the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire.

RESULTS. At 6 months, 29 of 42 patients (69%) had achieved a CR after a median of 83 days. The CR rate was not related to diagnosis, gender, or previous therapy. Nineteen patients completed the planned 2-year treatment in CR. No thromboembolic or bleeding complications were observed. Phlebotomy requirements were reduced in the majority of patients with PV. Five of 14 patients (36%) who initially were positive for PRV-1 achieved normalized PRV-1 expression under PEG-IFN treatment. Side effects were the cause of therapy failure in 16 of 23 patients. However, only 8 of 19 patients reported any side effects at 2 years. The QLQ-C30 revealed clinically significant impairments in several aspects of QoL at 6 months; however, at 2 years, QoL measurements were not different from baseline.

CONCLUSIONS. PEG-IFN effectively reduced platelet counts in 29 of 42 patients, but only 19 patients maintained a CR at 2 years. The reversal of PRV-1 positivity noted in a subset of patients suggested that PEG-IFN may have an effect on the malignant clone. PEG-IFN is a valuable therapeutic alternative for patients who tolerate its initial side effects. *Cancer* 2006;106:2397–405.
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Chronic myeloproliferative disorders (MPDs) are a group of related disorders, all of which are characterized by neoplastic proliferation of ≥ 1 hematopoietic cell lines. One of the most prevalent clinical challenges in the treatment of MPDs is thrombocythemia, which always is present in essential thrombocythemia (ET) and also is frequent in polycythemia vera (PV). Predisposing factors, such as previous thromboembolic incidents, long disease duration, and age older than 60 years, increase the risk for thrombosis.[1–3] When PV and ET occur in young individuals, the initial clinical presentation may be alarming, and life-threatening complications at diagnosis are not uncommon.[4] Modern treatment, however, has improved the prognosis for patients with PV and ET dramatically, mainly through the avoidance of thromboembolic complications.[5] A prospective trial of hydroxyurea versus observation in high-risk patients with ET who had platelet counts $>1500 \times 10^9$/L showed a marked reduction in the rate of thrombosis in the hydroxyurea arm.[6] Conversely, it also has been shown that, with long-term follow-up, the clinical course of patients with ET and PV can include thromboembolic complications in from 40% to 75% of patients.[1–3] Therefore, the current treatment for patients with PV and ET should aim at avoiding thromboembolic complications by using phlebotomy to maintain a venous hematocrit $<45\%$ in patients with PV[7]; and, in most patients with PV and ET, bone marrow-suppressive therapies also will be employed during the course of the disease to control thrombocythemia. Such treatments ideally should not increase the risk of acute leukemia.

Hydroxyurea generally is considered the treatment of choice for MPD-associated thrombocythemia and recently showed superior activity over anagrelide in patients with ET.[8] In the largest cohort study performed to date, no excess risk of leukemia was observed in hydroxyurea-treated patients.[9] However, when hydroxyurea was used in patients who previously received alkylating agents[10] or in combination with radioactive phosphorus,[11] an increased risk of secondary neoplasms clearly was demonstrated. Therefore, other nonleukemogenic treatment options are of potential importance in the management of MPD.

Interferon (IFN) first demonstrated effectiveness in correcting thrombocythemia in patients with ET and PV and later demonstrated ability to control the excess red cell mass in patients with PV.[12–15] Some case reports have shown that IFN can cause normalization of chromosomal abnormalities in PV.[16,17]

Lengfelder et al. summarized treatment results with IFN in 279 patients with PV and 273 patients with ET.[18,19] In addition to correction of thrombocythemia in approximately 90% of patients, a reduction of splenomegaly was observed in 77% of patients. Control of pruritus was achieved in 81% of patients with PV; and, in 82%, the frequency of phlebotomies was reduced.

Clear disadvantages associated with conventional IFN therapy are the need for frequent subcutaneous injections and a relatively high rate of side effects, leading to discontinuation of therapy in 21% of patients with PV and in 25% of patients with ET (meta-analyses[18,19]) and in up to 66% of patients with ET in individual trials.[19] Pegylated IFNα-2b (PegIntron®; Schering-Plough Nordic Biotech) is a polyethyleneglycol-conjugated formulation of IFN (PEG-IFN) that provides prolonged activity compatible with once-weekly dosing. When the current trial was started in January 2001, no trials had been published of PEG-IFN therapy in patients with PV or ET, but it was known that responses were observed in patients with chronic myeloid leukemia who were refractory to conventional IFN.[20] Therefore, we conducted the current prospective, Phase II trial of PEG-IFN therapy in patients with PV and ET that was designed to investigate the feasibility of PEG-IFN therapy, its biologic effects, and its impact on quality of life (QoL).

MATERIALS AND METHODS
Patients
This was a prospective, open label, Phase II clinical trial of 42 patients, including 21 patients with PV and 21 patients with ET (20 females and 22 males). Patients were included between January 2001 and May 2003, and all patients were followed for 24 months. Inclusion criteria were a diagnosis of PV or ET and a platelet count $>400 \times 10^9$/L in patients who had a previous thromboembolic episode or ongoing microcirculatory symptoms, a platelet count $>1000 \times 10^9$/L in asymptomatic patients age 18 years and older, and signed informed consent. Exclusion criteria were previous IFN therapy; ongoing therapy with another myelosuppressive agent; previous severe autoimmune disease; previous endogenous depression requiring medical therapy; pregnancy; cardiac failure (New York Heart Association Grades III and IV); serum creatinine or alanine aminotransferase levels >1.5 and >3 times the upper normal reference value, respectively; or another concurrent malignancy. The median age was 54 years (mean, 53 years; range, 29-77 years), and the median

disease duration was 0.80 years (mean, 3.1 years; range, 0.01-30.2 years). Twenty-two patients had a previous thromboembolic event, which included stroke in 9 patients, transient ischemic attack in 2 patients, pituitary apoplexy in 1 patient, myocardial infarction in 1 patient, peripheral arterial thrombosis in 1 patient, splenic infarction in 1 patient, deep vein thrombosis in 3 patients, pulmonary embolism in 1 patient, sinus thrombosis in 1 patient, retinal vein thrombosis in 1 patient, and superficial thrombophlebitis in 1 patient. The time from these complications to study inclusion was 30 months (mean range, 0.5-132 months). Four patients had ongoing microcirculatory symptoms, and 16 patients were asymptomatic. Twenty-seven patients had not received prior cytoreductive treatment, whereas 7 patients had received anagrelide, 6 patients had received hydroxyurea, 1 patient had received busulfan, and 1 patient had received radioactive phosphorus. Twenty-eight patients were on low-dose aspirin at study inclusion. In patients with PV, phlebotomy was used to maintain a venous hematocrit <45%.

The study was designed by the Nordic Study Group for Myeloproliferative Disorders (NMPD) and was conducted in accordance with the ethical principles of the declaration of Helsinki. Written informed consent was obtained from all patients. The study protocol was approved by the ethics committees at all participating hospitals.

Study Design and Treatment

The primary objective of this study was to evaluate the feasibility of PEG-IFN therapy in patients with PV and ET with regard to reaching preset objectives of platelet reductions, which were defined as achieving a platelet count $<400 \times 10^9$/L in patients who had a previous thromboembolic episode or ongoing microcirculatory symptoms or achieving a platelet count $<600 \times 10^9$/L in asymptomatic patients who were without previous thromboembolic complications. Having achieved this objective for at least 4 weeks was defined as a complete platelet response (CR), and all other patient outcomes were defined as failures. Secondary objectives were to evaluate efficacy with regard to thromboembolic events, cessation of phlebotomy requirement in patients with PV, overall survival, spleen size, polycythemia rubra vera-1 (PRV-1) expression, and bone marrow cytogenetics. Another secondary objective was to delineate the impact of PEG-IFN treatment on QoL.

All patients were treated with self-administered subcutaneous PEG-IFN once weekly at a starting dose of 0.5 μg/kg. In patients who failed to achieve a platelet count $<400 \times 10^9$/L (symptomatic patients) or $<600 \times 10^9$/L (asymptomatic patients) after 12 weeks at the initial dose level, the dose was increased to 1.0 μg/kg once weekly. When the preset objective for platelet reduction was reached (i.e., CR), the dose of PEG-IFN was reduced gradually to the lowest dose that maintained the CR. Patients were taken off study if they had not reached CR after 6 months or at any time if they did not tolerate side effects.

Efficacy and Safety Assessment

Patients underwent clinical examination in the outpatient clinic before the start of therapy and monthly during the first 3 months. Thereafter, patients were seen every third month or more frequently if clinically indicated. All adverse reactions were documented and graded according to the World Health Organization (WHO) standard toxicity scale. QoL evaluations were performed before the start of treatment and after 3 months, 6 months, 12 months, and 24 months. To obtain a standardized point of measurement, the patients were asked to complete the questionnaires before their medical examination. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire (version 3.0) was used. The QLQ-C30 questionnaire consists of 30 items, including 5 functional scales, 9 symptom scales, and a global health/QoL scale.[21,22] The Hospital Anxiety and Depression (HAD) scale, which was developed for the assessment of anxiety and depressive symptoms in patients with somatic diseases,[23,24] also was employed. The HAD scale consists of 14 items, including 7 items that measure anxiety and 7 items that measure depressive symptoms, and each item is scored in 4 response categories (scored from 0 to 3). The maximum score for each subscale is 21: An HAD scale cut-off score ≥8 is recommended for identifying potentially clinical cases, and a cut-off score >11 is recommended for clinical cases.

Additional Clinical and Biologic Studies

Patients underwent bone marrow biopsies before treatment, at 6 months, and at end of the study (after 2 years). Conventional cytogenetic analyses and spleen size measurements with computed tomography scans or ultrasound imaging were obtained before therapy and after 2 years. The expression of PRV-1 messenger RNA was quantitated in peripheral blood neutrophils precisely as described previously.[25]

Statistical Analyses

All 42 patients who were included in the current trial received PEG-IFN therapy and were evaluable for response assessment. Platelet response rates at 6 months and 24 months were analyzed by using the
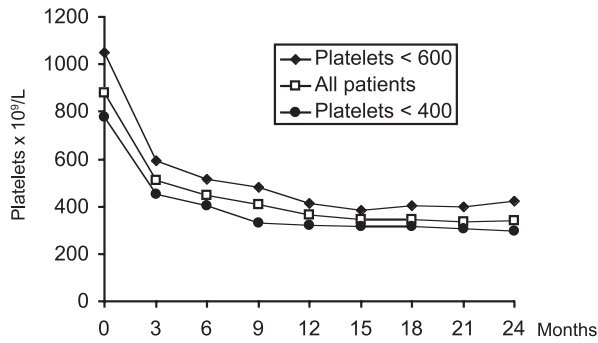
FIGURE 1. The platelet-lowering effect of pegylated interferon therapy during the trial is illustrated. Mean curves are shown for all patients (open squares), for patients with a treatment objective of platelets $<400 \times 10^9$/L (black circles), and for patients with a treatment objective of platelets $<600 \times 10^9$/L (black diamonds). The number of patients evaluated at different time points (n) is indicated.

Fisher exact test according to the following subgroups; patients with PV versus patients with ET, female patients versus male patients, and previously treated patients versus previously untreated patients. QoL questionnaires were analyzed according to the manual for the EORTC QLQ-C30 and the original HAD publication. QoL data are presented descriptively. Changes in mean values ≥ 5 were considered clinically significant.[26]

RESULTS
Efficacy of Treatment—Platelet Reduction
All patients were alive after 2 years of follow-up. No thromboembolic or hemorrhagic complications were observed, compared with 12 thrombotic events in 42 patients (29%) in the 24 months preceding inclusion, highlighting the importance of controlling thrombocythemia in patients with MPD who have had a previous thrombosis. The mean platelet count was 881×10^9/L at baseline and 512×10^9/L, 448×10^9/L, 362×10^9/L, and 341×10^9/L at 3 months, 6 months, 12 months, and 24 months, respectively. At 6 months, 29 of 42 patients (69%) had achieved a CR and were still on therapy. The failure rate was 31% (13 of 42 patients). Of those 13 patients, 4 patients went off study early because of side effects, another 2 patients also were taken off study at 6 months because of side effects, and 7 patients had not reached a platelet CR at 6 months despite a maximal PEG-IFN dose of 1.0 μg/kg once weekly. The median time to CR was 83 days, as shown in Figure 1, and the median PEG-IFN dose that was required to obtain a CR was 0.6 μg/kg
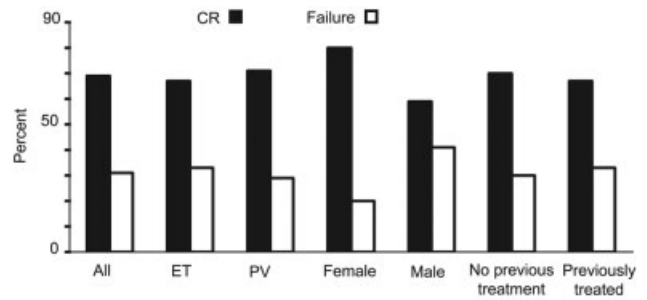

FIGURE 2. Platelet response to pegylated interferon α is illustrated at 6 months. The response rate was not related significantly to diagnosis, gender, or previous therapy. CR: complete platelet response; ET: essential thrombocythemia; PV: polycythemia vera.

(mean, 0.75 μg/kg). After a CR had been reached, the platelet count remained stable during dose reduction until the end of study in patients who continued therapy. Platelet responses at 6 months and at 24 months were not related significantly to diagnosis ($P = 1.00$), gender ($P = .19$), or previous therapy ($P = 1.00$), as depicted in Figure 2.

At 12 months, another 9 of 29 patients who achieved a CR at 6 months had discontinued therapy because of side effects; all of those patients were in CR when therapy was stopped. There was no difference in the median age of patients who continued therapy after 12 months (median age, 54 years) and patients who stopped therapy before 12 months (median age, 53 years). One additional patient went off therapy at 15 months, whereas the remaining 19 patients (12 patients with PV and 7 patients with ET) continued therapy for the planned 24 months and achieved a CR rate of 45% (19 of 42 patients) and a failure rate of 55% (23 of 42 patients) at 2 years. The mean platelet count was 341×10^9/L in all 19 patients at 24 months, 295×10^9/L in patients who had an objective of platelets $<400 \times 10^9$/L, and 422×10^9/L in patients who had the therapeutic objective to maintain a platelet count $<600 \times 10^9$/L. The mean PEG-IFN dose at 24 months was 0.4 μg/kg per week (range, 0.1-0.6 μg/kg per week). Five of 19 patients maintained a CR with a low dose of PEG-IFN (0.1-0.2 μg/kg per week). There was no significant difference in the dose administered to patients with ET and to patients with PV.

Other Clinical Benefits
Nine of 12 patients with PV who were treated for 24 months required phlebotomy in the 6 months preceding PEG-IFN therapy. At 24 months, 4 of 9 patients had no need for phlebotomy to maintain a stable hematocrit $<45\%$, 3 of 9 patients had at a reduction $\geq 50\%$ in their phlebotomy requirement; whereas, in 2 patients,

the need remained unchanged. Only 2 of 19 patients had an enlarged spleen before therapy. In both of those patients, PEG-IFN conferred reductions in the greatest perpendicular dimension of 3 cm and 2 cm, respectively. All 15 patients out of 19 who completed 2 years of treatment and were analyzed cytogenetically had a normal karyotype at the start of treatment. Eight of those patients were reanalyzed after 2 years, and their karyotype remained normal. Evaluation of bone marrow biopsies by local pathologists indicated no major impact on bone marrow morphology or bone marrow reticulin fibrosis after 24 months of therapy; however, no firm conclusions can be drawn until a planned, centralized, blinded review has been conducted that will be reported separately.

Effect on PRV-1 Expression

Of 29 patients who had pretherapeutic blood samples available, 21 patients had samples that overexpressed PRV-1 (13 patients with PV and 8 patients with ET), and 8 patients had samples with normal levels. The 8 PRV-1-negative patients (6 patients with ET and 2 patients with PV) remained negative at all subsequent evaluations. Six-month follow-up data were available for 20 of 21 patients who initially were positive for PRV-1; 16 patients remained PRV-1-positive, and 4 patients with ET had normalized PRV-1 expression. Three of those 4 patients continued to display normal PRV-1 levels after 24 months of treatment, 1 discontinued treatment at 15 months. Of the 16 patients who remained PRV-1 positive after 6 months of treatment, 11 patients were available for analysis at 24 months. Two of those patients, both with PV, had normalized PRV-1 levels, whereas 9 patients remained PRV-1-positive. Overall, 5 of 14 patients who initially were positive for PRV-1 (36%) and who had 24-month samples available achieved normalized PRV-1 expression during PEG-IFN treatment. All of those patients had a normal platelet count at 24 months.

Side Effects and Impact on Quality Of Life

Side effects were reported by all patients at some time during the study and were the same type of side effects that have been reported with conventional IFN (Table 1). The majority of side effects were WHO Grade 1 or 2, although some patients had Grade 3 side effects, most notably fatigue and flu-like symptoms. There was no significant difference in the frequency or severity of side effects between patients with ET and patients with PV. Only 8 of 19 patients who completed 24 months of therapy reported any side effect at the end of study.

Side effects were the cause for discontinuation of therapy in 16 of 23 patients, and the dominating prob-

TABLE 1
Percentages of the Patient Population that Reported a Side Effect at Any Time During the Trial*

Side effect	WHO Grade 1	WHO Grade 2	WHO Grade 3
Fatigue	37	24	15
Injection site reaction	54	10	0
Flu-like symptoms	32	22	10
Headache	37	15	5
Muscle pain	34	15	2
Depression	12	20	2
Insomnia	14	10	0
Alopecia	17	2	0
Weight loss	17	0	0
Other	24	20	7

WHO: World Health Organization.

* In each patient, the highest WHO grade during the study for the various side effects is given.

lem was fatigue in 6 patients, muscle pain in 3 patients, headache in 2 patients, flu-like symptoms in 1 patient, depression in 1 patient, erythema in 1 patient, hair loss in 1 patient, and tachycardia in 1 patient. In 14 of 16 patients, the treating physician and the patient concurred that PEG-IFN therapy should be stopped; in 2 patients, PEG-IFN was discontinued solely at the request of the patient.

Mild elevations were noted in serum alanine aminotransferase levels in 19 patients (1.05 ± 0.37 μkat/L; normal value, <0.8 μkat/L), creatinine levels in 3 patients (129 ± 9 μmol/L; normal value, <84 μmol/L), and thyroid-stimulating hormone levels in 3 patients (8.0 ± 2.6 mU/L; normal value, <5 mU/L). One patient developed clinical and laboratory signs of hyperthyroidism after 24 months of therapy that may have been treatment related, because withdrawal of PEG-IFN led to a full recovery within 5 months without any further intervention. Other clinically significant events that occurred during the trial included was 1 each of the following; atrial fibrillation, pneumonia, hypertension, endocarditis after a foot injury with large skin abrasion, basal cell carcinoma, and multiple sclerosis. It was considered unlikely that these events were associated with PEG-IFN therapy.

Mean values and standard deviations on the QLQ-C30 subscales are presented in Table 2. Clinically significant decreases (difference in mean values ≥ 5) from baseline to the 6-month assessment were found for 3 of 5 functional scales (physical, role, and social) and for global QoL. Correspondingly, the patients reported significant increases in 6 of 9 symptom scales, namely, fatigue, pain, dyspnea, sleeping problems, appetite loss, and diarrhea, compared with baseline. In patients who continued therapy, no clinically signifi-

TABLE 2
Mean Values and Standard Deviations for the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 Subscales at 5 Points of Assessment

Subscale	EORTC QLQ-C30 Scores: Mean ± Standard Deviation				
	Baseline (N = 37-38)	3 Mos (N = 35)	6 Mos (N = 37-38)	12 Mos (N = 23-24)	24 Mos (N = 17-19)
Physical functioning*	90.6 ± 11.5	84.6 ± 17.8	84.2 ± 16.7	85.2 ± 15.8	88.2 ± 14.4
Role functioning*	81.5 ± 24.5	77.6 ± 27.7	73.9 ± 27.9	81.9 ± 27.0	84.2 ± 30.2
Emotional functioning*	82.4 ± 17.1	82.1 ± 18.3	78.6 ± 18.5	82.3 ± 17.8	84.6 ± 18.3
Cognitive functioning*	86.7 ± 17.4	85,7 ± 19.0	84.2 ± 18.6	87.0 ± 18.8	88.6 ± 15.8
Social functioning*	89.6 ± 18.6	85.2 ± 23.5	79.7 ± 26.1	83.3 ± 22.5	82.5 ± 26.3
Global QoL*	72.1 ± 23.4	68.0 ± 21.0	67.1 ± 24.4	68.1 ± 21.5	70.6 ± 24.0
Fatigue†	23.1 ± 24.1	31.1 ± 24.1	36.9 ± 27.7	31.9 ± 24.1	26.3 ± 20.4
Nausea/emesis†	2.6 ± 6.2	3.3 ± 8.9	5.3 ± 12.3	1.4 ± 4.7	2.6 ± 6.2
Pain†	15.4 ± 25.2	19.0 ± 29.5	22.4 ± 24.9	16.7 ± 26.5	15.7 ± 31.7
Dyspnea†	10.6 ± 15.7	18.1 ± 26.0	22.8 ± 27.0	22.2 ± 27.2	12.3 ± 16.5
Sleeping problems†	19.3 ± 27.5	22.9 ± 26.5	26.3 ± 33.0	23.6 ± 30.3	15.8 ± 23.2
Appetite loss†	2.6 ± 9.1	7.6 ± 14.2	14.0 ± 22.8	9.7 ± 20.8	3.5 ± 10.5
Constipation†	4.4 ± 13.8	8.6 ± 14.8	7.9 ± 16.3	4.2 ± 11.3	5.3 ± 12.5
Diarrhea†	4.4 ± 11.4	14.3 ± 20.3	15,8 ± 24.2	12.5 ± 21.6	8.8 ± 18.7
Financial difficulties†	7.2 ± 17.8	3.8 ± 10.8	4.4 ± 11.4	4.2 ± 11.2	3.5 ± 10.5

EORTC: European Organization for Research and Treatment of Cancer; QLQ: Quality-of-Life Questionnaire; QoL: quality of life.

* Higher values represent better functioning.

† Higher values represent higher levels of symptoms.

TABLE 3
Mean Scores, Standard Deviations, and the Number and Proportion of Patients Categorized as No Case, Possible Clinical Case, and Clinical Case

Subscale	No. of Patients (%)				
	At Start (N = 39)	3 Mos (N = 31)	6 Mos (N = 38)	12 Mos (N = 29)	24 Mos (N = 21)
HAD anxiety					
Mean ± SD score*	4.74 ± 3.13	4.42 ± 3.55	4.73 ± 3.38	3.66 ± 3.91	3.95 ± 3.12
No case (score >8)	31 (79)	24 (77)	30 (79)	25 (86)	19 (90)
Possible clinical case (score 8-11)	7 (18)	5 (16)	6 (16)	1 (4)	2 (10)
Clinical case (score >11)	1 (3)	2 (7)	2 (5)	3 (10)	0 (0)
HAD depression					
Mean ± SD score	3.36 ± 3.53	3.65 ± 3.76	4.45 ± 4.49	3.21 ± 3.61	3.81 ± 3.97
No case (score >8)	34 (87)	27 (87)	32 (84)	26 (90)	18 (86)
Possible clinical case (score 8-11)	3 (8)	2 (6.5)	1 (3)	0 (0)	1 (5)
Clinical case (score <11)	2 (5)	2 (6.5)	5 (13)	3 (10)	2 (9)

HAD: Hospital Anxiety and Depression scale; SD: standard deviation.

* Mean scores: range, 0 to 21.

cantly differences were observed between the baseline assessment and the 24-month follow-up.

One patient who had a history of previous depressive tendency developed clinical signs of depression and was taken off study after 8 months. The mean values and standard deviations and the numbers and proportions of patients who were categorized as "no case," "possible case," and "clinical case" according to the HAD analyses are presented in Table 3.

DISCUSSION

Conventional IFN is effective in the treatment of MPDs, but its use has been hampered by frequent withdrawals from therapy[18,19] and by significant impairment of QoL.[27] The main finding of the current study was that PEG-IFN treatment appeared to induce a similar frequency and severity of side effects during long-term use compared with conventional IFN. Even though side effects diminished to some extent during

TABLE 4
Comparison of Results from 4 Trials of Pegylated Interferon Therapy in Patients with Essential Thrombocythemia and Polycythemia Vera

Study	No. of Patients	Response Rate: Best/End of Study (%)	Off Study (%)	Follow-Up (Mos)
Verstovsek et al., 2004[29]	16	69/Not given	Not given	Not given
Gugliotta et al., 2005[31]	90	79/53	39	24
Langer et al., 2005[32]	36	67/64	36	23
Current study	42	69/45	55	24

the first months of PEG-IFN therapy, large numbers of patients still experienced the same intensity of side effects after several months of treatment, as indicated by a long median drop-out time (202 days; range, 27-425 days). Twenty-three of 42 patients (55%) stopped treatment within 2 years, including 16 patients who stopped because of side effects that significantly decreased their QoL. However, in patients who were able to continue therapy, these differences abated with time; and, at the 24-month assessment, their QoL was not different from baseline. A comparison between the study group at the 24-month QLQ-C30 assessment and norm values for the Swedish population[22] revealed no clinically significant differences for any of the functioning scales or with respect to global QoL, and there were no clinically significant differences in the symptom scales except for fatigue, in which the study group scored higher levels of symptoms.

The 45% of patients who still were on treatment after 2 years had a good and sustained clinical effect of the drug and had either no or relatively mild side effects. The platelet-lowering effect of the drug did not decrease during the study period, indicating that this agent may be useful for long-term therapy.

During the completion of the current trial, 3 other Phase II trials of PEG-IFN use in patients with MPD have been reported. Those results largely are consistent with ours and are summarized in Table 4. The first published pilot study by Alvarado et al.[28] included 11 patients with ET who received high doses of PEG-IFN (1.5-4.5 μg/kg once weekly, subcutaneously). All patients reached a CR, which was defined as a normal platelet count, after 4 months. However, toxicity was high: the median duration on therapy was short (only 9 months), and 5 patients were lost to follow-up. An update of that trial[29] has been published that includes 34 patients. The overall response rates (CRs plus partial responses) in evaluable patients were 9 of 13 patients with ET (69%), 2 of 3 patients with PV (66%), and 0 of 11 patients with idiopathic myelofibrosis. Only 15 of 34 patients remained on the study at the time of

that report. The largest trial to date was performed by Gugliotta et al.,[30] who investigated 90 patients with ET (median age, 45 years; i.e., from 8 to 10 years younger than the age reported in other trials). A lower initial PEG-IFN dose of 25 μg per week was used, and the dose was increased gradually to a maximal dose of 100 μg per week. After 39 weeks, a best response rate of 72% was obtained by using a median dose of 50 μg per week. The side-effect profile was similar to that in our current report. With longer follow-up, only 55 of 90 patients still were receiving therapy at 2 years, with 48 of 90 patients (53%) having a sustained response.[31] Finally, Langer et al.[32] treated 36 patients with ET using PEG-IFN doses similar to those employed in our study, starting at 50 μg per week and gradually increasing the dose to a maximum of 150 μg/week. In that study, a platelet count $<450 \times 10^9$/L was obtained in 58% of patients at 6 months and in 67% of patients at 12 months. After a median observation of 24 months, 23 patients (64%) remained on therapy.

The current results also were very similar to our previous experience with anagrelide. It was claimed initially that the side effects of anagrelide were mild[33]; however, in our nonrandomized study in 60 MPD patients of long-term tolerance over 2 years, we observed a drop-out rate of 50%, which mainly was caused by side effects.[34] The remaining 30 patients had a continued platelet response with few or no side effects. Other studies[35-37] have corroborated our findings with similar discontinuation rates. In addition, anagrelide was discontinued in 148 of 405 patients (37%) in the primary thrombocythaemia-1 trial.[8]

The normalization of initially elevated PRV-1 expression in a significant proportion (36%) of patients documents the efficacy of PEG-IFN treatment at a molecular level, suggesting a suppression of the malignant clone in some patients. IFN is the only therapy for MPD that has been shown to modulate the fundamental, abnormal biologic processes observed in these disorders. The documented biologic effects of IFN include reversal of chromosome abnormalities,[16,17] restoration of polyclonal hematopoiesis in individuals with previously monoclonal hematopoiesis,[38] the suppression of erythropoetin-independent erythroid colony growth,[38] and single case reports of normalization of PRV-1 expression.[39] Such biologic effects have not been demonstrated for either hydroxyurea[40] or anagrelide, the other therapeutic options currently used most in this patent population. Fruehauf et al.[39] previously published results on the normalization of PRV-1 expression in 4 consecutive patients with PV. From the results of our current study, we cannot confirm this uniform effect; rather, we observed an effect in a large subgroup of patients.

Our data provide a strong rationale for the initiation of prospective studies with long-term follow-up to determine whether the biologic modulation observed in a subset of patients will translate into clinical benefits for these individuals.

In conclusion, the current results and the work by other investigators have documented that PEG-IFN is effective in reducing platelet counts in patients who have thrombocythemic MPD, and PEG-IFN has a toxicity similar to that of conventional, unmodified IFN. Because side effects remain a major clinical problem that may lead to the discontinuation of both PEG-IFN and anagrelide in a substantial proportion of patients, trials using combinations of these drugs at lower doses seem warranted.

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