

Changes in haemoglobin during interferon alpha-2b plus ribavirin combination therapy for chronic hepatitis C virus infection

M. S. Sulkowski,¹ R. Wasserman,² L. Brooks,³ L. Ball⁴ and R. Gish³ ¹Johns Hopkins University, Viral Hepatitis Center, Baltimore, MD, USA; ²Hepatitis Resource Center, Walnut Creek, CA, USA; ³California Pacific Medical Center Liver Clinic, San Francisco, CA, USA; and ⁴Hepatitis Resource Network, Puyallup, WA, USA

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SUMMARY. Interferon alpha and ribavirin (RBV) combination therapy is associated with decreases in haemoglobin (Hb) concentrations and anaemia. The aim of this analysis was to better characterize the magnitude and frequency of Hb changes and risk factors. This retrospective analysis evaluated treatment-related changes in Hb in 677 patients who participated in either of two interferon alpha-2b plus RBV studies for chronic hepatitis C virus (HCV) infection. Study 1 included 192 interferon alpha-naïve patients randomized to receive RBV 1000–1200 mg/day plus interferon alpha-2b 3 million IU daily or three times weekly for 48 weeks. Study 2 included 485 interferon alpha-experienced patients randomized to receive RBV 1000–1200 mg daily plus interferon alpha-2b 3 million IU daily or three times weekly for 4 weeks, followed by three times weekly dosing for 44 weeks. More than 50% of all patients experienced a decrease in Hb ≥ 30 g/L. Women were 4.4 times as likely as men to experience a Hb level of < 100 g/L; however,

men were at a 40% higher risk to experience a Hb decline of > 30 g/L from baseline. Daily use of interferon alpha-2b did not impact the magnitude of Hb decrease. In this pooled analysis, RBV dose reduction resulted in increases in Hb concentration of approximately 10 g/L. Lower baseline creatinine clearance, higher baseline Hb levels and increased age were independently associated with increased risk of Hb decreases of $> 27.7\%$. Lower baseline weight was not associated with increased risk of Hb decrease. Substantial Hb decreases occur frequently with interferon alpha/RBV combination therapy. Sex, the magnitude of the Hb decline and renal function are potentially important factors to consider in patients receiving RBV. Further research is needed to determine the impact on virological response and to develop strategies to manage the medical consequences.

Keywords: anaemia, haemolytic, hepatitis C, interferon, ribavirin.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection is the most common cause of chronic liver disease in the United States and Europe, leading to cirrhosis, end-stage liver disease and hepatocellular carcinoma among some infected persons. Currently, chronic HCV infection is the most frequent indication for liver transplantation and accounts for an estimated 8000–10 000 deaths each year in the United States [1,2]. Consequently, effective treatments for chronic hepatitis C are needed. The addition of ribavirin (RBV), a synthetic guanosine nucleoside

analogue, to standard interferon alpha substantially increases the sustained viral response (SVR) rate compared with interferon alpha alone among treatment-naïve [3–7] and nonresponding or relapsed interferon alpha-experienced patients [8–10]. More recently, two large, randomized, controlled trials have demonstrated that combination therapy with pegylated interferon alpha plus RBV is superior to standard interferon alpha-2b and RBV, resulting in SVR in 54–56% of treated patients [11,12]. Furthermore, among patients infected with HCV genotype 1, peginterferon alpha-2a in combination with higher dose RBV (1000–1200 mg daily) was significantly more effective than in combination with lower dose RBV (800 mg daily) [13].

While effective, both interferon alpha and RBV can decrease haemoglobin (Hb) concentrations and result in anaemia. Both standard and pegylated interferon alpha rapidly suppress bone marrow function [14]. Monotherapy with standard interferon alpha-2b causes a dose-dependent bone marrow suppression, resulting in decreases in Hb

Abbreviations: ALT, alanine transaminase; ANOVA, analysis of variance; CBC, complete blood count; CrCL, creatinine clearance; Hb, haemoglobin; HCV, hepatitis C virus; RBV, ribavirin; RR, relative risk; SVR, sustained viral response; TIW, three times weekly.

Correspondence: Mark S. Sulkowski MD, Viral Hepatitis Center, Johns Hopkins University, 1830 E. Monument Street, Suite 448, Baltimore, MD 21205, USA. E-mail: msulkows@jhmi.edu

of ≥ 20 g/L in approximately 26% of patients and Hb concentrations of 95 to 109 g/L in approximately 1–3% of patients [15,16]. RBV is well recognized to cause a dose-dependent, haemolytic anaemia that is slowly reversible upon drug discontinuation [17]. Combination therapy with RBV plus standard or pegylated interferon alpha is associated with an average Hb decline of 20–30 g/L over the first 4 weeks of therapy, which is accompanied by a compensatory reticulocytosis; however, for many patients this response is impaired by concomitant interferon-related bone marrow suppression [18]. Approximately 8–9% of patients receiving combination therapy experience decreases in Hb concentrations to < 100 g/L; 12–22% of patients require RBV and/or interferon alpha dose reduction and 6–26% discontinue combination therapy because of adverse events or intolerance [3,8,11,12].

Despite the impact of treatment-associated anaemia, the magnitude and frequency of Hb changes and risk factors for significant Hb declines during combination therapy have not been well characterized. The objective of this study was to evaluate the incidence and severity of anaemia among HCV-infected patients treated with daily or thrice weekly interferon alpha plus RBV and to determine risk factors for the development of significant decreases in Hb during therapy.

METHODS

Changes in Hb among 677 patients prospectively enrolled in two combination therapy (interferon alpha-2b/RBV) studies were retrospectively evaluated. All patients had chronic HCV infection, had Hb levels > 120 g/L (women) or > 130 g/L (men) and were treated with interferon alpha-2b and RBV [Rebetron[®] Combination Therapy; Intron[®] A (interferon alpha-2b, recombinant) Injection plus Rebetol[®] (ribavirin, USP) Capsules; Schering Corporation, Kenilworth, NJ, USA]. Patients with other types of liver disease (e.g. hepatitis B virus, alcoholic liver disease), haemoglobinopathies (e.g. thalassaemia), decompensated liver disease and/or HIV co-infection were excluded.

In study 1, interferon alpha-naïve patients were randomized to treatment with RBV 1000–1200 mg daily plus interferon alpha-2b 3 MIU daily or three times weekly (TIW) for 48 weeks (Fig. 1). In study 2, interferon alpha-experienced patients were randomized to treatment with RBV 1000–1200 mg daily plus interferon alpha-2b 3 MIU daily or TIW for 4 weeks, followed by RBV 1000–1200 mg daily plus interferon alpha-2b 3 MIU TIW for 44 weeks. In both studies, patients whose Hb concentrations fell below 100 g/L were required to decrease their daily RBV dose to 600 mg.

Baseline demographics and clinical assessments included sex, age, race/ethnicity, weight, serum creatinine concentration, serum alanine transaminase (ALT) concentration, complete blood count (CBC) and HCV viral load and genotype. Hb concentrations were measured at treatment weeks

0, 1, 2 and 4, and then monthly to week 48 (study 1 and 2), and at post-treatment weeks 4, 8, 12, 24 and 48 (study 2).

Descriptive statistics (e.g. sample size, mean, SD, quartiles) were used for continuous variables. Categorical variables were summarized using frequency statistics (e.g. frequencies, percentages). All data were analysed using SAS[®] software (Cary, NC, USA) or equivalent. Analysis of variance (ANOVA) were performed to test for treatment-by-study interaction. None were found, so the studies were combined for subsequent analyses reported here. Baseline variables significantly ($P < 0.05$) associated with the largest Hb decreases were identified by univariate analysis. These variables were then entered into a stepwise multivariate regression model to identify the variables independently associated with the largest Hb decreases. Creatinine clearance (CrCl) was estimated by the Cockcroft–Gault equation, which includes age, sex and body weight [19].

RESULTS

Of 677 patients enrolled in both HCV treatment studies, data from 595 patients (145 patients from study 1 and 450 patients from study 2) who had a baseline and at least one subsequent Hb measurement were analysed. The other 82 patients did not meet the criterion of having at least one Hb measurement or were early dropouts. The mean age was 45 years, and 64% were men. The mean Hb was 150 g/L, and men had higher Hb concentrations at baseline compared with women (Table 1). More than 80% of women had baseline Hb ≥ 130 g/L and more than 90% of men had baseline Hb ≥ 140 g/L. Following the initiation of interferon alpha-2b/RBV combination therapy, mean Hb concentrations decreased rapidly, with most of the decline occurring by treatment week 4 (Fig. 2). After treatment discontinuation (week 48), Hb concentrations increased, returning to pretreatment levels within 12 weeks.

With regard to nadir Hb concentrations, overall, 10.1% (95% CI: 7.8–12.8%) of patients had a Hb concentration of < 100 g/L. As shown in Fig. 3, the incidence of a Hb of < 100 g/L was approximately 4.4-fold higher in women (20%, 95% CI: 14.7–26.1%) than in men (4.5%, 95% CI: 2.7–7.2%) [relative risk (RR): 4.4, 95% CI: 2.6–7.6]. Conversely, while 54% of all patients experienced Hb decrease of ≥ 30 g/L (Fig. 4), the incidence of Hb decrease of ≥ 30 g/L was significantly higher in men compared with women, 60 and 44%, respectively (RR: 1.4, 95% CI: 1.2–1.6). Overall, 102 anaemic patients (17.1%) (mean Hb concentration = 107 g/L) underwent RBV dose reduction to 600 mg daily, which was associated with a mean Hb increase of 11 g/L, at 4–8 weeks following the RBV dose change.

With regard to relative Hb decreases, more than 35% of patients experienced Hb decreases exceeding 25% from baseline values (95% CI: 32–40%). The percentage decrease from baseline Hb was used to stratify patients into quartile 1 ($< 15.4\%$, $n = 149$), quartile 2 (15.4–21.2%, $n = 152$),

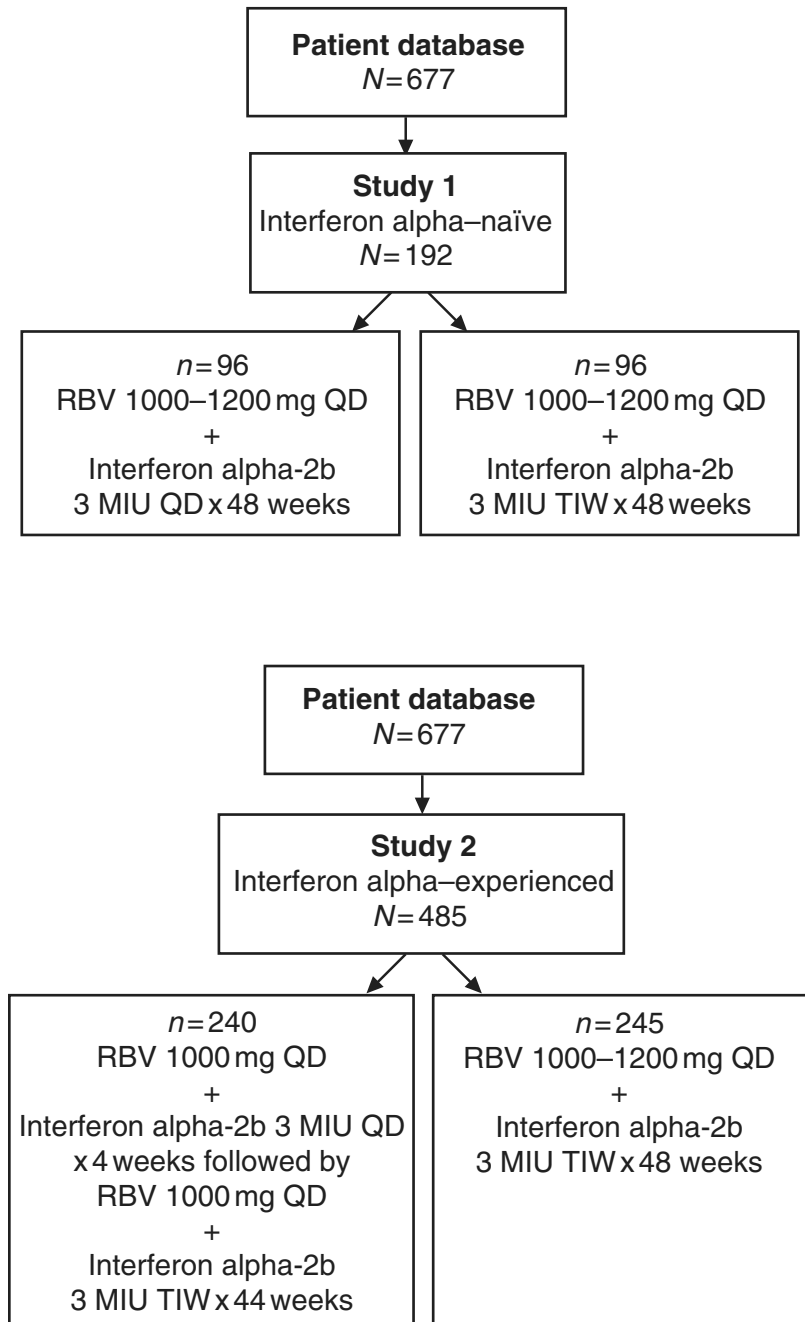


Fig. 1 Randomization during treatment of interferon alpha-naïve (study 1) and interferon alpha-experienced (study 2) HCV-infected patients.

quartile 3 (21.3–27.7%, $n = 153$) and quartile 4 ($>27.7\%$, $n = 141$) (Fig. 5). The mean baseline Hb values in quartiles 1, 2, 3 and 4 were 134, 146, 155 and 167 g/L, respectively. While patients with the highest Hb concentrations at baseline experienced the greatest absolute Hb decreases during the course of therapy, the mean percentage decreases (20–23%) from baseline were similar across baseline Hb quartiles. Patients receiving daily interferon alpha-2b therapy did not experience a greater decline in Hb compared with those who received interferon alpha-2b three times weekly by treatment week 4 in study 1 (-26 g/L vs -26 g/L for daily and TIW dosing, respectively; $P = 0.98$) or study 2

(-22 g/L vs -20 g/L for daily and TIW dosing, respectively; $P = 0.28$), nor at any additional time point in study 1.

While all subjects had baseline serum creatinine levels less than the upper limit of normal, significantly greater decreases in absolute and relative Hb concentrations were associated with lower estimated rates of CrCl (Table 2). Interestingly, changes in absolute and relative Hb concentrations were not associated with baseline body weight (Table 3). In univariate logistic regression analysis, older age, lower baseline CrCl, higher baseline Hb and lower baseline platelet count were significantly ($P < 0.05$) associated with the largest relative decrease in Hb

Table 1 Patient demographics and baseline characteristics

Characteristic	Patients evaluated (N = 595)
Mean age (years)	45.4
Sex*, n (%)	
Male	433 (64)
Female	243 (36)
Race/ethnicity†, %	
Caucasian	76.2
Hb, g/L (mean ± SD)	
All	150 ± 13
Men	155 ± 11
Women	141 ± 11
WBC × 10 ⁹ /L (mean ± SD)	0.0064 ± 0.0018
Platelets × 10 ⁹ /L (mean ± SD)	197 ± 55
Serum creatinine, µmol/L (mean ± SD)	78.7 ± 15.9

WBC, white blood cells.

*Data missing for one patient.

†Complete race data included Caucasian, Hispanic, Black, Asian and other.

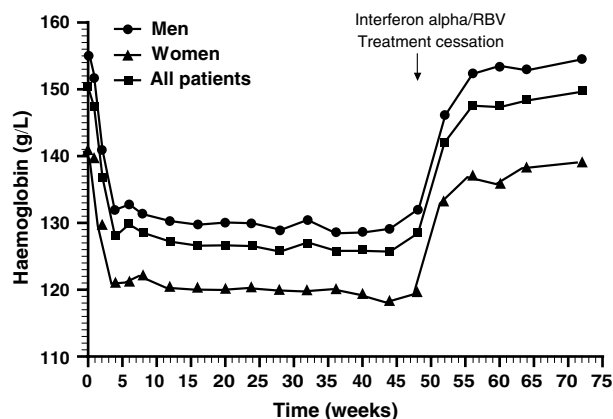


Fig. 2 Time course of Hb concentrations in HCV-infected patients treated with interferon alfa-2b/RBV combination therapy.

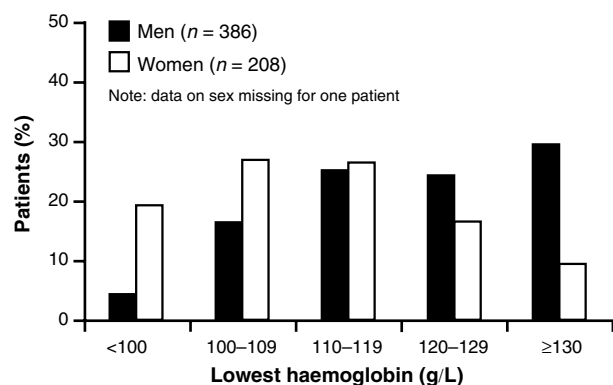


Fig. 3 Summary of lowest Hb during study.

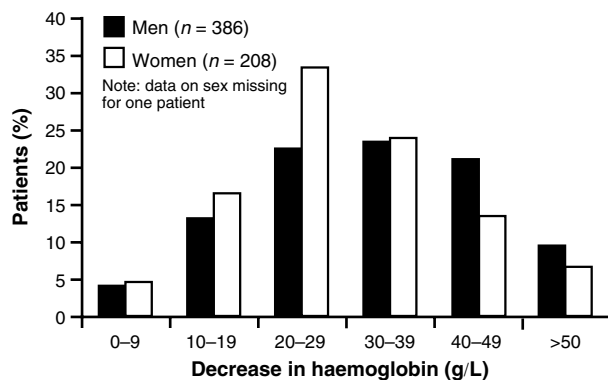


Fig. 4 Magnitude of Hb decrease.

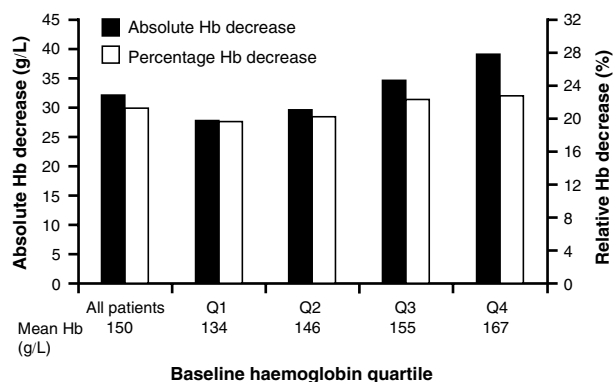


Fig. 5 Mean Hb decrease stratified by baseline Hb quartile.

concentrations, defined as >27.7% of the baseline Hb concentration (quartile 4). Of note, significant relative decreases in Hb concentrations were not associated with baseline weight, sex, race, or interferon dose/frequency. In stepwise multivariate logistic regression analysis, significant relative decreases in baseline Hb concentration were independently associated with lower baseline CrCl, higher baseline Hb concentration and older age (Table 4).

DISCUSSION

Our data indicate that more than 95% of men and women treated with standard interferon alpha-2b/RBV experienced a decrease in Hb concentration of ≥ 10 g/L and nearly 10% of men and 7% of women experienced a drop in Hb of ≥ 50 g/L. Furthermore, approximately 5% of men and nearly 20% of women experienced a Hb decrease to < 100 g/L, suggesting that women are significantly more likely to undergo RBV dose reduction in accordance with current guidelines for the management of treatment-associated anaemia.

With respect to clinical impact of treatment-associated anaemia, we found that the strategy of decreasing the daily RBV dose to 600 mg was associated with a relatively modest increase in Hb concentration of approximately 10 g/L within 4–8 weeks of dose reduction. While we were unable

Table 2 Relationship of absolute and relative decrease in Hb concentration and pretreatment estimated CrCl

	CrCl* estimate (mL/s per 1.73 m ²)				P-value†
	<1.65 (n = 133)	1.65–1.93 (n = 136)	1.94–2.37 (n = 134)	>2.37 (n = 135)	
Absolute Hb decline, g/L (mean ± SD)	330 (250–430)	350 (240–460)	310 (200–415)	280 (180–380)	<0.01
Percent Hb decline (%) (mean ± SD)	23 (17–29)	23 (17–29)	21 (14–28)	20 (13–25)	<0.001

CrCl, creatinine clearance; Hb, haemoglobin.

*CrCl estimated using the Cockcroft–Gault equation, incorporating baseline body weight, age, sex and serum creatinine concentration.

†Kruskal–Wallis test.

Table 3 Relationship of absolute and relative decrease in Hb concentration and pretreatment body weight

	Baseline weight (kg)				P-value*
	<73.9 (n = 131)	73.9–82.9 (n = 132)	83.0–95.2 (n = 144)	>95.2 (n = 138)	
Absolute Hb decline, g/L (mean ± SD)	290 (220–410)	310 (225–430)	330 (240–425)	330 (210–420)	0.76
Percent Hb decline (%) (mean ± SD)	21 (16–28)	21 (15–29)	22 (16–27)	22 (14–28)	0.89

H, haemoglobin.

*Kruskal–Wallis test.

Table 4 Risk factors for significant relative decreases in baseline Hb concentrations (>27.7% of baseline Hb concentration) by stepwise multivariate regression analysis

Variable	Odds ratio	95% CI	P-value
Baseline CrCl (mL/s per 1.73 m ²)			
1.65–1.93	4.5	2.1–9.5	<0.001
1.94–2.37	3.8	1.8–7.8	<0.001
>2.37	2.7	1.3–5.7	0.009
Higher baseline Hb (g/L)	1.6	1.3–1.9	<0.001
Baseline age (years)			
40–49	1.5	0.73–3.0	0.276
≥50	2.2	1.0–4.6	0.047

Hb, haemoglobin; CrCl, creatinine clearance.

to assess the effect of RBV dose reduction on virological treatment outcomes in our study, several recent studies have suggested that higher doses of RBV in conjunction with pegylated interferon may be associated with higher rates of viral eradication. Among 1105 treatment-naïve patients receiving standard interferon alpha-2b/RBV, Jen *et al.* reported that higher serum concentrations of RBV at week 4 of therapy were associated with increased rates of viral response at treatment week 24 [20]. In addition, using logistic regression analysis, Manns *et al.* reported that RBV

doses of >10.6 mg/kg were associated with higher rates of viral eradication among patients receiving peginterferon alpha-2b/RBV [11]. Similarly, in a prospective study, Hadziyannis *et al.* reported significantly higher sustained virological response rates among patients infected with HCV genotype 1, randomized to receive peginterferon alpha-2a plus RBV 1000–1200 mg daily compared with those randomized to lower dose RBV (800 mg daily) [13]; in this study, approximately 19% of patients randomized to receive higher dose RBV discontinued the drug because of an adverse event or laboratory abnormality. Fried *et al.* reported that sustained virological response rates were similar among patients receiving peginterferon alpha-2a plus RBV who had substantial dose reductions (to <80% of both agents) and those who maintained the full dosing schedule (67 and 75%, respectively); however, discontinuation despite an early virological response was associated with a substantial reduction in efficacy (12% sustained virological response) [12]. Taken together, these data suggest higher doses of RBV may be associated with increased antiviral efficacy; however, further research is needed to determine the impact of RBV-associated anaemia on the effectiveness of peginterferon alpha/RBV therapy.

In our study, more than one third of all patients experienced a relative Hb decrease exceeding 25% of their baseline concentration. Given the high observed incidence of significant Hb decreases, clinicians should be aware of pretreatment factors associated with its development in patients

receiving interferon alpha/RBV combination therapy. We found that significant relative decreases in Hb were independently associated with increasing age and baseline Hb concentrations and with decreasing CrCl as estimated by the Cockcroft–Gault equation, which includes age, sex, body weight and serum creatinine. Interestingly, in univariate analysis, significant relative decreases in Hb were not associated with sex or body weight, suggesting that the most important factors in the development of substantial Hb declines are renal function and age. Of interest, while age was a component of the equation used to estimate CrCl, we also found that older age was independently associated with the development of substantial Hb declines, suggesting that increasing age may be associated with other factors, such as greater erythrocyte susceptibility to oxidative membrane damage leading to increased RBV-associated haemolysis and/or decreased bone marrow responsiveness in the face of interferon alpha/RBV therapy.

Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted by the renal system, and several studies have indicated that the serum RBV concentration is related to renal function. In single-dose pharmacokinetic studies, serum concentrations of RBV were increased nearly threefold in patients with mild-to-moderate renal insufficiency [16]. Interestingly, Lindahl *et al.* recently reported that the decrease in Hb was not correlated with the dose of RBV based on body weight, but, rather, was correlated in a nonlinear fashion with serum RBV concentration, lending further support for dosing of RBV based on renal function [21]. Similarly, among patients with normal and impaired renal function, Bruchfeld *et al.* reported that RBV clearance was linearly dependent on renal function and that estimated CrCl was a significantly better predictor of RBV clearance than body weight alone, although there was a significant 40% interindividual variability in RBV total clearance that was not explained by estimated CrCl and body weight [22]. This interindividual variability in RBV clearance has been reported recently by others [23]. Bruchfeld *et al.* also reported that adequate plasma concentrations were maintained with low daily doses of RBV (170–300 mg) in patients with end-stage renal disease requiring chronic haemodialysis [24]. Accordingly, the researchers suggest that RBV dosage should be based mainly on renal function and not on body weight alone and suggest that RBV monitoring may be useful for optimizing treatment not only in the patients with impaired renal function but in other patients as well, given the lengthy time to achieve steady state and the variability in RBV clearance [22].

Our findings have several important clinical implications. While the impact of such Hb decreases on the tolerability and virological efficacy of interferon alpha/RBV is unknown, studies in patients with malignancy [25–27] or HIV infection [28,29] indicate that decreases in Hb are independently associated with increased fatigue and decreased quality of life. Our data suggest that clinicians should consider both

relative and absolute changes in Hb concentrations when evaluating patients with treatment-related adverse effects such as fatigue or dyspnoea on exertion. Furthermore, based on data suggesting that higher SVR rates may be obtained with the administration of higher doses of RBV, clinicians should be aware of the potential negative impact of RBV dose reduction or discontinuation, which occurred in nearly 20% of patients in one study [13].

A greater understanding of clinical factors associated with significant relative decreases in Hb may be useful in the management of patients during treatment as well as in determining the most appropriate dose of RBV for an individual patient. For example, current guidelines suggest that RBV should be administered according to patient weight with the intention of delivering ≥ 10.6 mg/kg of RBV daily. Our data suggest that baseline body weight is not independently associated with the development of significant Hb decreases in patients receiving interferon alpha/RBV, whereas renal function (estimated by calculated CrCl rates) and age were independently associated with a significantly higher risk of substantial Hb decline. It is important to note that our study included only patients with normal serum creatinine concentrations at baseline who were relatively young (mean age = 47 years). Additional studies are needed to further define appropriate RBV dosing schedules to enhance antiviral efficacy and minimize toxicity, particularly among those with renal insufficiency and of older age. Estimation of CrCl by the Cockcroft–Gault equation is based on readily available parameters (i.e. age, body weight, sex and serum creatinine) and is a reliable measure of glomerular filtration rate, even in patients with liver disease [30]. Thus, calculation of the estimated CrCl prior to treatment may be useful to prospectively assess the risk of significant Hb declines during interferon alpha/RBV therapy. Current data suggest that patients at increased risk for significant Hb declines may be safely treated with interferon alpha/RBV but may require closer monitoring and/or aggressive management of treatment-associated anaemia. Clinicians should be aware of the potential for increased risk of significant Hb declines among patients with even mild degrees of renal insufficiency, particularly those who are older. Additional studies are required to determine if monitoring of RBV concentrations during HCV treatment will lead to further improvement in the efficacy and safety of RBV therapy.

Similarly, studies are needed to evaluate the role of novel strategies for the management of interferon alpha/RBV-associated anaemia [31–33]. For example, in an open-label, randomized, parallel-group study, 64 HCV-infected patients receiving interferon alpha-2b/RBV who experienced Hb concentrations of ≤ 120 g/L were randomized to receive recombinant human erythropoietin (r-HuEPO; epoetin alpha) plus standard of care for anaemia management (i.e. transfusions, RBV dose reduction or discontinuation) or standard of care for anaemia management alone [31]. After 16 weeks of epoetin alpha therapy, the mean Hb

concentration (142 g/L) in patients receiving epoetin alpha was significantly ($P < 0.05$) higher than in the patients receiving standard of care alone (112 g/L) and 83% of epoetin alpha-treated patients maintained RBV dosages of ≥ 800 mg/day, compared with 54% of patients receiving standard of care alone ($P < 0.008$) [31]. Further studies are being conducted to define the role of epoetin alpha in the management of Hb decreases in patients receiving interferon alpha/RBV.

In conclusion, we found that the majority (95%) of patients treated with interferon alpha-2b/RBV experienced a decrease in Hb concentration of ≥ 10 g/L, whereas more than 7% of patients experienced a decline of > 50 g/L. In addition, the incidence of decreases in Hb to < 100 g/L was more than fourfold higher in women compared with men, suggesting that the use of this absolute Hb concentration for RBV dose reduction may not take into account potentially important factors such as sex and the magnitude of the relative Hb decline. We found that more than one third of treated patients experienced a $> 25\%$ decline from baseline Hb concentrations. Furthermore, our data indicate that significant decreases in Hb concentration are independently related to baseline Hb level, renal function and age. Consequently, in addition to body weight, clinicians should consider these factors, particularly estimated CrCl, when considering RBV dosing and the potential risk for significant Hb decline. Our data underscore the need to carefully monitor Hb in patients receiving combination interferon alpha/RBV therapy to ensure patient safety as well as to minimize adverse effects and enhance antiviral outcomes. Further research is needed to determine the impact of significant relative decreases in Hb concentration on important clinical parameters such as adherence to treatment, fatigue and quality of life and virological response, as well as the role of novel management strategies such as the use of epoetin alpha to improve these outcomes.

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