

A Phase III Study of the Safety and Efficacy of Viramidine Versus Ribavirin in Treatment-Naïve Patients with Chronic Hepatitis C: ViSER1 Results

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Pegylated interferon (peg-IFN) and ribavirin (RBV) are effective in eradicating the hepatitis C virus in more than half of patients. However, anemia arising from RBV-induced hemolysis can prompt dose reductions and lower sustained virologic response (SVR) rates. In early clinical trials, Viramidine (VRD, renamed taribavirin), an RBV prodrug, was associated with less anemia and VRD given at 600 mg twice daily (BID) appeared to provide the best safety with comparable efficacy to RBV. The phase III Viramidine's Safety and Efficacy versus Ribavirin 1 (ViSER1) study randomized 972 treatment-naïve patients with chronic hepatitis C to fixed-dose VRD (600 mg BID) or weight-based RBV (1000 or 1200 mg/day), each given with peg-IFN alfa-2b at 1.5 µg/kg/week. The primary efficacy endpoint was SVR rate, and the primary safety endpoint was hemoglobin (Hb) event rate (percent of patients with Hb < 10 g/dL or at least a 2.5-g/dL decrease from baseline). SVR rates were 37.7% with VRD (244/647) and 52.3% with RBV (170/325). Thus, the ViSER1 study failed to demonstrate the primary noninferiority efficacy endpoint. Significantly fewer patients had Hb events with VRD (353/647; 54.6%) compared to those with RBV (272/325; 83.7%) ($P < 0.001$), and significantly fewer developed anemia (Hb < 10 g/dL) with VRD (34/647; 5.3%) compared to those with RBV (76/325; 23.5%) ($P < 0.001$). **Conclusion:** Fixed doses of VRD failed to demonstrate noninferiority to RBV in producing SVR rates. The incidence of anemia was approximately four-fold significantly lower with VRD than with RBV. These results suggest fixed-dose VRD given 600 mg BID is insufficient to treat patients with chronic hepatitis C; a weight-based dosing trial of viramidine is currently under way. (HEPATOLOGY 2009;50:717-726.)

Combination therapy with pegylated interferon alfa (peg-IFN) and ribavirin (RBV) is the standard of care for the treatment of patients with chronic hepatitis C, resulting in overall sustained virologic response (SVR) rates of 54%-56%.^{1,2} However, adherence to the prescribed regimen of peg-IFN and RBV, especially during the first 12 weeks of treatment, is critical to viral clearance.³ A recent study showed that when pa-

tients infected with hepatitis C virus (HCV) genotype 1 maintained less than 80% of their cumulative RBV dose, the SVR rate was 52% compared with 67% for those who maintained more than 97% of their RBV dose.⁴

Patient characteristics such as ethnicity (African American) and coinfection with human immunodeficiency virus, as well as viral genotype (1, 4, 5, or 6) and adverse effects, may impair treatment outcomes and lower SVR

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; CI, confidence interval; FW, follow-up week; Hb, hemoglobin; HCV, hepatitis C virus; ITT, intent-to-treat; peg-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response; TW, treatment week; ViSER1, Viramidine's Safety and Efficacy versus Ribavirin 1 study; VRD, viramidine.

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rates. Adverse effects, in particular dose-limiting hemolytic anemia caused by RBV, are associated with lower SVR rates.^{3,5-7} Treatment-associated anemia can cause fatigue and affect quality of life, resulting in dose reductions.^{2,8,9} Although the molecular mechanism of RBV-associated antiviral activity remains uncertain, it may be due in part to its ability to up-regulate double-stranded RNA-activated protein kinase activity¹⁰; the anemia appears to be due to an accumulation of the triphosphate form of RBV within erythrocytes, leading to RBV-induced oxidative stress with subsequent membrane damage to and, ultimately, destruction of erythrocytes.^{11,12} Peg-IFN therapy contributes to hemolytic anemia by suppressing the production of erythrocytes in the bone marrow.¹³

Viramidine (VRD, renamed taribavirin) is a novel RBV prodrug being developed for administration with peg-IFN for the treatment of chronic hepatitis C. VRD is a guanosine analogue that preferentially targets the liver and is rapidly converted to RBV by adenosine deaminase.^{14,15} Pharmacokinetic multiple-dose studies of VRD in nonhuman primates revealed that VRD-derived RBV is concentrated in the liver in amounts three-fold higher than those seen after administration of RBV.¹⁶ A phase II dose-ranging comparison of VRD and RBV, both given in combination with peg-IFN, evaluated VRD doses of 400, 600, and 800 mg administered twice daily (BID) and RBV administered at a weight-based dose of 1000 or 1200 mg/day.¹⁷ Results showed similar virologic response with VRD 400, 600, and 800 mg BID and RBV 1000 or 1200 mg/day, each in combination with peginterferon alfa-2a in a dose of 180 $\mu\text{g}/\text{week}$.¹⁷

The current phase III, double-blind, multicenter Viramidine's Safety and Efficacy versus Ribavirin 1 (ViSER1) study was performed to compare the safety and efficacy of fixed-dose VRD (600 mg BID) and RBV (1000 or 1200 mg/day) when each is administered with peg-IFN alfa-2b in treatment-naïve patients with compensated chronic hepatitis C. The VRD dose of 600 mg BID was chosen for evaluation based on the earlier phase II study, which suggested that this dose provided the best safety profile while maintaining efficacy that appeared comparable to RBV.

Patients and Methods

Study Patients

The total planned enrollment for the study was 900 patients, with 600 randomized to receive VRD (Viramidine; Valeant Pharmaceuticals International, Aliso Viejo, CA) and 300 to receive RBV (ribavirin, Rebetol; Schering

Corp., Kenilworth, NJ). Patients were eligible for inclusion if they were treatment naïve, were at least 18 years of age, had compensated chronic hepatitis C, had HCV RNA levels >2000 copies/mL based on NGI Super-Quant assay (LabCorp, Burlington, NC), and showed histologic changes consistent with chronic hepatitis C as demonstrated on liver biopsy within the 2 years prior to screening. Patients were also required to have elevated alanine aminotransferase (ALT) levels at screening or within the preceding 6 months or histologic evidence of HCV infection and a detectable HCV RNA load. Patients were excluded from the study if they had previously received IFN or peg-IFN with or without RBV. Other reasons for exclusion included low hemoglobin (Hb) concentrations (<13 g/dL in men; <12 g/dL in women), neutropenia (absolute neutrophil count $<1200/\text{mm}^3$), thrombocytopenia ($<90,000$ platelets/ mm^3), serum creatinine concentrations ≥ 2 mg/dL, concomitant infection with hepatitis B virus or human immunodeficiency virus, or chronic hepatic disease other than hepatitis C.

Study Objective

The objective of this study was to compare the safety and efficacy of VRD dose of 600 mg BID versus that of RBV 1000 or 1200 mg/day in divided doses when administered in combination with peg-IFN alfa-2b in treatment-naïve patients with compensated chronic hepatitis C.

Study Design

This study was a randomized, double-blind, multicenter, phase III investigation conducted at 87 sites worldwide. Patients were enrolled by investigators and randomized to treatment groups using an interactive voice response system (Fig. 1). Eligible patients were randomly assigned in a 2:1 ratio to receive VRD 600 mg BID or RBV 1000 or 1200 mg/day in divided doses. Patients weighing ≤ 75 kg at screening were assigned to receive RBV 1000 mg/day, and those weighing >75 kg were assigned to receive RBV 1200 mg/day. This RBV dose regimen required weight-based dosing of RBV for all patients, regardless of genotype, and was the standard of care when this study was designed.

The study drug was initiated within the 24 hours after randomization. All patients also received open-label treatment with subcutaneous peg-IFN alfa-2b (peginterferon alfa-2b, PegIntron; Schering Corp., Kenilworth, NJ) 1.5 $\mu\text{g}/\text{kg}/\text{week}$.

Potential conflict of interest: Dr. Afdhal is a consultant for, advises, and received grants from Valeant, Echosens, GlaxoSmithKline and Vertex. He is a consultant for, advises, received grants from, and is on the speakers' bureau of Schering-Plough, Gilead, and Novartis. He received grants from Valeant Pharmaceuticals, Idenix, and Quest. He is a consultant for and advises Biogen, Idera Pharmaceuticals, Boehringer Ingelheim, Human Genome Sciences, Biolex, Ono Pharmaceuticals, and Fibrogen. He is also on the speakers' bureau of Bristol Myers Squibb. Dr. Shiffman is a consultant for, advises, is on the speakers' bureau of, and received grants from Roche. He advises Pfizer and Vertex. He is a consultant for, is on the speakers' bureau of and received grants from Schering-Plough. He is also a consultant for and received grants from Valeant. Dr. Pockros is a consultant for and received grants from Valeant.

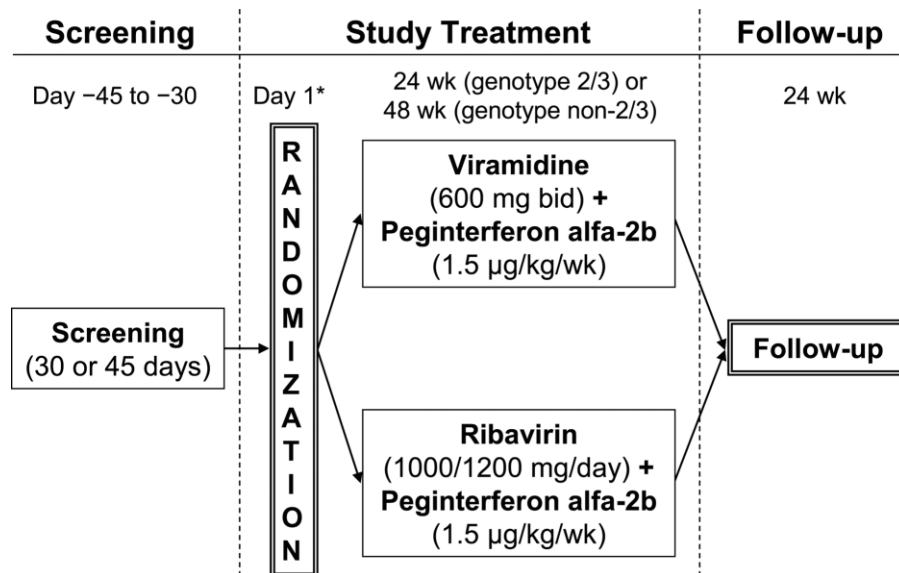


Fig. 1. ViSER1 study schematic. *Took place within 30 days of screening visit.

Patients were stratified according to HCV RNA genotype (genotypes 2 or 3 versus genotypes 1, 4, 5, 6, mixed, or untypeable [genotype non-2/3]), screening HCV RNA titers (≤ 2 million or > 2 million copies/mL), and baseline weight (≤ 75 or > 75 kg). Patients were assessed for disease stage using a nonstandard fibrosis scoring system. The high number of patients entering the study with long-term HCV infection required investigators to assess fibrosis using either the Metavir or Knodell scoring system, based on available biopsy records. Scores from both five-point scales were then combined and expressed using three descriptors: "cirrhosis" (Metavir and Knodell scores of 4), "bridging fibrosis" (scores of 3 or 2), and "no advanced fibrosis" (scores of 1 or 0).

Study treatment was initiated on Day 1, and clinic visits occurred at Treatment Weeks (TWs) 1, 2, 4, 8, 12, 18, and 24, as well as post-treatment at Follow-up Weeks (FWs) 4, 8, 12, 18, and 24. Patients infected with genotype 2/3 were treated for 24 weeks, and patients infected with genotypes other than 2 or 3 (genotype non-2/3) were treated for 48 weeks. All patients were followed for 24 weeks after the end of treatment to determine SVR rates. Only patients with HCV genotype non-2/3 attended clinic visits at TWs 30, 36, 42, and 48 because of their longer duration of treatment. All patients received three capsules of study drug twice daily with their morning and evening meals.

The sample size determination was calculated based on the primary efficacy variable, which was the proportion of patients with SVR at the end of the 24-week follow-up. The expected SVR rate in the test group (VRD) was estimated to be equal to or within 2% of the rate in the control group (RBV). Therefore, the power and sample size calculation assumed that the SVR rate in the VRD group was equal to or slightly lower than the rate in the

RBV group. The 900-patient sample size ($n = 600$, VRD group; $n = 300$, RBV group) allowed rejection of the null hypothesis with a power of 92% when the true SVR rates were the same between treatment groups and a power of 80% when the true SVR rate for the VRD group was 2% lower than the RBV group, based on the primary modified intent-to-treat (ITT) population.

The protocol was approved by the Investigational Review Boards of the participating institutions and conforms to the ethical guidelines of the Declaration of Helsinki (modified in 2004). All patients provided written informed consent. The study was conducted in accordance with the provisions of Good Clinical Practices.

Efficacy Assessments

The primary efficacy endpoint was SVR rate, defined as the proportion of patients with undetectable plasma HCV RNA levels (< 100 copies/mL) at the end of the 24-week follow-up. Additional predetermined efficacy variables included the number and proportion of patients with undetectable HCV RNA load or at least a 2-log_{10} decrease from baseline at TWs 4, 12, and 24 (all genotypes) and TW 48 (genotypes non-2/3), as well as FWs 4, 12, 18, and 24 by treatment; normalization of ALT levels at TW 24 and FW 24 by treatment; and the proportion of patients achieving SVR by genotype, baseline viral load, and other clinical and demographic characteristics.

Lack of efficacy was defined as less than a 2-log_{10} drop or detectable levels of HCV RNA (copies/mL) at TWs 12 or 24. Relapse rates were calculated by measuring proportion of responding patients whose plasma HCV levels changed from undetectable at end of treatment to detectable at FW 24.

Safety Assessments

The primary safety variable was the percentage of patients experiencing an Hb event at any time during treatment. An Hb event was defined as Hb concentrations <10 g/dL or at least a 2.5-g/dL decrease from baseline or at any point during treatment if no baseline measurement was available. Patients who discontinued treatment early were categorized as having an event if their Hb concentrations met this criterion, and patients without Hb measurements during treatment were considered not to have had an event.

Additional analyses for the primary safety variable were performed for subgroups that were based on HCV genotype, baseline plasma HCV RNA titers, and baseline weight. The proportion of patients with Hb concentrations <10 g/dL during treatment and with concentrations <10 g/dL or at least a 2.5 g/dL decrease from baseline at each scheduled visit were determined by treatment group for each of these subgroups.

If a dose reduction of study drug (VRD or RBV) was required because of an adverse event (AE), the dose was reduced to 600 mg once daily, to be taken in the morning. Once the dose was reduced, no increase was allowed for the duration of the study, but patients could remain in the study. If an AE necessitated interruption of any study drug for more than 14 consecutive days, or if a patient experienced a life-threatening AE, all study drugs were discontinued and the patient was removed from the study.

Statistical Analyses

This study had two coprimary measures of safety and efficacy. Safety analyses were conducted with data from the ITT population. The primary efficacy analysis was performed using data from the ITT and per-protocol populations; the secondary efficacy analysis considered data from the per-protocol population only. Hochberg's method was used to simultaneously control the overall experiment-wise Type I error rate at 0.05 for the two coprimary measures of safety and efficacy, with equal priority. All other statistical analyses were performed using a two-sided hypothesis test at the overall 5% level of significance. The stratification factors were those used for randomization (i.e., genotype, screening HCV RNA, and baseline weight) with a binary cutoff. If the upper limit of the confidence interval (CI) for the difference between RBV and VRD was less than 12%, the VRD group was considered noninferior to the RBV group. Continuous data were summarized using descriptive statistics unless otherwise noted: n, mean, standard deviation, median, minimum (min), and maximum (max). Categorical variables were summarized using frequency counts and percentages. All analyses were conducted using SAS (Cary, NC) version 8.2 or later.

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

Results

Study Patients

Enrollment began in December 2003, and the last patient completed the study on December 28, 2005. A total of 972 patients with HCV were randomized in a 2:1 ratio to receive peg-IFN alfa-2b in combination with either VRD 600 mg BID ($n = 647$) or RBV 1000 mg/day or 1200 mg/day ($n = 325$). All randomized patients received at least one dose of study drug and were included in the ITT population and analyzed for safety and efficacy. A total of 73% (470/647) of the patients in the VRD group and 76% (246/325) of the patients in the RBV group completed the study (Fig. 2); 177 (27.4%) patients in the VRD group and 79 (24.3%) in the RBV group discontinued study drug during treatment. The most commonly cited reasons for discontinuation in the VRD and RBV groups were AEs (9.6% and 9.8%, respectively) and lack of efficacy (11.7% and 7.4%, respectively). Baseline characteristics were similarly distributed between the two treatment groups (Table 1).

Efficacy

Sustained Virologic Response. The overall SVR rate at FW 24 in the ITT population was lower among VRD-treated patients (37.7%) than RBV-treated patients (52.3%); difference in proportions between RBV and VRD 0.15 (95% CI 0.09, 0.21) (Table 2). The upper limit of the 95% CI for the difference between the VRD and RBV groups exceeded 12%; thus, the noninferiority of VRD compared with RBV was not demonstrated. Mean changes in viral load from baseline over the course of the study were lower in the VRD group than the RBV group at every study visit. Patients in the VRD group had lower rates than the RBV group of undetectable HCV RNA at TWs 12 and 24 (Fig. 3). Relapse rates were 30.8% in the VRD group and 21.3% in the RBV group ($P = 0.0003$).

Subgroup Analysis. Lower SVR rates were seen in the VRD group compared to the RBV group for the following demographic and disease characteristics, which have been known to affect SVR: genotype, baseline viral load, sex, age, body weight, African-American ethnicity, and disease stage (Table 2). Interestingly, age was an important variable for response in comparing VRD to RBV. In patients younger than 45 years, efficacy of VRD was similar to that of RBV (51% versus 56%, respectively), but VRD clearly was less efficacious in patients older than 45

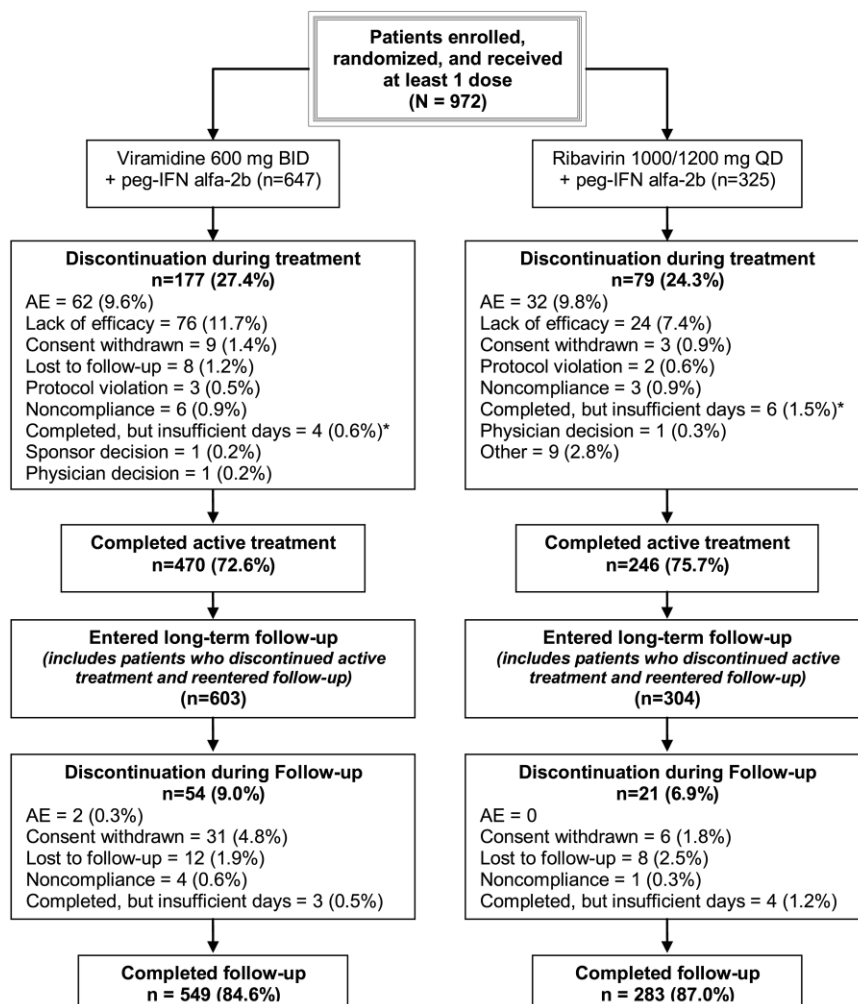


Fig. 2. Disposition of patients during treatment. *Completed per case study form but did not meet the criteria for minimum treatment weeks.

years. In these patients, response to VRD was only 26.9% compared with 50.9% seen with RBV ($P < 0.004$).

A post-hoc subgroup analyses indicated that greater exposure to VRD (per kilogram of body weight) was associated with higher SVR rates (Fig. 4). The SVR rate among patients receiving VRD at doses greater than 18 mg/kg was 48.8% (78/160); in contrast, the SVR rate among those receiving 13 mg/kg or less was 28.8% (38/132).

ALT Normalization. Compared with the RBV group, the VRD group had fewer patients with abnormal ALT levels at baseline. A greater proportion of patients receiving RBV achieved normal ALT values at every study visit.

Safety

Anemia. The primary safety endpoint was the proportion of patients with an Hb event, defined as Hb concentrations <10 g/dL or at least a 2.5-g/dL decrease from baseline, at any time during the treatment period. Significantly fewer patients in the VRD group

(5.3%, 34/647) had severe anemia (Hb < 10 g/dL) than did those in the RBV group (23.4%, 76/325); odds ratio = 0.16; $P < 0.001$ (Fig. 5A). Fewer patients in the VRD group had an Hb event than did those in the RBV group (54.6%, 353/647 versus 83.7%, 272/325, respectively); odds ratio = 0.21; $P < 0.001$. At each study visit, fewer Hb reductions of at least 25% from baseline occurred in VRD-treated patients (range, 0.3%-8.7%) than in RBV-treated patients (range, 3.4%-28.9%) (Fig. 5B). Mean Hb concentrations decreased from baseline in both treatment groups throughout the study, although the mean decrease was greater in the RBV group (Fig. 5C). A post-hoc analysis of patients with severe anemia (Hb < 10 g/dL) assigned to weight-based dose subgroups was performed to correspond with the efficacy subgroup analysis (Fig. 5D). Higher rates of anemia were seen with increased exposure to VRD (range, 3.8%-6.9%) but were smaller compared with increased exposure to RBV (range, 11.1%-36.8%).

Table 1. Patient Demographics and Baseline Characteristics (ITT Population)

Characteristic	Viramidine (n = 647)	Ribavirin (n = 325)	Total (n = 972)
Male, n (%)	399 (61.7)	210 (64.6)	609 (62.7)
Mean age, years (range)	44.3 (18-73)	45.1 (20-75)	44.6 (18-75)
Race, n (%)			
White	560 (86.6)	271 (83.4)	831 (85.5)
African-American	26 (4.0)	12 (3.7)	38 (3.9)
Asian	15 (2.3)	14 (4.3)	29 (3.0)
Hispanic	35 (5.4)	22 (6.8)	57 (5.9)
Other	11 (1.7)	6 (1.8)	17 (1.7)
Mean BMI, kg/m ² (range)	26.8 (16-49)	26.9 (18-43)	26.8 (16-49)
Weight category, n (%)			
≤75 kg	284 (43.9)	144 (44.3)	428 (44.0)
>75 kg	363 (56.1)	181 (55.7)	544 (56.0)
Geographic region			
North America	303 (46.8)	179 (55.1)	482 (49.6)
Europe	211 (32.6)	78 (24.0)	289 (29.7)
Other	133 (20.6)	68 (20.9)	201 (20.7)
HCV genotype (%)			
HCV genotype 2/3	174 (26.9)	89 (27.4)	263 (27.1)
HCV genotype 1	439 (67.9)	226 (69.5)	665 (68.4)
HCV genotype non-1, 2, 3	34 (5.3)	10 (3.1)	44 (4.5)
Plasma HCV RNA >2 million copies/mL (780 IU/mL), n (%)	453 (70.0)	223 (68.6)	676 (69.5)
Mean plasma HCV RNA, log ₁₀ copies/mL (range)	6.51 (3.2-7.7)	6.51 (4.1-7.7)	6.51 (3.2-7.7)
Liver biopsy, n (%)			
No advanced fibrosis	415 (64.1)	216 (66.5)	631 (64.9)
Bridging fibrosis	189 (29.2)	84 (25.8)	273 (28.1)
Cirrhosis	43 (6.6)	25 (7.7)	68 (7.0)
Mean Hb, g/dL (range)	15.02 (11.6-18.2)	14.99 (11.4-19.6)	15.01 (11.4-19.6)

BMI, body mass index; Hb, hemoglobin.

Hb event rates peaked at TW 24 for patients receiving VRD, at 31.8% (206/647; 95% CI: 28.26, 35.58) and at TW 12 for patients receiving RBV, at 61.8% (201/325; 95% CI: 56.32, 67.15). Patients in the VRD group had fewer Hb events early in treatment compared with the RBV group; at TWs 4 and 12, the respective rates of Hb events were 10.0% (65/647; 95% CI: 7.84, 12.63) and 26.1% (169/647; 95% CI: 22.77, 29.69) in the VRD group and 44.6% (145/325; 95% CI: 39.13, 50.20) and 61.8% (201/325; 95% CI: 56.32, 67.15) in the RBV group. Hb events after TW 24 through TW 48 remained considerably higher in the RBV group (range, 48.7%-53.4%) than the VRD group (range, 29.2%-31.5%). There was no statistically significant relationship between Hb < 10 g/dL and SVR rates at any point during the study.

AEs, Serious AEs, Dose Modifications or Discontinuations, and Hematology Changes. The most common AEs reported in this study were similar to those known to be associated with RBV plus peg-IFN therapy (Table 3). There were no unexpected AEs reported with the use of combination therapy with RBV and peg-IFN therapy. The percentages of patients experiencing the most common AEs were similar between the two treatment arms, with the exception of diarrhea. The rate of diarrhea was significantly higher in the VRD group (30.1%; 195/647) than in the RBV group (20%; 65/325) ($P < 0.001$). Moderate or severe

diarrhea occurred in a greater proportion of VRD-treated patients (9.7%) than RBV-treated patients (4.6%). There was no effect of weight-based drug exposure on the rates of diarrhea. Serious AEs related to hospitalizations for treatment of diarrhea-induced dehydration occurred in seven patients receiving VRD at 600 mg BID and in one receiving RBV.

Diarrhea prompted drug discontinuation in 1.9% (12/647) and dose modification in 2.6% (17/647) of VRD-treated patients. There were no discontinuations or dose modifications among RBV-treated patients due to diarrhea (Table 3). Anemia was the most common AE leading to dose interruption or modification, occurring more often among RBV-treated patients (17.8%; 58/325) than among VRD-treated patients (3.4%; 22/647). Overall, AEs led to dose interruption or modification in fewer patients receiving VRD (11.1%; 72/647) than RBV (27.4%; 89/325). In all, 91% of patients in the VRD group were compliant with at least 80% of the prescribed dose of study drug compared with 77% of patients who were compliant with at least 80% of the dose in the RBV group.

At baseline, mean neutrophil counts were similar for both treatment groups ($56.97 \times 10^9/L$ in the VRD group and $55.79 \times 10^9/L$ in the RBV group). By TWs 4, 24, and 48, mean neutrophil counts decreased from baseline to a slightly greater extent in the VRD treatment group (range $-1.99 \times 10^9/L$ to $-2.07 \times 10^9/L$) than the RBV

Table 2. SVR Rates by Treatment Group and Subgroup

SVR, n (%)	Viramidine n = 647	Ribavirin n = 325	P Value*
Overall	244 (37.7)	170 (52.3)	Difference of proportions 0.150 (0.09, 0.21) 0.181
Sex			
Male	135/399 (33.8)	109/210 (51.9)	
Female	109/248 (44.0)	61/115 (53.0)	
Age (years)			0.004
<45	152/298 (51.0)	79/141 (56.0)	
45 to <65	89/331 (26.9)	89/175 (50.9)	
≥65	3/18 (16.7)	2/9 (22.2)	
Race			0.179
Caucasian	215/560 (38.4)	150/271 (55.4)	
African-American	5/26 (19.2)	3/12 (25.0)	
Asian	10/15 (66.7)	10/14 (71.4)	
Hispanic	7/35 (20.0)	5/22 (22.7)	
Other	7/11 (63.6)	2/6 (33.3)	
BMI category (kg/m ²)			0.406
<30	206/513 (40.2)	141/248 (56.9)	
≥30	38/131 (29.0)	29/77 (37.7)	
Baseline weight (kg)			0.600
≤75	127/284 (44.7)	83/144 (57.6)	
>75	117/363 (32.2)	87/181 (48.1)	
Geographic region			0.462
North America	100/303 (33.0)	82/179 (45.8)	
Europe	86/211 (40.8)	43/78 (55.1)	
Other	58/133 (43.6)	45/68 (66.2)	
HCV Genotype			0.393
1	120/439 (27.3)	94/226 (41.6)	
2/3	108/174 (62.1)	71/89 (79.8)	
Non-1,2,3	16/34 (47.0)	5/10 (50.0)	
Baseline HCV RNA			0.694
≤2 million copies/mL	112/200 (56.0)	70/102 (68.6)	
>2 million copies/mL	132/447 (29.5)	100/223 (44.8)	
Disease stage			0.782
No advanced fibrosis	169/415 (40.7)	121/216 (56.0)	
Genotype 2/3	71/107 (66.4)	43/56 (76.8)	
Genotype non-2/3	98/308 (31.8)	78/160 (48.8)	
Cirrhosis/bridging fibrosis	75/232 (32.3)	49/109 (45.0)	
Genotype 2/3	37/67 (55.2)	28/33 (84.8)	
Genotype non-2/3	38/165 (23.0)	21/76 (27.6)	

*Homogeneity of the odds ratio tested by the Breslow-Day statistic.

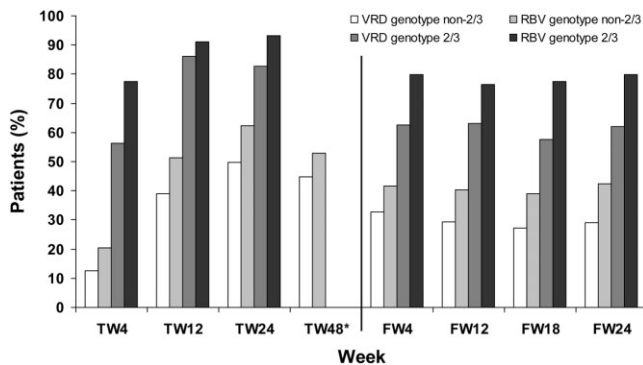


Fig. 3. Proportions of patients with undetectable HCV RNA by study visit (ITT population). *Patients with HCV genotype 2/3 received treatment only through TW24.

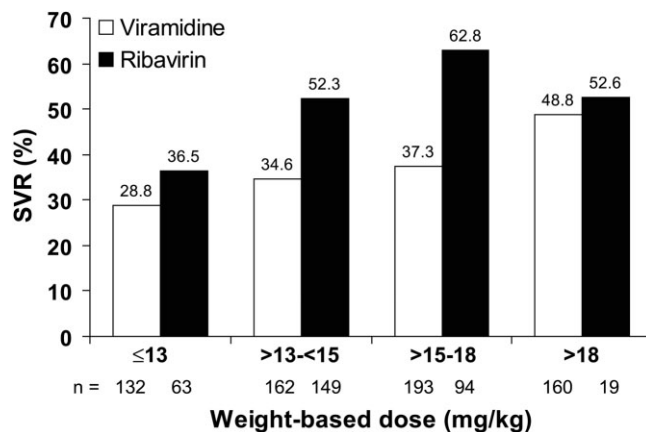


Fig. 4. SVR by weight-based doses of viramidine and ribavirin (ITT population).

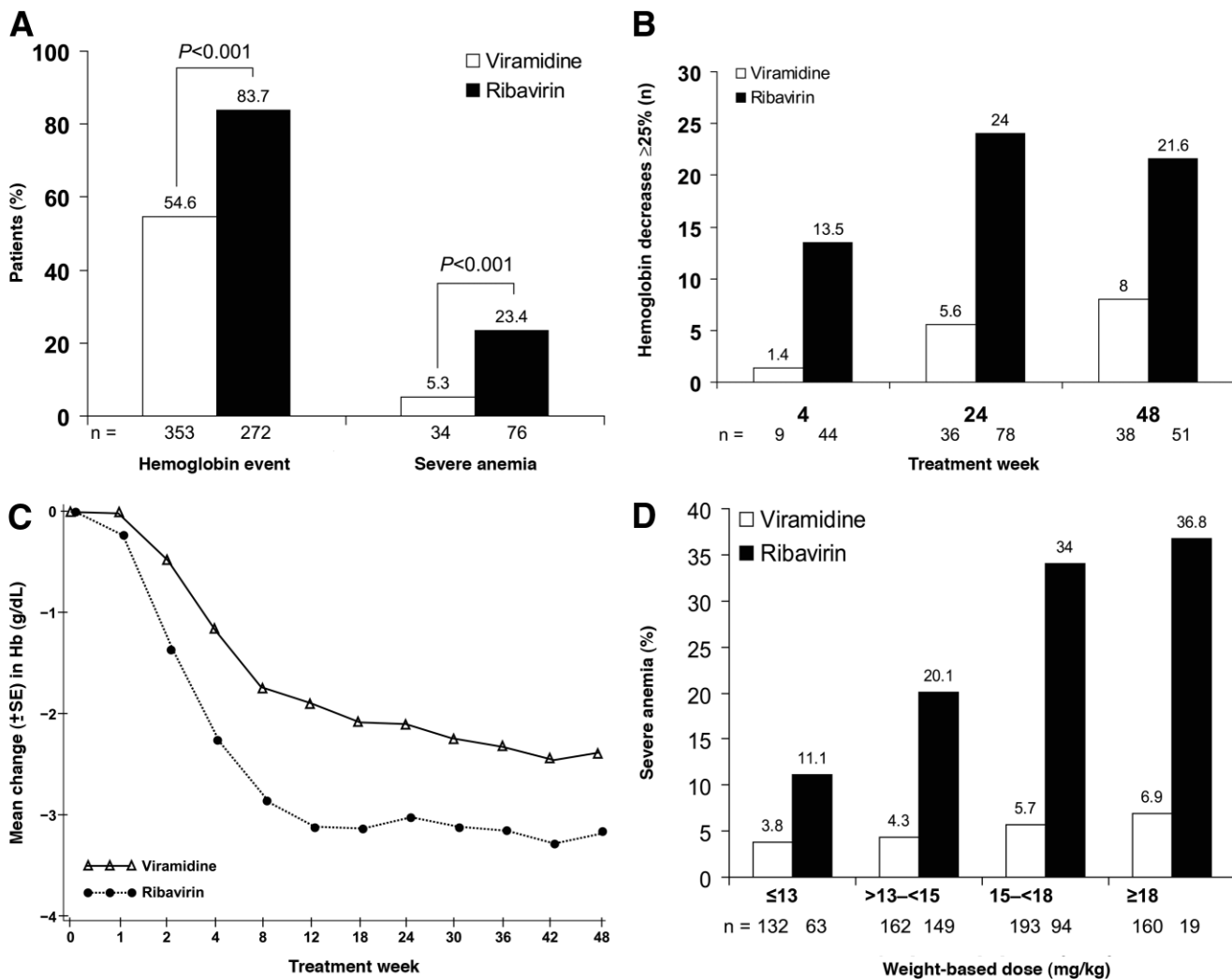


Fig. 5. (A) Incidence of Hb events (Hb < 10 g/dL or a ≥ 2.5 g/dL decrease from baseline) and severe anemia (Hb < 10 g/dL) any time during treatment (safety population). (B) Patients experiencing a decline in Hb of $\geq 25\%$ from baseline. †Excludes patients with missing baseline Hb concentrations. ‡48-week assessment includes only genotype non-2/3 patients (safety population). (C) Mean change from baseline in Hb over time (safety population). SE, standard error. (D) Patients with severe anemia (Hb < 10 g/dL) at any time during treatment, by weight-based doses of viramidine and ribavirin.

treatment group (range $-1.88 \times 10^9/L$ to $-1.98 \times 10^9/L$). By FW 24, mean neutrophil counts returned to near-baseline levels in both treatment groups. The percentages of patients with neutropenia (all grades) at any point during the study were similar between the two treatment groups (10%, 65/647 for VRD and 10.2%, 33/325 for RBV). All but one patient with neutrophil counts of grade 4 toxicity were in the VRD-treated group (1.7%, 11/644 and 0.3%, 2/325, respectively). However, grade 3 or 4 neutropenia occurred in a higher proportion of RBV-treated patients (37.2%, 121/325) than in VRD-treated patients (30.4%, 197/647). No patients in either treatment group developed grade 4 thrombocytopenia.

Discussion

The current ViSER1 trial showed that VRD did not meet the noninferiority criteria for the primary efficacy

analysis of SVR rate compared with RBV. A smaller proportion of patients treated with VRD than those treated with RBV had undetectable HCV RNA at every time point during the study, and relapse rates were higher in the overall VRD group. These data suggest that an inferior dose of RBV was delivered with the VRD 600 mg BID fixed dosing. The fixed VRD 600 mg BID dose was chosen on the basis of a previous dose-finding study and was believed to represent the best balance between safety and efficacy¹⁷; however, this dosing regimen was likely insufficient in the population studied here.

Fixed dosing of VRD was not as efficacious as weight-based dosing of RBV in the ViSER1 study. Similar to RBV, VRD may show increased efficacy when given based on body weight. Indeed, if the dose of VRD administered during this study was calculated on the basis of body weight, an increase in SVR was observed as the VRD dose, in mg/kg, was in-

Table 3. Common Adverse Events (Reported in >15% of Treated Patients) and Most Common Adverse Events Leading to Dose Discontinuation or Modification

AdverseEvent, n (%)	Viramidine (n = 647) n (%)	Ribavirin (n = 325) n (%)
Headache	350 (54.1)	187 (57.5)
Pyrexia	336 (51.9)	181 (55.7)
Fatigue	309 (47.8)	169 (52.0)
Myalgia	250 (38.6)	106 (32.6)
Nausea	229 (35.4)	116 (35.7)
Influenza-like illness	176 (27.2)	87 (26.8)
Diarrhea*	195 (30.1)	65 (20.0)*
AEs leading to drug discontinuation or dose modification		
Drug discontinuation		
Diarrhea	12 (1.9)	0
Anemia	4 (0.6)	6 (1.8)
Dose modification		
Anemia	22 (3.4)	58 (17.8)
Diarrhea	17 (2.6)	0
Decreased Hb concentrations	2 (0.3)	10 (3.1)
Fatigue	4 (0.6)	4 (1.2)
Nausea	4 (0.6)	1 (0.3)
Depression	3 (0.5)	2 (0.6)

* $P < 0.001$

creased (Fig. 4).¹⁸ When VRD was given at doses of 19-22 mg/kg, the SVR rate was 50%, with a 6% incidence of anemia.^{19,20} Although the current study was not powered to directly compare the two treatment groups based on the effects of weight-based dosing, these analyses suggest that VRD at a dose of at least 18 mg/kg may produce SVR rates comparable to that of weight-based RBV, with a lower incidence of anemia (Figs. 4 and 5D).^{19,21,22}

The rationale for weight-based dosing of RBV was recently confirmed in the Win-R trial, which randomized patients to peg-IFN alfa-2b at 1.5 $\mu\text{g}/\text{kg}/\text{week}$ plus either fixed-dose (800 mg/day) or weight-based (800-1400 mg/day) RBV.²³ Weight-based dosing of RBV was 800 mg for patients weighing <65 kg; 1000 mg for patients weighing >65-85 kg; 1200 mg for patients weighing >85-105 kg; and 1400 mg for patients weighing >105 kg but <125 kg. SVR rates were significantly greater in the weight-based groups compared with fixed-dosed group (44.2% versus 40.5%; $P < 0.008$). The investigators concluded that weight-based dosing was more efficacious than fixed dosing and provided equivalent efficacy across all weight groups.

The use of a fixed dose of VRD and weight-based dosing of RBV in the current study may therefore have led to lower SVR rates in the VRD group.²⁴ A phase IIb study was recently undertaken to compare the safety and efficacy of three weight-based VRD doses (53 patients received between 20 and 30 mg/kg of VRD per day) versus weight-based RBV, both administered with peg-IFN, in therapy-naïve patients with HCV genotype 1 infection.²⁵

The results should continue to clarify the role of VRD in the treatment of patients with chronic hepatitis C.

In contrast with the efficacy results, ViSER1 safety findings showed significantly lower rates of anemia for fixed-dose VRD 600 mg BID compared with RBV 1000 or 1200 mg/day, and thus met the primary safety endpoint. There were significantly fewer patients with an Hb event or severe anemia in the VRD group versus the RBV group. Patients in the RBV group had more Hb events early in treatment (TWs 4 to 12), which is consistent with reports in the literature.¹³ It is important to note that the dose of RBV used in this study could have affected the anemia rates. The recommended dose of RBV for HCV genotypes 2 and 3 is 800 mg/day. Further, the label for peg-IFN alfa-2b (PEGIntron) recommends an RBV dose of 800 mg/day for all HCV genotypes. The use of 1000/1200 mg/day of RBV for HCV genotype 2/3 in the current study may have created an artificially inflated difference in anemia rates among patients treated with RBV, conferring an advantage on VRD. Future studies will need to explore if the lower anemia rates will be maintained with weight-based dosing of VRD as well as provide greater VRD-derived RBV exposure to patients.

The AEs seen in the VRD treatment group have also been reported with combination peg-IFN and RBV therapy. However, there were more patients in the VRD arm with diarrhea (30.1%) compared to the RBV arm (20%). The incidence of moderate or severe diarrhea in VRD-treated patients was double that in RBV-treated patients (9.7% versus 4.6%, respectively). This led to slightly more patients in the VRD group discontinuing for VRD dose modification due to diarrhea, but this difference was insubstantial when compared with the much higher percentage of patients who developed RBV-associated severe anemia.

Although protease and polymerase inhibitors and other immune-modulating therapies are currently being investigated for patients with chronic hepatitis C,²⁶⁻²⁸ peg-IFN and RBV are likely to remain the backbone of long-term hepatitis C therapy for the foreseeable future. Some of these new protease and polymerase inhibitors have already been shown to exacerbate the anemia observed with peg-IFN and RBV.^{29,30} This strongly suggests that there will remain a need to use an RBV analogue that is less likely to cause hemolytic anemia. Therefore, further study of VRD given on a weight-based dosing schedule is warranted to determine the optimal dosing efficacy that maintains the safety profile.

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