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Ribavirin dose management in HCV patients receiving ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin

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Abstract

Background & Aims: Some individuals with hepatitis C virus infection treated with direct-acting antivirals require ribavirin to maximize sustained virological response rates. We describe the clinical management of ribavirin dosing in hepatitis C virus-infected patients receiving ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin.

Methods: We performed a post hoc analysis of patients receiving ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 12 or 24 weeks in six phase 3 trials. Multivariate stepwise logistic regression models assessed predictors associated with ribavirin dose adjustments and with developing anaemia.

Results: Of 1548 patients, 100 (6.5%) modified ribavirin dose due to haemoglobin declines, of which 99% achieved sustained virological response at 12 weeks post-treatment. Median time to first ribavirin dose reduction was 37 days. Low baseline haemoglobin was significantly associated with an increased risk of requiring ribavirin dose modification (odds ratio: 0.618 [0.518, 0.738]; $P < .001$) and developing anaemia (odds ratio: 0.379 [0.243, 0.593]; $P < .001$).

Conclusions: Ribavirin dose reductions were infrequent, occurred early in treatment, and did not impact sustained virological response at 12 weeks post-treatment. Patients with low baseline haemoglobin should be monitored for on-treatment anaemia.

KEYWORDS

anaemia, dasabuvir, ombitasvir, paritaprevir, ribavirin

1 | INTRODUCTION

In combination with standard interferon and pegylated interferon (pegIFN), ribavirin (RBV) has been shown to significantly decrease

Abbreviations: AASLD, American Association for the Study of Liver Diseases; BMI, body mass index; CrCl, creatinine clearance; DAA, direct-acting antivirals; DSV, dasabuvir; GT, genotype; HCV, hepatitis C virus; LLOQ, lower limit of quantification; OBV, ombitasvir; pegIFN, pegylated interferon; PTV, paritaprevir; RBV, ribavirin; r, ritonavir; SD, standard deviation; SVR12, sustained virological response 12 weeks post-treatment; SVR, sustained virological response.

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the risk of post-treatment viral relapse and increase rates of sustained virological response (SVR) in patients with hepatitis C virus (HCV) infection.^{1,2} Despite improving the efficacy of IFN-based therapy, RBV is associated with haemolytic anaemia,^{3,4} a phenomenon driven by accumulation of RBV in erythrocytes and oxidative damage within the red blood cells.⁵ RBV-associated decline in haemoglobin levels is dose-dependent and can be exacerbated by the suppressive effects of interferon on bone marrow,⁶ which suppresses compensatory reticulocytosis.⁷

In the current era of all-oral, IFN-free, direct-acting antivirals (DAAs) for the treatment of HCV, clinical trial data have shown that

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the addition of RBV to DAA treatment regimens can result in higher SVR rates by reducing post-treatment viral relapse and limiting selection of HCV resistance-associated variants among some difficult-to-cure individuals.⁸⁻¹⁰

Six phase 3 trials evaluated the all-oral DAA regimen of ombitasvir (OBV, an NS5A inhibitor), paritaprevir (an NS3/4A protease inhibitor identified by AbbVie and Enanta, and dosed with ritonavir, PTV/r) and dasabuvir (DSV, a non-nucleoside NS5B RNA polymerase inhibitor) with or without RBV in HCV genotype (GT)1-infected patients that were either treatment naïve or pegIFN experienced, with or without compensated cirrhosis.^{8,11-14} Overall, the frequency and clinical severity of anaemia were low across the six trials; 6.5% of subjects had a decrease in haemoglobin levels to <10 g/dL during treatment with OBV/PTV/r + DSV + RBV, and <1% had a haemoglobin decrease to <8 g/dL.^{8,11-14}

Anaemia-related adverse events can be effectively managed through adjustments in RBV dose. However, optimal clinical management of anaemia requires an understanding of (1) when clinically significant declines in haemoglobin levels are likely to occur, (2) the characteristics of patients that are likely to require RBV dose reductions and (3) the impact of RBV dose reductions on treatment outcomes. This post hoc pooled analysis describes the clinical management of RBV dosing in GT1-infected patients receiving OBV/PTV/r + DSV + RBV in six phase 3 trials.

2 | PATIENTS AND METHODS

Patients in the phase 3 SAPPHERE-I and -II, PEARL-II, -III and -IV, and TURQUOISE-II studies received OBV/PTV/r (25/150/100 mg once daily) and DSV (250 mg twice daily) for 12 weeks (non-cirrhotic patients), or for either 12 or 24 weeks (cirrhotic patients). Where administered, RBV was dosed according to body weight with a total daily dose of 1000 mg (<75 kg) or 1200 mg (≥75 kg). The design, patient characteristics, and overall efficacy and safety outcomes of these studies have been described previously.^{8,11-14}

RBV dose modifications were protocol-specified for (1) patients without cardiac disease with a haemoglobin decline to <10 g/dL, or a haemoglobin decline ≥4 g/dL in two consecutive visits; (2) patients with cardiac disease with a haemoglobin decline to <12 g/dL, or a haemoglobin decline ≥2 g/dL during 4 weeks of treatment and (3) any patient with a confirmed calculated creatinine clearance (CrCl) <50 mL/min. RBV dose was reduced according to the local Prescribing Information for RBV.

The percentage of patients with first and with second RBV dose modifications, and the mean and median time to first and secondary modifications were calculated. Mean haemoglobin concentrations over time were plotted for patients with and without RBV dose modifications.

Stepwise logistic regression models ($\alpha = 0.10$ to enter and to remain in the model) assessed predictors associated with RBV dose modification and predictors associated with developing anaemia. Among all patients, stepwise logistic regression modelled RBV dose

Key points

- Among 1548 patients treated with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 12 or 24 weeks in six phase 3 trials, ribavirin dose reductions due to haemoglobin declines were infrequent, occurring in 100 (6.5%) patients
- Ribavirin dose reductions with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin occurred early in treatment and did not impact sustained virological response at 12 weeks post-treatment
- Low baseline haemoglobin was significantly associated with an increased risk of requiring ribavirin dose modification and developing anaemia
- Patients with low baseline haemoglobin should be monitored for on-treatment anaemia with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin treatment

modification as the dependent variable, and among the 100 patients with a RBV dose modification, anaemia (haemoglobin <10 g/dL) was modelled as the dependent variable. Independent variables in both regression models included age, sex, race, ethnicity, prior pegIFN/RBV treatment experience, baseline cirrhosis status, and baseline values for body mass index (BMI), haemoglobin, CrCl, albumin and platelet count.

All patients in the studies provided written informed consent before any study-specific procedures were carried out. The studies were conducted in accordance with the International Conference on Harmonisation guidelines, applicable regulations and the principles of the Declaration of Helsinki. The study protocols were approved by each of the independent ethics committees (IECs) or institutional review boards (IRBs) at each of the participating study sites (a list of IECs/IRBs can be found in Table S1).

3 | RESULTS

In the six phase 3 studies, the overall rate of patients requiring a RBV dose modification was low. Of 1548 patients receiving RBV, only 100 (6.5%) reduced the RBV dose due to haemoglobin declines. A total of 715 (46.2%) of these patients received an OBV/PTV/r + DSV + RBV regimen that is recommended by the current (2016) guidelines of the American Association for the Study of Liver Diseases (AASLD).¹⁵ Five patients received erythropoietin (four patients in TURQUOISE-II and one patient in SAPPHERE-I); none received a blood transfusion.^{11,16}

At first dose adjustment, the majority of patients (56/100; 56%) were managed with a reduction in RBV dose to 600 mg, and only 10 patients (10/100; 10%) were reduced to 400 mg or lower. The

TABLE 1 Patient characteristics associated with increased risk of RBV dose modification and anaemia^a

	Odds ratio	95% CI	P
Increased risk of RBV dose modification			
Baseline haemoglobin level (continuous, g/dL)	0.618	0.518, 0.738	<.001
Baseline CrCl (continuous, mL/s)	0.261	0.123, 0.554	<.001
Age (continuous, years)	1.06	1.02, 1.09	<.001
Baseline BMI (continuous, kg/m ²)	1.08	1.02, 1.15	.013
Increased risk of anaemia (haemoglobin <10 g/dL) among patients with RBV dose modifications			
Baseline haemoglobin level (continuous, g/dL)	0.379	0.243, 0.593	<.001

^aIndependent baseline variables that were considered in the stepwise multivariate logistic regression models were age (years), prior pegIFN/RBV experience (yes, no), sex (male, female), race (black, Asian, white), ethnicity (Hispanic/Latino, other), baseline cirrhosis status (yes, no), and baseline values for BMI (kg/m²), haemoglobin (g/dL), CrCl (mL/s), platelet count (10⁹/L), albumin (g/L). BMI, body mass index; CrCl, creatinine clearance; RBV, ribavirin.

majority (65%) of RBV dose reductions occurred within the first 6 weeks of treatment, and the median time to first dose reduction was 37 days (95% CI 36.0, 44.0; Table S2).

Of the 100 patients that modified the RBV dose, 20 required a second RBV dose reduction. The majority (14/20; 70%) of secondary dose adjustments occurred within 8 weeks of starting treatment, on median day 48 (Table S2). Three (15%) of the 20 patients with at least two reductions in RBV dose had an increase in RBV dose before the second RBV dose reduction.

Logistic regression analyses demonstrated that low baseline haemoglobin level ($P < .001$), low CrCl rate ($P < .001$), older age ($P < .001$) and higher baseline BMI ($P = .013$) were associated with a significantly increased likelihood of requiring a RBV dose modification (Table 1). Differences between these characteristics in patients with and without RBV dose modifications are presented in Table S2.

In patients with RBV dose reductions, mean haemoglobin declines were observed within 4 weeks of receiving OBV/PTV/r + DSV + RBV, after which haemoglobin levels plateaued until the end of treatment (Figure 1). The mean (\pm SD) maximum decline in haemoglobin level was -4.1 ± 1.26 g/dL, compared with -2.7 ± 1.19 g/dL in patients without RBV dose reductions. Laboratory-confirmed anaemia (haemoglobin <10 g/dL) was observed in 63 of the 100 patients that reduced the RBV dose, and haemoglobin levels declined to <8 g/dL in four patients. Mean haemoglobin levels returned to near baseline values by post-treatment week 4 (Figure 1). After RBV dose reduction, recovery of haemoglobin levels during treatment led to an increase in RBV dose in 16 patients (16/100; 16%), as per the study protocols.

Regression analysis among the 100 patients with RBV modifications identified low baseline haemoglobin ($P < .001$) as the only factor significantly associated with developing anaemia (Table 1).

Ribavirin (RBV) dose reductions, including secondary reductions, did not impact the ability of patients to achieve a sustained virological response 12 weeks post-treatment (SVR12) in the phase 3 trials. The SVR12 rate among patients that required a reduction in RBV dose was 99% (99/100); only one 64-year-old white male with an

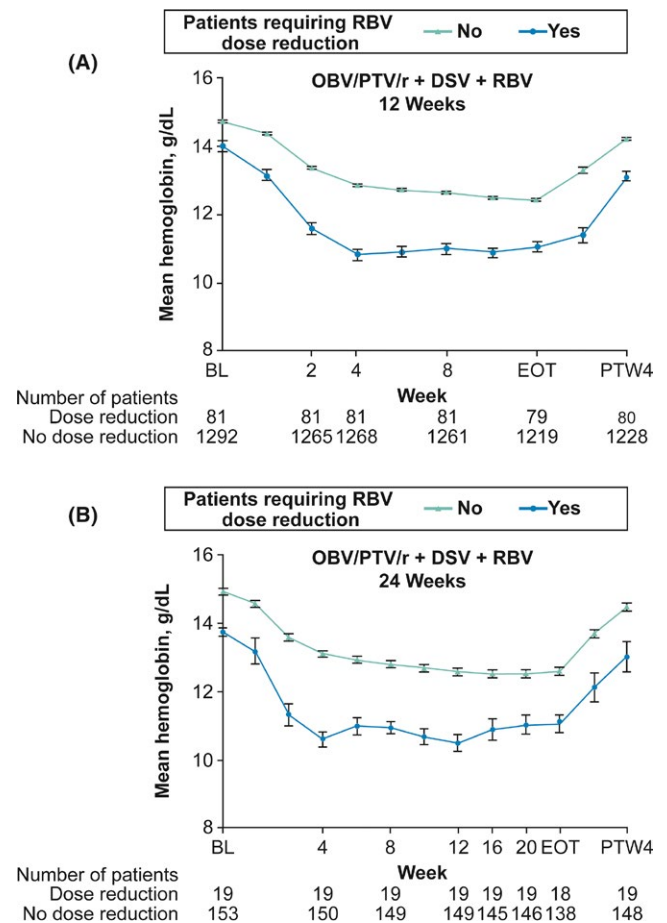


FIGURE 1 Mean (\pm SE) haemoglobin level declines in patients with or without a ribavirin dose reduction following OBV/PTV/r + DSV + RBV treatment for 12 weeks (A) or 24 weeks (B). The mean plot is shown across time for haemoglobin levels in patients that received ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in six phase 3 trials

IL28B non-CC genotype and HCV GT1a infection without cirrhosis did not achieve SVR12. Furthermore, reducing the RBV dose prior to achieve HCV RNA below the lower limit of quantification (LLOQ;

25 IU/mL) did not affect response rates. All seven patients that required a dose reduction before HCV RNA <LLOQ achieved SVR12. The one patient who did not achieve SVR12 had HCV RNA <LLOQ at Study Day 15, prior to reduce RBV dose at Study Day 29.

4 | DISCUSSION

Across six phase 3 studies of OBV/PTV/r + DSV + RBV, RBV dose reductions were required in only 6.5% of patients, compared with approximately 20% of patients receiving pegIFN/RBV therapy in past studies.^{1,2} Head-to-head studies have recently reported RBV dose reductions to be lower in patients receiving OBV/PTV/r + DSV + RBV compared with those receiving the first-generation protease inhibitor, telaprevir, in combination with pegIFN/RBV.¹⁷

The majority of RBV dose modifications occurred early in the course of treatment, and successfully halted haemoglobin declines with only 20% of patients requiring further RBV dose decreases. The majority of patients were managed with a reduction in RBV dose to 600 mg. Moreover, reducing RBV dose prior to achieve HCV RNA below the LLOQ had no negative impact on achieving SVR12. Previous studies evaluating pegIFN/RBV therapy also concluded that mild to moderate RBV dose reductions do not adversely affect SVR rates.^{18,19}

In the present analysis, low baseline haemoglobin levels and low baseline CrCl rates, as well as older age, were identified as predictive factors associated with RBV dose modifications, and these observations are in keeping with previously reported predictors of anaemia.^{20,21} Higher BMI was identified as a predictor in the presence of the other predictors although with a low odds ratio (OR: 1.08; $P = .013$). There was no significant difference in BMI between patients with and without RBV dose reductions ($P = .396$; Table S3).

The majority (63%) of patients that received a RBV dose modification had declines in haemoglobin to <10 g/dL (Grade 2 anaemia); only 4% had declines in haemoglobin to <8 g/dL (Grade 3 anaemia). Across the phase 3 studies, the highest rates of anaemia occurred in patients with compensated cirrhosis (TURQUOISE-II),^{8,11-14} a patient population that typically has higher rates of HCV-treatment-related adverse events.²² In the recent TURQUOISE-III study, OBV/PTV/r + DSV achieved 100% SVR12 in GT1b-infected patients with compensated cirrhosis, demonstrating that RBV is not required in these patients.²³

Using multivariate logistic regression, the only significant factor associated with anaemia among subjects with RBV dose modifications was lower baseline haemoglobin levels. Therefore, our data suggest that patients with low baseline haemoglobin levels should be monitored most carefully for RBV-associated declines in haemoglobin and managed through RBV dose reductions. The same principles also apply to patients with decompensated cirrhosis for whom current guidelines recommend the use of ribavirin, either weight-based or low initial dose.^{15,24} However, it is important to note that, like all protease-inhibitor-containing regimens, OBV/PTV/r + DSV

should not be used in patients with Child-Pugh B/C cirrhosis due to an increased risk of hepatotoxicity.²⁵⁻²⁷

In summary, although haemoglobin decreases were more common with OBV/PTV/r + DSV + RBV than without the use of RBV (haemoglobin <10 g/dL did not occur in any patients receiving the RBV-free regimen across the six trials), significant anaemia was uncommon and was managed with RBV dose reductions alone in most patients, without any negative impact on SVR12.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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