Poster #1851

Treatment-Related Anemia Is Associated With Higher SVR Rates Among Persons Treated With Peginterferon (PEG)/Ribavirin (RBV): Results From the IDEAL Study

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Abstract

Background: Anemia due to peginterferon/ribavirin (PEG/RBV) affects ~30% of persons treated. Epoetin alfa (EPO) has been used to increase hemoglobin (Hb) levels to improve quality of life and RBV dose. The relationship of anemia, EPO use, and sustained viral response (SVR) is unknown.

Methods: 3070 HCV genotype 1–infected patients (pts) were randomized (1:1:1) and treated for 48 weeks with PEG 2b 1.5 µg/kg/wk or PEG 2b 1.0 µg/kg/wk + RBV 800-1400 mg/d, or PEG 2a 180 µg/wk + RBV 1000-1200 mg/d. Patients with virologic failure at treatment week (TW) 12 or 24 stopped therapy. Anemia was defined as Hb <10 g/dL. Anemic patients underwent protocol-defined RBV dose reduction, after which EPO was permitted at investigator discretion. Viral response rates (ITT) were assessed in 3 groups: 1) No anemia; 2) Anemia/No EPO; 3) Anemia/EPO.

Results: No anemia was observed in 2158 pts (70%), of whom 67% were male and 83% were older than 40 years; median Hb maximum decline was –3.60 g/dL. Anemia was observed in 865 pts (28%), of whom 41% were male and 90% were older than 40 years; median Hb maximum decline was –4.65 to –5.20 g/dL. EPO was used in 449 (52%) anemic pts. Median nadir Hb level and median Hb maximum decline were similar in anemic pts with and without EPO use. Median RBV exposure (mg/kg/d) during treatment: (PEG 2b 1.5/PEG 2b 1.0/PEG 2a, respectively) – No anemia, 12.6/12.6/13.5, Anemia/No EPO, 11.7/12.0/12.6, Anemia/EPO, 11.9/11.9/12.5. The proportion of pts completing ≥12 weeks of therapy: No anemia, 94%; Anemia/No EPO, 92%; Anemia/EPO, 99%. Discontinuation due to adverse events (AEs)/virologic nonresponse: No anemia, 10%/31%; Anemia/No EPO, 18%/20%; Anemia/EPO, 12%/19%. End-of-treatment, relapse, and SVR rates are shown in Figure 4. *P*-value < 0.0001 using Mantel-Haenszel test for the association of Anemia with SVR adjusting for treatment.

Conclusions: Compared to those with no anemia, anemic pts were less likely to have virologic nonresponse and significantly more likely to achieve SVR despite receiving less RBV (mg/kg/d) during treatment. Although potential selection bias for comparing the groups may exist, this suggests that other host and treatment factors (e.g., plasma RBV concentration) contribute to viral response in this group. Among anemic pts, EPO use was associated with lower AE-related discontinuation and higher on-treatment viral response but not a substantially higher SVR rate.

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]
- Although these treatments are efficacious, they are associated with unwanted side effects
- Hemolytic anemia is a well-described side effect of RBV that can lead to dose reductions and treatment discontinuations, potentially resulting in lower rates of SVR[3]
  - Erythropoietin (EPO) supplementation helps maintain RBV dose levels and improves patient quality of life[4,5]
- EPO use was evaluated 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 infection[6]

Aim

- To evaluate the relationship between anemia and the use of EPO and their impact on SVR in the IDEAL study

Patients and Methods

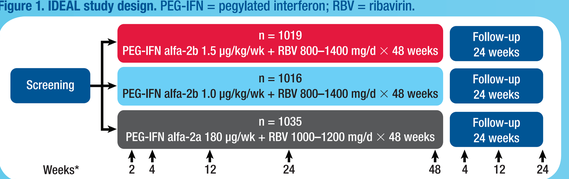
Patients

- 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 double-blind treatment, and PEG-IFN alfa-2a and RBV were administered as open-label treatments

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



*HCV RNA assessments.

- Patients had their treatment discontinued for therapeutic failure, defined as:
  - <2 $\log_{10}$ decrease from baseline in HCV RNA at treatment week (TW) 12
  - ≥2 $\log_{10}$ decrease from baseline in HCV RNA that remained detectable at TW 12 and detectable HCV RNA at TW 24
- Per protocol, anemia was defined as a decrease in hemoglobin level to <10 g/dL. After anemia developed, patients were required to reduce the RBV dose according to the protocol-defined 1-step (PEG-IFN alfa-2a) or 2-step (PEG-IFN alfa-2b) schema. At the discretion of the site investigator and the patient, EPO use was permitted (but not provided by the study) after RBV dose reduction. Patients were permitted to increase the RBV dose after correction of anemia
  - RBV dose reduction in the PEG-IFN alfa-2b + RBV arms
    - Decrease from full dose of 800-1200 mg/d by 200 mg (first dose reduction) and then by 200 mg (second dose reduction), or
    - Decrease from full dose of 1400 mg/d by 400 mg (first dose reduction) and then by 200 mg (second dose reduction)
  - RBV dose reduction in the PEG-IFN alfa-2a + RBV arm
    - Decrease from full dose of 1000-1200 mg/d to 600 mg/d (per prescribing information)

Assessments

- Hemoglobin concentrations were assessed at TWs 2, 4, 8, 12, 18, 24, 30, 36, 42, and 48/end of treatment and follow-up weeks 4, 12, and 24
- HCV RNA levels were assessed at TWs 2, 4, 12, 24, and 48/end of treatment and follow-up weeks 4, 12, and 24
  - HCV RNA was measured using COBAS® TaqMan® (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)
- Study centers recorded EPO use throughout the study period

Results

Patient Characteristics

- Patients (n = 3070) had similar characteristics across the 3 treatment groups (see Poster 1850, 1868, or 1869 for characteristics by treatment group)
- Differences between patients who did not develop anemia and those who developed anemia with or without EPO use during treatment are shown in **Table 1**

Table 1. Baseline Patient Characteristics Categorized by Development of Anemia

	No Anemia (A) n = 2158	With Anemia n = 865				
		No EPO (B) n = 416	EPO (C) n = 449	*P* A vs B	*P* A vs C	*P* B vs C
Male, %	67	38	44	<0.0001	<0.0001	0.0667
Race, %						
Caucasian	72	68	72	0.0958	0.8048	0.2689
African American/Black	17	21	20	0.0595	0.2422	0.5704
Age, y, mean (SD)	46.8 (7.9)	48.7 (8.2)	50.2 (7.6)	<0.0001	<0.0001	0.0040
Weight, kg, mean (SD)	84.7 (16.1)	79.8 (16.9)	80.5 (15.9)	<0.0001	<0.0001	0.5281
Baseline HCV RNA >600,000 IU/mL, %	83	77	84	0.0048	0.3971	0.0053
Steatosis,[a] %						
Absent	36	38	38	0.3415	0.4020	0.9134
Present	60	58	55	0.6161	0.0528	0.2826
METAVIR fibrosis score,[a] %						
F0/1/2	85	85	80	0.6419	0.0021	0.0614
F3/4	10	12	13	0.2175	0.0675	0.6896
Baseline hemoglobin concentration, g/dL, mean (SD)	15.2 (1.2)	14.3 (1.1)	14.3 (1.2)	<0.0001	<0.0001	0.4108
Baseline creatinine, µmol/L, mean (SD)	74.5 (14.1)	72.7 (13.5)	74.2 (15.2)	0.0185	0.6731	0.1384
Baseline estimated creatinine clearance,[b] mL/min,mean (SD)	123.3 (31.6)	110.2 (30.8)	108.9 (28.9)	<0.0001	<0.0001	0.4976

EPO = erythropoietin; HCV = hepatitis C virus.
[a]Data were missing for 147 patients. [b]Using Cockcroft-Gault equation.

- No anemia was observed in 2158 of 3070 (70%) patients
  - 83% were older than 40 years
  - Baseline mean and median hemoglobin concentrations were higher than in patients who developed anemia
- Anemia was observed in 865 of 3070 (28%) patients
  - 59% were female
  - 90% were older than 40 years
- EPO was used in 449 of 865 (52%) patients who developed anemia

Hemoglobin Concentrations During Treatment

- In patients without anemia, median hemoglobin maximum decline was –3.60 g/dL (**Table 2**)
- In patients with anemia, median hemoglobin maximum decline ranged from –4.65 to –5.20 g/dL
  - In patients with anemia who used EPO, median hemoglobin maximum decline was –4.90 to –5.20 g/dL
  - Median nadir hemoglobin concentration and median hemoglobin maximum decline were similar in patients with anemia regardless of EPO use

Table 2. Median Nadir Hemoglobin Concentration and Median Hemoglobin Maximum Decline

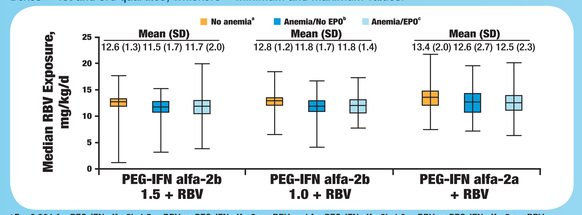
		PEG-IFN alfa-2b 1.5 + RBV			PEG-IFN alfa-2b 1.0 + RBV			PEG-IFN alfa-2a + RBV		
		Median Nadir Hb Level	Median Days to Hb Nadir (IQR)	Median Hb Max Decline (IQR)	Median Nadir Hb Level	Median Days to Hb Nadir (IQR)	Median Hb Max Decline (IQR)	Median Nadir Hb Level	Median Days to Hb Nadir (IQR)	Median Hb Max Decline (IQR)
No Anemia		11.50	126 (58, 217)	–3.60 (–4.5, –2.8)	11.60	122 (57, 211)	–3.60 (–4.4, –2.7)	11.40	127 (61, 253)	–3.60 (–4.6, –2.7)
Anemia	No EPO	9.50	145 (71, 215)	–5.10 (–5.9, –4.1)	9.60	127 (64, 210)	–5.00 (–5.9, –4.1)	9.60	142 (65, 252)	–4.65 (–5.7, –4.1)
	EPO	9.30	88.5 (56, 168)	–5.20 (–5.9, –4.2)	9.40	103 (57, 175)	–5.10 (–5.9, –4.3)	9.45	101 (43, 171)	–4.90 (–6.0, –3.8)

EPO = erythropoietin; Hb = hemoglobin; IQR = 1st and 3rd quartiles; PEG-IFN = pegylated interferon; RBV = ribavirin.

RBV Exposure

- During treatment, median and mean RBV exposures were higher among patients receiving PEG-IFN alfa-2a than among those receiving PEG-IFN alfa-2b, regardless of EPO use and development of anemia (**Figure 2**)

Figure 2. Median RBV exposure according to presence of anemia and use of EPO. EPO = erythropoietin; PEG-IFN = pegylated interferon; RBV = ribavirin; 1.5 = 1.5 µg/kg/wk; 1.0 = 1.0 µg/kg/wk.
Boxes = 1st and 3rd quartiles; whiskers = minimum and maximum values.

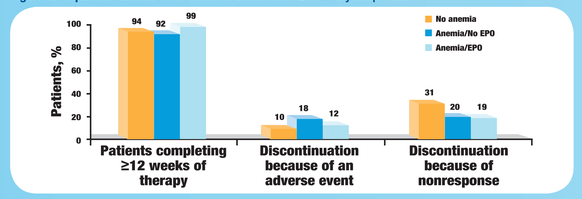


[a]$P < 0.001$ for PEG-IFN alfa-2b 1.5 + RBV vs PEG-IFN alfa-2a + RBV and for PEG-IFN alfa-2b 1.0 + RBV vs PEG-IFN alfa-2a + RBV; $P = 0.012$ for PEG-IFN alfa-2b 1.5 + RBV vs PEG-IFN alfa-2b 1.0 + RBV.
[b]$P < 0.001$ for PEG-IFN alfa-2b 1.5 + RBV vs PEG-IFN alfa-2a + RBV; $P = 0.002$ for PEG-IFN alfa-2b 1.0 + RBV vs PEG-IFN alfa-2a + RBV; $P = 0.270$ PEG-IFN alfa-2b 1.5 + RBV vs PEG-IFN alfa-2b 1.0 + RBV.
[c]$P < 0.001$ for PEG-IFN alfa-2b 1.5 + RBV vs PEG-IFN alfa-2a + RBV; $P = 0.001$ for PEG-IFN alfa-2b 1.0 + RBV vs PEG-IFN alfa-2a + RBV; $P = 0.616$ for PEG-IFN alfa-2b 1.5 + RBV vs PEG-IFN alfa-2b 1.0 + RBV.

Impact of Anemia on Treatment Adherence

- Fewer patients with anemia completed ≥12 weeks of therapy (**Figure 3**); this effect of anemia was reversed by the use of EPO ($P < 0.001$ for No Anemia or Anemia/No EPO vs Anemia/EPO)
- More patients who developed anemia that was not treated with EPO discontinued treatment because of an adverse event than did patients who did not develop anemia ($P < 0.001$ for No Anemia vs Anemia/No EPO; **Figure 3**); this effect of anemia was reversed by the use of EPO ($P = 0.017$ for Anemia/No EPO vs Anemia/EPO)
- The discontinuation rate because of virologic nonresponse at TWs 12 and 24 was highest among patients who did not develop anemia (**Figure 3**) ($P < 0.001$ for No Anemia vs Anemia/No EPO and Anemia/EPO)

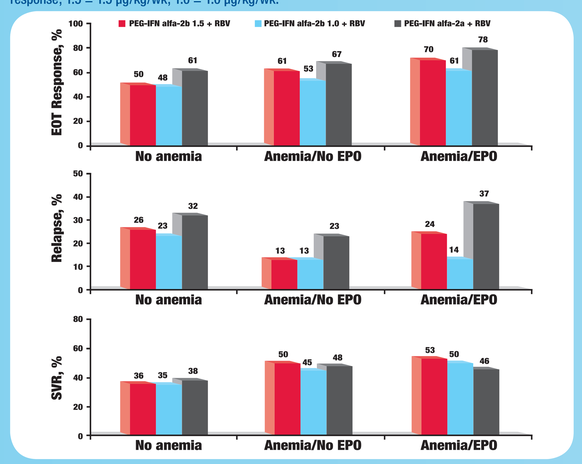
Figure 3. Impact of anemia on treatment adherence. EPO = erythropoietin.



Virologic Outcomes

- End-of-treatment response, relapse, and SVR rates are shown in **Figure 4**
- $P < 0.0001$ using Mantel-Haenszel test for the association of anemia with SVR adjusting for treatment

Figure 4. Virologic outcomes according to development of anemia. EOT = end of treatment; EPO = erythropoietin; PEG-IFN = pegylated interferon; RBV = ribavirin; SVR = sustained virologic response; 1.5 = 1.5 µg/kg/wk; 1.0 = 1.0 µg/kg/wk.



Safety

- Adverse events during the study are shown in **Table 3**

Table 3. Adverse Events

Patients	No Anemia	Anemia[a]	
		No EPO	EPO
Treatment-emergent adverse events, %	99	100	100
Serious adverse events, %	9	12	14
Relevant adverse events, %			
Fatigue	64	67	74
Anemia[b]	9	87	97
Aplastic anemia	0	0	<1
Dyspnea	15	23	24
Exertional dyspnea	5	7	10
Hypertension	4	4	4
Increased blood pressure	1	<1	1
Myocardial infarction	<1	<1	<1
Coronary artery disease	<1	<1	0
Angina pectoris	<1	0	0
Pulmonary embolism	<1	0	<1
Deep venous thrombosis	<1	0	1
Congestive heart failure	0	<1	<1
Cerebrovascular accident	0	0	<1
Cerebral hemorrhage	<1	0	0
Malignant melanoma	<1	0	<1

EPO = erythropoietin.
[a]Anemia based on hemoglobin <10 g/dL.
[b]Anemia based on adverse event as listed by the investigator.

Conclusions

- Patients with anemia were significantly more likely to attain end-of-treatment response and SVR than were those without anemia, despite having received less RBV (mg/kg/d) during treatment after the development of anemia
- Among patients with anemia, EPO use was associated with a lower adverse event–related discontinuation rate and a higher on-treatment viral response rate but not with a substantially higher SVR rate
- Although potential selection bias for comparing the nonrandomized groups may exist, these data suggest that other host and treatment factors (eg, plasma or hepatocyte RBV concentration) contribute to higher rates of viral response in patients who develop anemia
- These data support the hypothesis that treatment-related anemia may be a pharmacodynamic marker of patient exposure to the active moiety, RBV triphosphate
- Further modeling is under way to assess the role of EPO in this study

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Disclosures

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