Virologic Response Rates of Weight-Based Taribavirin Versus Ribavirin in Treatment-Naive Patients with Genotype 1 Chronic Hepatitis C

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Ribavirin-induced hemolytic anemia can prompt dose reductions and lower sustained virologic response (SVR) rates in the treatment of patients with chronic hepatitis C. The study aimed to determine if weight-based dosing of taribavirin (TBV), an oral prodrug of ribavirin (RBV), demonstrated efficacy comparable to RBV while maintaining its previously demonstrated anemia advantage with fixed dose administration. A U.S. phase 2b randomized, open-label, active-controlled, parallel-group study was conducted in 278 treatment-naive patients infected with genotype 1 who were stratified by body weight and baseline viral load. Patients were randomized 1:1:1:1 to receive TBV (20, 25, or 30 mg/kg/day) or RBV (800-1400 mg/day) with pegylated interferon alfa-2b for 48 weeks. The SVR rates in this difficult-to-cure patient demographics (mean age, 49 years; 61% male; 30% African American or Latino; high viral load; advanced fibrosis; and mean weight, 82 kg) were 28.4%, 24.3%, 20.6%, and 21.4% in the 20, 25, and 30 mg/kg TBV groups and the RBV group, respectively. There were no statistical differences in the efficacy analyses. Anemia rates were significantly lower ($P < 0.05$) in the 20 and 25 mg/kg/day TBV treatment groups (13.4% and 15.7%, respectively) compared to RBV (32.9%). The most common adverse events in all groups were fatigue, diarrhea, and insomnia. Diarrhea, reported in 38% of TBV patients versus 21% of RBV patients, was generally mild and not dose-limiting. *Conclusion:* All TBV doses demonstrated efficacy and tolerability comparable to that of RBV; however, the 25 mg/kg dose demonstrated the optimal balance of safety and efficacy. Anemia rates were significantly lower for TBV given at 20-25 mg/kg than RBV. These data suggest weight-based dosing with TBV provides a safe and effective treatment alternative to RBV for chronic hepatitis C. American Association for the Study of Liver Diseases.
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Ribavirin (RBV) is essential for the treatment of chronic hepatitis C virus (HCV) infection. When used in combination with peginterferon alfa (peg-IFN alfa), it significantly enhances on-treatment virologic response and reduces relapse.[1-3] RBV has been demonstrated to be essential in achieving high rates of sustained virologic response (SVR) when used in combination with direct-acting antiviral agents.[4-6] One of the most significant toxicities of RBV is hemolytic anemia.[5,7] When used as monotherapy, RBV-induced hemolytic anemia is marginal because of a compensatory reticulocytosis.[8,9] However, peg-IFN alfa suppresses the bone marrow and significantly reduces reticulocytosis. Therefore, anemia associated with the combination of IFN and RBV therapy is much greater. Approximately 25%-30% of patients receiving peg-IFN and RBV develop a decline of 4 g

Abbreviations: AE, adverse event; ESA, erythropoiesis-stimulating agent; EVR, early virologic response; FW, follow-up week; Hb, hemoglobin; HCV, hepatitis C virus; IFN, interferon; ITT, intent to treat; RBV, ribavirin; SVR, sustained virologic response; TBV, taribavirin; TW, treatment week; WBD, weight-based dosing.

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or greater in hemoglobin (Hb).[1,2,10] This significantly impairs quality of life and leads to dose reduction and premature discontinuation of treatment in 15%-30% of patients.[1,3,11,12] Decreasing the dose of RBV to below 10.6 mg/kg body weight/day during the first 12 weeks of treatment has been shown to increase relapse rates and reduce SVR in both treatment-naive patients and during retreatment.[11,13,14]

Taribavirin (TBV), formerly known as Viramidine, is a nucleoside analogue and oral prodrug of RBV that is converted from TBV to RBV by adenosine deaminase. Its structural difference from RBV, a positively charged carboxamidine group at position 3, significantly reduces the ability of this agent to enter red cells. Because accumulation of RBV within red blood cells is the primary mechanism causing hemolytic anemia, TBV should therefore be associated with significantly less anemia.

Two previous phase 3 clinical trials, ViSER 1 and ViSER 2 (Viramidine's Safety and Efficacy versus Ribavirin), compared a fixed dose of TBV 600 mg twice a day to weight-based dosing (WBD) of RBV 1000 mg/1200 mg ($\leq$75 kg/$>$75 kg body weight), in combination with either peg-IFN alfa-2b or peg-IFN alfa-2a, respectively.[15,16] Both ViSER studies met the primary safety endpoint defined as Hb $<$ 10 g/dL or at least a 2.5 g/dL decrease from baseline at any time point during therapy. Statistically less anemia was observed in patients treated with TBV compared to RBV. However, the primary efficacy endpoint of these studies—a noninferior SVR between the TBV and RBV groups—was not achieved. Detailed subgroup analyses of the data suggested the reasons for the lower SVR in TBV-treated patients were: fixed dose as opposed to WBD and the selection of an inadequate dose. The present study explored several higher WBD regimens of TBV to determine a dosage regimen that was able to deliver comparable responses to RBV with less anemia.

Patients and Methods

Study Patients. Approximately 260 patients were planned for enrollment in the study, with approximately 65 patients in each of the four treatment groups. Eligible patients were treatment-naive, at least 18 years of age, diagnosed with chronic HCV genotype 1 infection ($>$2000 copies/mL or $>$780 IU/mL), and showed histologic changes consistent with chronic HCV as demonstrated on liver biopsy within 3 years of screening. Patients were excluded from the study if they had histologic evidence of cirrhosis (F4), low Hb concentrations (men, $<$13 g/dL; women, $<$12 g/dL), neutropenia (absolute neutrophil count $<1200 \times 10^3/\mu$L), thrombocytopenia ($<90 \times 10^3$ platelets/μL) or serum creatinine levels $\geq$1.5 mg/dL. Additional exclusion criteria included chronic hepatic disease other than HCV, human immunodeficiency virus, or hepatitis B coinfection; severe psychiatric disorders; alcoholism or drug addiction within 1 year of screening; use of erythropoiesis-stimulating agents (ESAs); and presence of comorbid conditions considered significant by the investigator.

Study Design. This was a phase 2b, multicenter, randomized, open-label, active-control, and parallel-group trial. Although the study was open-label, the sponsor was blinded to treatment allocation and viral load results until treatment week 12. Patients were enrolled at 51 centers in the United States. Patients were stratified by serum HCV RNA titers ($\leq$780,000 IU/mL or $>$780,000 IU/mL) and baseline weight ($\leq$75 or $>$75 kg). An interactive voice response system was used to randomize patients in a 1:1:1:1 ratio to receive weight-based TBV 20 mg/kg/day, 25 mg/kg/day, or 30 mg/kg/day (Valeant Pharmaceuticals North America, Aliso Viejo, CA) or weight-based RBV at 800, 1000, 1200, or 1400 mg/day (Copegus; Hoffmann-La Roche, Nutley, NJ) in combination with peg-IFN alfa 2b (PegIntron; Schering Corp., Kenilworth, NJ). All patients received doses twice daily with their morning and evening meals.

Patients were treated for 48 weeks, but treatment was discontinued for evidence of nonresponse defined as $<$2-log decline at week 12 or a positive viral load at week 24. Study treatment was initiated on day 1 and clinic visits occurred at treatment weeks (TWs) 1, 2, 3, 4, 8, 12, 18, 24, 30, 36, and 48, as well as post-treatment follow-up weeks (FWs) 4, 12, 20, and 24. All patients who completed treatment with study drug or discontinued treatment prematurely (except nonresponders) immediately entered a 24-week follow-up period.

The study protocol was approved by the institutional review boards of participating institutions and was conducted in accordance with the Declaration of Helsinki and provisions of Good Clinical Practices. All patients provided written informed consent.

Study Objective. The objective of this study was to select an optimal dose of TBV by comparing the efficacy and safety of three TBV dose levels versus RBV based on body weight, both administered with peg-IFN alfa-2b to therapy-naive compensated patients with genotype 1 chronic hepatitis C.

Efficacy Assessments. The primary efficacy endpoint was early virologic response (EVR) defined as the

proportion of patients with at least a 2-log decrease from baseline in serum HCV RNA levels at TW12. Additional efficacy endpoints assessed in the trial included SVR; undetectable HCV RNA at TW4, TW24, and TW48; and viral relapse for those who were responders at the end of treatment. Subgroup analyses were carried out to determine the impact of various baseline demographic factors such as sex, age, race, weight, baseline HCV RNA, and fibrosis score on response.

Lack of efficacy was defined as less than a 2-log decrease of HCV RNA (IU/mL) at TW12 or detectable HCV RNA at TW24. Relapse rates were calculated by measuring the proportion of responding patients whose plasma HCV levels changed from undetectable at end of treatment to detectable at FW24.

Safety Assessments. The primary safety endpoint was the proportion of patients with Hb $<$ 10 g/dL at any time during the treatment period. Subgroup analyses were carried out to determine the impact of various baseline demographic factors such as sex, age, race, weight, baseline HCV RNA, and fibrosis score on safety. Safety assessments included laboratory values, vital signs, and monitoring of adverse events (AEs) at each study visit. Patients who discontinued therapy prematurely due to an AE were followed to study completion. Stepwise reductions in peg-IFN, RBV, and TBV dosages were allowed to manage AEs or laboratory abnormalities that had reached predetermined thresholds of severity. If a dose modification of TBV or RBV was required for nonhematologic AEs, the dose was decreased in a stepwise manner, starting with a reduction of approximately 20% of the assigned dose. Hematologic AEs, except anemia, initially required a dose reduction of 50%. Anemia AEs were managed according to presence or absence of cardiac disease. Upon AE resolution, increases of peg-IFN, RBV, or TBV dose in a reverse stepwise manner could be attempted at the investigator's discretion. Use of ESAs was prohibited.

Because diarrhea was identified as an AE of special interest in previous clinical trials, a more extensive diarrhea history was obtained at baseline, and a diarrhea-specific AE report form was developed and employed in this trial. Diarrhea was classified on the form by common toxicity criteria grades of 1 to 4 (mild to severe). A diarrhea management plan was developed and employed. An independent data monitoring committee convened at various time points during the study treatment period to assess safety but also to determine the risk-benefit ratio considering the higher dosages studied.

Pharmacokinetic Analyses. Serial plasma samples for the determination of TBV and RBV concentrations were collected across the first dosing interval (0-12 hours) of the twice daily dosing regimen at TW4 and TW12 in a representative subset of the patients at select sites for noncompartmental pharmacokinetic analysis and assessment of dose linearity. In addition, predose plasma samples for determination of TBV and RBV concentrations were obtained at each treatment week with an assessment of steady state at TW4.

Statistical Analyses. There were 275 patients enrolled in the study, with approximately 70 patients in each of the four treatment groups. The projected study power was 70% to detect a linear trend in proportions as well as to detect noninferiority of TBV versus RBV using a margin of 12%.

Analysis of the primary efficacy and safety variables used data from the intent-to-treat (ITT) population, defined as patients who were randomized and received at least one dose of study drug.

The per-protocol population, defined as ITT patients with no major protocol deviations, no use of prohibited concomitant medications, and who completed treatment with $>$80% compliance, was used for the sensitivity analysis at TW12, TW24, and TW48 and FW4, FW12, and FW24.

Unless otherwise noted, all tests of hypotheses were two-sided at the overall 5% level of significance. The trend test determined the dose response relationship of the three TBV treatment groups, and the Fisher's exact test was performed for the various treatment group comparisons. For each of these three comparisons, the difference in responder rate and associated 95% confidence interval was determined. Once the optimum TBV dose was identified, a test of noninferior efficacy was performed by comparing the proportions of responders at TW12 in the optimal TBV and RBV treatment arms. Chi-squared or the Fisher's exact test compared anemia rates between the TBV and RBV groups with a 95% confidence interval.

Secondary efficacy measures included the SVR defined as HCV RNA $<$100 copies/mL (39 IU/mL) and/or at least a 2-log decrease from baseline at TW4, TW24, TW48 and FW4 and FW12 and relapse rates at FW4, FW12, and FW24. Secondary safety measures included the comparison of incidence of treatment-emergent adverse events.

Subgroup analysis by HCV RNA levels at baseline, body weight, age, sex, race, and baseline fibrosis were performed using the trend test and the Fisher's exact test for the primary endpoint. In addition, the Cochran-Mantel-Haenszel procedure, with the Breslow-Day

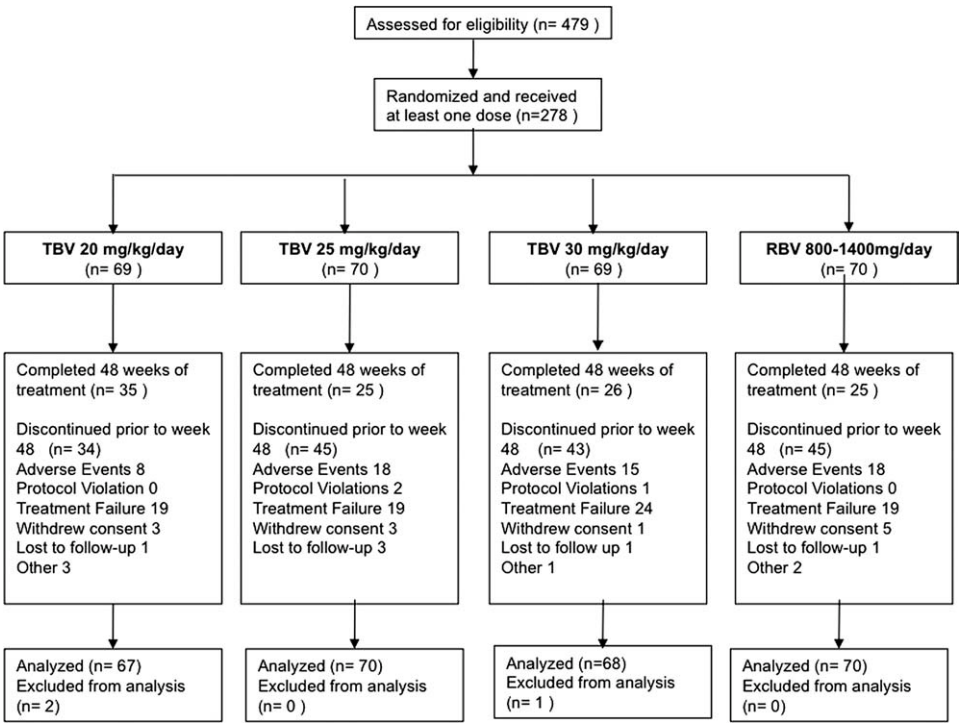

Fig. 1. Disposition of patients during treatment.

test was used to examine the homogeneity of treatment effect across strata.

The investigators and the sponsor managed the data for this study. The sponsor completed the statistical analysis. The authors had access to the clinical study report and have either written or provided intellectual input to the manuscript.

Results

Study Patients. A total of 278 patients were randomized at 51 U.S. centers between March 2007 and October 2008. A total of 86 (41%) of patients in the TBV arms and 25 (36%) in the RBV arm completed treatment and follow-up. Overall, 122 (59%) patients withdrew prematurely in the TBV arms compared to 45 (64%) in the RBV group. The most commonly cited reasons for premature withdrawal were lack of response (29%) and adverse events (20%). Figure 1 shows the disposition of patients during treatment.

Baseline characteristics across the four treatment groups were similar (Table 1). The majority of patients were male (61%) with a mean weight of 82.1 kg and mean age of 49 years. African American or Latino patients accounted for 30% of the study population and 81% had high viral load defined as >400,000 IU/mL at baseline.

Efficacy. The proportions of patients in the ITT population with an EVR, the primary endpoint of this

Table 1. Patient Demographic Characteristics at Baseline

Characteristic	TBV 20 mg/kg (N = 67)	TBV 25 mg/kg (N = 70)	TBV 30 mg/kg (N = 68)	RBV 800-1400 mg (N = 70)	Total (N = 275)
Mean age, ± SD	48.5 ± 9.39	47.5 ± 9.42	49.6 ± 7.24	49.7 ± 8.30	48.8 ± 8.63
Male, n (%)	32 (47.8)	45 (64.3)	43 (63.2)	48 (68.6)	168 (61.1)
Race, n (%)					
Caucasian	50 (74.6)	41 (58.6)	42 (61.8)	45 (64.3)	178 (64.7)
African American	10 (14.9)	14 (20.0)	13 (19.1)	12 (17.1)	49 (17.8)
Asian	2 (3.0)	4 (5.7)	3 (4.4)	2 (2.9)	11 (4.0)
Latino	4 (6.0)	10 (14.3)	9 (13.2)	10 (14.3)	33 (12.0)
Other	1 (1.5)	1 (1.4)	1 (1.5)	1 (1.4)	4 (1.5)
Mean weight (kg) ± SD	81.5 ± 16.86	82.6 ± 16.77	82.2 ± 17.99	82.3 ± 17.08	82.1 ± 17.09
Mean BMI (kg/m^2) ± SD	28.1 ± 5.23	27.2 ± 4.14	27.2 ± 4.21	28.2 ± 5.09	27.7 ± 4.69
Mean HCV RNA × 10^6 ± SD	6.6 ± 0.71	6.6 ± 0.78	6.6 ± 0.78	6.5 ± 0.84	6.6 ± 0.77
>400,000 IU/mL (%)	82.1	80.0	79.4	81.4	81
Bridging fibrosis, N (%)	16 (23.9)	17 (24.3)	21 (30.9)	29 (41.4)	83 (30.2)

All patients received study drug in combination with peg-interferon alfa-2b.
BMI, body mass index; RBV, ribavirin; SD, standard deviation; TBV, taribavirin.

Table 2. Efficacy Analysis—ITT Population

Study Drug Daily Dose	TBV 20 mg/kg N = 67	TBV 25 mg/kg N = 70	TBV 30 mg/kg N = 68	RBV 800-1400 mg N = 70	*P* Value ns = nonsignificant
TW4*	11 (16.4%)	10 (14.3%)	11 (16.2%)	8 (11.4%)	ns
TW12*	28 (41.8%)	29 (41.4%)	17 (25.0%)	22 (31.4%)	ns
EVR†	43 (64.2%)	40 (57.1%)	37 (54.4%)	36 (51.4%)	ns
TW24*	35 (52.2%)	30 (42.9%)	27 (39.7%)	27 (38.6%)	ns
TW48*	30 (44.8%)	27 (38.6%)	23 (33.8%)	26 (37.1%)	ns
SVR*	19 (28.4%)	19 (27.1%)	19 (27.9%)	19 (27.1%)	ns

*HCV RNA undetectable<39 IU/mL.

†EVR-undetectable (<39 IU/mL) or a >2-log decline in HCV RNA from baseline at TW12.

study, were comparable between all groups with no statistical difference versus RBV. EVR was achieved in 64.2% (43 of 67) in the 20 mg/kg group, 57.1% (40 of 70) in the 25 mg/kg group, 54.4% (37 of 68) of the 30 mg/kg group and 51.4% (36 of 70) in the RBV group. Virologic response for TW4, 12, 24, and 48 as well as SVR are shown in Table 2. The proportion of patients with undetectable HCV RNA at every time point was similar between the TBV and RBV groups. Although responder rates were numerically lower at TW12 in the TBV 30 mg/kg group and somewhat higher at TW24 and TW48 in the TBV 20 mg/kg group, they were not significantly different for any of the TBV doses compared with RBV.

The relapse rates for the TBV groups (35%, 20 mg/kg; 21%, 25 mg/kg; 14%, 30 mg/kg) were inversely proportional to the TBV dose and are most likely indicative of the recognized effects of RBV dosing (Fig. 2). The lowest TBV dose resulted in the lowest RBV exposure and subsequently, the greatest relapse rate (35%).

The SVR rates observed in the per-protocol population were 60%, 64%, 62%, and 62% for the 20, 25, and 30 mg/kg/day TBV groups and the RBV group, respectively, and there were no statistically significant differences between the groups. These results were more than double the ITT SVR demonstrating maximal response as RBV or TBV exposure increases with adherence to therapy.

Safety. The most common AEs were typical of those previously reported for chronic hepatitis C therapy with peg-IFN and RBV. However, diarrhea and insomnia were more common (>10% different) in the groups that received TBV, whereas anemia was more common (>10% different) in the RBV group (Table 3). The mean insomnia rate of the TBV arms was 35% compared to 24% for the RBV arm and was not considered clinically relevant. The mean TBV diarrhea rate was 39% versus 23% in the RBV group.

Diarrhea, which was previously noted to occur more frequently in the ViSER studies, was also reported more frequently in the current study. It occurred predominantly during the first 12 weeks of therapy and was generally mild, not dose-limiting and of short duration. Through FW24, cumulative diarrhea rates occurred in 40.3%, 37.1%, and 36.8% of patients on 20, 25, and 30 mg/kg/day TBV respectively. This indicates no apparent TBV dose relationship. In the majority of cases diarrhea classification was "mild" or "moderate." Serious diarrhea AEs (grade 3) were reported in two patients and were determined by their physician assessment as un-related to study medication and due to concomitant disease. There were no grade 4 diarrhea events reported. During the 24-week follow up period, the incidence of diarrhea returned to baseline at a frequency similar to that of RBV.

The cumulative incidence of anemia throughout the trial is shown in Table 4. The 20 and 25 mg/kg groups were statistically significantly lower than the RBV group ($P < 0.05$) at all time points. The anemia rate of TBV 30 mg/kg was lower than that observed with RBV but did not achieve statistical significance, other than at week 4. The pharmacokinetic analysis showed this effect correlated with RBV plasma exposure in the TBV group. Exposure of RBV associated with TBV dosing was consistently lower compared to RBV exposure due to RBV dosing by pharmacokinetic measures (data not shown) until after TW18. At that

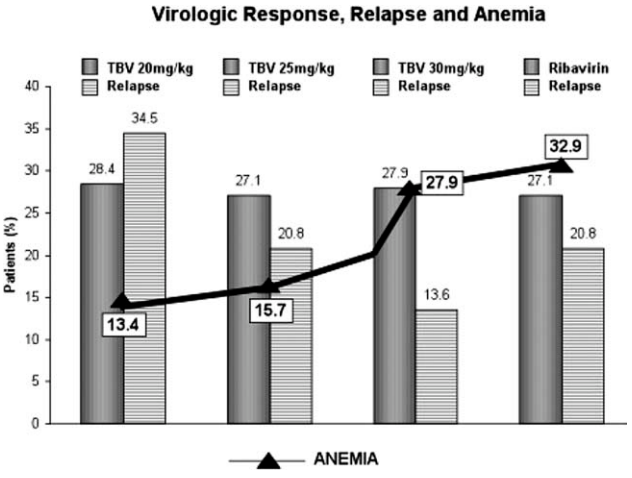

Fig. 2. Virologic response, relapse, and anemia.

Table 3. Most Common Treatment Emergent Adverse Events

Study Drug Daily Dose	TBV 20 mg/kg N = 67 (%)	TBV 25 mg/kg N = 70 (%)	TBV 30 mg/kg N = 68 (%)	RBV 800-1400 mg N = 70 (%)	*P* Value vs RBV
Fatigue	43 (64.2)	37 (52.9)	43 (63.2)	36 (51.4)	ns
Headache	30 (44.8)	35 (50)	22 (32.4)	28 (40)	ns
Nausea	30 (44.8)	24 (34.3)	29 (42.6)	29 (41.4)	ns
Diarrhea	27 (40.3)†	26 (37.1)†	25 (36.8)†	15 (21.4)	<0.05
Insomnia	23 (34.3)	26 (37.1)	23 (33.8)	17 (24.3)	ns
Flu-like symptoms	13 (19.4)	22 (31.4)	15 (22.1)	10 (14.3)	ns
Rash	9 (13.4)	13 (18.6)	12 (17.6)	12 (17.1)	ns
Anemia*	9 (13.4)†	11 (15.7)†	19 (27.9)	23 (32.9)	<0.05
Depression	13 (19.4)	22 (31.4)†	15 (22.1)	10 (14.3)	<0.05

*Hemoglobin <10 g/dL on treatment.

†Indicates those values that are significantly different from RBV.

time, TBV 30 mg/kg/day generated RBV plasma trough levels that exceeded the levels observed due to RBV oral administration. In addition, the exposure of TBV and RBV due to TBV were dose linear over the dosage range 20-30 mg/kg/day evaluated.

Adverse Events Requiring Dose Modification or Discontinuation. The percentages of patients with AEs leading to dose reduction or discontinuations are shown in Table 5. Dose modifications of TBV or RBV were most common in the TBV 30 mg/kg/day and RBV groups. Dose reductions were less frequent in the 20 and 25 mg/kg TBV groups compared to RBV by 21% and 12.9%, respectively. The proportion of patients withdrawn from the study as a result of adverse events were 12%, 25%, 19%, and 26% for the 20, 25, 30 mg/kg TBV groups and RBV group, respectively. The proportion of patients withdrawn for anemia adverse events was 1%, 4%, 4%, and 6%, for the 20, 25, and 30 mg/kg groups and the RBV group, respectively. The corresponding number of patients withdrawn for diarrhea AEs was 1%, 1%, 3%, and 0%. Dose reductions due to anemia were 7.5%, 12.9%, 20.6%, and 30% for the 20, 25, and 30 mg/kg TBV groups and the RBV group, respectively. Stepwise reductions in peg-IFN, RBV, and TBV dosages were used primarily to manage anemia AEs.

Discussion

The present study demonstrated that WBD TBV achieved comparable efficacy to RBV as demonstrated by SVR. This was observed in all three TBV WBD treatment groups, which met the study's primary endpoint. Notably, patients treated with TBV had less than half the anemia and a 13%-21% lower dose modification rate compared to RBV treated patients treated. These results suggest WBD of TBV can significantly improve the tolerability of HCV treatment while maintaining efficacy. Specifically, the 25 mg/kg dose offered the optimal balance of efficacy and safety in this patient population.

The relapse rates for the TBV groups were inversely proportional to the TBV dose and are most likely indicative of the recognized effects of RBV dosing. The similar SVR and higher relapse rates observed in the 20 mg/kg group are a reflection of higher end of treatment response rates. The high on-treatment response can be explained by the greater percentage of women and Caucasians randomized to this group. The higher relapse rate observed in the 20 mg/kg group is likely due to the lower TBV/RBV exposure.

The overall response rates observed in this trial appeared lower than expected for a Caucasian based genotype 1 trial. However, the demographics of this patient population were quite different than in many other controlled clinical trials reported to date. Approximately 20% of enrolled patients were African American, which was more than double many previous controlled clinical trials.[1,3] African Americans with genotype 1 HCV, have lower response rates to peg-IFN/RBV than Caucasians.[17] Recent studies also demonstrated that African Americans have a much lower population frequency of a gene associated with SVR.[18] A genetic predisposition for nonresponse in these patients is not likely to be overcome by a more

Table 4. Cumulative Incidence of Anemia

Anemia*	TBV 20 mg/kg N = 67	TBV 25 mg/kg N = 70	TBV 30 mg/kg N = 68	RBV 800-1400 mg N = 70	*P* Value
TW4	0†	3 (4.3%)†	0†	8 (11.4%)	<0.05
TW12	6 (9.0%)†	5 (7.1%)†	10 (14.7%)	17 (24.3%)	<0.05
TW24	9 (13.4%)†	8 (11.4%)†	13 (19.1%)	21 (30.0%)	<0.05
TW48	9 (13.4%)†	11 (15.7%)†	19 (27.9%)	23 (32.9%)	<0.05

*Hemoglobin <10 g/dL on treatment.

†Indicates those values that are statistically different compared to RBV.

Table 5. Dose Reductions or Discontinuation Due to Adverse Events

Study Drug Daily Dose	TBV 20 mg/kg N = 67 (%)	TBV 25 mg/kg N = 70 (%)	TBV 30 mg/kg N = 68 (%)	RBV 800-1400 mg N = 70 (%)	*P* Values
Treatment discontinuation (peg-IFN + TBV/RBV)	9 (13.4)	17 (24.3)	13 (19.1)	17 (24.3)	ns
Treatment discontinuation due to anemia	1 (1)	3 (4)	3 (4)	4 (6)	ns
Peg-IFN dose reduction	15 (22.4)	13 (18.6)	12 (17.6)	16 (22.9)	ns
TBV/RBV dose reduction	8 (11.9)*	14 (20)	19 (27.9)	23 (32.9)	0.0034

*Indicates those values that are statistically significantly different compared to RBV. ns, not significant.

favorable treatment, though the addition of direct acting antiviral agents should improve SVR rates in these populations. In addition to a high percentage of African and Latino races, other poor response characteristics present in the study population were: 81% of patients had high viral load; a higher age than reported in previous registration trials and up to 40% of patients had bridging fibrosis.[1-3] The drop out rate in this trial was approximately 10% higher than other U.S.-based trials and this difference is likely related to the poor response characteristics described above.

Similar to dosing experiences with RBV, we found WBD with TBV provides optimal RBV exposure. The pharmacokinetics of TBV administered at doses of 20, 25, and 30 mg/kg/day demonstrated steady state by TW4 for both prodrug and parent drug. This is equivalent to what is seen of RBV exposure from a RBV weight adjusted dosage of 800-1400 mg/day. TBV pharmacokinetics were dose linear, predictable and consistently generated RBV plasma levels that were lower than seen by RBV administration, without an impact on efficacy. The lower RBV concentrations positively affected the critical safety concern for RBV-anemia. The TBV 25 mg/kg/day dose had similar efficacy results as WBD RBV with significantly lower anemia rates.

As was reported in previous TBV clinical trials, an increase in the frequency of diarrhea was observed in all TBV cohorts when compared to RBV. Diarrhea was considered an adverse event of special interest in this study, therefore a more rigorous medical history specific to diarrhea was collected prospectively and this likely accounted for increased reporting frequency. The majority of cases across all treatment groups were classified as common toxicity criteria grade 1, occurred early in therapy and were single episode. The exact mechanism of action leading to diarrhea in patients receiving TBV remains unknown. After the end of treatment, the incidence of diarrhea returned to baseline, suggesting it is treatment related, and reversible.

Anemia is considered to be significant when the Hb falls below 10 g/dL. Patients treated with TBV had lower rates of anemia throughout the entire 48 weeks of treatment. Within the first 12 weeks of treatment, when maintaining the dose of RBV has been shown to be most critical, significant anemia was observed in only 7%-15% of patients treated with TBV compared to 24% of patients treated with RBV. As a result, fewer patients treated with TBV required dose reductions (13%-28%) compared to 32% of patients treated with RBV. Less frequent dose modification in patients treated with TBV may alleviate the need to use ESAs. Several studies have now demonstrated the use of ESAs can significantly decrease the need to dose reduce RBV and leads to an improvement in the quality of life during HCV treatment,[19-21] but fail to improve the SVR.[22] However, the use of ESAs adds significant cost to HCV treatment and is associated with significant adverse events including thrombosis and red cell aplasia.[19,23] Thus, limiting anemia during HCV treatment is clearly desirable.

The future of HCV treatment will incorporate potent antiviral agents such as protease and polymerase inhibitors, with peg-IFN and RBV. Despite its toxicity, RBV remains critical to optimizing SVR rates of hepatitis C and is unlikely to be replaced by the first generation direct acting antiviral agents.[4-6] Data from the new small molecule trials have demonstrated that anemia is a common consequence of treatment of protease inhibitors and when used with RBV there appears to be a significant need to either dose modify RBV or use ESAs to limit anemia.[4-6] Therefore, TBV should be considered as a RBV substitution to future clinical trials with peg-IFN and protease inhibitors as it may yield a significant treatment advantage over RBV.

Other potential TBV opportunities that need to be explored in clinical trials would be in patients susceptible to anemia and where RBV is contraindicated (including chronic renal failure and hemoglobinopathies). Patients who are slow to respond and may require 72 weeks of treatment may also benefit from using TBV as opposed to RBV. The lower anemia rates associated with TBV may allow these patients to remain on a prolonged course to achieve SVR. Finally, TBV may be particularly useful in liver transplant recipients with recurrent HCV and in patients coinfected with HCV and human immunodeficiency virus. Many of these patients have preexisting anemia and

this worsens considerably during treatment with peg-IFN and RBV. The low SVRs in these populations are at least in part secondary to anemia and the inability to optimize RBV dosage.

In conclusion, TBV administered in a weight-based fashion demonstrated similar rates of efficacy to RBV via SVR with significantly less anemia and lower rates of dose modification. The recommended dose of TBV for future development in patients with chronic hepatitis C genotype 1 is 25 mg/kg. These data suggest TBV may be an effective agent to substitute for RBV in the future and could be incorporated in upcoming trials using emerging small molecules for HCV treatment.

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