Predicting the Ability to Achieve a Sustained Virologic Response (SVR) in the First 12 Weeks: Results From the IDEAL Study

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Abstract

Background: Less than half of all patients with HCV genotype 1 achieve sustained virologic response (SVR) when treated with peginterferon (PEG) + ribavirin (RBV). In addition, these medications contribute to adverse events. It is therefore important to minimize exposure to these medications in patients who are unable to achieve SVR. Identifying early on-treatment factors associated with SVR is important. These may differ with various peginterferon preparations/RBV dosing regimens.

Methods: Treatment-naive patients with HCV genotype 1 were randomized (1:1:1) to receive either 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 for 48 weeks. Treatment was terminated in patients for lack of virologic response at week 12 or 24. HCV RNA was determined at treatment weeks (TWs) 2, 4, and 12. Positive predictive value (PPV) for achieving SVR was calculated.

Results: Patients (n = 3070) had similar baseline 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%; fibrosis 3/4, 11%. End-of-treatment (EOT) response, relapse, and SVR rates: PEG2b 1.5/RBV, 53.2%, 23.5%, 39.8%; PEG2b 1.0/RBV, 49.2%, 20%, 38%; PEG2a/RBV, 64.4%, 31.5%, 40.9%. PPV for SVR at weeks 2, 4, 12, and 24 are shown in Figures 3 and 5. Adherence based upon receiving 80% of both study treatments for 80% of the 48-week duration were PEG2b 1.5/RBV, 70%; PEG2b 1.0/RBV, 74%; PEG2a/RBV, 61%. Adverse events (AEs) were similar across groups. Serious AEs/discontinuations due to AEs: PEG2b 1.5, 9%/13%; PEG2b 1.0, 9%/10%; PEG2a, 12%/13%.

Conclusions: For the first time data are available in a large randomized study showing PPV for TW 2 is highly predictive of SVR. However, the numbers of subjects who achieve an undetectable HCV RNA at TW 2 is small. TWs 4 and 12 remain the mainstay for physicians to make decisions regarding the ability of patients to achieve SVR.

Note: Abstract has been updated since submission.

Background

- 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}
- It is important to minimize exposure to PEG-IFN alfa + RBV in patients who are unlikely to attain SVR because these antiviral medications are associated with unwanted side effects
- Data from studies that assessed virologic response at treatment week (TW) 12 have resulted in a treatment algorithm that recommends discontinuing therapy in HCV G1-infected patients who are unlikely to respond to PEG-IFN alfa + RBV³
- Identifying additional early on-treatment virologic factors associated with SVR, which may differ with various PEG-IFN alfa + RBV dosing regimens, is also important and was assessed in the Individualized Dosing Efficacy vs Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study
- IDEAL investigated the efficacy and safety of weight-based PEG-IFN alfa-2b + weight-based RBV and fixed PEG-IFN alfa-2a + semi-weight-based RBV in patients with chronic hepatitis C caused by HCV G1 infection⁴

Δim

To identify early on-treatment virologic response associated with SVR

Patients and Methods

Patients

- Chronic hepatitis C, genotype 1
- Treatment naive
- Weight, 40 to 125 kgCompensated liver disease

Study Design

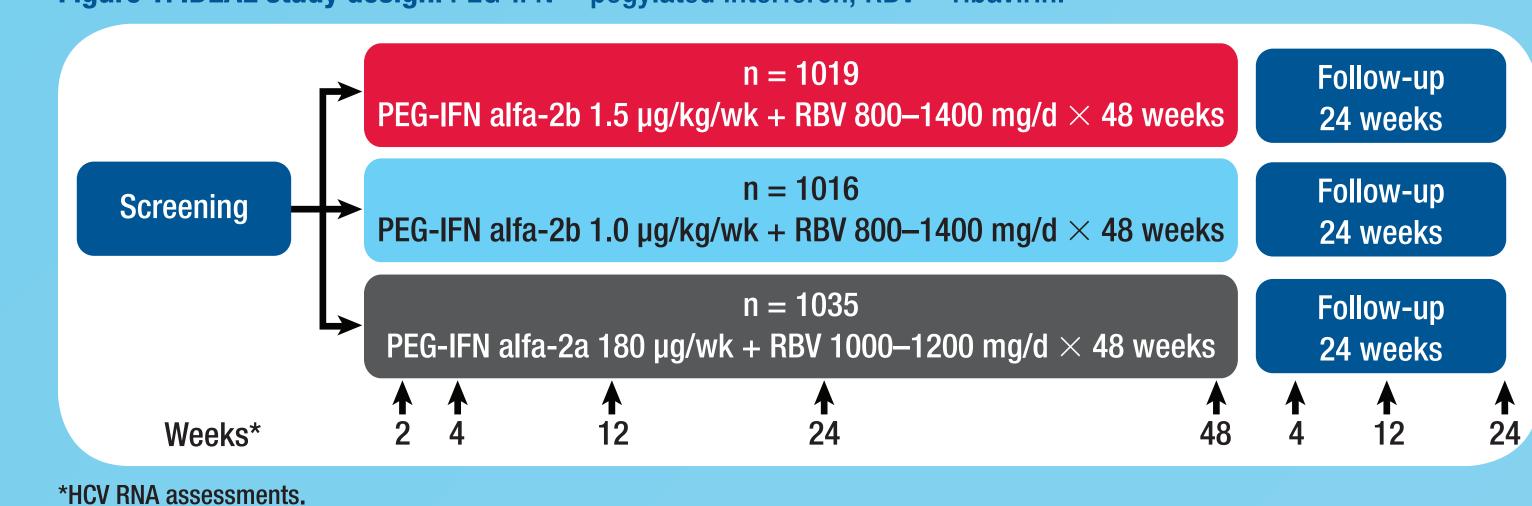
Age, 18 to 70 years

- 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 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.



Assessments

HCV RNA levels were assessed 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® TaqMan® 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 missing, week 12)</p>

Results

^aData were missing for 147 patients

Patient Characteristics

• Patients (n = 3070) had similar characteristics across the 3 treatment arms (Table 1)

• Positive predictive values (PPVs) of on-treatment HCV RNA levels for attaining SVR were calculated

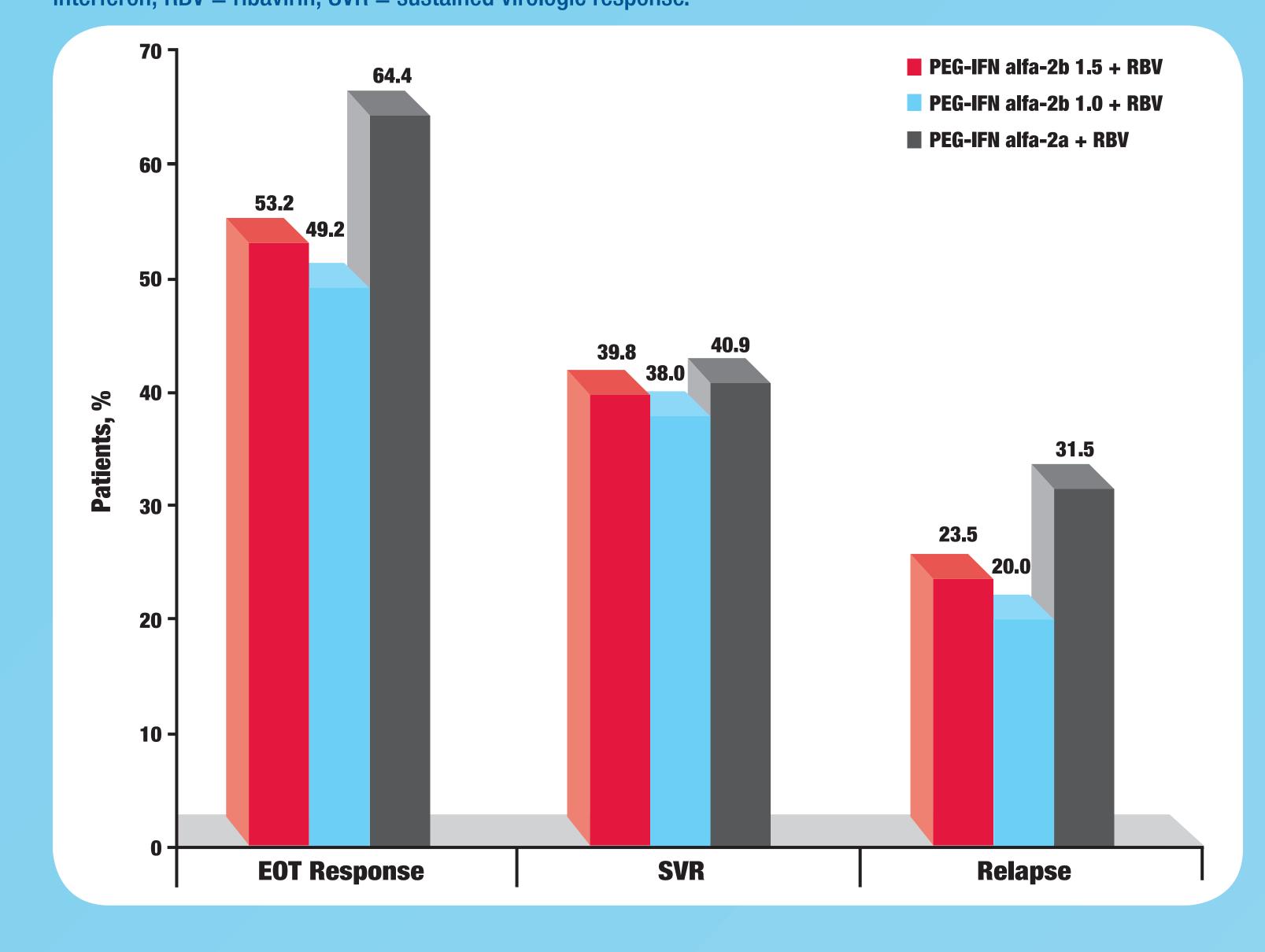
Table 1. Baseline Patient Characteristics

	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

End-of-Treatment Response, SVR, and Relapse Rates

• End-of-treatment response, SVR, and relapse rates are shown in Figure 2

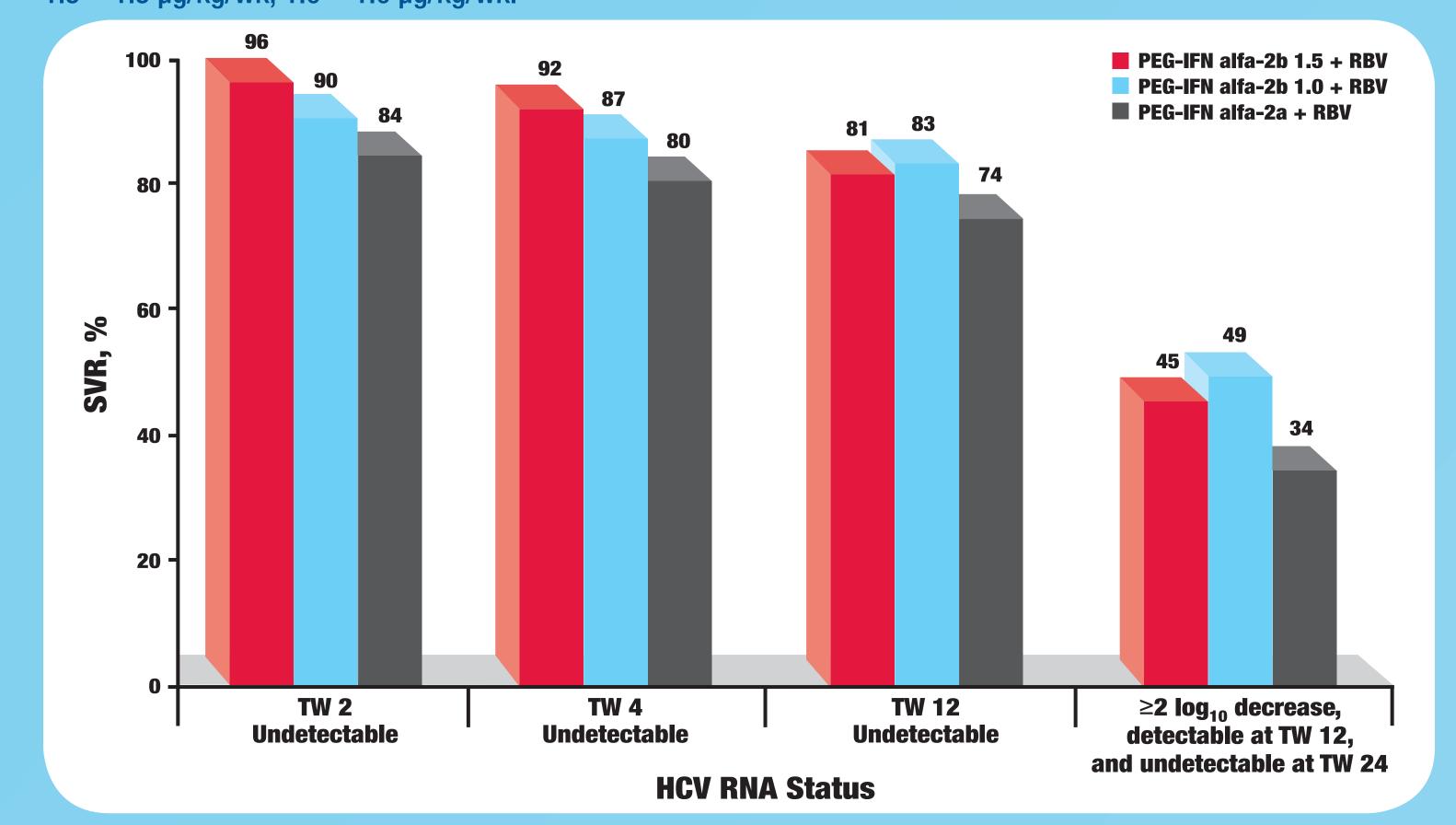
Figure 2. EOT response, SVR, and relapse rates after treatment with PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV, PEG-IFN alfa-2b 1.0 μg/kg/wk + RBV, and PEG-IFN alfa-2a 180 μg/wk + RBV. EOT = end-of-treatment; PEG-IFN = pegylated interferon; RBV = ribavirin; SVR = sustained virologic response.



• PPVs of HCV RNA levels at TWs 2, 4, 12, and 24 for SVR are shown in Figures 3 and 5

- 4% of all patients had undetectable HCV RNA at TW 2, resulting in SVR rates ranging from 84% to 96%
- PEG-IFN alfa-2b 1.5 + RBV had the highest PPV of attaining SVR compared with PEG-IFN alfa-2b 1.0 + RBV and PEG-IFN alfa-2a + RBV at TWs 2 and 4

Figure 3. Positive predictive values for SVR categories by undetectable HCV RNA levels at TWs 2, 4, 12, and 24. PEG-IFN = pegylated interferon; RBV = ribavirin; SVR = sustained virologic response; TW = treatment week; $1.5 = 1.5 \mu g/kg/wk$; $1.0 = 1.0 \mu g/kg/wk$.



• The proportions of patients who attained undetectable HCV RNA levels for the first time at TWs 2, 4, 12, and 24 are shown in Figure 4

Figure 4. Proportions of patients who first attained undetectable HCV RNA levels at each time point among patients who attained undetectable HCV RNA while on treatment. PEG-IFN = pegylated interferon; RBV = ribavirin; TW = treatment week; $1.5 = 1.5 \mu g/kg/wk$; $1.0 = 1.0 \mu g/kg/wk$.

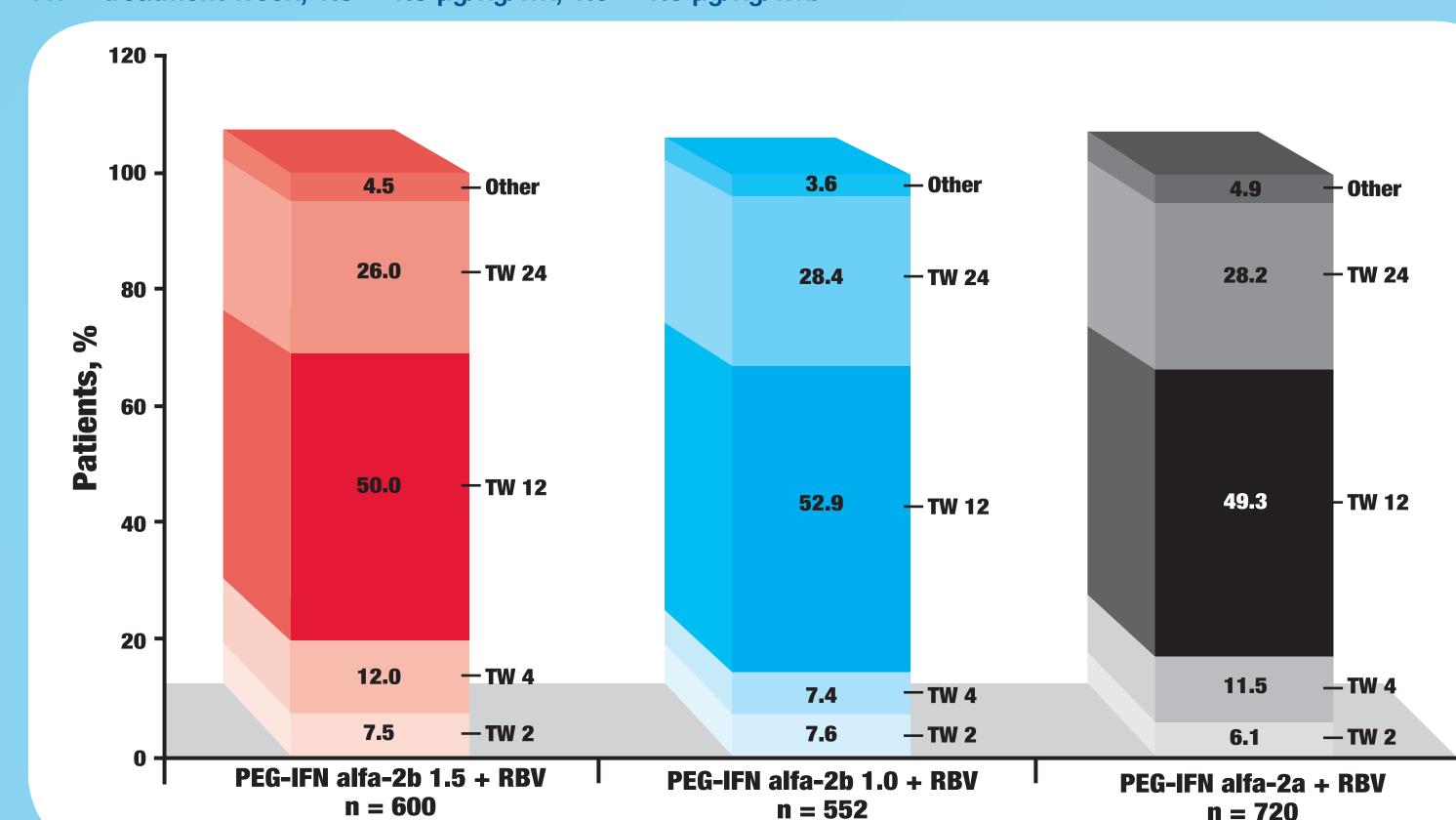
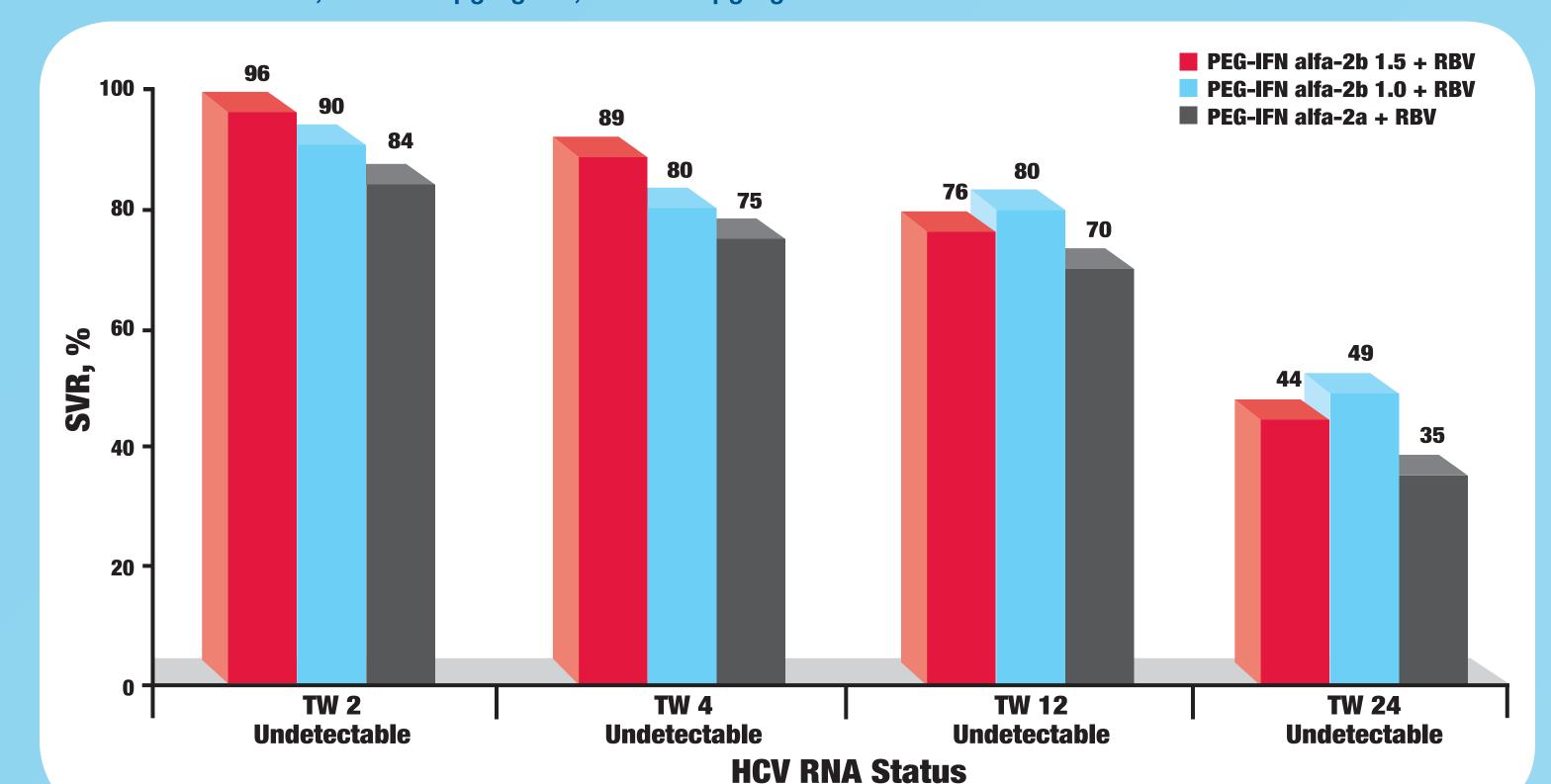


Figure 5. Positive predictive values for SVR categorized by the first treatment week during which patients attained undetectable HCV RNA levels. PEG-IFN = pegylated interferon; RBV = ribavirin; SVR = sustained virologic response; TW = treatment week; $1.5 = 1.5 \mu g/kg/wk$; $1.0 = 1.0 \mu g/kg/wk$.



Adherence

- 46% (1426/3070) of patients received ≥80% of both their PEG-IFN alfa + RBV doses for ≥80% of the expected duration of therapy (80/80/80) and were, therefore, considered adherent to the initially assigned dosing regimen⁵
- SVR rates for each of the treatment arms for patients adherent to treatment (≥80% of PEG-IFN alfa + RBV for ≥80% of the 48-week duration) are shown in **Table 2**

Table 2. Effect of Adherence to Initially Assigned Doses and Duration on SVR Rate

			SVR I	Rate		
	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	
	% (n/n)	95% CI	% (n/n)	95% CI	% (n/n)	95% CI
≥80% adherence to PEG-IFN alfa + RBV for ≥80% duration	70.0 (319/456)	65.7, 74.2	74.0 (327/442)	69.6, 78.1	61.4 (324/528)	57.2, 65.5
<80% adherence to PEG-IFN alfa and/or RBV or <80% duration, excluding treatment failures	28.9 (87/301)	23.8, 34.0	27.2 (59/217)	21.3, 33.1	32.8 (97/296)	27.4, 38.1

CI = confidence interval; PEG = peginterferon; RBV = ribavirin; SVR = sustained virologic response.

Safety

Adverse events (AEs) were similar across the 3 treatment arms

- Most common AEs (≥25% incidence) were fatigue, headache, nausea, insomnia, chills, pyrexia, anemia, myalgia, neutropenia, depression, irritability, and rash
- Incidences of serious AEs and discontinuations because of AEs are shown in **Table 3**

Table 3. Serious Adverse Event and Study Discontinuation Rates by Treatment Group

	SAE, %	Discontinuation, %
PEG-IFN alfa-2b 1.5 μg/kg/wk + RBV	9	13
PEG-IFN alfa-2b 1.0 μg/kg/wk + RBV	9	10
PEG-IFN alfa-2a 180 μg/wk + RBV	12	13

Conclusions

- Results from this large randomized trial show for the first time that attaining undetectable HCV RNA at TW 2 is highly predictive of attaining SVR
- However, the number of patients who attained undetectable HCV RNA at TW 2 was small (4% in each treatment arm)
- TWs 4 and 12 remain the foundation for assessing the likelihood that a patient will attain SVR
 High SVR rates can be attained with optimal therapy (80/80/80)

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