Poster #889

Asian and White Patients With Chronic Hepatitis C (CHC) Achieve Similar Response Rates With Peginterferon (PEG-IFN) Alfa-2b Plus Ribavirin (RBV) in Genotypes (G) 2 and 3: Subanalysis of the REDD 2/3 Study

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Abstract

Purpose: Ethnicity as a factor in prevalence, disease progression, and treatment outcome of CHC is well described in African Americans and whites but less well described in Asians. Global differences in variables such as obesity, nutrition, infections and alcohol consumption may also affect treatment response. Data on the efficacy of PEG-IFN plus RBV are sparse in the Asian population. Our aim was to evaluate efficacy and safety of PEG-IFN alfa-2b plus RBV in Asian vs white subjects with CHC G2 or G3 infection.

Method: REDD 2/3 was an open-label, multicenter, parallel group study. Subjects were randomized 1:1:1 to receive 24 weeks (group A) or 16 weeks (group C) of PEG-IFN alfa-2b 1.5 µg/kg/wk plus 800-1200 mg/day RBV (WBD RBV), or 24 weeks PEG-IFN alfa-2b 1.0 µg/kg/wk plus WBD RBV (group B). REDD 2/3 comprised 2 cohorts: an investigator-initiated (real-life) German study (HepNet Cohort) and an industry-sponsored study (International Cohort) conducted in India, Indonesia, Israel, Malaysia, Poland, Singapore, and Thailand. This report is a subanalysis of treatment response in Asian vs white subjects in the International Cohort only as it represented both ethnicities. Primary endpoint was sustained virologic response (SVR), defined as undetectable HCV RNA 24 weeks after receiving last dose of therapy.

Results: As in the overall REDD 2/3 population, the International Cohort was primarily G3 (84.8% vs 15.2% G2). Mean duration of HCV infection was 11.4 y, and 57% had baseline viral load ≥600,000 IU/mL. This cohort comprised 52.8% Asians and 47.2% whites. Overall SVR was 74.6% group A, 68.8% group B, and 66.1% group C. SVR was similar in Asian and white subjects (Table). Although not statistically significant, SVR was higher in group A vs groups B and C for both Asians and whites. Adverse event profile was consistent with that previously reported with PEG-IFN alfa-2b/RBV therapy.

Conclusion: This study, consisting of >80% CHC G3 subjects, appears to be the largest study to date in Asian G3 subjects. SVR rates were similar in Asian and white subjects. This study demonstrates that PEG-IFN alfa-2b 1.5 µg/kg/wk plus WBD RBV is effective at treating Asian and white patients with CHC G2 or G3.

SVR According to Race

	Group A PEG 1.5/RBV (24 wk)	Group B PEG 1.0/RBV (24 wk)	Group C PEG 1.5/RBV (16 wk)
Overall			
Asian	75.4% (43/57)	69.5% (41/59)	65.6% (40/61)
White	73.7% (42/57)	68% (34/50)	66.7% (34/51)
Genotype 2			
Asian	100% (1/1)	83.3% (5/6)	80% (4/5)
White	70% (7/10)	58.3% (7/12)	70.6% (12/17)
Genotype 3			
Asian	75% (42/56)	67.9% (36/53)	64.3% (36/56)
White	74.5% (35/47)	71.1% (27/38)	64.7% (22/34)

PEG=peginterferon alfa-2b; RBV=ribavirin.

Background

- The standard of care regimen for treating patients with chronic hepatitis C (CHC) genotype (G) 2 or 3 infection is peginterferon (PEG-IFN) alfa plus ribavirin (RBV) for 24 weeks. However, a few studies have shown that a reduced treatment duration of 12 or 16 weeks is effective in patients who have attained rapid virologic response.[1-4] Additionally, for selected patients a reduced dose does not appear to be associated with a lower rate of sustained virologic response (SVR)[1,3]
- Ethnicity also has an impact on treatment outcomes in patients with CHC, with African-American and Hispanic patients typically having poorer SVR rates compared with Asian and white patients. While the impact of ethnicity on CHC is well described in African Americans and whites, it is less well described in the Asian population
- REDD 2/3 was a prospective, randomized, international study to assess the efficacy and safety of a reduced dose or treatment duration of PEG-IFN alfa-2b (PegIntron®; Schering-Plough) in patients with CHC G2 or G3 infection

Aim

- Assess efficacy and safety of reduced dose or reduced treatment duration of PEG-IFN alfa-2b plus RBV in Asian vs white subpopulations in the REDD 2/3 trial

Methods

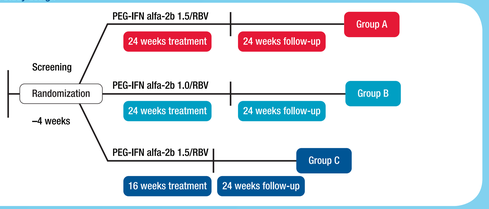
Patients

- Previously untreated patients with CHC G2 or G3 infection and with compensated liver disease were enrolled. Patients with HIV or hepatitis B coinfection were excluded

Study Design

- Open-label, multicenter, randomized, parallel-group study
- This study was originally an investigator-initiated ("real-life") study conducted in Germany (Hep-Net Cohort), and was later expanded to an industry-sponsored study conducted in India, Indonesia, Israel, Malaysia, Poland, Singapore, and Thailand (International Cohort)
- The results presented here are a subanalysis of the Asian vs white populations in the International Cohort only
  - The overall results of the REDD 2/3 study, including Hep-Net and International cohorts, were presented previously[6]
- All patients randomized in the International Cohort (n = 335) were included in the efficacy analysis
- After a 4-week screening period, patients were randomized 1:1:1 to receive
  - PEG-IFN alfa-2b (1.5 µg/kg/wk) + RBV (800-1200 mg/d) for 24 weeks (group A)
  - PEG-IFN alfa-2b (1.0 µg/kg/wk) + RBV (800-1200 mg/d) for 24 weeks (group B)
  - PEG-IFN alfa-2b (1.5 µg/kg/wk) + RBV (800-1200 mg/d) for 16 weeks (group C)
  - In all treatment arms, RBV was administered according to patient body weight (<65 kg, 800 mg/d; 65-85 kg, 1000 mg/d; >85 kg, 1200 mg/d)

Figure 1. REDD 2/3 study design



Efficacy Assessments

- The primary efficacy end point was the proportion of patients attaining SVR, defined as undetectable HCV RNA 24 weeks after the end of treatment
- Additional analyses included
  - Relapse rate: Undetectable HCV RNA at the end of treatment and detectable HCV RNA at the follow-up visit
  - Completers analysis: Patients who attended ≥80% of scheduled study visits and adhered to ≥80% of PEG-IFN alfa-2b therapy and RBV therapy
- Quantitative HCV RNA was measured by polymerase chain reaction (PCR) at screening, baseline, weeks 4 and 12, end of treatment (week 16 or week 24), and 24 weeks after the last dose
  - All HCV RNA testing was performed by local laboratories
- All efficacy measurements were performed on the intent-to-treat (ITT) population (primary population for the statistical analysis)
- Noninferiority criteria were used to determine differences in response rates between group A and group B, and group A and group C. Noninferiority was concluded if the lower bound of the one-sided 95% confidence interval of B–A or C–A in SVR rates was greater than the noninferiority margin of –10%. The Hochberg procedure was used to adjust for the multiple comparisons (B–A) and (C–A)
  - The study was not adequately powered for noninferiority comparisons within only the International Cohort

Safety Assessments

- Safety and tolerability were assessed at baseline and at each clinic visit during treatment and follow-up
- The safety population included all randomized patients who received at least 1 dose of study medication

Results

Patient Characteristics

- A total of 696 patients were randomized in the REDD 2/3 study, with 335 patients included in the International Cohort (**Table 1**)
  - 37 patients (11%) in the International Cohort were withdrawn from the study, with "lost to follow-up" being the primary reason for withdrawal (n = 7 before end of treatment; n = 14 after end of treatment)
- There was a higher proportion of patients with G3 compared with G2 (84.8% vs 15.2%)
- 57% of patients had high baseline viral load (≥600,000 IU/mL) compared to 43% with low baseline viral load (<600,000 IU/mL)

Table 1. Baseline Demographics in the International Cohort

	Group A PEG-IFN alfa-2b 1.5/RBV (24 weeks) n = 114	Group B PEG-IFN alfa-2b 1.0/RBV (24 weeks) n = 109	Group C PEG-IFN alfa-2b 1.5/RBV (16 weeks) n = 112	Total N = 335
Age, mean (SD), y	39.7 (10.4)	39.4 (11.0)	41.3 (11.1)	40.2 (10.8)
Sex, n (%)				
Male	70 (61.4)	79 (72.5)	77 (68.8)	226 (67.5)
Female	44 (38.6)	30 (27.5)	35 (31.3)	109 (32.5)
Race, n (%)				
White	57 (50.0)	50 (45.9)	51 (45.5)	158 (47.2)
Asian	57 (50.0)	59 (54.1)	61 (54.5)	177 (52.8)
HCV genotype, n (%)				
2	11 (9.6)	18 (16.5)	22 (19.6)	51 (15.2)
3	103 (90.4)	91 (83.5)	90 (80.4)	284 (84.8)
Body weight, mean (SD), kg	72.2 (15.7)	72.4 (13.7)	70.3 (14.4)	71.6 (14.6)
HCV exposure, mean (SD), y	11.9 (8.14)	10.9 (8.02)	11.3 (9.96)	11.4 (8.71)
Baseline HCV RNA, n (%)				
<600,000 IU/mL	49 (43.0)	50 (45.9)	45 (40.2)	144 (43.0)
≥600,000 IU/mL	65 (57.0)	59 (54.1)	67 (59.8)	191 (57.0)
Baseline ALT, n (%)				
<40 IU/L	16 (14.0)	10 (9.2)	14 (12.5)	40 (11.9)
≥40 IU/L	98 (86.0)	99 (90.8)	98 (87.5)	295 (88.1)

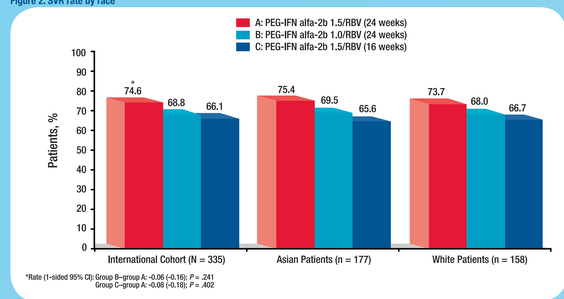
ALT = alanine aminotransferase; HCV = hepatitis C virus; PEG-IFN = peginterferon; RBV = ribavirin; RNA = ribonucleic acid; SD = standard deviation.

Efficacy

Sustained Virologic Response

- Overall, SVR was similar among treatment arms (**Figure 2**)
  - Low-dose PEG-IFN alfa-2b plus RBV for 24 weeks failed to demonstrate noninferiority compared with standard-dose PEG-IFN alfa-2b plus RBV for 24 weeks
  - Standard-dose PEG-IFN alfa-2b plus RBV for 16 weeks failed to demonstrate noninferiority compared with standard-dose PEG-IFN alfa-2b plus RBV for 24 weeks
- SVR in Asian and white patients was consistent with International Cohort results (**Figure 2**)
  - SVR was similar between Asian and white patients within treatment arms

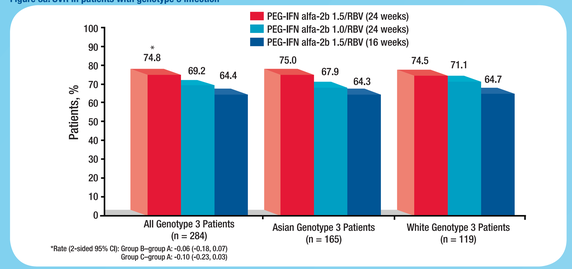
Figure 2. SVR rate by race



*Rate (1-sided 95% CI): Group B–group A: -0.06 (-0.16); *P* = .241
Group C–group A: -0.08 (-0.18); *P* = .402

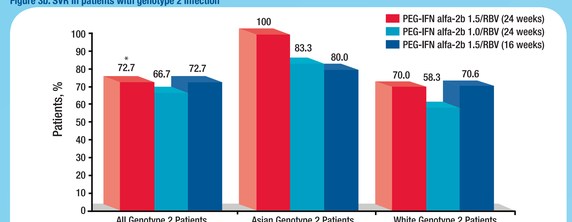
- SVR rates were similar between Asian and white patients with G3 infection (**Figure 3a**)
  - Because of the small patient numbers, no meaningful assessment of SVR by ethnicity can be made for Asian G2 patients (**Figure 3b**)

Figure 3a. SVR in patients with genotype 3 infection



*Rate (2-sided 95% CI): Group B–group A: -0.06 (-0.18, 0.07)
Group C–group A: -0.10 (-0.23, 0.03)

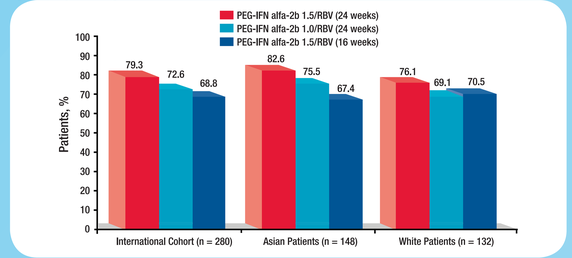
Figure 3b. SVR in patients with genotype 2 infection



*Rate (2-sided 95% CI): Group B–group A: -0.06 (-0.40, 0.28)
Group C–group A: -0.00 (-0.32, 0.32)

- Results from the completers analysis are consistent with data from the primary analysis population (**Figure 4**)

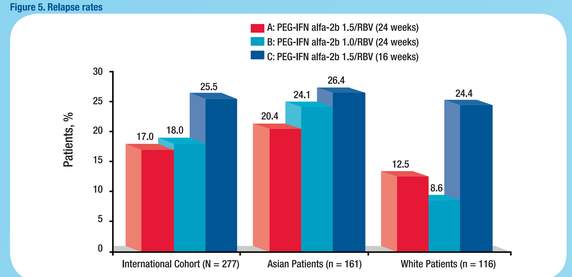
Figure 4. Completers analysis



Relapse Rate

- Overall, relapse rates were higher in the 16-week treatment arm compared with the 24-week treatment arms (**Figure 5**)
  - This result is consistent with the overall results of the REDD 2/3 study[6]
  - Relapse rates were numerically lower in white patients compared with Asian patients

Figure 5. Relapse rates



Safety

- The type and incidence of the most common treatment-emergent adverse events (TEAE) were similar across all treatment groups in the International Cohort (**Table 2**)
- The most common TEAEs were pyrexia, asthenia, headache, and myalgia
  - Within each treatment arm, TEAEs were similar in Asian and white patients
  - TEAEs in the International Cohort were similar to those observed in the overall REDD 2/3 study results

Table 2. Most Common Treatment-Emergent Adverse Events in the International Cohort*

Adverse Event, n (%)	Group A PEG-IFN alfa-2b 1.5/RBV (24 weeks) n = 114	Group B PEG-IFN alfa-2b 1.0/RBV (24 weeks) n = 109	Group C PEG-IFN alfa-2b 1.5/RBV (16 weeks) n = 112
Any adverse event	105 (92.1)	102 (93.6)	105 (93.8)
Pyrexia	65 (57.0)	68 (62.4)	75 (67.0)
Asthenia	39 (34.2)	50 (45.9)	43 (38.4)
Headache	30 (26.3)	26 (23.9)	30 (26.8)
Alopecia	27 (23.7)	17 (15.6)	20 (17.9)
Myalgia	26 (22.8)	23 (21.1)	26 (23.2)
Cough	17 (14.9)	14 (12.8)	19 (17.0)
Fatigue	16 (14.0)	16 (14.7)	8 (7.1)
Pain	16 (14.0)	13 (11.9)	12 (10.7)
Nausea	15 (13.2)	14 (12.8)	20 (17.9)
Anorexia	15 (13.2)	8 (7.3)	15 (13.4)
Arthralgia	15 (13.2)	11 (10.1)	8 (7.1)
Anemia	14 (12.3)	10 (9.2)	18 (16.1)
Diarrhea	14 (12.3)	13 (11.9)	12 (10.7)
Insomnia	14 (12.3)	10 (9.2)	8 (7.1)
Dizziness	13 (11.4)	5 (4.6)	9 (8.0)
Influenza-like illness	12 (10.5)	11 (10.1)	9 (8.0)
Injection-site erythema	11 (9.6)	15 (13.8)	7 (6.3)
Weight decrease	10 (8.8)	7 (6.4)	13 (11.6)
Dyspepsia	9 (7.9)	20 (18.3)	13 (11.6)
Irritability	8 (7.0)	13 (11.9)	10 (8.9)
Pruritus	7 (6.1)	18 (16.5)	10 (8.9)
Decreased appetite	5 (4.4)	11 (10.1)	11 (9.8)

*Occurring at a frequency of ≥10% in any treatment arm in descending order of frequency in group A.

Conclusions

1. This is the largest study to date in Asian patients with hepatitis C G3 infection
2. Overall, SVR rates were similar in Asian and white patients
3. Results for Asian and white patients with G3 infection were similar (75% and 74.5 %, respectively) and did not differ despite genetic and environmental differences
4. Overall, relapse rates in the International Cohort were higher in the 16-week arm compared with the 24-week arms
   - The lower relapse rates in white compared with Asian patients may be attributable to both environmental and genetic factors
5. Low-dose PEG-IFN alfa-2b failed to reach noninferiority compared with the standard-of-care regimen
   - However, the encouraging rates of SVR in the low-dose arm suggest that physicians can confidently reduce the PEG-IFN alfa-2b dose for patients who do not tolerate the standard-of-care regimen

References

1. Mangia A et al. *N Engl J Med.* 2005;352(25):2609-17.
2. Lagging M et al. *Hepatology.* 2008;47(6):1837-45.
3. von Wagner M et al. *Gastroenterology.* 2005;129(2):522-7.
4. Dalgard O et al. *Hepatology.* 2008;47(1):35-42.
5. Manns MP et al. *Lancet.* 2001;358(9286):958-65.
6. Manns MP et al. Presentation at the 44th Annual Meeting of The European Association for Study of the Liver, April 26, 2009, Copenhagen, Denmark.

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Disclosures

M. P. Manns consults for Bristol-Myers Squibb, Valeant, Idenix, Vertex, GlaxoSmithKline, Merck, Astra/Arrows, Boehringer Ingelheim, Gilead, Schering-Plough, Roche, and Tibotec, and receives grant/research support from Schering-Plough, Roche, Gilead, Novartis, Boehringer Ingelheim, Bristol-Myers Squibb. Y. Ilan is a member of the board for Exalenz Bioscience and Alcobra, and consults for Immuron, ENZO Biochem, and ChiasmaPharma. Y. Lurie receives grant/research support from Human Genome Sciences, Inc. A. Horban receives grant/research support from Gilead Sciences. H. Wedemeyer receives grant/research support from Roche, Schering-Plough, Bristol-Myers Squibb, Gilead, and Abbott and speaks and teaches for Roche, Schering-Plough, Novartis, Bristol-Myers Squibb, Gilead, Siemens, and Abbott. X. Yu, E. I. Chaudhri, and L. Pedicone are employees of and hold stock in Schering-Plough. R. Faruqi consulted for Schering-Plough. M. I. Merican, S. M. Abu-Mouch, A. Sood, D. N. Reddy, and S. Sharmila have nothing to disclose.

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