

Epoetin Alfa Maintains Ribavirin Dose in HCV-Infected Patients: A Prospective, Double-Blind, Randomized Controlled Study

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Background & Aims: Combination therapy with interferon α (IFN- α) and ribavirin (RBV) or pegylated IFN- α (PEG-IFN- α)/RBV for chronic hepatitis C virus (HCV) infection often causes anemia, prompting RBV dose reduction/discontinuation. This study assessed whether epoetin alfa could maintain RBV dose, improve quality of life (QOL), and increase hemoglobin (Hb) in anemic HCV-infected patients. **Methods:** HCV-infected patients (n = 185) on combination therapy who developed anemia (Hb \leq 12 g/dL) were randomized into a U. S. multicenter, placebo-controlled, clinical trial of epoetin alfa, 40,000 U subcutaneously, once weekly vs. matching placebo. The study design used an 8-week, double-blind phase (DBP) followed by an 8-week, open-label phase (OLP), in which placebo patients were crossed over to epoetin alfa. **Results:** At the end of the DBP, RBV doses were maintained in 88% of patients receiving epoetin alfa vs. 60% of patients receiving placebo ($P < 0.001$). Mean QOL scores at the end of the DBP improved significantly on all domains of the Linear Analog Scale Assessment (LASA) and on 7 of the 8 domains of the Short Form-36, version 2 (SF-36v2). Mean Hb increased by 2.2 ± 1.3 g/dL (epoetin alfa) and by 0.1 ± 1.0 g/dL (placebo) in the DBP ($P < 0.001$). Similar results were demonstrated in patients who switched from placebo to epoetin alfa in the OLP. Epoetin alfa was well tolerated; the most common adverse effects were headache and nausea. **Conclusions:** Epoetin alfa maintained RBV dose and improved QOL and Hb in anemic HCV-infected patients receiving combination therapy.

Anemia frequently complicates interferon α (IFN- α)/ribavirin (RBV) combination therapy for chronic hepatitis C virus (HCV) infection.¹⁻⁴ Regardless of the form of IFN- α —standard or pegylated IFN- α (PEG-IFN- α)—used in combination with RBV, hemoglobin (Hb) levels decrease during treatment in the majority of

patients.^{3,4} Mean maximal Hb decreases within the first 12 weeks of therapy have been reported to be 2.9–3.1 g/dL,³ and a recent study found that 54% of patients on combination therapy experienced Hb decreases of ≥ 3 g/dL.⁴ The cause of anemia is multifactorial; RBV induces a dose-dependent hemolytic anemia,⁵ whereas IFN- α suppresses bone marrow function, inducing anemia by suppressing erythroid progenitor cell and red blood cell production.^{6,7} Together, these drugs act to produce a “mixed” anemia. Additionally, for reasons not fully elucidated, combination therapy has been associated with a blunted erythropoietic response to this anemia. Preliminary data suggest that, although levels of serum erythropoietin are increased from baseline, they are not sufficient to correct the anemia. Patients, therefore, usually remain anemic for the course of their HCV therapy.⁸

Previously, the only available option to manage HCV treatment-induced anemia was to reduce or discontinue the RBV dose. Recent clinical trials have suggested that anemia during combination therapy results in 22% of patients requiring RBV dose modification² and premature discontinuation of HCV therapy in up to 36% of patients.⁹ However, increasing evidence indicates that decreasing the RBV dose may compromise treatment success.^{1,10,11} In addition, both anemia and HCV combination therapy are associated with decreased quality of life (QOL).¹² The impact of anemia on QOL may also

Abbreviations used in this paper: AE, adverse event; DBP, double-blind phase; EA/EA, epoetin alfa/epoetin alfa; EVR, early virologic response; Hb, hemoglobin; HCV, hepatitis C virus; IFN- α , interferon α ; LDH, lactate dehydrogenase; OLP, open-label phase; P/EA, placebo/epoetin alfa; PEG-IFN- α , pegylated interferon α ; QOL, quality of life; RBV, ribavirin; SAE, serious adverse event; SVR, sustained virologic response.

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decrease HCV treatment adherence. Thus, interventions to correct anemia may improve outcomes. In a proof-of-principle, randomized, open-label, multicenter study, epoetin alfa 40,000 units (U) administered subcutaneously (SC) once weekly was effective in increasing Hb levels and maintaining RBV dose in anemic (Hb \leq 12 g/dL) HCV-infected patients treated with combination therapy.¹³ These promising results led to further investigation of the benefits of epoetin alfa in the current, larger, placebo-controlled study.

The objective of the current study was to assess, in anemic (Hb \leq 12 g/dL) HCV-infected patients on combination therapy, the ability of epoetin alfa to maintain RBV dose, improve QOL, and correct anemia.

Materials and Methods

Study Design

Patients who developed anemia while receiving HCV combination therapy (either first course of treatment or re-treatment for previous relapse or nonresponse) were eligible for enrollment. Study inclusion criteria were as follows: patients 18–75 years of age; Hb \leq 12 g/dL at randomization; chronic HCV infection and on combination therapy with a planned treatment duration of at least 16 additional weeks; HIV negative; and willing and able to sign an informed consent form. Patients were excluded from the study if they had any one of the following: contraindication to epoetin alfa therapy (e.g., known sensitivity to mammalian cell-derived products, known hypersensitivity to human albumin), inadequate iron stores reflected by serum ferritin level $<$ 50 ng/mL (in that functional and/or actual iron deficiency limits the efficacy of epoetin alfa therapy), or significant atherosclerotic heart disease (a contraindication to RBV therapy). Other reasons for exclusion included history of any primary hematologic disease, history of or current uncontrolled hypertension (diastolic blood pressure $>$ 100 mm Hg), or uncontrolled seizure disorder. In addition, patients were excluded if they were currently pregnant or lactating, of childbearing potential and not taking adequate birth control measures, currently active substance abusers, or if they had exposure to epoetin formulations within 6 months before enrollment.

The study consisted of 2 treatment phases: (1) an 8-week, double-blind, placebo-controlled, parallel-group phase (DBP; epoetin alfa vs. placebo) and (2) an 8-week, open-label, modified crossover phase (OLP) during which eligible patients (who had received either epoetin alfa or placebo in the DBP) received epoetin alfa. After the end of this study period, patients were allowed to be maintained on epoetin alfa for the remainder of their HCV therapy and followed only for safety. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutional review committees of the investigators' respective institutions or central institutional review board (IRB). Figure 1 outlines the design of the total 16-week study

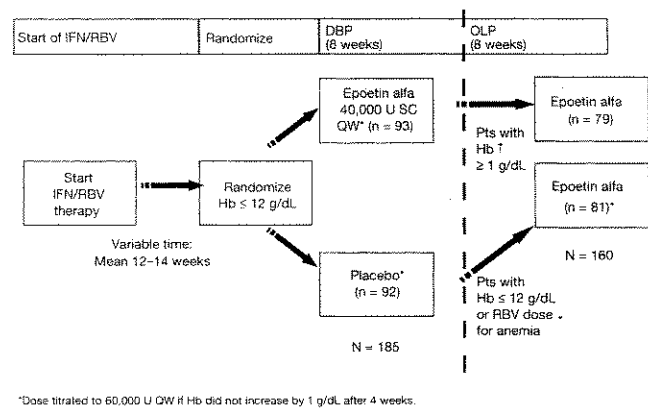


Figure 1. Study design. Dashed vertical line indicates division between DBP and OLP.

period. Each end point was measured at the end of the DBP and the OLP.

In the 8-week DBP, anemic HCV-infected patients receiving any combination of IFN- α /RBV were randomized to treatment with epoetin alfa (PROCRIT [epoetin alfa]; Ortho Biotech Products, L.P., Bridgewater, NJ) 40,000 U once weekly or matched placebo. An independent contract research organization generated the randomization schedule using permuted blocks. Based on this randomization code, the study drug was packaged and labeled for each patient. Each individual site enrolled participants. Each eligible patient was assigned a patient number in strict sequential order according to the patient number on the study drug container. To maintain the blind, the study drug container had a 2-part, tear-off label with directions for use and other information on each part. The tear-off section of the label contained a concealed area identifying the study drug (epoetin alfa or placebo) and was removed and attached to the patient's case report form when the drug was administered. The second part of the label contained all identifying information except for the identity of the drug. Study drugs were identical in appearance and were packaged in identical containers.

Study drug doses were administered by SC injection. The initial dose of study drug was 40,000 U once weekly; this dose or matching placebo was titrated to 60,000 U once weekly if the Hb level did not increase by 1 g/dL from randomization after 4 weeks of study drug treatment. Patients were eligible to receive epoetin alfa in the OLP if they had a Hb increase of at least 1 g/dL from randomization in response to blinded epoetin alfa in the DBP or, for those on blinded placebo, if they had RBV dose reduction because of anemia or ended the DBP with Hb \leq 12 g/dL.

Weight-based RBV dosing was recommended, according to the following guidelines: 800 mg/day for patients $<$ 65 kg, 1000 mg/day for patients 65–85 kg, 1200 mg/day for patients 86–105 kg, and 1400 mg/day for patients $>$ 105 kg, or as recommended by the instructions on the package insert. To maintain therapeutic RBV dosing once patients entered the study, the RBV dose was adjusted according to Hb changes at

the investigator's discretion. In patients who had an RBV dose reduction from the initial RBV dose at the start of HCV treatment, the protocol suggested an increase in the RBV dose by 200 mg/day for each 1-g/dL increase in Hb, up to one 200-mg/day increase per week, to a maximum of the initial RBV dose. The RBV dose could be reduced when Hb decreased to <10 g/dL or when clinically indicated, at the discretion of the investigator. Dose reductions could be carried out according to the following recommendations: reduce to 600 mg/day for patients <65 kg, reduce to 800 mg/day for patients 65–104 kg, reduce to 1000 mg/day for patients 105 kg or greater, or as recommended by the instructions on the package insert, or as clinically indicated. Discontinuation of RBV was recommended when Hb decreased to <8.5 g/dL or when clinically indicated. These recommendations for RBV dosing were provided as guidelines only; strict adherence by study investigators was not required. Final decisions about RBV dose adjustments were made by the investigators after complete assessment of patients' individual clinical situations.

Study End Points

The primary efficacy end point was RBV dose maintenance at the end of the 8-week DBP. RBV dose maintenance was defined as an ending RBV dose (weeks 4–8) greater than or equal to the dose at randomization. Failure to maintain RBV dose was defined as either (1) ending (weeks 4–8) RBV dose less than the dose at randomization, (2) study withdrawal before the end of week 4 because of any reason, or (3) all withdrawals because of anemia, regardless of RBV dose. The proportion of patients maintaining RBV dose in each group during the 8-week DBP was compared.

Secondary end points were RBV dose (absolute and change from randomization, assessed at the end of week 8 and week 16), QOL self-assessments (change from randomization, assessed at weeks 9 and 17), and Hb levels (absolute and change from randomization, assessed at weeks 9 and 17). The tools used to assess QOL were the Linear Analog Scale Assessment (LASA) and the Medical Outcomes Survey Short Form-36, version 2 (SF-36v2). Per protocol, QOL assessments were to be completed by the patient before any other study-related procedures were undertaken for that visit. To minimize the bias in QOL measurements, patients were to be kept blinded to Hb, hematocrit, liver function tests, and HCV viral load results until all study procedures were completed for the visit.

Safety

At screening (up to 14 days prior to randomization), clinical laboratory tests, including chemistry and liver function tests, and a physical examination were carried out. At randomization and week 5 (or early withdrawal), an interim physical exam (including weight, pulse, respirations, and temperature) was performed. Chemistry and liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, lactate dehydrogenase [LDH], bilirubin [total and direct], total albumin, and γ -glutamyl transferase [GGT]), as well as HCV viral load, were carried out

up to 14 days prior to randomization and at weeks 9 and 17, or on early withdrawal. The study protocol recommended monitoring for functional iron deficiency and suggested that iron supplementation be considered in such cases. Study procedures required that, at each visit, the incidence and severity of adverse events (AEs) and the use of concomitant medications were to be recorded on the case report form. All AEs were coded using the World Health Organization Adverse Reaction Terms (WHOART) dictionary.¹⁴

Statistical Analyses

Based on results obtained in the proof-of-principle, randomized, open-label, multicenter study of epoetin α treatment of anemic HCV-infected patients on combination therapy,¹³ it was estimated that 90 patients per arm would provide 90% power to detect differences between the 2 groups ($\alpha = 0.05$, 2-sided). All analyses were conducted using the intent-to-treat (ITT) population with the last value carried forward (LVCF) to impute missing values. The 2-sided Fisher exact test was used to compare the treatment groups for proportion of RBV dose maintenance and proportion of AE occurrence. RBV doses were analyzed using the Wilcoxon-Mann-Whitney test and Wilcoxon signed rank test. Analysis of covariance (ANCOVA) was used to compare treatment groups for QOL scores and Hb responses, adjusting for baseline values. The paired *t* test was used to compare within-group changes. Post hoc analyses were conducted to determine (1) the proportion of patients in each group who maintained or increased their RBV dose at the end of the DBP and OLP (or early withdrawal) vs. RBV dose at the start of HCV treatment and (2) the proportion of patients who maintained or did not maintain RBV dose, counting all withdrawals as failure to maintain RBV dose.

Results

Patient Characteristics and Disposition

Demographics, HCV status, and HCV treatment profiles were similar between patients in the epoetin α and placebo groups (Table 1). The study was initiated on November 1, 2001, and the OLP was concluded on November 22, 2002. A total of 185 patients were randomized in the DBP and evaluated for efficacy (epoetin α , $n = 93$; placebo, $n = 92$). In each study group, the distribution of men and women was relatively equal, and whites were the largest ethnic group. The majority of patients in each group were infected with HCV genotype 1, and 64% were naïve to HCV treatment. At randomization, patients in the epoetin α and placebo groups had been on HCV therapy for an average of 12 and 14 weeks, respectively, prior to receiving the first dose of study drug. The percentage of patients with undetectable HCV viral load at randomization was slightly greater in the epoetin α group than in the placebo group (58% vs.

Table 1. Demographics, HCV Status, and HCV Treatment Profiles

	Epoetin Alfa (n = 93)	Placebo (n = 92)
Mean age, yr (\pm SD, range)	49.5 (9.0, 24–77)	50.5 (7.2, 33–70)
Sex, n (%)		
Male	45 (48)	42 (46)
Female	48 (52)	50 (54)
Ethnicity, n (%)		
White	71 (76)	69 (75)
Black	10 (11)	13 (14)
Hispanic	10 (11)	8 (9)
Asian	2 (2)	1 (1)
Other	0	1 (1)
Mean weight, kg (\pm SD, range)	81.5 (17.3, 48.2–128.6)	79.4 (17.0, 41.1–130.5)
HCV genotype, n (%)		
1	67 (72)	70 (76)
2	14 (15)	13 (14)
3	9 (10)	5 (5)
Other	3 (3)	4 (4)
HCV treatment status, n (%)		
Naïve	64 (69)	55 (60)
Experienced	29 (31)	37 (40)
Mean number of weeks of combination therapy prior to first dose of study drug (\pm SD, range)	12 (8, 1–33)	14 (11, 3–55)
HCV viral load ^a (% undetectable), n (%)	54 (58)	45 (49)
Patients with marked fibrosis and cirrhosis, n (%)	31 (33)	34 (37)

SD, standard deviation.

^aAt randomization.

49%, respectively). The percentage of patients with marked fibrosis and cirrhosis did not differ between groups (33% for the epoetin α group and 37% for the placebo group).

A total of 10 patients in the epoetin α group and 9 patients in the placebo group withdrew from the study during the DBP, for reasons including the following: AE (epoetin α , n = 3; placebo, n = 2), early discontinuation of HCV therapy (epoetin alfa, n = 4; placebo, n = 3), patient request (placebo, n = 2), lost to follow-up (epoetin alfa, n = 1; placebo, n = 1), protocol violation (placebo, n = 1), and other (epoetin alfa, n = 2). During the DBP, the HCV therapy discontinuation rate was 4% for the epoetin alfa group and 3% for the placebo group.

One hundred sixty patients continued on to the OLP (epoetin alfa, n = 79; placebo, n = 81; see Figure 1). Six patients were not eligible to cross over to the OLP for the following reasons: epoetin alfa nonresponder (Hb level did not increase by at least 1 g/dL from randomization; n = 3 in the epoetin alfa group), permanent discontinuation of RBV therapy (n = 1 in the epoetin alfa group), and Hb > 12 g/dL (n = 2 in the placebo group). Five patients in the epoetin alfa/epoetin alfa (EA/EA) group and 9 patients in the placebo/epoetin alfa (P/EA) group withdrew from the study, for reasons including the following: AE (n = 1 in the P/EA group), early discontinuation of HCV therapy (n = 2 in the EA/EA group, n = 5 in the P/EA group), patient request (n = 1 in the

EA/EA group), lost to follow-up (n = 1 in the EA/EA group), and other (n = 1 in the EA/EA group, n = 3 in the P/EA group). During the OLP, the HCV therapy discontinuation rate was 3% for the EA/EA group and 6% for the P/EA group.

Primary End Point: RBV Dose Maintenance

The mean RBV dose at the start of HCV therapy was similar in both study groups (1011 ± 205 mg/day in the epoetin alfa group and 1024 ± 175 mg/day in the placebo group). At randomization, mean RBV doses were also similar in both study groups (925 ± 236 mg/day in the epoetin alfa group and 948 ± 231 mg/day in the placebo group). As shown in Figure 2A, a significantly greater number of patients receiving epoetin alfa maintained their randomization RBV dose (88%) compared with patients receiving placebo (60%; $P < 0.001$). For patients who received epoetin alfa in the DBP, 83% (43 of 52) with no, mild, or moderate fibrosis were able to maintain RBV dose (and had a mean Hb of 13.1 ± 1.2 g/dL), whereas 68% of patients (21 of 31) with marked fibrosis or cirrhosis were able to maintain RBV dose (mean Hb = 12.9 ± 1.7 g/dL) ($P = \text{NS}$). However, for patients who received placebo in the DBP, 36% (17 of 47) with no, mild, or moderate fibrosis were able to maintain RBV dose (mean Hb = 11.1 ± 0.8 g/dL), whereas 50% (17 of 34) with marked fibrosis or cirrhosis were able to maintain RBV dose (mean Hb = $11.1 \pm$

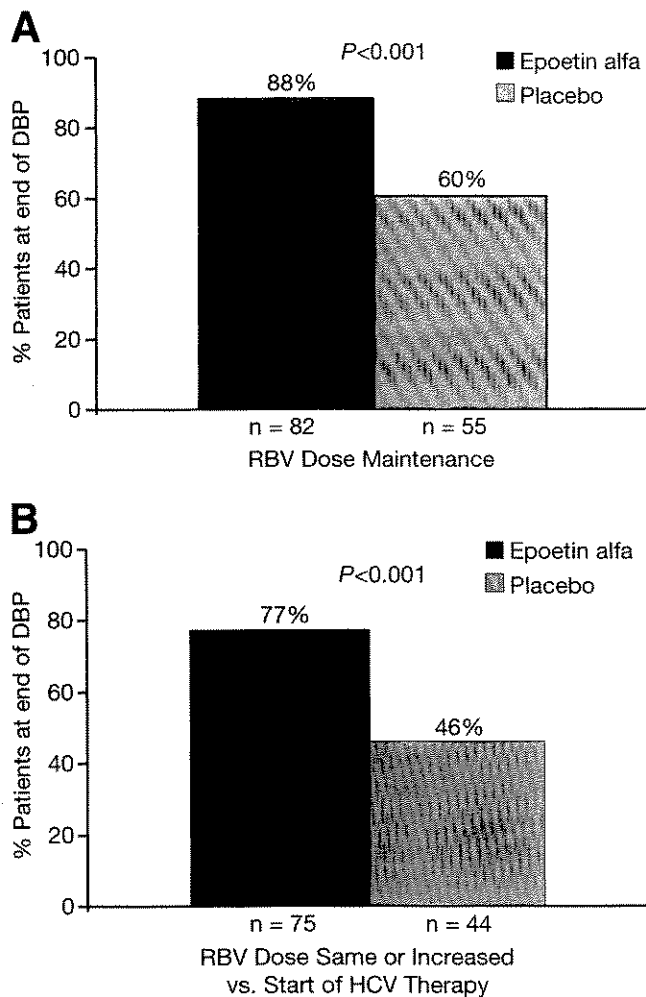


Figure 2. Ribavirin dose maintenance with epoetin alfa vs. placebo. (A) RBV dose maintenance is indicated by the percentages of patients in each group who, at the end of the DBP, maintained or increased their randomization RBV dose (primary efficacy end point). (B) Percentages of patients in each group who, at the end of the DBP, maintained or increased their RBV dose compared with their RBV dose at start of HCV combination therapy.

0.8 g/dL) ($P = NS$). In addition, a significantly greater number of patients who received epoetin alfa had an RBV dose at the end of the DBP that was greater than or equal to the RBV dose at the start of HCV therapy (77% of epoetin alfa-treated patients vs. 46% of placebo-treated patients; $P < 0.001$; Figure 2B). Four patients in each group had an RBV dose at the end of the DBP greater than that at the start of HCV therapy.

Figure 3A illustrates the mean change in RBV dose from randomization over time. In the epoetin alfa group, the mean RBV dose had not changed significantly from randomization (925 ± 236 mg/day) to the end of the DBP (953 ± 214 mg/day); however, a significant decrease in mean RBV dose from randomization (948 ± 231 mg/day) to the end of the DBP (854 ± 239 mg/day)

was apparent in the placebo group ($P < 0.001$). In contrast, the percentages of patients at the end of the DBP who maintained their randomization IFN- α dose and their IFN- α dose at the start of HCV therapy did not differ between the epoetin alfa group (80% and 72%, respectively) and the placebo group (79% and 71%, respectively).

Results of additional analyses showed that epoetin alfa was similarly effective in heavier patients vs. lighter patients and in patients receiving higher vs. lower RBV doses. Within each treatment group, patients were divided into quartiles by weight at randomization (Q1, lightest 25% [41.4–68.4 kg]; Q2, weight $> 25\%$ and $\leq 50\%$ [68.5–78.2 kg]; Q3, weight $> 50\%$ and $\leq 75\%$ [78.4–90.5 kg]; Q4, heaviest 25% [90.7–129.5 kg]), and the RBV dose maintenance rates at the end of the DBP were determined for each quartile. The RBV dose maintenance rate was significantly higher in the epoetin alfa group than in the placebo group in Q3 (90% vs. 59%, respectively; $P = 0.025$) and Q4 (88% vs. 58%, respectively; $P = 0.035$). In Q1 and Q2, a strong trend

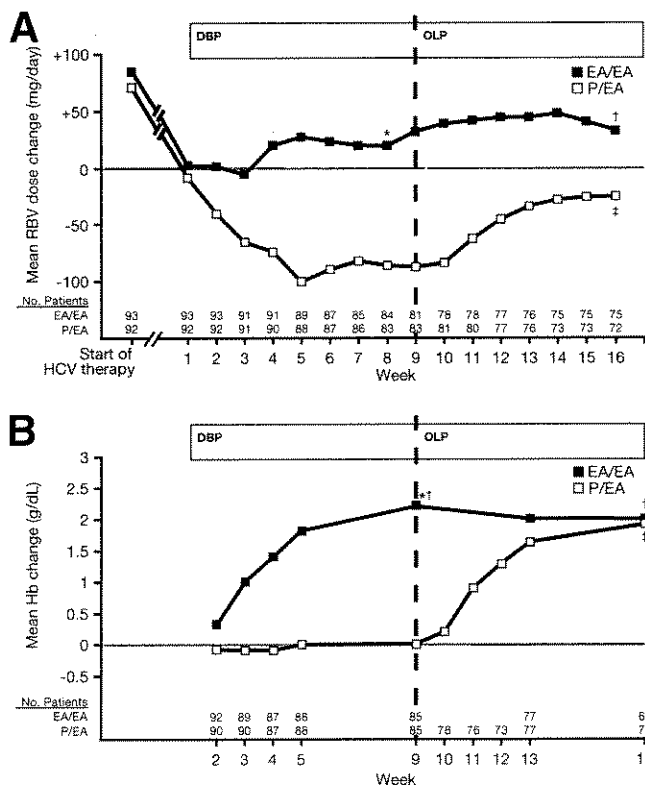


Figure 3. EA/EA, epoetin alfa/epoetin alfa; P/EA, placebo/epoetin alfa. Dashed vertical line indicates division between DBP and OLP. (A) Mean change in ribavirin dose over time. * $P < 0.001$, epoetin alfa vs. placebo (at the end of the DBP). † $P < 0.004$, EA/EA vs. P/EA (at the end of the OLP). ‡ $P < 0.001$, P/EA (OLP vs. DBP). (B) Mean change in hemoglobin levels over time. * $P < 0.001$, epoetin α vs. placebo (at the end of the DBP). † $P < 0.001$, EA/EA (vs. randomization). ‡ $P < 0.001$, P/EA (OLP vs. DBP).

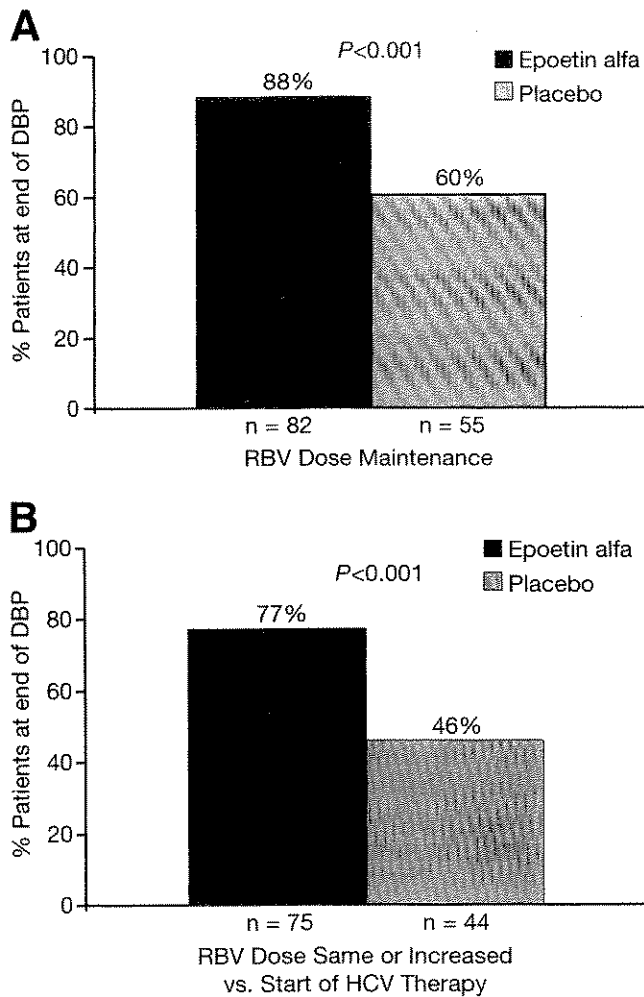


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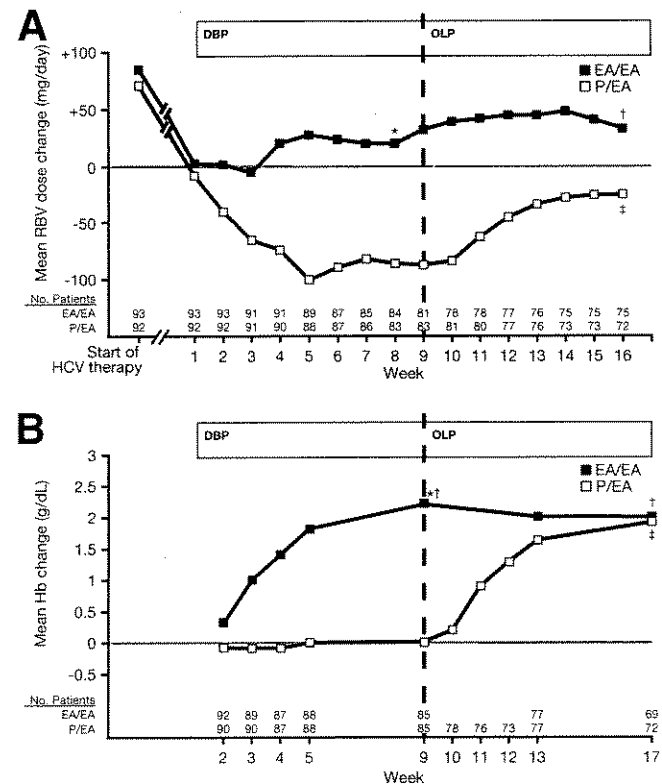


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over from placebo to epoetin alfa. QOL scores increased in the P/EA group on all 3 scales of the LASA at the end of the OLP ($P < 0.001$ for all domains, OLP vs. DBP). Similarly, in the P/EA group, significant increases in QOL scores from the end of the DBP to the end of the OLP were seen on 7 of 8 domains of the SF-36v2 in the OLP, with the exception of bodily pain (Figure 4C). QOL improvements achieved at the end of the DBP were maintained at the end of the OLP in the EA/EA group.

Effects of epoetin alfa treatment on Hb levels.

At the start of HCV therapy, mean Hb levels were similar in both study groups (14.3 ± 1.2 g/dL in the epoetin α group and 14.2 ± 1.5 g/dL in the placebo group). Both groups also had similar mean Hb levels at randomization (10.8 ± 0.8 g/dL in the epoetin α group and 10.8 ± 1.0 g/dL in the placebo group). As shown in Figure 3B, patients receiving epoetin alfa had significantly increased Hb levels from randomization to the end of the DBP, compared with placebo. Mean Hb levels at the end of the DBP were 13.0 ± 1.3 g/dL for the epoetin alfa group and 10.9 ± 1.1 g/dL for the placebo group ($P < 0.001$), representing a mean Hb change from randomization of 2.2 ± 1.3 g/dL in the epoetin alfa group ($P < 0.001$) and 0.1 ± 1.0 g/dL in the placebo group ($P = 0.515$). Furthermore, at the end of the DBP, 57% of patients in the epoetin alfa group had Hb increases ≥ 2 g/dL, and 84% of patients in the epoetin alfa group had Hb increases ≥ 1 g/dL. In contrast, 5% and 17% of patients in the placebo group had Hb increases in these ranges, respectively.

For patients entering the OLP, the mean Hb level was 13.1 ± 1.3 g/dL in the EA/EA group and 10.8 ± 0.9 g/dL in the P/EA group. The results demonstrated in the OLP for patients who had crossed over from placebo to epoetin alfa were similar to those in the DBP for patients who had been randomized to epoetin alfa. Mean Hb levels increased significantly in the P/EA group by the end of the OLP (mean change of 2.0 ± 1.4 g/dL; $P < 0.001$ vs. end of DBP); Hb levels were maintained over time in the OLP in the EA/EA group (-0.3 ± 1.4 g/dL). Mean Hb levels at the end of the OLP did not differ significantly between groups (12.8 ± 1.6 g/dL in the EA/EA group and 12.7 ± 1.5 g/dL in the P/EA group).

Safety Results

Liver function. Liver function, measured at randomization and at the end of the DBP and OLP, did not differ significantly between groups or change appreciably over time. The mean LDH level was the only index to show a statistically significant change between groups at the end of the DBP (345.7 ± 224.0 in the epoetin alfa group vs. 276.0 ± 180.1 in the placebo group, $P <$

0.001) and within the epoetin α group from randomization to the end of the DBP (284.3 ± 197.0 at randomization vs. 345.7 ± 224.0 at the end of the DBP, $P < 0.001$), possibly reflecting increased red blood cell turnover in the epoetin alfa group.

HCV viral load. To ensure that epoetin alfa treatment did not adversely impact HCV clearance during HCV therapy, patients' HCV RNA levels were measured at randomization and the end of the DBP and OLP. The proportion of patients with undetectable HCV RNA on treatment remained similar between groups at all time points measured following randomization (end of DBP: 65% for epoetin alfa, 65% for placebo [$P = 0.531$]; end of OLP: 73% for EA/EA, 69% for P/EA [$P = 0.804$]).

Adverse Events

As expected among patients receiving HCV combination therapy, AEs were common. The AEs occurring in $\geq 10\%$ of patients during the DBP and OLP are listed in Table 2. Although nausea was more common in the epoetin alfa group in the DBP, the majority of cases were classified as mild. One patient receiving placebo in the DBP reported severe nausea. Six serious AEs (SAEs) occurred during the DBP (5 in the epoetin alfa group and 1 in the placebo group; Table 2). Of these, 1 SAE was considered by the investigator to be possibly related to study drug (cerebrovascular disorder/cerebral thrombosis) and resolved without sequelae. Examination of the case details indicated that, by this female patient's fifth week of epoetin alfa treatment, Hb had increased to 14.3 g/dL from 11.0 g/dL at randomization (Hb was 14.6 g/dL prior to the start of HCV therapy). Platelets and blood pressure did not change significantly during her 5-week treatment period. No other episodes of thrombosis were reported in this study. Two other SAEs occurred during the OLP and were considered by the investigators to be not related to study drug. To date, in the safety phase following the OLP (during which all patients receive epoetin alfa) or off study, 10 SAEs have occurred, including 2 deaths during this period. Of these 10 SAEs, 9 have been considered by the investigators to be not related to study drug, and the relationship to study drug of the remaining SAE was considered doubtful. A total of 3 deaths occurred (each was considered by the investigator to be not related to study drug): 1 in the DBP in a patient in the epoetin alfa group with pneumonia, renal failure, and hepatic failure; 1 after week 17 in a patient receiving epoetin alfa with esophageal and gastric variceal bleeds; and 1 off study (12 weeks after the last dose of epoetin alfa) because of a massive stroke.

Table 2. Adverse and Serious Adverse Events Occurring During the 16-week Study Period

AE ^a or SAE	Epoetin	
	Alfa n (%)	Placebo n (%)
DBP		
Headache	18 (19)	12 (13)
Nausea	15 (16)	4 (4) ^b
Rash	14 (15)	15 (16)
Fatigue	11 (12)	18 (20)
Insomnia	9 (10)	9 (10)
Patients with any SAE	5 (5)	1 (1)
Neuropathy	1 (1)	0
Pneumonia	1 (1) ^c	
Renal failure		
Hepatic failure		
Hepatocellular carcinoma	1 (1)	0
Bacterial infection		
Coronary artery disorder	0	1 (1)
Depression	1 (1)	0
Cerebrovascular disorder/cerebral thrombosis	1 (1) ^d	0
OLP		
Headache	9 (11)	7 (9)
Alopecia	8 (10)	3 (4)
Nausea	5 (6)	9 (11)
Fatigue	1 (1)	10 (12) ^e
Patients with any SAE	2 (3)	0
Syncope	1 (1)	0
Acute Coombs-positive hemolytic anemia	1 (1)	0

^aAEs occurring in $\geq 10\%$ of patients.

^b $P = 0.014$.

^cOutcome = death.

^dPossibly related to study drug. All other SAEs considered not related to study drug.

^e $P = 0.009$.

Discussion

The results of this study demonstrate that once weekly, subcutaneous administration of epoetin alfa 40,000 U to anemic HCV-infected patients on combination therapy maintains RBV dose, improves QOL, and corrects anemia. Patients who received epoetin α in both the DBP and the OLP maintained the RBV dose, QOL, and Hb benefits throughout the 16-week study period. Epoetin alfa was generally well tolerated, with the most commonly reported AEs being headache and nausea.

Although the current study was not designed to examine the effects of epoetin alfa on virologic response, maintenance of higher RBV doses has been shown in other studies to be associated with increased sustained virologic response (SVR) rates.^{1,10} For patients infected with HCV genotype 1, the likelihood of achieving an SVR is highest when at least 80% of the RBV dose and at least 80% of the IFN- α dose is maintained for at least 80% of the time,¹⁰ and one study has prospectively demonstrated that, in such patients, higher RBV doses

are associated with higher SVR rates.¹¹ Epoetin alfa was able to maintain RBV dose in 88% of patients in this study compared with only 60% on placebo, and the placebo group had a mean 170-mg RBV dose reduction from their initial therapeutic dose. The ability of epoetin alfa to maintain RBV dose effectively could potentially lead to improvements in virologic response rates.

In addition, treatment with epoetin alfa significantly improved patient QOL, as evidenced by results of patients given epoetin alfa during the DBP and patients switched from placebo to epoetin alfa in the OLP. Highly significant improvements were recorded in the areas of vitality, social functioning, and physical and emotional states. These results are particularly notable and encouraging because QOL in patients with chronic HCV infection is decreased compared with that of patients with other chronic conditions and that of healthy individuals.^{15,16} These improvements in QOL may lead to improved adherence to combination therapy.

Treatment with epoetin alfa significantly improved HCV therapy-induced anemia as well. Patients who received epoetin alfa in the DBP demonstrated a mean increase in Hb of >1 g/dL by week 4, with further increases thereafter. Interestingly, no increase in mean Hb levels was observed in the placebo group in the DBP; this result is likely a reflection of the stabilization of Hb levels that would occur secondary to the RBV dose reduction that those patients experienced. When placebo-treated patients crossed over to receive epoetin alfa in the OLP, these patients (P/EA group) showed significant increases in Hb (mean increase in Hb of >1 g/dL by week 12 [3 weeks after receiving epoetin alfa]), similar to the experience in the DBP of the patients randomized to receive epoetin alfa (EA/EA group). An initial small pilot study had suggested that antioxidant use with supplemental vitamin E and C might be beneficial in reducing RBV-induced hemolysis.¹⁷ However, several larger studies demonstrated no clinical benefit of antioxidants on RBV-induced hemolysis,^{18,19} and, thus, antioxidant use was not monitored in this study.

Collectively, the responses to epoetin α demonstrated by these 3 end points illustrate that a proactive approach to treating anemia in HCV-infected patients may impact treatment outcomes. For both the epoetin α and the placebo group, the mean Hb level at randomization in this study was 10.8 g/dL. Given the success achieved with epoetin alfa intervention at this Hb level, perhaps earlier intervention at the first appearance of anemia (Hb ≤ 12 g/dL) before any RBV dose reduction may provide additional clinical benefit.

The current study was designed to evaluate epoetin alfa in patients with already established anemia, and a significant proportion of patients had already had an RBV dose reduction prior to randomization, which occurred at a mean of 13 weeks into combination therapy. Clearly, recent data from the ongoing Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial demonstrated that, in prior nonresponders to HCV therapy who were retreated with PEG-IFN- α /RBV, a mean reduction in RBV dose (but not PEG-IFN- α dose) was associated with a significant decline in the end-of-treatment response and SVR rates.²⁰ Data from another study indicate that a reduction in RBV dosage before week 12 of therapy below 80% of the starting dose diminishes the chance of an early virologic response (EVR) from 80% to 60% with combination PEG-IFN- α /RBV treatment.²¹ This information suggests that RBV dose maintenance during the first 12 weeks of therapy is a critical predictor of EVR, which, in turn, has a strong predictive value for SVR. Thus, the opportunity to achieve an SVR may be compromised in many patients by early RBV dose reduction. It is presently unknown whether patients who have early RBV dose reduction followed by RBV dose increase have the same chance for successful HCV treatment outcome as patients who are never dose reduced. The design of our study did not allow for the assessment of virologic outcomes for efficacy, although data on virologic response were collected for safety. A study designed to evaluate the effect of epoetin alfa on virologic response could randomize patients before early dose reduction, but it would likely need criteria in addition to an absolute Hb value at which to initiate epoetin alfa therapy. Thus, the optimal timing of intervention with epoetin alfa (possibly before rather than after the development of anemia and RBV dose reduction) remains to be defined further in this patient population.

The design of this study has some other inherent limitations. Although the first 8 weeks of the study were blinded, QOL and Hb improvements were significant enough that investigators and patients may have suspected which patients were receiving epoetin alfa. Although the protocol specified that QOL questionnaires were to be completed before any procedures were performed or results were given to patients, the blind could have been somewhat compromised because it could have been evident to the investigators that patients with increasing/unchanged Hb and improved QOL were most likely receiving epoetin alfa. Similarly, it could have been evident to the patients who were feeling better that they may have received active treatment with epoetin alfa.

Nevertheless, the symmetry of the observed changes in QOL scores across the 2 phases of the study—that is, score changes on each SF-36 domain were similar for epoetin alfa-treated patients at the end of the DBP compared with score changes among the P/EA patients at the end of the OLP—suggests a real and substantial effect of epoetin α treatment on several domains of QOL, with the greatest impact on the vitality domain. A CNS effect independent of Hb increases is unlikely because regression analyses of these data show that patients who had Hb decreases from baseline to the end of the DBP did not have QOL increases.²²

In conclusion, we have shown that epoetin alfa 40,000 U SC administered once weekly is effective in maintaining RBV dose and improving QOL and Hb in anemic HCV-infected patients receiving combination therapy. Treatment with epoetin alfa, through its effects on tolerability of combination therapy and QOL, also has the potential to improve adherence rates, which may in turn improve virologic response rates. Future studies should focus on the pharmacoeconomic benefits of epoetin alfa therapy as well as its impact on virologic response rates.

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