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The incidence, predictors and management of anaemia and its association with virological response in HCV/HIV coinfecting persons treated with long-term pegylated interferon alfa 2a and ribavirin

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SUMMARY

Background—The association of anaemia with outcomes in the HCV/HIV coinfecting persons undergoing HCV treatment remains unclear.

Aims—To study the incidence, predictors and management of anaemia, and its association with outcomes among persons treated with pegylated interferon and weight-based ribavirin.

Methods—Retrospective analysis of a prospective controlled treatment trial of HCV/HIV coinfection.

Results—Among 329 subjects enrolled, 40% developed anaemia during the first 12–18 weeks of treatment (median haemoglobin decrease at week 4: 2.2 g/dL). Among 169 subjects who achieved early virological response and received therapy for 72 weeks, 55% eventually developed anaemia. However, median haemoglobin levels stayed stable after 12–18 weeks of initial therapy. Among these 169 subjects, 45% were prescribed an erythropoiesis stimulating agent (ESA), with 17% receiving it prior to a drop in haemoglobin meeting protocol definition of anaemia. Only 27% completed the study without any ribavirin dose modification. Age >40 years, lower BMI, zidovudine use and lower entry haemoglobin were significant predictors of anaemia in the multi-covariate model. Among all 329, sustained virological response (SVR) rate was similar in those with or without anaemia (23% vs. 30%; $P = 0.17$) with no evidence of association between anaemia or ESA use and treatment response.

Conclusions—Anaemia is common in HCV/HIV coinfecting persons undergoing HCV treatment, and only a minority of them are able to maintain ribavirin dose. Persons with age >40 years, lower baseline haemoglobin and lower baseline BMI should be monitored carefully.

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Prescription of erythropoiesis stimulating agent is common, but anaemia or erythropoiesis stimulating agent use is not associated with SVR.

INTRODUCTION

The prevalence of hepatitis C virus (HCV) in persons infected with the human immunodeficiency virus (HIV) ranges from 16% to 34%.^{1, 2} Treatment of HCV in HIV coinfecting persons is less effective than in HCV monoinfected persons.^{3, 4} In actual clinical settings, a minority of patients infected with HCV are ever initiated on treatment,⁵ and the rate of treatment initiation is even lower among those coinfecting with HIV.⁶ Anaemia is nearly twice as common in HCV/HIV coinfecting persons compared with HCV monoinfected persons,⁶ and pre-treatment anaemia is one of the strongest predictors of non-initiation of treatment,⁶ and premature discontinuation of treatment among those who are started on treatment.^{7, 8} In some studies of genotype-1 HCV monoinfected persons, development of anaemia has been associated with a higher virological response, which is likely a reflection of higher ribavirin exposure,^{9, 10} but a recent review of literature and a study of HCV/HIV co-infected subjects did not confirm this association.^{11, 12} On the other hand, pre-treatment anaemia is also one of the strongest predictors of mortality in this population.¹³

Anaemia may develop early in the course of treatment, or may be delayed. The relative frequency, predictors and implications of early and late anaemia are poorly understood. It is critical to further describe the precise nature and relationship of anaemia to HCV treatment, its effect upon virological response and to devise optimal strategies to manage anaemia in the HCV/HIV coinfecting population. We therefore sought to describe the incidence, severity and time to development of anaemia, identify its predictors and to describe management with erythropoiesis stimulating agents (ESA) and ribavirin (RBV) dose modifications among persons treated with pegylated interferon alfa 2a (PEG) and weight-based ribavirin (WBR) in a prospective controlled treatment trial in HCV/HIV coinfection.

METHODS

Study design

A5178 was a prospective, open-label, controlled trial (National Institutes of Health Registration number NCT00078403) designed to determine the effects of PEG maintenance therapy on fibrosis progression in HCV/HIV coinfecting subjects who failed to respond to 12 weeks of treatment with PEG and WBR. Evaluations of anaemia and use of erythropoiesis stimulating agents were prespecified secondary aims. The study schema is shown in Figure 1. Briefly, eligible subjects were treated with PEG 180 mcg SQ per week plus WBR (1000 mg for ≤ 75 kg; 1200 mg for > 75 kg) for 12–18 weeks (Step 1). The 6-week window at the end of Step 1 was allowed to complete screening evaluations for subsequent step. Subjects who had at least a two $\log_{10}$ reduction in HCV RNA from baseline or undetectable virus (< 600 IU/mL) at week 12 were classified as having an early virological response (EVR) and, if they had tolerated PEG on Step 1, were entered into a treatment continuation step to complete a total 72-week course of PEG and WBR (Step 3). Those who failed to achieve an EVR were randomised to receive maintenance therapy with PEG or observation only (Step 2). Here, we report the results of anaemia in subjects in Steps 1 and 3, as only subjects in these arms received PEG and WBR.

Subject eligibility

A complete list of eligibility criteria for the parent study has been previously published.¹⁴ Briefly, subjects ≥ 18 years of age, coinfecting with HCV and HIV were enrolled if they had

HIV-1 RNA <50 000 copies/mL, a CD4 count of >200 cells/mm³, and HCV viraemia, defined as detectable levels of HCV RNA by RT-PCR or bDNA. Subjects could be HCV treatment naïve or experienced. Other laboratory criteria required for entry included absolute neutrophil count (ANC) ≥1000/mm³; haemoglobin ≥11 for men and ≥10 g/dL for women; platelets ≥70 000/mm³; creatinine ≤1.5 mg/dL; international normalised ratio (INR) <1.5; alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase ≤10× upper limit of normal (ULN); direct bilirubin <1.5 mg/dL; lipase ≤1.5× ULN; and a normal thyroid-stimulating hormone (TSH) or normal thyroid function on full thyroid panel.

Subjects were excluded if they had an AIDS-defining opportunistic infection within 12 weeks prior to study entry, evidence of decompensated liver disease or other significant liver disease (including HBV, HAV, hemochromatosis), systemic corticosteroid use within 14 days of study entry, active drug/alcohol abuse that, in the opinion of the site investigator, would interfere with study adherence, uncontrolled seizure disorder, uncontrolled depression, history of autoimmune processes, or history of major organ transplantation.

Definition of anaemia

Protocol-defined toxicity management for anaemia recommended ribavirin dose reduction at haemoglobin decrease to <11 g/dL for men and <10 g/dL for women. Decreases in haemoglobin below to <10 g/dL in men and 9 g/dL in women required temporary or permanent discontinuation of ribavirin. Use of ESA was permitted at the discretion of the investigator with no protocol-specified guidance. Therefore, anaemia was defined as a drop in haemoglobin to below 11 g/dL for men and 10 g/dL for women for this analysis.

Statistical analysis

The rate of anaemia was summarised with two-sided 95% Binomial confidence interval. Kaplan–Meier survival analysis was used to estimate time to development of anaemia with follow-up censored at initiation of ESA or RBV dose reduction or discontinuation. Subjects who were initiated on ESA and/or had a RBV dose reduction immediately prior to developing anaemia were considered events. For these cases, the time to ESA initiation or RBV dose reduction, whichever occurred earlier, was considered the time of anaemia.

Age, gender, race, ZDV use, HCV genotype, cirrhosis, prior HCV treatment, and entry body mass index (BMI), CD4 cell count, HIV RNA, HCV RNA, ALT and haemoglobin were assessed as predictors of anaemia. Medians with lower (*Q1*) and upper quartile (*Q3*) are provided to summarise continuous variables. Wilcoxon rank-sum tests were used to test statistical significance of differences between two groups in continuous measures. Comparisons of categorical measures between two groups used exact tests. Time-adjusted univariate and multi-covariate logistic regression analyses were used to identify factors associated with development of anaemia. As development of anaemia may be related to duration of exposure to RBV and use of ESA, the logistic regression analyses were adjusted for follow-up time censored at initiation of ESA or RBV dose reduction or discontinuation. As there were significant differences in entry haemoglobin between some subsets (e.g. gender, race and entry HIV RNA, ALT), analysis of all other factors were conducted controlling for entry haemoglobin level. Two-sided *P*-values <0.05 were considered statistically significant. No adjustment for multiple testing was made in this exploratory analysis. Statistical analysis was performed using Statistical Analysis System, Version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

Ethical issues

The study protocol was reviewed and approved by National Institute of Allergy and Infectious Diseases and Institutional Review Boards at each performance site. All subjects

provided informed consent prior to enrolment. An independent Study Monitoring Committee provided monitoring and oversight during the conduct of the trial.

RESULTS

A total of 329 subjects started treatment with PEG and WBR in Step 1 of the study. Of these, 184 (55.9%) achieved an EVR. Of those 184, 169 continued treatment with PEG and WBR in Step 3. We report the incidence, predictors, time to development of anaemia and outcomes in all 329 during the first 12–18 weeks of the study (Step 1) and in up to 96 weeks of follow-up from Step 1 entry to the end of Step 3 in the 169 EVRs who entered Step 3.

Anaemia during the first 12–18 weeks of treatment (Step 1)

The median age (*Q1–Q3*) was 48 (42–52) years, 83% were male, 43% were white, 37% black, and 15% Hispanic. Thirty-two per cent had received any prior HCV treatment and 23% were on a zidovudine (ZDV)-based antiretroviral (ARV) regimen at study entry. Further baseline characteristics are provided in Table 1.

One hundred and thirty-three (40.4%, 95% CI: 35.1–45.9%) developed anaemia. Most anaemia was observed within the first weeks of starting the therapy with PEG and WBR (Figure 2a). The median drop in haemoglobin from baseline to week 4 was 2.2 g/dL (1.1–3.3 g/dL) and remained at a stable level at week 8 (median drop from baseline of 2.1 g/dL, 1.3–3.0 g/dL) and at week 12 (2.0 g/dL, 1.1–3.0 g/dL) (Figure 3).

On Step 1, 120 subjects (36.5%) were prescribed an ESA, with 44 of these prescribed ESA prior to a drop in haemoglobin that was sufficient to diagnose anaemia per protocol. Twenty-seven subjects were prescribed ESA, but never developed anaemia on Step 1 (Table 2). Among the 166 (50.5%) subjects who had a change in RBV prescription, ribavirin dose was reduced in 36.1%, temporarily held in 29.5% and prematurely discontinued due to any reason in 34.3% (Table 2). A total of 89/329 subjects (27.1%) both had a RBV dose reduction and were prescribed ESA on Step 1.

Anaemia among subjects who received long-term PEG and WBR (Step 1 and Step 3)

Of the 169 subjects who achieved EVR, tolerated PEG on Step 1 and received long-term treatment with PEG and WBR on Step 3, 89% were male; 52% White, 29% Black and 14% Hispanic. The median age at study entry was 47 years (42, 51). Twenty-nine percent were HCV treatment experienced and 19% were on a ZDV-containing ARV regimen (Table 1).

Ninety-three (55.0%, 95% CI: 47.2–62.7%) experienced anaemia between Step 1 entry and the end of Step 3. Of those, 34 subjects (36.6%) first experienced anaemia on Step 3. The median drop in haemoglobin from study entry to end of treatment at week 72 was 2.15 g/dL (0.2–3.25 g/dL) (Figure 4). There was no further drop in median haemoglobin for the group who entered Step 3 from Step 3 entry until end of therapy (72 weeks of treatment with PEG and WBR). Time to development of anaemia with follow-up censored at initiation of ESA or RBV modification is illustrated in Figure 2b.

Of the 169 who received long-term treatment with PEG and WBR, 76 subjects (45.0%) were prescribed an ESA, with 29 (17.2%) subjects having been prescribed before a drop in haemoglobin met the protocol-specified definition of anaemia. Median time of initiation of an ESA was week 8.1 (3.9–14.0) and total duration of prescription was 56.1 weeks (30.1–66.43) (Table 2). Among 123 subjects who had a change in ribavirin prescription, the worst ribavirin modification experienced over the course of treatment was dose reduction (30.9%), temporary stop (22.8%) and premature discontinuation in (46.3%) (Table 2). A total of

68/169 subjects (40.2%) both had a RBV dose reduction and were prescribed ESA on Step 1 or Step 3.

Anaemia on Step 2

Subjects who entered Step 2 (i.e. those who did not achieve early virological response at week 12 and were then randomised to maintenance PEG or observation only) recovered their haemoglobin rapidly and maintained it while on Step 2. (Figure 3).

Predictors of anaemia (Step 1 and Steps 1 + 3)

Among the 329, entry haemoglobin, and age ≥ 40 years, lower BMI, male gender and ZDV use controlling for entry haemoglobin were significantly associated with odds of developing anaemia on Step 1 in univariate analyses. In the multi-covariate model, older age, male gender, ZDV use and lower entry haemoglobin remained significant (Table 3).

Among the 169, older age, lower BMI, ZDV use and lower entry haemoglobin were significant predictors of anaemia in the multi-covariate model (Table 3).

Anaemia, ESA use and HCV treatment response

Among the 329 subjects enrolled, the EVR rate was higher in those who did not experience anaemia in Step 1, but the observed difference was not statistically different; EVR was achieved in 51.9% with anaemia and 58.7% without ($P = 0.26$). SVR was achieved in 22.6% of those with anaemia and 29.6% of those without anaemia ($P = 0.17$) (Figure 5). There was no evidence of association between ESA use on Step 1 and HCV treatment response.

Among the 120 subjects who received ESA on Step 1, 55.8% achieved EVR, 41.7% cEVR and 26.7% SVR compared to 56.0%, 43.1% and 26.8% among the 209 subjects who did not receive ESA on Step 1 ($P = 1.0, 0.82$ and 1.0 respectively).

Among the 169 subjects who achieved EVR in Step 1 and entered Step 3, the SVR rate was 57.0% among those who experienced anaemia ($N = 93$) and 46.1% among those who did not experience anaemia ($N = 76$; $P = 0.17$). Among the 76 subjects who were prescribed ESA, the SVR rate was 50.0% compared to 53.8% among the 93 subjects who did not receive ESA ($P = 0.65$).

As some previous studies have reported a drop in haemoglobin of >3 g/dL, we conducted additional analysis using this definition. In our study, 170/329 (51.7%) Step 1 subjects had a >3 g/dL drop in haemoglobin from baseline during Step 1. Among the 169 Step 3 subjects (i.e. those who went on to receive 72 weeks of therapy with PEG-IFN and RBV), 127 (75.1%) had a >3 g/dL drop in haemoglobin compared to entry during Steps 1 or 3. Of these 127, 42 first had a >3 g/dL drop on Step 3. Therefore, the overall proportion of subjects with a >3 g/dL haemoglobin drop was 64.4%.

We also analysed the association between adherence to ribavirin and presence of anaemia at week 12 on Step 1 among all Step 1 subjects ($N = 329$) and among Step 3 subjects ($N = 169$) at Step 3 entry, Step 3 study weeks 12, 24, 48 and at the completion of treatment at study week 72. Non-adherence to ribavirin was not associated with anaemia at any of the time points (data not presented).

DISCUSSION

Anaemia is among the strongest risk factors associated with non-initiation and noncompletion of HCV treatment among HCV and HCV/HIV coinfecting persons.⁶⁻⁸ In our study, 40.4% of the subjects developed anaemia in the first 12–18 weeks of therapy, and

only 49.5% of the subjects completed the first 12 weeks without any changes in ribavirin prescription, with 17.3% of the subjects discontinuing ribavirin in this time period. Anaemia developed rapidly, and haemoglobin values reached a nadir by the fourth week of therapy with smaller fluctuations seen in the subsequent period. Among the subjects who stopped ribavirin therapy, haemoglobin values recovered almost as rapidly as the decline in the earlier period. Among Step 1 + 3 subjects (i.e. those who were able to complete the first 12 weeks of therapy, achieved an early virological response at week 12, and continued to receive PEG and WBR), 55.0% developed anaemia over the full duration of study, and only 27.2% were able to maintain the dose of ribavirin throughout the study. These data are remarkable in that such a high proportion of subjects developed anaemia or required ribavirin dose modification or discontinuation. It also demonstrates that anaemia may develop late in therapy, and providers should remain vigilant even after the patients appear to have reached a steady state in the initial weeks of therapy.

We found that lower entry haemoglobin, older age, and zidovudine use were strongly predictive of anaemia on treatment. Controlling for entry haemoglobin which was lower in women, men were more likely to develop anaemia. Unfortunately, the number of women was too small for detailed analyses comparing men and women. Zidovudine is associated with anaemia even in the absence of concomitant ribavirin administration in HIV infected persons as well as healthy volunteers.^{15–17} While administration of any effective combination antiretroviral therapy to anaemic HIV infected persons improves haemoglobin levels, the time to improvement is longer among those who receive a zidovudine-based regimen.¹⁸ As the most recent treatment guidelines do not recommend zidovudine as part of a preferred first line antiretroviral regimen, the potentiation of anaemia by co-administration of zidovudine and ribavirin would appear to be of lesser concern in HIV-infected persons contemplating their first antiretroviral regimen. However, among treatment experienced patients who require anti-HCV therapy, the providers need to be mindful of this effect. If treatment for HCV is being contemplated in persons ≥ 40 years old, more aggressive monitoring of haemoglobin and minimization of any other risk factors should be undertaken. The role of improving pre-treatment haemoglobin using ESA is a potential strategy that has not been adequately tested in this setting.

Over one-third of the subjects were prescribed an ESA during the initial period of treatment, with a significant proportion being prescribed an ESA prior to meeting the definition of anaemia by haemoglobin criteria. Among those who achieved early virological response and continued on PEG and WBR to complete the total of 72 weeks of treatment almost a half received ESA. Use of ESA is a costly strategy, but has been associated with enhanced rates of maintained ribavirin dosing,¹⁹ improvements in target haemoglobin levels,²⁰ and improved health-related quality of life measures.¹⁹ Compared with ribavirin dose reduction, treatment with ESA has been advocated as cost effective, with estimates ranging from US \$33 382 to 64 311 per additional quality-adjusted life-year gain, depending on the agent used.²¹ These potential benefits should be carefully weighed against possible risks of ESA use demonstrated in the non-HCV population.^{22–24} In a recent small study, ESA use was not associated with increased risk of cardiovascular events, malignancy, thrombosis, or death in HCV-infected patients during receipt of HCV therapy or in the period after completion.²⁰

A major concern regarding development of anaemia and subsequent reduction in RBV dosing or its temporary or permanent discontinuation is the potential for virological failure. However, we did not see evidence of a difference in EVR or SVR among those with and without anaemia, although the rates of both EVR and SVR were slightly higher among subjects who did not experience anaemia. We also did not observe an effect of ESA prescription upon virological response. The role of anaemia upon SVR is controversial. A study by Nunez *et al.* found no association between development of anaemia and SVR in

HCV/HIV coinfecting persons enrolled in the PRESCO trial.¹¹ This is in contrast to two recent studies in HCV monoinfected subjects which reported higher rate of SVR among those who developed anaemia.^{9, 10} In the study by Sulkowski *et al.*⁹ subjects who received an ESA in the first 8 weeks of therapy and did not require dose reduction of RBV had higher SVR compared with those who did not receive an ESA. The percentage of intended dose of RBV delivered was significantly higher among those who received an ESA compared with those who did not, 64% vs. 43% ($P < 0.001$) suggesting that the effect is primarily mediated through a higher RBV exposure. In the study by Sievert *et al.*,¹⁰ subject who developed anaemia during week 5–48 of therapy had a higher SVR, but those who developed anaemia in the first 4 weeks had no association with SVR. The reason for this remains unclear, but it is possible that subjects who developed anaemia in the first 4 weeks may have had dose reductions in RBV or treatment discontinuation, and the rest of the subjects had a higher exposure to RBV.

Other than zidovudine use, HIV-related factors were not associated with an increased risk of anaemia. Although reasonable control of HIV replication and a relatively preserved CD4+ lymphocyte count are usually required for enrolment in many clinical trials as well as in actual clinical setting when treating HCV infected persons, evidence supporting this practice is sparse. Similarly, no HCV-specific factors were associated with the risk of anaemia in our study. Recently, genetic variants leading to inosine triphosphatase (ITPA) deficiency have been shown to protect against anaemia in patients treated for HCV.²⁵ Such information was not available at the time our study was conducted, and the prevalence and effect of such gene variants among our study subjects remain unknown.

There is some discrepancy in the rates of anaemia in our study compared with some previously published studies, which have reported the rate of anaemia to be in the 12–16% range.^{10, 16, 17} This is likely due to the different definition of anaemia. Most studies define anaemia as a drop in haemoglobin to <10 g/dL, without accounting for gender differences or baseline haemoglobin. The definition of anaemia has long been debated and was discussed by Beutler *et al.* in an elegant and critical review.²⁶ One consistent aspect of defining a 'normal' haemoglobin has been the difference based on gender. Numerous studies cited in the above article unanimously use different levels for men and women. Most studies that have attempted to define the 'normal' haemoglobin have consistently found the lower limit of normal to be 13–14 g/dL for men and on average 1 g/dL lower for women. Additionally, a drop in haemoglobin to less than 10 g/dL translates to a nearly 30% drop in haemoglobin for men based on average baseline haemoglobin for most studies. The median baseline haemoglobin in our study was 14.8 g/dL for men and 13.1 g/dL for women, and a drop to 11 g/dL and 10 g/dL for men and women represents a 26% and 24% drop from baseline respectively. On the basis of these data, we felt that using a uniform definition for men and women is not appropriate and that our defined limits are more clinically relevant and appropriate. When we compare studies which reported a drop in haemoglobin from baseline, our results are closer to the previously results. For example, compared to 64% of subjects who had a drop in haemoglobin >3 g/dL in our study, 61% of subjects on an AZT-based regimen in the study by Alvarez *et al.*,¹⁶ and 76% of the subjects in the CHARLOT study had at 3 g/dL decline in haemoglobin.¹⁰ In the RIBAVIC study, 24% of the subjects had at least 25% drop in haemoglobin on treatment.¹⁷

Strengths of our study include a large, well-characterised population, rigorous prospective design and repeated, uniform measurements in all subjects. We believe that adjusting our analysis for the entry haemoglobin values, initiation of ESA and actual time on prescribed treatment provides the most robust estimates of anaemia in this population. The limitations of the study include the retrospective analysis and that ESA use was not regulated by the protocol leading to inconsistent use of such agents. We used a definition of anaemia

different from that in other recent trials, which makes any comparison with other trials difficult.

In summary, anaemia is very common in HCV/HIV-infected persons who are treated with PEG and WBR. While anaemia develops in a majority of subjects in the first 12 weeks of therapy, a substantial portion develop late anaemia. Baseline haemoglobin, lower BMI, age over 40 years and zidovudine use are strong predictors of anaemia. The majority of subjects are not able to maintain the originally prescribed dose of ribavirin. Strategies to improve management of anaemia are urgently required in the HIV-coinfected population.

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Figure 1.
The schema for A5178 study.

Anaemia with long-term treatment in HCV/HIV coinfectd persons

Figure 2.

(a) Time to anaemia (Step 1). (b) Time to anaemia (Steps 1 + 3). Follow-up was censored at the initiation of an erythropoiesis stimulating agent, ribavirin dose reduction or discontinuation. Step 1 refers to all subjects who entered the trial ($N = 329$); Step 3 refers to subjects who completed at least 12 weeks of therapy, demonstrated an early virological response defined as a drop in HCV RNA of at least $2 \log_{10}$ at week 12, and were assigned to continue treatment with pegylated interferon and weight-based ribavirin for a total of 72 weeks.

Figure 3.

Change in haemoglobin from study entry. * Medians with interquartile range are plotted at each time point. Step 1 refers to all subjects who entered the trial ($N = 329$); Step 3 refers to subjects who completed at least 12 weeks of therapy, demonstrated an early virological response defined as a drop in HCV RNA of at least 2 $\log_{10}$ at week 12, and were assigned to continue treatment with pegylated interferon and weight-based ribavirin for a total of 72 weeks.

Figure 4.

Change in haemoglobin among subjects who entered Step 3, by gender. * Medians with interquartile range are plotted at each time point. ** FUP0, FUP12, FUP24 are follow-up visits at 0, 12 and 24 weeks after treatment discontinuation respectively.

Figure 5.

Anaemia on Step 1 and response to treatment. * EVR = early virological response defined as at least a 2 log₁₀ drop from HCV RNA from entry or undetectable (<600 IU/mL) HCV RNA at week 12; cEVR = complete early virological response defined as undetectable HCV RNA at week 12; SVR = sustained virological response defined as undetectable (<60 IU/mL) HCV RNA at 24 weeks after treatment discontinuation.

Table 1

Demographics and clinical characteristics at study entry

	Step 1 <i>N</i> = 329 Median (<i>Q1</i> , <i>Q3</i>)	Steps 1 + 3 <i>N</i> = 169 Median (<i>Q1</i> , <i>Q3</i>)
Age, years	48 (42, 52)	47 (42, 51)
Age, <i>N</i> (%)		
<40	52 (15.8)	32 (18.9)
≥40	277 (84.2)	17 (81.1)
Gender, <i>N</i> (%)		
Male	274 (83.3%)	150 (88.8%)
Female	55 (16.7%)	19 (11.2%)
Race/Ethnicity, <i>N</i> (%)		
White	142 (43.2)	88 (52.1)
Black	123 (37.4)	49 (29.0)
Hispanic	50 (15.2)	23 (13.6)
Other/Unknown	14 (4.3)	9 (5.3)
HCV RNA, log ₁₀ IU/mL	6.6 (6.3, 6.9)	6.6 (6.0, 6.9)
HCV RNA, <i>N</i> (%)		
<800,000 IU/mL	55 (16.7)	37 (21.9)
≥800,000 IU/mL	274 (83.3)	132 (78.1)
Genotype, <i>N</i> (%)		
1	273 (83.0)	128 (75.7)
2	30 (9.1)	26 (15.4)
3	13 (4.0)	10 (5.9)
4	10 (3.0)	3 (1.8)
Unknown	3 (0.9)	2 (1.2)
HIV RNA<50 copies/mL, <i>N</i> (%)	245 (74.5)	126 (74.6)
CD4 count, cells/mm ³	498 (358, 706)	489 (347, 690)
CD4 count, <i>N</i> (%)		
<350 cells/mm ³	76 (23.1)	43 (25.4)
≥350 to <500 cells/mm ³	89 (27.1)	45 (26.6)
≥500 cells/mm ³	164 (49.8)	81 (47.9)
BMI, kg/m ²	25.7 (23.3–29.3)	25.5 (23.3, 28.0)
BMI, <i>N</i> (%)		
<25 kg/m ²	143 (43.5)	75 (44.4)
≥25 to <30 kg/m ²	113 (34.3)	60 (35.5)
≥30 kg/m ²	73 (22.2)	34 (20.1)
Zidovudine use, <i>N</i> (%)	75 (22.8)	33 (19.5)
Prior HCV treatment, <i>N</i> (%)	106 (32.2)	49 (29.0)

	Step 1 <i>N</i> = 329 Median (<i>Q1</i>, <i>Q3</i>)	Steps 1 + 3 <i>N</i> = 169 Median (<i>Q1</i>, <i>Q3</i>)
Cirrhosis, <i>N</i> (%)	43 (13.1)	15 (8.9)
Haemoglobin, g/dL	14.5 (13.5, 15.6)	14.8 (13.7, 15.7)
Male	14.8 (13.8, 15.8)	14.9 (14.0, 15.7)
Female	13.1 (12.2, 14.3)	13.1 (12.0, 14.3)
Alanine aminotransferase, U/L	60 (41, 89)	59 (42, 87)

BMI, body mass index.

Step 1 refers to all subjects who entered the trial (*N* = 329); Step 3 refers to subjects who completed at least 12 weeks of therapy, demonstrated an early virological response defined as a drop in HCV RNA of at least 2 log₁₀ at week 12, and were assigned to continue treatment with pegylated interferon and weight-based ribavirin for a total of 72 weeks.

Table 2

Anaemia characteristics (Step 1 and Steps 1 + 3)

	Step 1 (<i>N</i> = 329) <i>n</i> (%)	Steps 1 + 3 (<i>N</i> = 169) <i>n</i> (%)
Anaemia [95% CI]	133 (40.4) [35.1–45.9]	93 (55.0) [47.2–62.7]
ESA use		
Any use	120 (36.5)	76 (45.0)
Before anaemia by haemoglobin criteria	44 (13.4)	29 (17.2)
ESA before developing anaemia	27 (8.2)	18 (10.7)
ESA but never developed anaemia	17 (5.2)	11 (6.5)
At study entry	6 (1.8)	3 (1.8)
Ribavirin modification *		
No dose reduction	163 (49.5)	46 (27.2)
Dose reduction	60 (18.2)	38 (22.5)
Temporary hold	49 (14.9)	28 (16.6)
Premature discontinuation	57 (17.3)	57 (33.7)

ESA, erythropoiesis stimulating agent.

Step 1 refers to all subjects who entered the trial (*N* = 329); Step 3 refers to subjects who completed at least 12 weeks of therapy, demonstrated an early virological response defined as a drop in HCV RNA of at least 2 log₁₀ at week 12, and were assigned to continue treatment with pegylated interferon and weight-based ribavirin for a total of 72 weeks.

* The worst dose modification during the respective time period was counted for each subject, the worst being premature discontinuation followed by temporary hold and dose reduction.

Table 3

Predictors of anaemia in Step 1 and Steps 1 + 3

Univariate analyses*					
Predictor variable	Effect	Step 1 OR (95% CI)	P-value	Steps 1 + 3 OR (95% CI)	P-value
Age, years	per 10 years	1.42 (0.97–2.08)	0.070	2.26 (1.35–3.79)	0.002
Age, years	≥40 vs. <40	2.42 (1.13–5.20)	0.024	4.31 (1.70–10.93)	0.002
Gender	Female vs. Male	0.32 (0.14–0.71)	0.005	0.84 (0.22–3.20)	0.803
Race	Black vs. White	0.65 (0.35–1.23)	0.186	1.38 (0.56–3.40)	0.489
	Hispanic vs. White	0.71 (0.31–1.59)	0.402	0.15 (0.05–0.48)	0.001
BMI, kg/m ²	per 1 kg/m ²	0.94 (0.89–0.99)	0.031	0.87 (0.79–0.95)	0.002
BMI, kg/m ²	≥30 vs. <25	0.75 (0.37–1.53)	0.431	0.48 (0.18–1.32)	0.157
	[25–30) vs. <25	0.71 (0.39–1.32)	0.285	0.82 (0.36–1.87)	0.636
CD4, cells/mm ³	<350 vs. ≥500	0.54 (0.27–1.08)	0.082	0.57 (0.23–1.40)	0.222
	≥350 to <500 vs. ≥500	0.67 (0.35–1.28)	0.224	0.58 (0.24–1.41)	0.229
HIV RNA, copies/mL	≥50 vs. <50	0.54 (0.29–1.00)	0.051	0.62 (0.26–1.47)	0.279
ZDV use	Yes vs. No	11.34 (5.78–22.24)	<0.001	13.48 (4.53–40.14)	<0.001
HCV genotype	1, 4 vs. 2, 3	1.10 (0.50–2.43)	0.809	1.64 (0.70–3.82)	0.255
HCV RNA, IU/mL	≥800 000 vs. <800 000	1.36 (0.66–2.78)	0.400	1.54 (0.64–3.70)	0.333
Prior HCV treatment	Yes vs. No	1.39 (0.77–2.49)	0.271	1.87 (0.79–4.43)	0.155
Cirrhosis	Yes vs. No	0.81 (0.37–1.77)	0.596	0.24 (0.06–0.93)	0.038
ALT, U/L	per 10 U/L	1.02 (0.98–1.07)	0.313	0.99 (0.94–1.05)	0.816
Haemoglobin, g/dL [†]		0.34 (0.27–0.42)	<0.001	0.34 (0.26–0.46)	<0.001
Multi-covariate analyses [‡]					
Predictor variable	Effect	Step 1 OR (95% CI)	P-value	Steps 1 + 3 OR (95% CI)	P-value
Age, years	per 10 years	1.58 (1.06–2.35)	0.024	2.57 (1.52–4.35)	<0.001
Gender	Female vs. Male	0.29 (0.13–0.68)	0.004		
BMI, kg/m ²	per 1 kg/m ²			0.84 (0.76–0.92)	<0.001

Univariate analyses*					
Predictor variable	Effect	Step 1		Steps 1 + 3	
		OR (95% CI)	P-value	OR (95% CI)	P-value
ZDV use	Yes vs. No	12.35 (6.18–24.69)	<0.001	23.14 (7.32–73.15)	<0.001
Haemoglobin, g/dL	per 1 g/dL	0.28 (0.22–0.37)	<0.001	0.34 (0.24–0.46)	<0.001

BMI, body mass index; ZDV, zidovudine; ALT, alanine aminotransferase.

Step 1 refers to all subjects who entered the trial ($N = 329$); Step 3 refers to subjects who completed at least 12 weeks of therapy, demonstrated an early virological response defined as a drop in HCV RNA of at least 2 log₁₀ at week 12, and were assigned to continue treatment with pegylated interferon and weight-based ribavirin for a total of 72 weeks.

* Estimates are from univariate logistic regression adjusted for follow-up time and controlling for entry haemoglobin (continuous), unless specified otherwise.

[†] Estimates are from univariate logistic regression for entry haemoglobin adjusted for follow-up time.

[‡] Estimates are from multi-covariate logistic regression adjusted for follow-up time.