Poster #1868

Probability of Sustained Virologic Response (SVR) Is Associated With the Magnitude of HCV RNA Reduction at Week 4 of Treatment With Peginterferon (PEG) Plus Ribavirin (RBV): Results of the IDEAL Trial

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Background: Clearance of HCV RNA at week 4 (rapid virologic response [RVR]) is highly predictive of SVR. We hypothesized that the magnitude of reduction of HCV RNA from baseline by treatment week (TW) 4 was predictive of increasing rates of SVR reaching a maximum with RVR.

Methods: Chronic hepatitis C patients infected with genotype 1 were randomized (1:1:1) and treated for 48 weeks with PEG2b 1.5 μg/kg/wk or PEG2b 1.0 μg/kg/wk + RBV 800-1400 mg/d, or PEG2a 180 μg/wk + RBV 1000-1200 mg/d. Patients with virologic failure at TW 12 (<2 log₁₀ drop from baseline) or 24 (detectable) terminated therapy. HCV RNA levels were assessed at baseline and at TWs 2, 4, 12, 24, 48 and follow-up weeks 4, 12, and 24. The change in HCV RNA level for each patient was categorized according to log₁₀ change from baseline: <1 \log_{10} ; 1-<2 \log_{10} ; 2-<3 \log_{10} ; 3-<4 \log_{10} ; \geq 4 \log_{10} and undetectable (<27 IU/mL, no HCV RNA detected) and assessed with regard to SVR rate. HCV RNA was assessed by Roche COBAS TaqMan (LLQ <27 IU/mL). Chi-square test was performed.

Results: Patients (n = 3070) had similar characteristics across groups: male, 60%; Caucasian, 71%; Black, 19%; mean age, 47.5 years; mean weight, 83.4 kg; HCV RNA >600,000 IU/mL, 82%; F3/4, 11%. The number (%) of patients in each category and the observed SVR rate are shown in Table 3 and Figure 2 (below). The magnitude of change in HCV RNA at TW 4 was highly associated with the likelihood of SVR (P < 0.0001).

Conclusions: Independent of PEG/RBV regimen, the magnitude of the change in HCV RNA after 4 weeks of treatment was predictive of subsequent SVR in adults infected with HCV genotype 1. Patients with a decline in HCV RNA from baseline ≥3 log₁₀ had a greater than 61% probability of SVR whereas those with a decline of <1 log, had a less than 5% probability of SVR. These data support the definition of "TW 4 null response" as achieving less than 1 log₁₀ decrease in HCV RNA from baseline and underscore the importance of monitoring HCV RNA response at TW 4 to determine an individual patient's probability of SVR. During treatment with PEG/RBV, clinicians should incorporate these TW 4 viral response data into clinical decision making for HCV genotype 1-infected patients.

Note: Abstract has been updated since submission.

- Standard of care for patients with chronic hepatitis C is pegylated interferon (PEG-IFN) alfa-2b (PegIntron®; Schering Plough) + ribavirin (RBV) or PEG-IFN alfa-2a (Pegasys®; Roche) + RBV
- With these treatments, patients infected with hepatitis C virus (HCV) genotype 1 (G1) attain sustained virologic response (SVR) rates of 42% to 46%^{1,2}
- Studies have shown that clearance of HCV RNA at treatment week (TW) 4 (rapid virologic response [RVR]) is highly predictive of attaining SVR and may be used to individualize therapy³⁻⁹
- Results from the Individualized Dosing Efficacy vs Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study confirmed that attaining RVR was highly predictive of attaining SVR (Table 1)
- IDEAL investigated the efficacy and safety of weight-based PEG-IFN alfa-2b + weightbased RBV and fixed PEG-IFN alfa-2a + semi-weight-based RBV in patients with chronic hepatitis C caused by HCV G1 infection¹⁰

Table 1. Attainment of SVR Among Patients With RVR in the IDEAL Study¹¹

PEG-IFN alfa-2b 1.5 + RBV PEG-IFN alfa-2b 1.0 + RBV PEG-IFN alfa-2a + RBV n = 79 n = 123n = 116

92.2 (87.4, 97.1)

87.3 (80.0, 94.7)

79.7 (72.6, 86.8)

PEG-IFN = pegylated interferon; RBV = ribavirin; SVR = sustained virologic response. Values in parentheses are 95% confidence intervals.

• To determine, with the use of data from the IDEAL study, whether the magnitude of reduction in HCV RNA from baseline to TW 4 is predictive of SVR, with undetectable HCV RNA (ie, RVR) providing the strongest positive predictive value

Patients and Methods

Patients

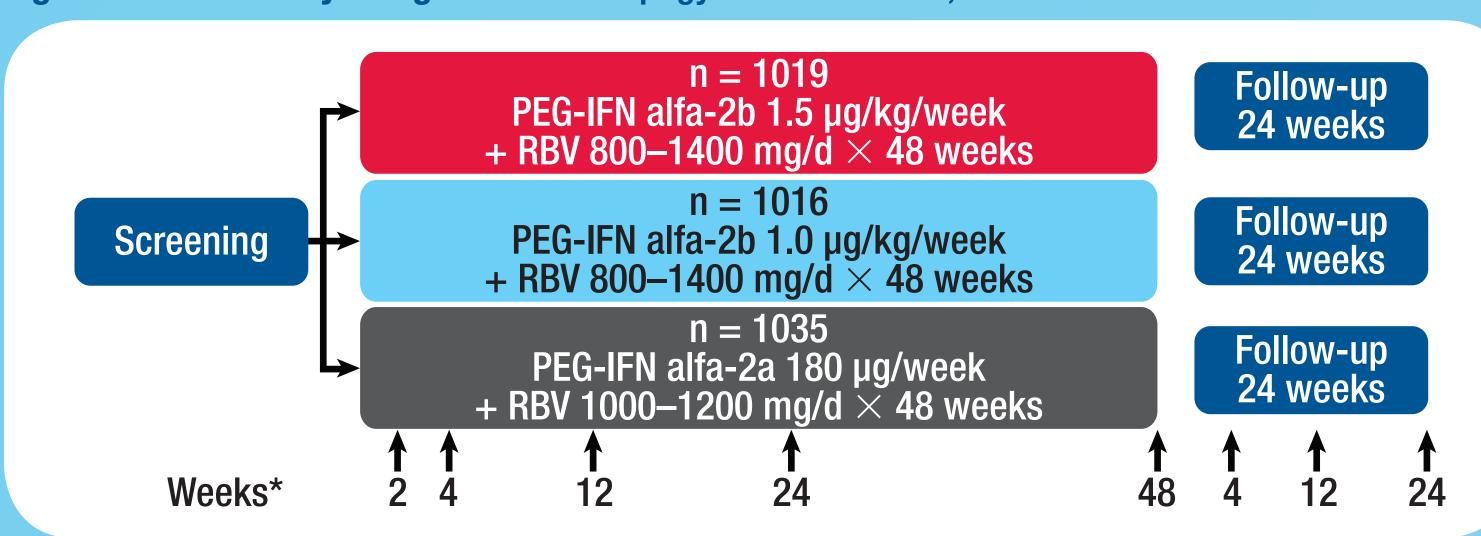
- Chronic hepatitis C, genotype 1
- Treatment naive
- Age, 18 to 70 years

- Weight, 40 to 125 kg
- Compensated liver disease

Study Design

- IDEAL was a phase 3b, randomized, parallel-arm trial conducted at 118 academic and community centers in the United States (Figure 1)
- PEG-IFN alfa-2b was administered as a double-blind treatment, and PEG-IFN alfa-2a and RBV were administered as open-label treatments
- Patients had their treatment discontinued for therapeutic failure, defined as:
- <2 log₁₀ decrease from baseline in HCV RNA at TW 12
- ≥2 log₁₀ decrease from baseline in HCV RNA that remained detectable at TW 12 and detectable **HCV RNA at TW 24**

Figure 1. IDEAL study design. PEG-IFN = pegylated interferon; RBV = ribavirin.



*HCV RNA assessments.

Assessments

- HCV RNA levels were assessed at baseline, at TWs 2, 4, 12, 24, and 48/end of treatment, and at follow-up weeks 4, 12, and 24
- HCV RNA was measured using the COBAS® TagMan® assay (Roche) (lower limit of quantitation, 27 IU/mL)
- SVR was defined as HCV RNA <27 IU/mL at the end of follow-up (week 24 or, if data were missing, week 12)
- Change in HCV RNA levels for each patient was categorized according to log₁₀ change from baseline to TW 4: <1 \log_{10} ; 1-<2 \log_{10} ; 2-<3 \log_{10} ; 3-<4 \log_{10} ; \geq 4 \log_{10} ; and undetectable (<27 IU/mL, no HCV RNA detected)
- SVR rates were assessed in each group
- Chi-square tests were performed to determine statistical significance

Results

Patient Characteristics

• Patients (n = 3070) had similar characteristics across the 3 treatment groups (**Table 2**)

Table 2. Baseline Patient Characteristics

	PEG-IFN alfa-2b 1.5 + RBV n = 1019	PEG-IFN alfa-2b 1.0 + RBV n = 1016	PEG-IFN alfa-2a + RBV n = 1035
Male, %	60	60	59
Race, %			
Caucasian	72	71	71
African American/Black	18	18	19
Age, y, mean (SD)	47.5 (7.8)	47.5 (8.1)	47.6 (8.2)
Weight, kg, mean (SD)	84 (17)	83 (16)	83 (17)
Baseline HCV RNA			
HCV RNA, log ₁₀ , mean (SD)	6.32 (0.69)	6.32 (0.70)	6.34 (0.64)
HCV RNA >600,000 IU/mL, %	82	82	82
Steatosis, ^a %			
Absent	38	35	36
Present	58	61	58
METAVIR fibrosis score, ^a %			
F0/1/2	85	85	83
F3/4	11	11	11

PEG-IFN = pegylated interferon; RBV = ribavirin. ^aData were missing for 147 patients.

Predictability of Change in HCV RNA From Baseline to Treatment Week 4 for SVR

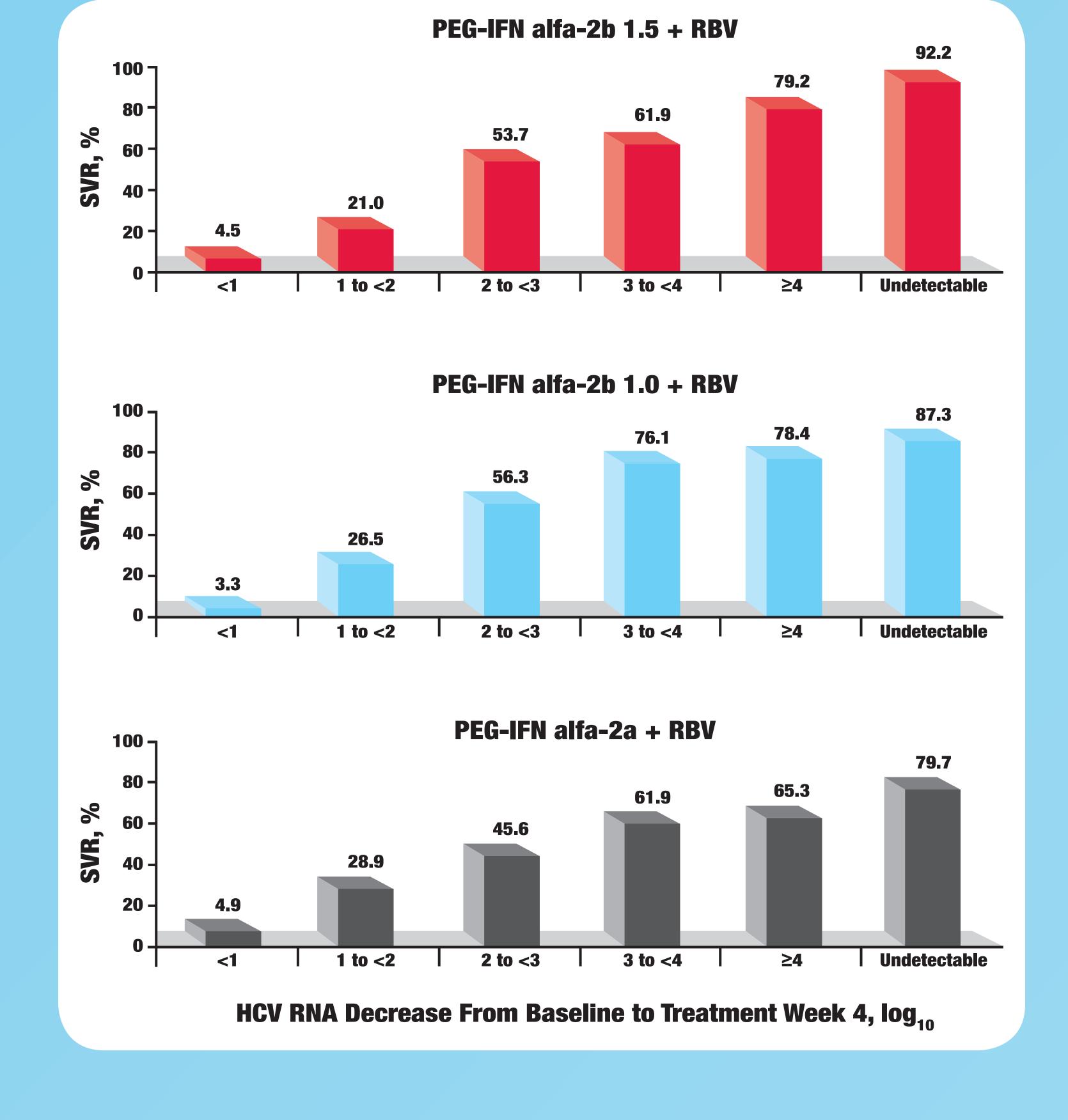
- SVR rate increased with the magnitude of reduction in HCV RNA from baseline to TW 4 (Table 3, Figure 2)
- The magnitude of reduction in HCV RNA from baseline to TW 4 was significantly associated with the likelihood of attaining SVR (P < 0.0001)

Table 3. Percentage of Patients in Each Treatment Group Categorized According to the Magnitude of Reduction in HCV RNA From Baseline to Treatment Week 4

Reduction in HCV RNA Level at Treatment Week 4	Patients, % (n)		
	PEG-IFN alfa-2b 1.5 + RBV n = 1019	PEG-IFN alfa-2b 1.0 + RBV n = 1016	PEG-IFN alfa-2a + RBV n = 1035
Detectable			
<1 log ₁₀	21.6 (220)	29.9 (304)	21.8 (226)
1 to <2 log ₁₀	23.8 (243)	24.5 (249)	22.4 (232)
2 to <3 log ₁₀	14.6 (149)	14.9 (151)	15.3 (158)
3 to <4 log ₁₀	12.4 (126)	11.1 (113)	14.2 (147)
≥4 log ₁₀	9.4 (96)	8.7 (88)	12.0 (124)
Undetectable	11.4 (116)	7.8 (79)	11.9 (123)

PEG-IFN = pegylated interferon; RBV = ribavirin.

Figure 2. SVR rates categorized according to the magnitude of reduction in HCV RNA level. Levels were measured from baseline to treatment week 4 after treatment with PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV (top), PEG-IFN alfa-2b 1.0 μg/kg/wk + RBV (middle), and PEG-IFN alfa-2a 180 μg/wk + RBV (bottom). PEG-IFN = pegylated interferon; RBV = ribavirin; SVR = sustained virologic response.



- The magnitude of reduction in HCV RNA level after 4 weeks of treatment was predictive of SVR attainment, independent of PEG-IFN alfa + RBV regimen, in adults infected with
- Patients with <1 log₁₀ decreases in HCV RNA from baseline to TW 4 had <5% probability of attaining SVR
- Patients with 3 to <4 log₁₀ decreases in HCV RNA from baseline to TW 4 had >61% probability of attaining SVR
- Patients with ≥4 log₁₀ decreases in HCV RNA or undetectable HCV RNA at TW 4 had even greater SVR rates
- These data support the concept of TW 4 null response, defined as attaining a <1 log₁₀ decrease in HCV RNA from baseline at TW 4
- These results underscore the importance of monitoring HCV RNA response at TW 4 to determine a patient's probability of attaining SVR
- Clinicians should incorporate TW 4 viral response data into clinical decision making during the treatment of HCV G1-infected patients

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References

- 1. Manns MP et al. *Lancet*. 2001:358:958-965. 2. Fried MW et al. N Engl J Med. 2002;347:975-982. 3. Zeuzem S et al. *J Hepatol*. 2006;44:97-103. 4. Reddy KR et al. Gastroenterology. 2005;128 (suppl 2):A-716.
- 5. Yu ML et al. *Hepatology*. 2008;47:1884-1893. 6. Jensen DM et al. *Hepatology*. 2006;43:954-960. 7. Berg T et al. *Gastroenterology*. 2006;130:1086-1097.
- 8. Ferenci P et al. *Gastroenterology*. 2008;135:451-458. 9. Sanchez-Tapias JM et al. Gastroenterology. 2006:131:451-460.
- 10. McHutchison J et al. *J Viral Hepat*. 2008;15:475-481. 11. Sulkowski M et al. 43rd Annual Meeting of the **European Association for the Study of the Liver**; April 23-27, 2008; Milan, Italy.

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