Poster #1869

Hematologic Safety Data From the IDEAL Trial: Neutropenia, Anemia, and Thrombocytopenia Profiles of Peginterferon alfa/Ribavirin

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Abstract

Background: The IDEAL trial compared 3 treatment regimens of peginterferon alfa plus ribavirin (RBV) in naive genotype 1 patients. Hematologic profiles are described.

Methods: 3070 patients were treated for 48 weeks with ribavirin 800-1400 mg/d plus PEG2b 1.5 µg/kg/wk (PEG1.5/RBV) or PEG2b 1 µg/kg/wk (PEG1/RBV), or PEG2a 180 µg/wk + ribavirin 1000-1200 mg/d (Peg2a/RBV). Dose reduction (DR)/ discontinuation (DC) was required for Hgb <10 and 8.5 g/dL, neutrophil count (neut) <0.75 and 0.50 × 10^9/L, or platelet count (plt) <50 and 25 × 10^9/L, respectively. Subsequent to required RBV DR, erythropoietin was allowed, and there were no differences in usage among arms.

Results: Baseline blood counts were similar in all arms. Lowest on-treatment means were calculated. Neut were significantly lower in the PEG2a/RBV arm (mean=1.09 × 10^9/L) compared to the PEG1.5/RBV (1.15 × 10^9/L) or the PEG1/RBV (1.29 × 10^9/L) arms ($P < 0.001$, Wilcoxon 2-sample test). Plts were significantly lower in the PEG2a/RBV arm (130 × 10^9/L) compared to the PEG1.5/RBV (145 × 10^9/L) or the PEG1/RBV (156 × 10^9/L) arms ($P < 0.001$) and for PEG1.5/ RBV compared to PEG1/RBV ($P < 0.001$). Hgb concentration was significantly lower for the Peg2a/RBV and PEG1.5/RBV arms compared to the PEG1/RBV ($P \leq 0.01$). In the Peg2a/RBV arm, 6% of patients reached the neut DC value compared to 3% in the PEG1.5/RBV and 2% in the PEG1/RBV arms. Neutropenia appeared to be related to body weight (BW) in the PEG2a/RBV arm only; 9% in 40-65 kg BW, 6% in 75-85 kg BW, and only 3% in >105 kg BW arm had neut <0.50 × 10^9/L. Similarly, Hgb <8.5 g/dL was seen in 4%, 3%, and 2% of those receiving Peg2a/RBV, PEG1.5/RBV, and PEG1/RBV, respectively, but a clear effect of BW was seen only in the Peg2a/RBV arm; 8% with BW 40-65 kg, 3% with BW 75-85, and 1% with BW>105 kg. Five patients in Peg2a/RBV had plts <25 × 10^9/L. Regressions for moving averages plots by arm for rates of decreased blood counts vs baseline BW demonstrated: 1) grade 3-4 neutropenia for the 3 arms diverging at <100 kg BW, with the steepest slope for the Peg2a/RBV arm; 2) for grades 2-4 anemia, both PEG/RBV arms showed a slight increase in anemia with decreasing BW, whereas there was a steep increase in anemia for the Peg2a/RBV arm below BW <90 kg, with a divergence from the other 2 arms for those with a BW of <70 kg; 3) grades 2-4 thrombocytopenia decreased with lower BW for both PEG2b/RBV arms but increased with lower BW in the Peg2a/RBV arm.

Conclusions: Treatment with Peg2a/RBV causes significantly more neutropenia and thrombocytopenia than either PEG/ RBV regimen, particularly with lower BW. This may reflect the increased bone marrow exposure to interferon on a BW basis in the Peg2a/RBV regimen as well as possible inherent differences between the different peginterferon molecules.

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, PEG-IFN alfa can result in bone marrow suppression that affects the 3 blood cell lines, and RBV can cause hemolytic anemia
- Hematologic side effects were 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 infection[3]

Aim

- To describe the hematologic safety profiles of patients in the IDEAL trial treated with PEG-IFN alfa + RBV

Patients and Methods

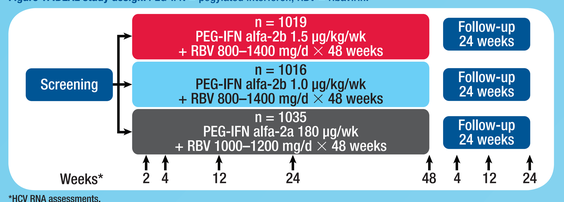
Patients

- 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
- 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

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



*HCV RNA assessments.

- PEG-IFN alfa dose reduction was required when either of the following occurred:
  - Neutrophil count was <0.75 × 10^9/L
  - Platelet count was <50 × 10^9/L
- RBV dose reduction was required when hemoglobin level was <10 g/dL
  - Use of erythropoietin was permitted with concurrent RBV dose reduction
- Discontinuation of PEG-IFN alfa + RBV was required when any of the following occurred:
  - Neutrophil count was <0.5 × 10^9/L
  - Platelet count was <25 × 10^9/L
  - Hemoglobin concentration was <8.5 g/dL

Assessments

- Absolute neutrophil counts, platelet counts, and hemoglobin concentrations were assessed at baseline and at TWs 2, 4, 8, 12, 18, 24, 30, 36, 42, and 48/end of treatment and at follow-up weeks 4, 12, and 24
- Lowest on-treatment mean values were calculated for neutrophil counts, platelet counts, and hemoglobin concentrations
- Wilcoxon 2-sample tests were conducted to determine statistical significance

Results

Patient Characteristics

- Patients (n = 3070) had similar characteristics across treatment arms (**Table 1**), including baseline blood counts
- No differences in erythropoietin use were observed among the 3 treatment arms (14%-17%)

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
Mean hematologic parameters (SD)			
Neutrophil counts, × 10^9/L	3.68 (1.35)	3.72 (1.36)	3.79 (1.55)
Platelet counts, × 10^9/L	229 (69)	228 (70)	228 (68)
Hemoglobin concentration, g/dL	15.0 (1.3)	15.0 (1.2)	14.9 (1.3)

PEG-IFN = pegylated interferon; RBV = ribavirin.
[a]Data were missing for 147 patients.

Hematologic Profiles

Neutrophil Counts

- Mean on-treatment neutrophil counts were significantly lower in the PEG-IFN alfa-2a + RBV arm than in the PEG-IFN alfa-2b + RBV arms ($P < 0.001$) (**Table 2**)
  - Mean on-treatment neutrophil counts were significantly lower in the PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV arm than in the PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV arm ($P < 0.001$)

Table 2. Mean Nadir On-Treatment Hematologic Values of Patients Treated

	PEG-IFN alfa-2b 1.5 + RBV n = 1019[a]	PEG-IFN alfa-2b 1.0 + RBV n = 1016[b]	PEG-IFN alfa-2a + RBV n = 1035[c]	PEG-IFN alfa-2b 1.5 + RBV vs PEG-IFN 2b 1.0 + RBV	PEG-IFN alfa-2b 1.5 + RBV vs PEG-IFN 2a + RBV	PEG-IFN alfa-2a + RBV vs PEG-IFN 2b 1.0 + RBV
					P[a]	
Neutrophil count, ×10^9/L (SD)	1.15 (0.55)	1.29 (0.67)	1.09 (0.56)	< 0.001	< 0.001	< 0.001
Platelet count, ×10^9/L (SD)	145 (53)	156 (57)	130 (51)	< 0.001	< 0.001	< 0.001
Hemoglobin concentration, g/dL (SD)	10.9 (1.5)	11.1 (1.4)	10.9 (1.5)	< 0.001	0.43	0.01

PEG-IFN = pegylated interferon; RBV = ribavirin.
On-treatment laboratory data were available for [a]989 of 1019 patients, [b]1001 of 1016 patients, and [c]1033 of 1035 patients. [a]Wilcoxon 2-sample test.

- Neutrophil counts <0.50 × 10^9/L, requiring discontinuation from study treatment, were seen in
  - 3% (28/1000) of patients receiving PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV
  - 2% (21/1008) of patients receiving PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV
  - 6% (61/1034) of patients receiving PEG-IFN alfa-2a + RBV

Platelet Counts

- Mean on-treatment platelet counts were significantly lower in the PEG-IFN alfa-2a + RBV arm than in the PEG-IFN alfa-2b + RBV arms ($P < 0.001$) (**Table 2**)
  - Mean on-treatment platelet counts were significantly lower in the PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV arm than in the PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV arm ($P < 0.001$)
- Platelet counts <25 × 10^9/L, requiring discontinuation from study treatment, were seen in
  - 0.5% (5/1034) of patients receiving PEG-IFN alfa-2a + RBV

Hemoglobin Concentrations

- Mean on-treatment hemoglobin concentrations were significantly lower in the PEG-IFN alfa-2a + RBV and PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV arms than in the PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV ($P \leq 0.01$) arm (**Table 2**)
- Hemoglobin concentrations <8.5 g/dL, requiring discontinuation from study treatment, were seen in
  - 3% (25/1000) of patients receiving PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV
  - 2% (21/1008) of patients receiving PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV
  - 4% (39/1034) of patients receiving PEG-IFN alfa-2a + RBV

Effect of Body Weight

Neutropenia

- Neutropenia was related to body weight in the PEG-IFN alfa-2a + RBV arm (**Table 3**)
  - Patients with lower body weights had higher rates of dose reduction and discontinuation than did those with higher body weights

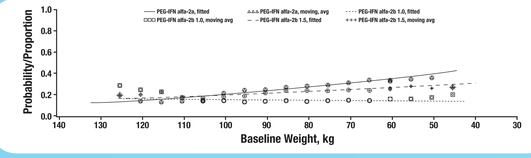
Table 3. Incidence of Neutropenia by Weight Category

Weight Range, kg	PEG-IFN alfa-2b 1.5 + RBV n = 1019[a] (%)		PEG-IFN alfa-2b 1.0 + RBV n = 1016[b] (%)		PEG-IFN alfa-2a + RBV n = 1035[c] (%)	
	DR 0.5-<0.75 × 10^9/L	DC <0.5 × 10^9/L	DR 0.5-<0.75 × 10^9/L	DC <0.5 × 10^9/L	DR 0.5-<0.75 × 10^9/L	DC <0.5 × 10^9/L
40-65	37/141 (26)	2/141 (1)	20/138 (14)	2/138 (1)	40/160 (25)	15/160 (9)
>65-<75	26/146 (18)	4/146 (3)	19/165 (12)	4/165 (2)	46/174 (26)	11/174 (6)
≥75-85	54/265 (20)	11/265 (4)	32/249 (13)	5/249 (2)	57/270 (21)	17/270 (6)
>85-105	58/341 (17)	6/341 (2)	41/379 (11)	8/379 (2)	64/322 (20)	15/322 (5)
>105	19/107 (18)	5/107 (5)	14/77 (18)	2/77 (3)	11/108 (10)	3/108 (3)

DC = discontinuation for neutrophil counts of <0.5 × 10^9/L; DR = dose reduction for neutrophil counts of 0.5-<0.75 × 10^9/L; PEG-IFN = pegylated interferon; RBV = ribavirin.
On-treatment laboratory data were available for [a]1000 of 1019 patients, [b]1008 of 1016 patients, and [c]1034 of 1035 patients.

- Grades 3-4 neutropenia (grade 3 = neutrophil count 0.5-<0.75 × 10^9/L; grade 4 = neutrophil count <0.5 × 10^9/L)
  - Fitted regression lines along with observed moving averages plotted by arm for rates of grades 3-4 neutropenia versus baseline body weight demonstrated grades 3-4 neutropenia rates for the 3 arms diverging at <100 kg, with the steepest slope for the PEG-IFN alfa-2a + RBV arm (**Figure 2**)
  - Pairwise comparisons of the slopes resulted in the following:
    - PEG-IFN alfa-2a + RBV versus PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV was statistically significant ($P = 0.003$)
    - PEG-IFN alfa-2a + RBV versus PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV was not statistically significant ($P = 0.141$)
    - PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV versus PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV was not statistically significant ($P = 0.109$)

Figure 2. Minimum neutrophil grades 3 and 4 by weight.



Thrombocytopenia

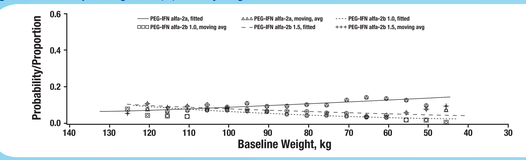
- Grades 2-4 thrombocytopenia (grade 2 = platelet count 50-<70 × 10^9/L; grade 3 = platelet count 25-<50 × 10^9/L; grade 4 = platelet count <25 × 10^9/L) decreased with lower body weight for both PEG-IFN alfa-2b + RBV arms but increased with lower body weight in the PEG-IFN alfa-2a + RBV arm (**Table 4, Figure 3**)
  - These differences were not clinically meaningful

Table 4. Incidence of Thrombocytopenia by Weight Category

Weight Range, kg	PEG-IFN alfa-2b 1.5 + RBV n = 1019[a] (%)		PEG-IFN alfa-2b 1.0 + RBV n = 1016[b] (%)		PEG-IFN alfa-2a + RBV n = 1035[c] (%)	
	DR 25-<50 × 10^9/L	DC <25 × 10^9/L	DR 25-<50 × 10^9/L	DC <25 × 10^9/L	DR 25-<50 × 10^9/L	DC <25 × 10^9/L
40-65	1/141 (1)	0/141	1/136 (1)	0/136	4/160 (3)	1/160 (1)
>65-<75	1/146 (1)	0/146	2/165 (1)	0/165	6/174 (3)	1/174 (1)
≥75-85	6/264 (2)	0/264	1/249 (<1)	0/249	5/270 (2)	2/270 (1)
>85-105	4/340 (1)	0/340	4/379 (1)	0/379	8/322 (2)	0/322
>105	2/107 (2)	0/107	2/77 (3)	0/77	0/108	1/108 (1)

DC = discontinuation for platelet count of <25 × 10^9/L; DR = dose reduction for platelet count of 25 to <50 × 10^9/L; PEG-IFN = pegylated interferon; RBV = ribavirin.
On-treatment laboratory data were available for [a]998 of 1019 patients, [b]1006 of 1016 patients, and [c]1034 of 1035 patients.

Figure 3. Minimum platelet grades 2, 3, and 4 by weight.



Anemia

- Anemia was also related to body weight in the PEG-IFN alfa-2a + RBV arm (**Table 5**)
  - Discontinuation rates were higher in patients with lower body weights

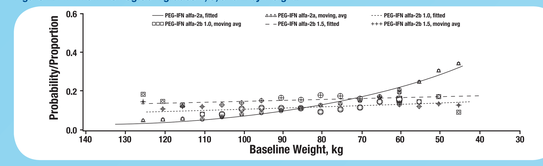
Table 5. Incidence of Anemia by Weight Category

Weight Range, kg	PEG-IFN alfa-2b 1.5 + RBV n = 1019[a] (%)		PEG-IFN alfa-2b 1.0 + RBV n = 1016[b] (%)		PEG-IFN alfa-2a + RBV n = 1035[c] (%)	
	DR 8.5-<10 g/dL	DC <8.5 g/dL	DR 8.5-<10 g/dL	DC <8.5 g/dL	DR 8.5-<10 g/dL	DC <8.5 g/dL
40-65	47/141 (33)	1/141 (1)	47/138 (34)	0/138	67/160 (42)	12/160 (8)
>65-<75	45/146 (31)	7/146 (5)	37/165 (22)	5/165 (3)	47/174 (27)	12/174 (7)
≥75-85	78/265 (29)	4/265 (2)	48/249 (19)	6/249 (2)	68/270 (25)	8/270 (3)
>85-105	84/341 (25)	12/341 (4)	87/379 (23)	8/379 (2)	69/322 (21)	6/322 (2)
>105	28/107 (26)	1/107 (1)	15/77 (19)	2/77 (3)	16/108 (15)	1/108 (1)

DC = discontinuation for hemoglobin concentration of <8.5 g/dL; DR = dose reduction for hemoglobin concentration of 8.5 to <10 g/dL; PEG-IFN = pegylated interferon; RBV = ribavirin.
On-treatment laboratory data were available for [a]1000 of 1019 patients, [b]1008 of 1016 patients, and [c]1034 of 1035 patients.

- Grades 2-4 anemia (grade 2 = hemoglobin 8.0-<9.5 g/dL; grade 3 = hemoglobin 6.5-<8.0 g/dL; grade 4 = hemoglobin concentration <6.5 g/dL)
  - Both PEG-IFN alfa-2b + RBV arms showed slight increases in anemia with decreasing body weight (**Figure 4**)
  - A steep increase in anemia for the PEG-IFN alfa-2a + RBV arm in patients weighing <90 kg was observed, and a divergence from the PEG-IFN alfa-2b + RBV arms was observed for patients weighing <70 kg (**Figure 4**)

Figure 4. Minimum hemoglobin grades 2, 3, and 4 by weight.



Conclusions

- Treatment with PEG-IFN alfa-2a + RBV caused significantly more neutropenia and thrombocytopenia than did either of the PEG-IFN alfa-2b + RBV regimens, particularly in patients with low body weight, though no clinically significant differences (infections or bleeding) were seen
  - This observation may reflect the increased bone marrow exposure to IFN alfa based on body weight in the PEG-IFN alfa-2a + RBV arm in the lower weight groups and possible inherent differences among the different PEG-IFN alfa molecules
- Treatment with PEG-IFN alfa-2b 1.0 µg/kg/wk + RBV resulted in fewer hematologic side effects than did treatment with PEG-IFN alfa-2b 1.5 µg/kg/wk + RBV or PEG-IFN alfa-2a + RBV

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Disclosures

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