Epoetin alfa Improves Quality of Life in Anemic HCV-Infected Patients Receiving Combination Therapy

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Anemia and decreased health-related quality of life (HRQL) are common in patients receiving combination therapy of interferon alfa (IFN) and ribavirin (RBV) for chronic hepatitis C virus (HCV) infection. In a randomized, prospective study evaluating the effectiveness of epoetin alfa in maintaining RBV dose, alleviating anemia, and improving HRQL in anemic (Hb ≤ 12 g/dL) HCV-infected patients receiving combination therapy, patients receiving epoetin alfa had significant improvements in HRQL compared with placebo. In this study, 185 patients were randomized to 40,000 units of epoetin alfa subcutaneously weekly or placebo for an 8-week double-blind phase (DBP), followed by an 8-week open-label phase during which all patients received epoetin alfa. To further assess the impact of epoetin alfa on HRQL, *post hoc* analyses were conducted in the same patient population to compare the HRQL of these patients at randomization with norms of other populations, and to determine the critical relationship between hemoglobin (Hb) levels and HRQL. Mean HRQL scores of anemic HCV-infected patients receiving combination therapy at randomization were significantly lower than those of both the general population and patients who had other chronic conditions. Patients receiving epoetin alfa who had the greatest Hb increases from randomization to the end of the DBP also had the largest improvements in HRQL. Hb improvement was an independent predictor of HRQL improvement in these patients. In conclusion, epoetin alfa provided clinically significant HRQL improvement in HCV-infected patients receiving IFN/RBV therapy. (HEPATOLOGY 2004;40: 1450–1458.)

Health-related quality of life (HRQL) is impaired in many disease states ranging from diabetes mellitus[1] to cancer.[2] Until recently, a common perception among treating physicians was that most patients infected with hepatitis C virus (HCV) did not experience a reduction in HRQL.[3] However, published data have suggested that HCV-infected patients have a decreased HRQL compared with the general population.[4] Studies have shown that HCV-infected patients who did not have cirrhosis but who were receiving treatment had a decreased HRQL when compared with groups of healthy individuals and patients infected with hepatitis B virus.[5,6] Similar decreases in HRQL have been demonstrated in cancer patients receiving chemotherapy, in whom HRQL was shown to correlate directly with hemoglobin (Hb) levels.[2,7] In these studies, patients receiving epoetin alfa treatment for their anemia not only experienced an increase in Hb but also exhibited clinically significant improvements in HRQL domains such as energy, activity, and overall quality of life.

Decreased Hb levels represent a common side effect of the interferon alfa (IFN) and ribavirin (RBV) combination or the pegylated interferon alfa (PEG-IFN) and RBV combination used to treat HCV infection, with 29% to 36% of treated patients developing anemia.[8] In a recent study, 54% of patients on this regimen experienced Hb decreases of 3 g/dL or more from pretreatment levels.[9] In

Abbreviations: HRQL, health-related quality of life; IFN, interferon alfa; RBV, ribavirin; HCV, hepatitis C virus; DBP, double-blind phase; Hb, hemoglobin; PEG-IFN, pegylated interferon alfa; SVR, sustained virological response; SF-36, Medical Outcomes Survey Short Form-36; LASA, linear analog scale assessment; OLP, open-label phase.

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a large clinical trial, anemia (defined as Hb < 12 g/dL) resulted in RBV dose reductions in 22% of patients,[10] and in a community-based setting, anemia resulted in the discontinuation of therapy in 36% of patients.[11] Decreased HRQL has also been associated with the discontinuation of therapy in HCV-infected individuals.[3] It is possible, in a manner similar to the situation with cancer patients receiving chemotherapy, that treatment to increase Hb levels in HCV-infected patients receiving IFN/RBV or PEG-IFN/RBV combination therapy may improve HRQL. These HRQL improvements may decrease discontinuation rates of IFN/RBV therapy, which could potentially result in a higher percentage of patients adhering to treatment, especially during the critical first 12 weeks of therapy.

A recent study by McHutchison and colleagues[12] examined treatment adherence in HCV-infected patients receiving combination therapy for 24 to 48 weeks. Results demonstrated that patients who maintained at least 80% adherence to therapy—which was defined as taking at least 80% of their RBV dose and at least 80% of their IFN dose for the entire course of treatment (or continuing treatment through week 36, at which point at least 80% of the expected treatment duration had been completed)—had sustained virological response (SVR) rates substantially higher than those who took less than 80% of each medication. A similar analysis of patients receiving PEG-IFN alfa-2b plus RBV showed that dose reductions of RBV alone or in combination with PEG-IFN significantly affected the early virological response rate.[13] Results from another trial that examined the retreatment of prior IFN or IFN/RBV nonresponders suggested that RBV dose reductions alone during the first 12 to 20 weeks of treatment resulted in a reduction of the SVR rate by more than 50%.[14] Maintenance of RBV dose has recently been shown to be of particular importance in patients infected with HCV genotype 1; results from a study comparing IFN/RBV therapy using a standard daily dose of RBV (1,000 mg or 1,200 mg) with IFN/RBV therapy using a lower dose of RBV (800 mg) demonstrated that the standard RBV dose was statistically superior to the lower dose, with an absolute difference in SVR rates of 11.9% between the standard and lower-dose treatment groups.[15]

A randomized, double-blind, placebo-controlled, multicenter clinical trial that evaluated the effectiveness of epoetin alfa versus placebo in maintaining RBV dose, alleviating anemia, and improving HRQL in anemic (Hb ≤ 12 g/dL) HCV-infected patients receiving combination therapy was recently published[16] (Fig. 1). The results of this study demonstrated that patients who received epoetin alfa (n = 93) experienced a significant

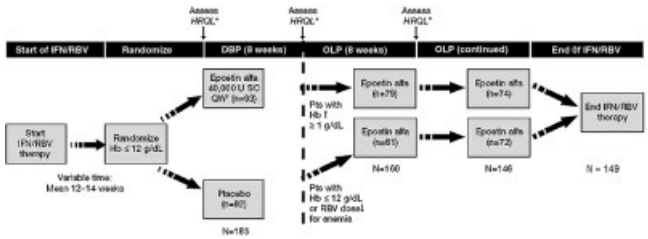

Fig. 1. Study design (adapted with permission from Afdhal et al.[16]). *Assessed using the SF-36 and the LASA. HRQL, health-related quality of life; IFN, interferon alfa; RBV, ribavirin; DBP, double-blind phase; OLP, open-label phase; SC, subcutaneously; Hb, hemoglobin.

increase in HRQL from randomization to the end of the double-blind phase (DBP)—measured using both the Medical Outcomes Survey Short Form-36 (SF-36) (version 2) and linear analog scale assessment (LASA)—when compared with patients who received placebo (n = 92). These increases were statistically significant in 7 of the 8 domains of the SF-36, as well as in all three categories measured by the LASA. Patients crossing over to epoetin alfa during the open-label phase (OLP) showed HRQL improvements that mirrored those in the epoetin alfa group during the DBP.

To further quantify and understand the effects of epoetin alfa on HRQL in HCV-infected patients, the objectives of this study were to compare the HRQL of anemic HCV-infected patients receiving IFN/RBV or PEG-IFN/RBV combination therapy (from the previously published trial[16]) with that of the general population, as well as with that of patients affected by other chronic conditions, and to retrospectively evaluate the relationship between HRQL and Hb levels in these patients.

Patients and Methods

Study Design. As previously reported by Afdhal et al.,[16] patients were eligible for enrollment in this study if they had developed anemia while receiving HCV combination therapy (either first course of treatment or retreatment for previous relapse or nonresponse). Inclusion criteria for the study were as follows: 18 to 75 years of age; Hb 12 g/dL or more at randomization; chronic HCV infection and on combination therapy with a planned treatment duration of at least 16 additional weeks; HIV-negative status; and willingness and ability 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 a serum ferritin level of less than 50 ng/mL; or significant atherosclerotic heart disease (a contraindication to

RBV therapy). Additional exclusion criteria included history of any primary hematological disease, history of or current uncontrolled hypertension (diastolic blood pressure > 100 mm Hg), or an uncontrolled seizure disorder. In addition, patients were excluded if they were currently pregnant or lactating, were of childbearing potential and not taking adequate birth control measures, were current active substance abusers, or had been exposed to epoetin formulations within 6 months prior to enrollment.

This study consisted of two treatment phases, followed by a 6-month safety monitoring period. The first treatment phase was an 8-week, double-blind, placebo-controlled, parallel-group phase (DBP; epoetin alfa vs. placebo); the second was an 8-week, open-label, modified crossover phase during which eligible patients (who had received either epoetin alfa or placebo in the DBP) received epoetin alfa. 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. Figure 1 outlines the design of the study from enrollment through the conclusion of the safety monitoring period.

In the 8-week DBP, eligible patients were randomized to treatment with 40,000 units of epoetin alfa (PROCRIT, Ortho Biotech Products, L.P., Bridgewater, NJ) weekly or matched placebo. An independent contract research organization generated the randomization schedule using permuted blocks, and the study drug was packaged and labeled for each patient based on this code. Each individual site enrolled participants who were 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 tear-off label that 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. Study drugs were identical in appearance and were packaged in identical containers.

The initial dose of the study drug was 40,000 units of subcutaneously weekly; this dose or matching placebo was titrated to 60,000 units weekly if Hb levels did not increase by 1 g/dL from randomization after 4 weeks of study drug treatment had been completed. 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 receiving placebo, if they had a RBV dose reduction due to anemia or ended the DBP with a Hb level of 12 g/dL or less.

Weight-based RBV dosing was suggested for all patients in the study. The RBV dose was to be reduced during the study when the Hb level fell below 10 g/dL and discontinued when it fell below 8.5 g/dL. These recommendations for RBV dosing were provided as guidelines only; final decisions regarding RBV dose adjustments were made by the investigators after complete assessment of patients' individual clinical situations.

HRQL was assessed at randomization and at the conclusion of the DBP and OLP using two instruments—the SF-36 and the LASA, both of which were administered by a health care professional. The SF-36 is a widely used, validated, generic HRQL instrument that measures eight different domains: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health.[17] The LASA is a patient-reported instrument that has been used extensively to evaluate HRQL in anemic patients and addresses three major constructs: activity level, energy level, and overall quality of life.[18] Both instruments use a 0 to 100 scoring scale for each domain or construct, with 0 representing the lowest possible score and 100 the best score. To minimize bias, the study protocol specified that these questionnaires be completed before any other study-related procedures were performed or test results given. Specifically, patients were kept blinded to laboratory values, including Hb, hematocrit, liver function tests, and HCV viral load until all study procedures were completed for the visit. Results from the assessment tools were checked immediately for thoroughness and completion, and attempts were made to capture missing information within 3 days of the office visit. The changes in HQRL between groups during the DBP and OLP were compared, as were the changes within each group during the DBP and OLP.

Safety. Patients were followed for safety throughout the DBP and OLP as described previously.[16] Patients remaining on epoetin alfa after the conclusion of the 8-week OLP were monitored for safety through the completion of their epoetin alfa and HCV combination therapy. Hb levels, HCV RNA (viral load), laboratory values, physical examination findings, and adverse events were monitored during this period and were evaluated during follow-up visits at 4 weeks, 3 months, and 6 months after completion of therapy.

Statistical Analyses. It was estimated that 90 patients per arm would provide 90% power to detect differences between the two treatment groups ($\alpha = .05$, two-sided) in the study. This estimation was based on results obtained in an earlier proof-of-principle, randomized, open-label, multicenter study of epoetin alfa treatment of anemic HCV-infected patients on combination therapy.[19] The intent-to-treat population with the last value carried forward to impute missing values was used in all analyses.

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

	Epoetin alfa (n = 93)	Placebo (n = 92)
Mean age, y (±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 (±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 (±SD, range)	12 (8, 1–33)	14 (11, 3–55)
HCV viral load (% undetectable), n (%)	54 (58)	45 (49)
Patients with marked fibrosis and cirrhosis, n (%)	31 (33)	34 (37)

*Reprinted from Afdhal et al.,[16] with permission from American Gastroenterological Association.

Post hoc analyses comparing the SF-36 HRQL values of study patients at randomization were compared with norms of other patient populations,[17,20] using independent sample *t* tests. These populations included age- and sex-matched controls from the general population, as well as patients with untreated chronic HCV infections,[20] congestive heart failure, clinical depression, or type II diabetes.[17] *Post hoc* analyses comparing HRQL in study patients with and without cirrhosis were performed at baseline, week 5, and the conclusion of the DBP.

Post hoc regression analyses of the relationship between Hb and HRQL were also conducted to determine whether increased Hb levels in anemic HCV-infected patients were associated with improved HRQL, regardless of the study drug received. Categorical analysis of change in HRQL related to change in Hb from randomization to the end of the DBP included the following groups: patients with a decrease in Hb; patients with a Hb increase from 0 to less than 2 g/dL; and patients with a Hb increase of 2 g/dL or more. These analyses controlled for age, sex, Hb level at randomization, Hb change between randomization and week 9, corresponding HRQL score for each domain at randomization, fibrosis status, RBV dose change, duration of HCV therapy, and HCV RNA levels (randomization and week 9 detectable/undetectable status). Regression models treated Hb change as either a continuous or a categorical variable. Multicollinearity for the variables in the regression model was evaluated prior to regression analysis.

Results

The study was initiated on November 1, 2001; the OLP concluded on November 22, 2002; and the follow-up phase concluded on November 6, 2003. A total of 185 patients were randomized in the DBP and were evaluable for efficacy (epoetin alfa, n = 93; placebo, n = 92). Patient demographics are summarized in Table 1.

Comparison of HRQL in HCV-Infected Patients With Population Norms. Mean SF-36 scores of anemic HCV-infected patients receiving combination therapy at study randomization were significantly lower than those of both the general population and patients who had untreated chronic HCV infection,[20] with the greatest disparities appearing in the physical functioning, role limitations (physical), vitality, and social functioning domains of the SF-36 (Table 2). Scores on the SF-36 domains of vitality, bodily pain, and social functioning for the study patients were consistently lower than those for all other populations in the analyses, which included groups of patients who had clinical depression, type II diabetes, and congestive heart failure.[17] By the conclusion of the OLP, these disparities had narrowed, with the scores of study patients on the SF-36 domain of vitality surpassing those of patients who had clinical depression.

Comparison of HRQL in Patients With and Without Cirrhosis. Liver biopsy reports were available for 164 patients. A total of 33 patients (epoetin alfa group, n = 15; placebo group, n = 18) had cirrhosis at baseline

Table 2. Study Population Mean Randomization SF-36 Scores Compared With Norms of Other Populations

SF-36 Domain	Study Population	Untreated Chronic HCV Infection	General Population*	Congestive Heart Failure	Type 2 Diabetes	Clinical Depression
Physical functioning	46.4	80.4†	79.4†	47.5	67.7†	71.6†
Role limitations (physical)	37.9	67.5†	72.8†	34.4	56.8†	44.4‡
Bodily pain	50.4	70.6†	71.4†	62.7†	68.5†	58.8†
General health	52.9	61.5†	70.7†	47.1‡	56.1	52.9
Vitality	25.1	52.4†	61.1†	44.3†	55.7†	40.1†
Social functioning	43.0	78.7†	79.1†	71.3†	80.0†	57.2†
Role limitations (emotional)	55.3	76.8†	78.5†	63.7‡	75.6†	38.9†
Mental health	61.0	73.1†	72.6†	74.7†	76.7†	46.3†

NOTE. The 0 to 100 scale was used for all scoring.
*Age and sex matched to study population.
†$P < .001$ versus study population.
‡$P < .05$ versus study population.

(Metavir score F4). HRQL measures in these patients were not significantly different than those in patients without cirrhosis ($P > .05$ for all domains of the SF-36 and LASA). In addition, there were no significant differences in HRQL between patients with and without cirrhosis when it was assessed at week 5 (patients with cirrhosis, n = 30; epoetin alfa group, n = 12; placebo group, n = 18) and week 9 (patients with cirrhosis, n = 26; epoetin alfa group, n = 11; placebo group, n = 15).

Analyses of Changes in Hb and HRQL. Patients who demonstrated the greatest Hb increases from randomization to the end of the DBP also had the greatest improvements in HRQL during that time. Hb increases of 2 g/dL or more were associated with improvements in SF-36 scores, with increases ranging from 3 to 20 points across all domains (Fig. 2A). In addition, patients with Hb increases of 2 g/dL or more had an increase of 17 to 22 mm on the 3 constructs measured by the LASA (Fig. 2B). Significant improvement in HRQL was also seen in patients with Hb increases of 0 to 2 g/dL. These patients demonstrated an increase of 0.5 to 7 points across all domains of the SF-36, and an increase of 6 to 10 mm in all constructs of the LASA. In contrast, patients whose Hb decreased during the DBP experienced a decrease in the role limitations (physical), general health, vitality, role limitations (emotional), and mental health domains of the SF-36 as well as the activity domain of the LASA, while showing only minimal increases in the other domains of both measurement tools.

Regression analysis demonstrated that Hb change was a significant independent predictor of HRQL change in all constructs of the LASA and in 6 of 8 domains of the SF-36. When Hb was evaluated as a continuous variable, the parameter estimates indicated increases in vitality and physical functioning (SF-36) and energy scores (LASA) of 4.26, 2.73, and 4.48, respectively, for each 1-g/dL increase in Hb relative to Hb at randomization. Among all of the variables used in the regression model (age, sex, Hb level at randomization, Hb change between randomization and week 9, corresponding HRQL score for each domain at randomization, fibrosis status, RBV dose change, duration of HCV therapy, and HCV RNA levels

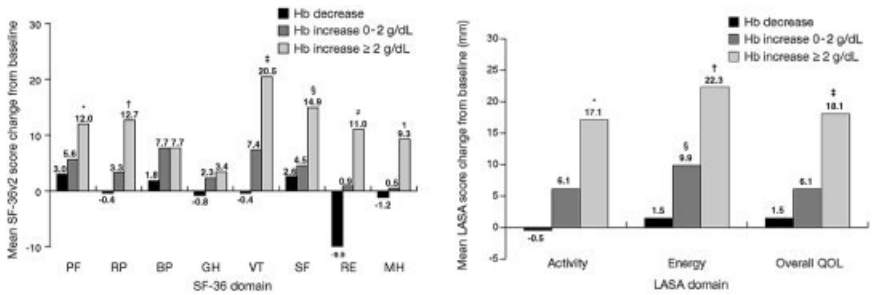

Fig. 2. Mean change in SF-36 and LASA scores by Hb change during the DBP. (A) Change in SF-36 scores in patients with Hb decrease, Hb increase of 0 to 2 g/dL, and Hb increase of 2 g/dL or more. *$P = .016$; †$P = .0008$; ‡$P < .0001$; §$P = 0.039$; #$P = 0.007$; ¶$P = .011$; all P versus Hb decrease. (B) Change in LASA scores in patients with Hb decrease, Hb increase of 0 to 2 g/dL, and Hb increase of 2 g/dL or more. *$P = .0004$; §$P = .0178$; †$P < .001$; ‡$P = .0010$; all P versus Hb decrease. Hb, hemoglobin; SF-36v2, Medical Outcomes Survey Short Form-36, version 2; PF, physical functioning; RP, role limitations, physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitations, emotional; MH, mental health.

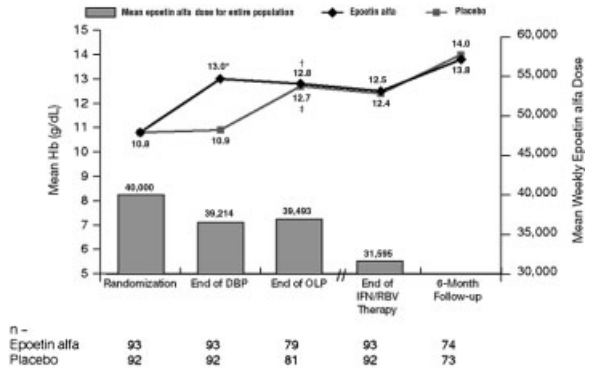

Fig. 3. Mean Hb levels from randomization through the 6-month follow-up period; mean weekly epoetin alfa dose (units) from randomization through the conclusion of combination therapy. †$P < .001$ versus epoetin alfa group at randomization; ‡$P < .001$ versus placebo crossover group at week 9; *$P < .001$ versus the placebo group. Hb, hemoglobin; DBP, double-blind phase; OLP, open-label phase; IFN, interferon alfa; RBV, ribavirin.

[randomization and week 9 detectable/undetectable status]), Hb change was the variable most strongly associated with HRQL improvement. When compared with the other variables in the model, Hb was also the most stable and consistent predictor for HRQL improvement across all domains.

The mean Hb of the study population from randomization to the end of the follow-up period is summarized in Fig. 3. The improved Hb levels relative to randomization attained by both treatment groups by the end of the OLP were maintained during the continuation of the OLP. Mean Hb levels returned to pre–HCV treatment levels by the end of the 6-month follow-up period after HCV therapy completion. Mean laboratory parameters, including total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma glutamyltransferase remained within the normal range from the conclusion of the OLP to the conclusion of HCV treatment.

Safety. The results of the safety analyses of the DBP and OLP have been previously reported.[16] A total of 20 serious adverse events occurred during the study, with 8 occurring during the continuation of the OLP (week 17 and thereafter). These events included fever, esophageal variceal bleed, gastric variceal bleed (the latter two events occurring in the same patient), chest pain, cholecystitis, foot drop, and involuntary muscle contractions (the latter two events occurring in the same patient). One patient developed hemolytic anemia while receiving epoetin alfa during the OLP, despite RBV dose adjustment; this patient received a transfusion and recovered without further sequelae. All 8 events were considered by investigators not to be related to the study drug. One death occurred during this period (the patient with esophageal and gastric variceal bleeds). The most common adverse events during the continuation of the OLP (N = 140) were headache (n = 14; 10%), diarrhea (n = 12; 9%), and insomnia (n = 12; 9%).

The percentages of patients with an undetectable viral load at randomization were 58% and 49% in the epoetin alfa and placebo groups, respectively; these percentages increased to 75% and 73%, respectively, by the conclusion of the OLP (week 17) (Fig. 4A). This increase was seen in patients regardless of prior treatment status; the percentage of treatment-experienced patients with an undetectable viral load increased from 42% to 70%, and the percentage of treatment-naïve patients with an undetectable viral load increased from 60% to 77% (Fig. 4B).

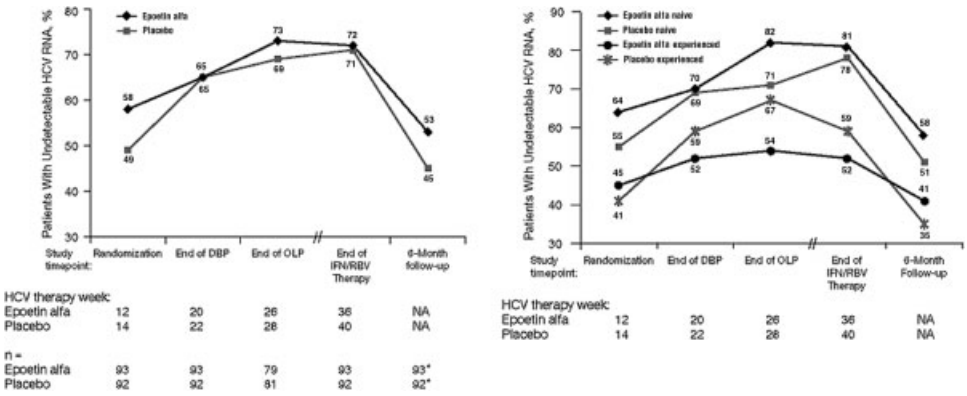

Fig. 4. Percentage of patients with undetectable HCV RNA throughout the study and follow-up period. (A) Overall percentage of patients with undetectable HCV-RNA, stratified by study treatment group. *Seventy-six patients (41%) (32 epoetin alfa, 44 placebo) had detectable HCV RNA; 19 patients (10%) (12 epoetin alfa, 7 placebo) had undetectable HCV RNA at the end of combination therapy, but did not have 6-month follow-up measurements. (B) Percentage of patients with undetectable levels of HCV RNA, stratified by treatment status (treatment-naïve or treatment-experienced), from randomization through 6 months after the completion of epoetin alfa and HCV combination therapy. HCV, hepatitis C virus; DBP, double-blind phase; OLP, open-label phase; IFN, interferon alfa; RBV, ribavirin; NA, not available.

Discussion

Recently published work by Afdhal et al.[16] has demonstrated that weekly dosing with 40,000 units of epoetin alfa maintained the RBV dose and increased Hb levels in anemic HCV-infected patients undergoing combination therapy. Furthermore, HRQL was significantly improved in these patients. The results of the current analyses further suggest that increases in Hb are independently associated with increases in HRQL in HCV-infected patients, with the largest Hb increases producing the greatest improvements in HRQL.

The increase in HRQL seen after epoetin alfa treatment in this trial is particularly important when considering the patient population studied. HCV-infected individuals receiving treatment for their disease had a lower randomization HRQL than both healthy controls and patients with chronic diseases such as diabetes mellitus, chronic depression, and congestive heart failure.[17,20] This disparity could be attributable to a number of factors, including side effects of HCV combination therapy. Known side effects of this regimen include not only anemia, but also fatigue, myalgia, flu-like symptoms, clinical depression, and alterations in concentration, mood, and libido.[3,21,22] In the current study, the differences in randomization SF-36 domain scores between the study population and the aforementioned chronic disease populations were especially apparent in the physical functioning, vitality, and social functioning domains. After completion of the OLP, score disparities in all domains between the study population and the other populations narrowed considerably, with scores of the study population actually surpassing those of other groups in certain domains.

Clinically significant improvement in HRQL was defined in a meta-analysis by Samsa et al.[23] to be represented by an increase in SF-36 domain scores of 3 to 5 points. Ware et al.[17] suggested that an increase of 10 points exerted a moderate effect on patients' HRQL. Using these criteria, the findings of the current study suggest that patients receiving epoetin alfa experienced clinically significant improvements in HRQL across all domains of the SF-36, with moderate improvements in the areas of physical functioning and role limitations (physical). The vitality and social functioning domain scores showed even greater improvement, increasing 15 to 20 points after epoetin alfa treatment. The clinical significance of changes in LASA scores was addressed in a study by Patrick et al.[24], who demonstrated that a score increase of 9 to 10 points in each domain represented the minimum score change that patients would perceive as having a beneficial effect on their HRQL. If these criteria are applied to the results of the current study, patients experienced a beneficial effect on their HRQL from epoetin alfa treatment as measured by all three constructs of the LASA, with increases of 16 to 22 mm from randomization achieved by the end of the OLP. It is important to note that HRQL improves in HCV-infected patients who achieve an SVR[25]; therefore, viral clearance may have contributed to the HRQL changes observed with epoetin alfa treatment in this study. However, the design of this study did not allow detection and evaluation of differences in this effect, nor was HRQL evaluated at the initiation of combination therapy. Furthermore, because the regression analyses were based solely on the results at the end of the 8-week DBP, the depth of the HRQL changes caused by increases in Hb may not have been fully revealed.

Previous studies have shown that both anemia and decreased HRQL are reasons often cited by patients for the discontinuation of combination therapy.[3,10,11] In this study, epoetin alfa treatment improved both of these factors and therefore has the potential to increase patient adherence to the combination regimen. This, in turn, may increase the percentage of patients achieving a SVR. Adherence to RBV therapy, in particular, has been shown to significantly impact SVR; recent data suggest that the reduction of RBV dose alone during the first 12 to 20 weeks of treatment results in a significant decrease in SVR rates in a retreatment population.[14] In addition, data from the safety portion of this trial indicated that epoetin alfa treatment not only maintained Hb levels for the duration of HCV combination therapy, it also did not adversely affect HCV RNA clearance. There was an 8–percentage point improvement in SVR in the epoetin alfa group relative to placebo (53% vs. 45%, respectively). This is not a trivial difference, especially considering that 20% of the patients enrolled in the epoetin alfa group had already reduced their dose of RBV prior to entering the study. Although these results strongly suggest that epoetin alfa therapy is likely to significantly increase SVR by preventing the need to reduce RBV dosage, this study was not designed to detect a significant difference of this magnitude (8%) at an alpha level of 0.05. In addition, because patients in this study were not stratified by genotype, prior therapy, or fibrosis score at enrollment, there were slightly fewer genotype 1 patients (72% vs. 76%) and patients with cirrhosis (33% vs. 37%) and slightly more treatment-naïve patients (69% vs. 60%) in the epoetin alfa group than in the placebo group. These imbalances could possibly account for some of the differences in SVR. Although the results of this study do not indicate that epoetin alfa improves SVR, they clearly provide support for additional studies with adequate sample size to deter-

mine if adjuvant epoetin alfa therapy is associated with a statistically significant improvement in SVR.

Future investigations prompted by this study could also focus on the marked improvement in mental functioning reported by study patients, because the contribution of the potential central nervous system effects of epoetin alfa to increases in HRQL has yet to be determined. With an appropriate study design, it might be possible to separate the HRQL improvements due to a direct central nervous system effect of epoetin alfa treatment from the improvements attributable to a rise in Hb. As previously mentioned, the relationship between increases in HRQL, treatment adherence, and SVR has yet to be determined.

These data show that the HRQL of anemic HCV-infected patients receiving combination therapy is lower than that of the general population, untreated HCV-infected patients, and individuals with other chronic conditions. The data also demonstrate that an increase in Hb is a strong independent predictor of HRQL improvement in these patients. Epoetin alfa therapy in the anemic HCV-infected population successfully increased Hb and provided patients with a clinically significant improvement in HRQL.

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