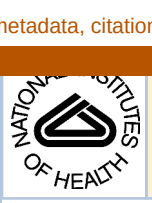

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Early Predictors of Anemia in Patients with Hepatitis C Genotype 1 Treated with Peginterferon alfa-2a (40KD) plus Ribavirin

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Abstract

Objective—Adherence to ribavirin is one factor that is critically important in the treatment of hepatitis C virus infection. However, ribavirin can be associated with clinically significant hemolytic anemia resulting in dose modifications in up to one-quarter of patients. Currently, baseline predictors of considerable anemia are not sufficiently discriminating for routine therapeutic intervention. The objective of this analysis was to elucidate baseline and on-treatment factors predictive of a considerable hemoglobin drop at week 4.

Methods—Multiple logistic regression analysis was used to explore possible predictors for considerable hemoglobin decline (≥2.5 g/dL) at week 4 among patients receiving peginterferon alfa-2a (40KD) and ribavirin (1000/1200 mg/day).

Results—A total of 555 patients were included in this analysis. At week 4, 236 patients exhibited a ≥2.5 g/dL decrease in hemoglobin. By regression analysis the most important independent variables associated with a decrease in hemoglobin of ≥2.5 g/dL were baseline creatinine clearance (p=0.0003) and a rapid decline in hemoglobin of ≥1.5 g/dL at week 2 (p<0.0001). Considerable hemoglobin decreases at week 4 were also significantly associated with early ribavirin dose reductions and a lower cumulative daily dose of ribavirin.

Conclusion—Patients with impaired renal function may be at an increased risk of ribavirin-related anemia and should be monitored accordingly. Furthermore, a hemoglobin drop of ≥1.5 g/dL by week 2 was an excellent early predictor for subsequent considerable hemoglobin decreases and might be used to identify candidates for early intervention against anemia in order to help maintain ribavirin dosing and avoid suboptimal exposure.

Keywords

HCV; PEGASYS; pegylated interferon; safety; hemoglobin

BACKGROUND

As many as 5 million Americans have been exposed to hepatitis C virus (HCV) and the majority will go on to develop chronic infection. Individuals with chronic hepatitis C infection are at

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risk for serious complications – for example, HCV is the principal cause of hepatocellular carcinoma, the major indication for liver transplantation – and HCV directly contributes to an estimated 13,000 deaths in the United States annually. The combination of peginterferon and ribavirin can achieve sustained virologic response (SVR; HCV RNA <50 IU/mL 24 weeks after treatment) in over 50% of those treated.[1,2] However, soon after the introduction of peginterferon and ribavirin it was recognized that adherence to treatment is critical to maintaining high rates of virologic clearance.[3] Unfortunately, peginterferon plus ribavirin therapy can be associated with side effects, some of which may lead to dose reductions, premature discontinuation of the drug, and subsequent treatment failure.[4]

As recently reviewed by McHutchison et al., ribavirin is associated with dose-dependent hemolytic anemia, which occurs in a considerable proportion of treated patients.[4] Although treatment-related side effects can make therapy unpleasant, most do not necessarily lead to disruption or discontinuation of therapy. However, hemolytic anemia associated with ribavirin frequently leads to ribavirin dose reductions. Indeed, in a peginterferon alfa-2a pivotal trial, it was reported that patients receiving peginterferon alfa-2a plus ribavirin had a median maximal decrease in hemoglobin of 3.7 g/dL, and this resulted in a ribavirin dose modification in 22% of patients.[1] High rates of anemia are not unique to that study; retrospective analyses of patients receiving combination therapy with ribavirin and interferon alfa-2b confirm the frequent occurrence of anemia. In one study more than 50% of patients experienced a decrease in hemoglobin of ≥3.0 g/dL,[5] and, in another study, by 24 weeks of treatment ribavirin dose reduction was required in 27.6% of patients, with a mean maximal decrease in hemoglobin of 4.0 g/dL.[6]

Although these studies suggest that multiple baseline factors may predict an increased risk of significant anemia, no analysis is sufficiently discriminating to justify therapeutic intervention. Following a prior analysis of 58 HCV genotype 1 (HCV-1) patients, a significant correlation was found between a decrease in hemoglobin of ≥1.5 g/dL from baseline to week 2 (rapid hemoglobin reduction, RHR) and a week 4 hemoglobin decline of ≥2.5 g/dL – a decline that may be clinically significant in many patients.[7] The objective of the present analysis was to elucidate baseline and on-treatment factors predictive of a considerable hemoglobin drop at week 4.

METHODS

Study design and patients

Data from two pivotal, prospective, randomized, international phase III trials in treatment-naive adults with HCV-1 infection were pooled for this *post hoc* analysis.[1,8] The objective was to evaluate baseline and on-treatment characteristics with the potential to predict considerable hemoglobin decreases (≥2.5 g/dL decrease in hemoglobin from baseline), and hence identifying patients at an increased risk of anemia, at treatment week 4. A hemoglobin decline of 2.5 g/dL was selected as a marker of potential clinically relevant anemia as this approximated the median decline in the overall population.

The study design methodology and the main findings of the studies have been published elsewhere.[1,8] Briefly, the studies recruited patients with anti-HCV antibodies, quantifiable HCV RNA (>600 IU/mL via COBAS AMPLICOR HCV MONITOR Test, v2.0; Roche Diagnostics, Branchburg, NJ, USA), increased serum alanine aminotransferase (ALT), and well-compensated liver disease. Liver biopsy findings were consistent with chronic hepatitis C. Patients were excluded with baseline neutropenia (neutrophil count $<1.5 \times 10^9$ cells/L), thrombocytopenia (platelet count $<90 \times 10^9$ cells/L), anemia (hemoglobin level <12 g/dL in women and <13 g/dL in men), HIV, hepatitis A or hepatitis B co-infection, decompensated liver disease, a serum creatinine level >1.5 times the upper limit of normal, poorly controlled

psychiatric disease, recent alcohol or drug dependence, or substantial coexisting medical conditions.

Only genotype 1 patients randomized to 48 weeks of treatment with subcutaneous peginterferon alfa-2a (40KD) (PEGASYS®; Roche, Basel, Switzerland) 180 μg once weekly plus oral ribavirin (COPEGUS®; Roche, Basel, Switzerland) were included in this analysis. Furthermore, in this subset, only patients who received at least one dose of study drug and had hemoglobin assessments before treatment and at week 4 during treatment were subsequently included.

Anemia assessments

Anemia assessments (serum hemoglobin) were obtained at baseline and weeks 1, 2, 4, 6, 8, and 12, and at 6-week intervals thereafter, in one trial,[8] and at baseline and weeks 1, 2, 4, 6, and 8, and at monthly intervals thereafter including weeks 52, 60, and 72, in a second trial.[1] Dose modification occurred per protocol: ribavirin was reduced to 800 mg/day or 600 mg/day[8] or to 600 mg/day[1] if the hemoglobin level dropped below 10 g/dL in patients without heart disease or decreased by ≥2 g/dL in patients with stable heart disease. Ribavirin was discontinued if hemoglobin fell below 8.5 g/dL.

Efficacy and safety end points

The primary efficacy end point for both studies was SVR, defined as undetectable serum HCV RNA (<50 IU/mL) by qualitative polymerase chain reaction (COBAS AMPLICOR HCV MONITOR Test, v2.0) at the end of a 24-week untreated follow-up phase. Creatinine clearance was calculated according to the Cockcroft and Gault equation.

The percentage of premature withdrawals, the percentage of patients with dose reductions due to anemia, the mean treatment duration, the cumulative dose, and the average dose of peginterferon alfa-2a (40KD) and ribavirin were determined for patients with and without a 2.5 g/dL decline in hemoglobin at week 4.

Statistical analysis

Various baseline and on-treatment characteristics, as well as SVR, in patients with and without hemoglobin declines (≥2.5 g/dL) at week 4 were compared using the chi-squared test for association in the case of categorical data or the Student's t-test in the case of continuous data. Univariate and multiple logistic regression analyses were used to assess the association between several possible predictors and hemoglobin decreases at week 4. Characteristics included are gender, race, age, body weight, body mass index, fibrosis/cirrhosis status, genotype subtype, HCV RNA titer, geographical region, hemoglobin, platelet and white blood cell counts, creatinine level, creatinine clearance, ribavirin start dose per kg of body weight, cumulative dose of ribavirin and peginterferon alfa-2a (40KD) per kg of body weight in the first 4 weeks, and achieving an RHR (week 2 hemoglobin reduction of ≥1.5 g/dL from baseline).

In the stepwise model building process of the multiple logistic regression analysis, a variable was added to the model if the adjusted chi-square statistic was significant at the 0.1 level and a variable was deleted from the model if the Wald chi-square statistic was not significant at the 0.05 level. For the resulting independent predictive factors, odds ratio and 95% confidence intervals (CI) were calculated. The functional association of continuous variables with considerable anemia was examined by generalized additive logistic regression models.

RESULTS

Five hundred and fifty-five patients fulfilled the criteria for analysis (Figure 1); 236 patients (42.5%) exhibited considerable hemoglobin decreases, defined as a drop of ≥2.5 g/dL at week 4. In these patients the median decrease at week 4 was 3.4 g/dL, with a range of 2.5–7.4 and interquartile range of 2.9, 4.1. Baseline characteristics for both groups were compared (Table 1).

Using univariate regression analysis, several factors, including age, race, baseline hemoglobin, creatinine clearance, and achieving an RHR, were predictive factors for considerable hemoglobin decrease at week 4 (Table 2). By multiple logistic regression analysis, baseline creatinine clearance and RHR had the strongest association (odds ratio 0.82 [95% CI: 0.73–0.91] and 23.3 [95% CI: 14.1–38.1], respectively). The ribavirin dose per kg of body weight in the first 4 weeks was excluded from the final multiple logistic regression analysis because the observed lower ribavirin dose in the first 4 weeks in patients with a considerable hemoglobin decrease seems to be a reaction to the developing anemia and cannot be used as an explanation for more pronounced anemia.

Plotting baseline creatinine clearance against hemoglobin reductions of ≥2.5 g/dL at week 4 (Figure 2a) shows that, as baseline creatinine clearance increases, the probability of hemoglobin reductions of ≥2.5 g/dL at week 4 decreases continuously across the entire range. This highlights the potential heightened risk of anemia in patients with impaired renal function at baseline.

The factor most strongly associated with considerable hemoglobin reductions at week 4 in the multiple logistic regression analysis was achieving an RHR. This is illustrated in Figure 2b, which shows that 84% of patients with a week 2 reduction of hemoglobin of ≥1.5 g/dL subsequently experienced more significant week 4 decreases (≥2.5 g/dL decrease from baseline) compared with only 18% of patients with a week 2 reduction of hemoglobin of <1.5 g/dL ($p<0.0001$). While this might be what one would expect, it confirms that relatively small hemoglobin declines at week 2 progress to more significant declines after a further 2 weeks on treatment.

Treatment adequacy

On-treatment characteristics of patients with and without week 4 hemoglobin drops of ≥2.5 g/dL in the two studies (Table 3) showed that these week 4 decreases significantly correlated with more and earlier ribavirin dose reductions due to anemia ($p<0.0001$), and thus a lower cumulative and average daily dose of ribavirin ($p=0.0005$ and $p<0.0001$ respectively). Furthermore, patients with hemoglobin declines of ≥2.5 g/dL at week 4 were significantly more likely to have their dose of ribavirin reduced, resulting in them receiving <60% of the target dose compared with patients with smaller declines in hemoglobin (30.1% versus 21.6%; $p=0.0234$ respectively). There was no correlation with cumulative peginterferon dose, mean treatment duration, or completion of treatment course.

Treatment efficacy

Despite significantly greater reductions in ribavirin exposure, the likelihood of SVR in patients with considerable hemoglobin decreases at week 4 was only slightly lower than that in patients without such decreases, a difference that was not found to be statistically significant (47.5% versus 51.7%; $p=0.3203$). However, when hemoglobin drop at week 2 was plotted as a continuous variable against the probability of achieving an SVR, it was evident that across the range of observed drops in hemoglobin at week 2 a relationship with the probability of achieving an SVR was clearly present (Figure 3). A similar relationship was also seen when

hemoglobin drop at week 4 was plotted as a continuous variable against the probability of achieving an SVR (data not shown).

DISCUSSION

This study demonstrates that considerable and potentially clinically significant decreases in hemoglobin from baseline can be predicted by a decrease in hemoglobin of ≥1.5 g/dL after only 2 weeks of therapy (RHR). This may provide clinicians with an early opportunity to evaluate the pros and cons of reducing the dose of ribavirin in patients at a high risk of developing anemia, or to consider the later use of hematological growth factors to treat ribavirin-associated anemia thereby enabling patients to maintain their ribavirin exposure. Early indicators of subsequent considerable anemia should prompt the physician to primarily consider early and small reductions in ribavirin dose (200 mg decrements) to reduce the risk of considerable anemia while maintaining adequate exposure to ribavirin. In addition, recent trials have demonstrated that higher starting doses of ribavirin can improve SVR rates in difficult-to-treat populations,[9–11] making the early identification of patients at risk of significant hemoglobin reductions increasingly important. Growth factors may be considered as an adjunct to dose reduction but should be used at the lowest dose to gradually increase hemoglobin concentrations to the lowest level sufficient to maintain ribavirin dosing – they should not be used to target hemoglobin levels >12 g/dL and should not result in increases of >1 g/dL over a 2-week period.[12]

In our analysis we identified several independent baseline factors, including race, cirrhosis, hemoglobin count, and creatinine clearance, that were predictive of subsequent development of considerable hemoglobin decreases at week 4, allowing physicians the opportunity to identify patients at heightened risk of developing anemia even before starting therapy.

Our findings confirm other recent reports of predictors of anemia. Although Spangler and colleagues found no baseline predictors of ribavirin-associated anemia in a small study of 58 patients infected with HCV-1, they did show that 81% of patients with a ≥1.5 g/dL drop in hemoglobin at week 2 had considerable anemia at week 4 compared with only 18% of patients with a <1.5 g/dL hemoglobin drop at week 2 ($p<0.001$).[7] These finding are remarkably similar to those of our own.

In a different analysis based upon a generalized additive logistic model, the probability of anemia has been calculated to increase from 6% to 16% as a function of ribavirin dose (from 12 mg/kg/day to 16 mg/kg/day).[13] A number of baseline characteristics were prognostic factors for anemia, including gender, baseline hemoglobin, age, baseline ALT, and cirrhosis. Interestingly, in our analysis, gender and age were not shown to be independent predictors of considerable hemoglobin decrease at week 4 in the multiple logistic regression analysis (both $p>0.05$).

Our results and those of others clearly show that anemia is a common and significant problem during treatment with interferon and ribavirin. A decline in hemoglobin begins shortly after initiation of treatment and generally reaches the lowest level after 4 to 6 weeks of therapy.[6,14] Indeed, treatment-induced anemia has been shown to be one of the most frequently reported adverse events in pivotal trials and contributes to dose reductions and treatment discontinuations.[1,2,6,8,15–18]

Although anemia is reversible when therapy is discontinued, it has a considerable impact on treatment outcome in relation to adequate ribavirin dosing. Compared with interferon or peginterferon monotherapy, the combination of interferon and ribavirin greatly increased the rate of SVR and decreased the risk of relapse after discontinuation of therapy.[1,2]

In our analysis, while the rate of SVR among those patients with hemoglobin decreases ≥2.5 g/dL was similar to that among patients without such decreases, it was shown that across the whole range of hemoglobin drops, either at week 2 or week 4, greater decreases in hemoglobin were associated with a lower probability of achieving an SVR. Consequently the failure to show a significant reduction in SVR in our analysis may be explained by dichotomizing the population at hemoglobin decreases of ≥2.5 g/dL and those with smaller decreases in hemoglobin.

It has been suggested that higher exposure to ribavirin (15 mg/kg) may greatly improve treatment efficacy, especially by decreasing the risk of relapse. However, this approach is anticipated to have a significantly higher association with anemia.[13,19] Certainly, ribavirin is not the only cause of treatment-related anemia, as interferon has been shown to suppress bone marrow hematopoiesis,[20] and erythropoietin production is blunted in patients with anemia receiving peginterferon and ribavirin.[21]

In conclusion, although associated with anemia, ribavirin is a critical component to the successful treatment of HCV. To maintain the highest likelihood of achieving an SVR the dose of ribavirin should be initiated at the highest appropriate dose and maintained for as long as possible. In our analysis, achieving an RHR (decline in hemoglobin of ≥1.5 g/dL at week 2) was a reliable predictor of greater and potentially clinically relevant decreases in hemoglobin later in the course of peginterferon and ribavirin therapy and provides an early indication that the dose of ribavirin may need to be modified. However, when warranted, the dose of ribavirin should be reduced by the smallest decrement possible (200 mg), avoiding reduction to ≤60% of the target dose since this is known to be associated with a significant reduction in the rate of SVR.

Study highlights

What is current knowledge?

- Anemia is common following interferon and ribavirin therapy
- Dose modifications of ribavirin for anemia may result in a diminished therapeutic response

What is new?

- Determination of >1.5 gm/dL decline in hemoglobin at week 2 strongly predicts >2.5 gm/dL decline at week 4.
- Independent variables associated with a decrease in hemoglobin: baseline creatinine clearance and a rapid decline in hemoglobin at week 2.

List of abbreviations

HCV, Hepatitis C virus; HCV-1, HCV genotype 1; SVR, Sustained virologic response; ALT, Alanine aminotransferase; CI, Confidence interval; RHR, Rapid hemoglobin reduction.

Acknowledgments

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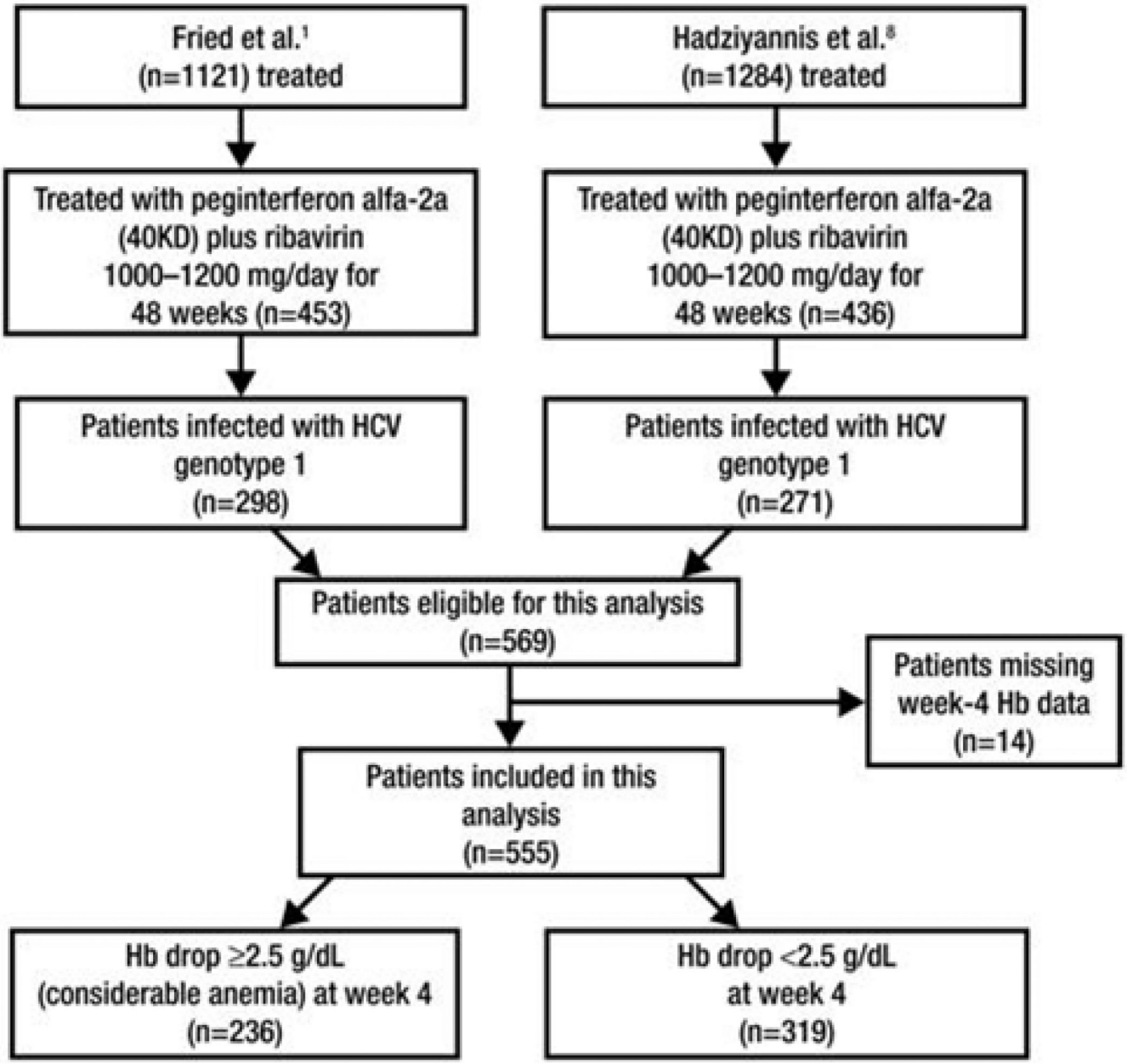

Figure 1.
Patients from the pivotal phase III studies who were included in this analysis and patients with and without hemoglobin decreases (≥2.5 g/dL) at week 4 (Fried 2002, Hadziyannis 2004)[1,8]
Hb = hemoglobin.

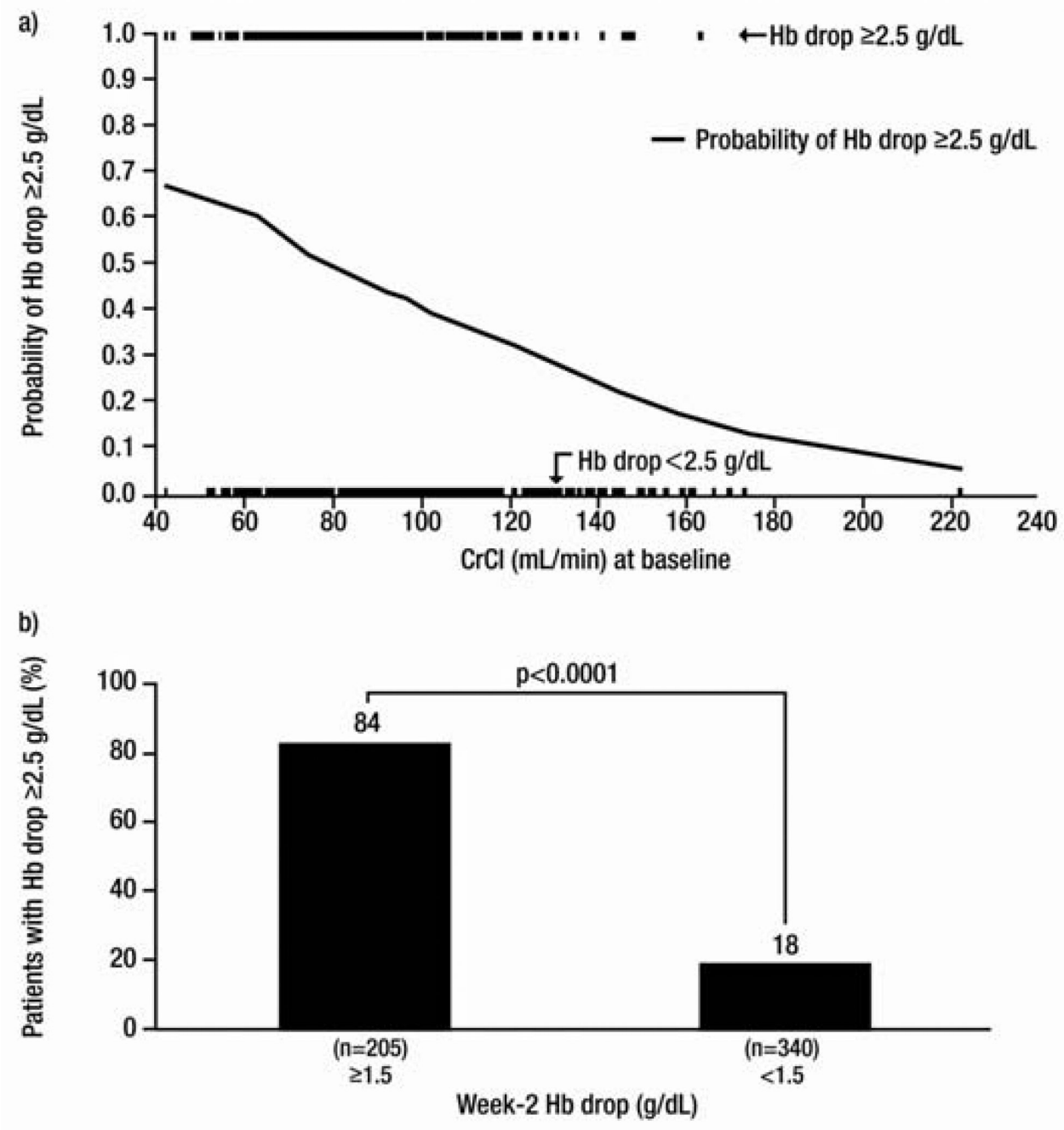

Figure 2.

Association between a hemoglobin drop of ≥2.5 g/dL at week 4 and (a) creatinine clearance (generalized additive logistic regression model using smoothing lines) and (b) week 2 hemoglobin drop (<1.5 g/dL versus ≥1.5 g/dL)

CrCl = creatinine clearance; Hb = hemoglobin.

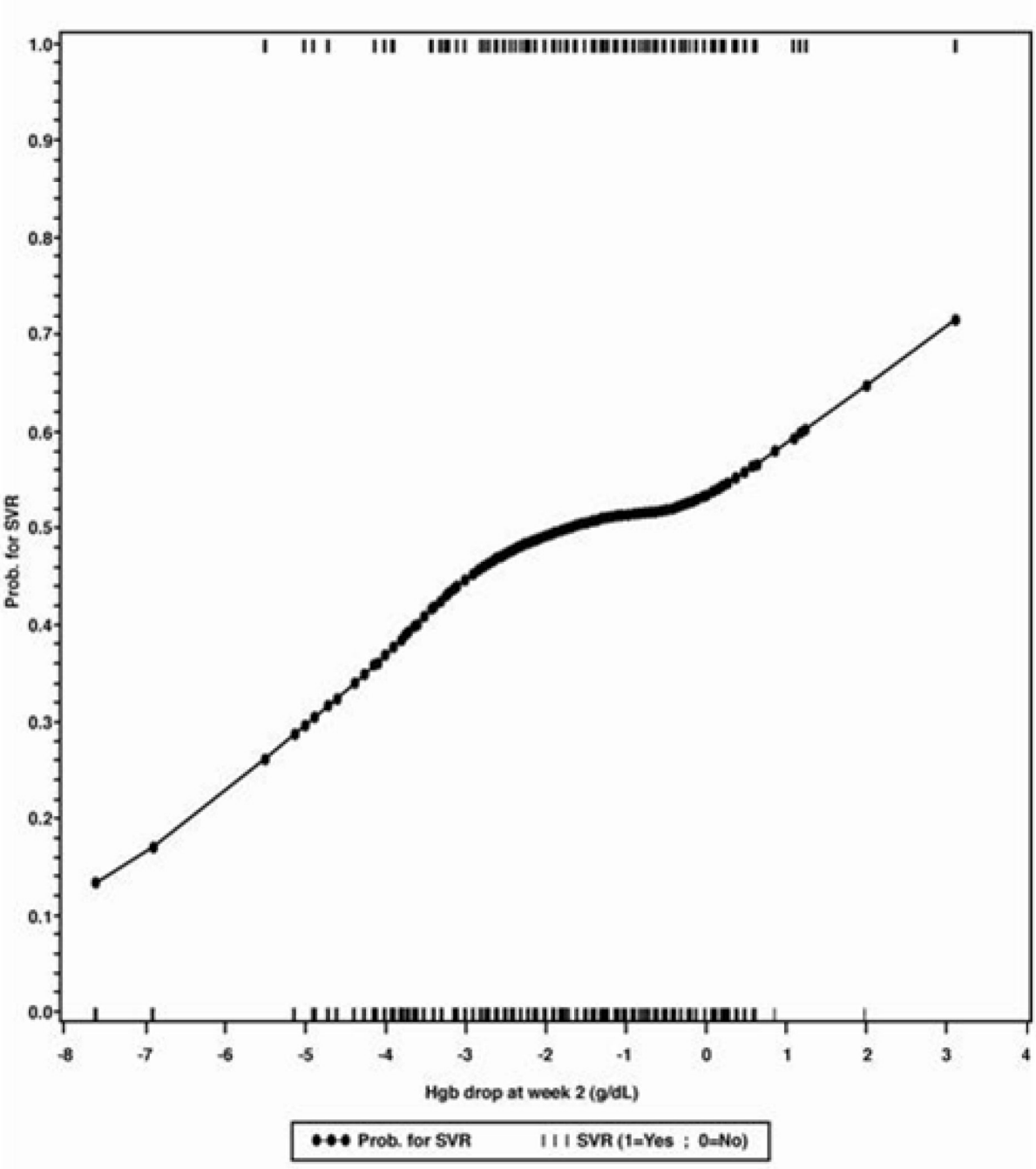

Figure 3.
Association between hemoglobin drop from baseline to week 2 and the probability of achieving an SVR (generalized additive logistic regression model using smoothing lines)
Hgb = hemoglobin.

Table 1

Baseline characteristics of patients with and without a week 4 hemoglobin decrease of ≥2.5 g/dL in the two studies[a]

Parameter	Patients with hemoglobin drop ≥2.5 g/dL at week 4 (N=236)	Patients with hemoglobin drop <2.5 g/dL at week 4 (N=319)	p-value
Region – n (%)			0.2582
North America	103 (43.6)	124 (38.9)	
Rest of world	133 (56.4)	195 (61.1)	
Gender – M/F (% male)	149/87 (63.1)	228/91 (71.5)	0.0373
Race			0.0033
Caucasian	206 (87.3)	267 (83.7)	
Black	11 (4.7)	18 (5.6)	
Hispanic	11 (4.7)	6 (1.9)	
Asian	4 (1.7)	26 (8.2)	
Other	4 (1.7)	2 (0.6)	
Cirrhosis – no/yes (% no)	180/56 (76.3)	263/56 (82.4)	0.0732
Age (years)	46.2 ± 10.7	41.9 ± 9.7	<0.0001
Weight (kg)	77.9 ± 16.4	80.5 ± 17.3	0.0724
Body mass index (kg/m^2)	26.7 ± 4.5	26.9 ± 5.1	0.6194
Hemoglobin (g/dL)	15.7 ± 1.1	15.2 ± 1.1	<0.0001
Creatinine clearance[b] (mL/min)	89.7 ± 23.0	101.2 ± 25.6	<0.0001
Ribavirin start dose 1000/1200 mg/day (% 1000)	102/134 (43.2)	123/196 (38.6)	0.2687

[a] Plus–minus values are means ± SD

[b] Creatinine clearance calculated according to Cockcroft and Gault equation

Table 2

Factors associated with considerable hemoglobin drop at week 4 (defined as a ≥2.5 g/dL decrease in hemoglobin) (N=544[a])

Factors associated with hemoglobin drop at week 4	Univariate logistic regression analysis p-value	Multivariate logistic regression analysis	
		p-value	Odds ratio (95% CI)
Age (per 10-yr increase)	<0.0001	NS	–
Gender (female vs. male)	0.0426	NS	–
Race (Black/Asian vs. other)[b]	0.0046	0.0035	0.31 (0.14–0.68)
Baseline hemoglobin (per 1.0 g/dL increase)[c]	<0.0001	0.0087	1.34 (1.08–1.66)
Creatinine clearance (per 10 mL/min increase)[c]	<0.0001	0.0003	0.82 (0.73–0.91)
Cirrhosis (yes vs. no)[b]	0.0808	0.0121	2.06 (1.17–3.61)
RHR vs. no RHR[b]	<0.0001	<0.0001	23.2 (14.1–38.1)
Peginterferon exposure weeks 1–4 (per 1 μg/week/kg increase)[c]	0.0275	0.0293	1.77 (1.06–2.95)

RHR = rapid hemoglobin reduction (≥1.5 g/dL decrease in hemoglobin at week 2 from baseline).

[a] Eleven patients were excluded from the logistic regression analyses due to missing data in at least one of the analyzed factors. Explanatory factors with a p-value >0.1 in the univariate analysis are not listed in Table 2.

[b] For discrete variables, the odds ratio is the ratio of the odds of the first category versus the opposite category.

[c] For continuous variables, the odds ratio relates to a unit change as specified (e.g., the odds of having a hemoglobin drop of ≥2.5 g/dL at week 4 in a patient with baseline hemoglobin of 11 g/dL is 34% higher than in a patient with baseline hemoglobin of 10 g/dL; odds ratio 1.34).

Table 3

On-treatment characteristics of patients with and without week 4 ≥2.5 g/dL drop in hemoglobin in the two studies[a]

Parameter	Patients with hemoglobin drop ≥2.5 g/dL at week 4 (N=236)	Patients with hemoglobin drop <2.5 g/dL at week 4 (N=319)	p-value
Completed treatment – yes/no (% yes)	181/55 (76.7)	241/78 (75.5)	0.7545
Duration of peginterferon therapy (weeks)	43 ± 11	42 ± 11	0.7054
Duration of ribavirin therapy (days)	292 ± 82.5	290 ± 85.6	0.8190
Dose reduction due to anemia[b] – yes/no (% yes)	89/147 (37.7)	40/279 (12.5)	<0.0001
Early dose reduction due to anemia[c] – yes/no (% yes)	18/218 (7.6)	1/318 (0.3)	<0.0001
Cumulative peginterferon dose (μg)	7265 ± 2062	7222 ± 2136	0.8106
Daily ribavirin dose[d] (mg)	954 ± 215	1064 ± 148	<0.0001
Cumulative ribavirin dose (g)	278 ± 103	308 ± 101	0.0005

[a] Plus–minus values are means ± SD.

[b] Dose reduction at any time due to anemia.

[c] Dose reduction in the first 4 weeks due to anemia.

[d] Mean daily dose between first and last treatment day. Interruptions were considered as weeks with dose 0.