Boceprevir Combined with Peginterferon Alfa-2b/Ribavirin in Treatment-Naïve HCV G1 Patients with Compensated Cirrhosis: SVR and Safety Subanalyses from the Anemia Management Study

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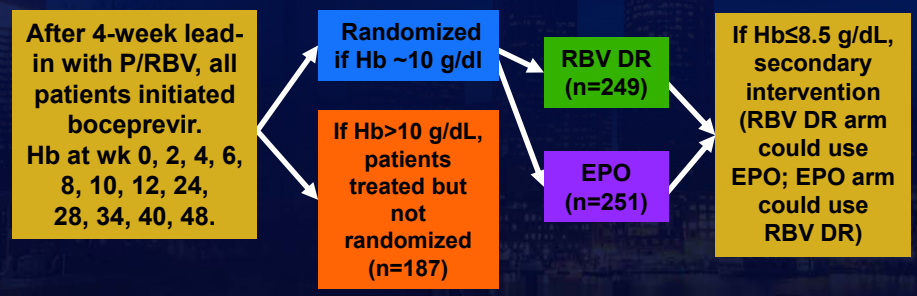
Abstract 50

Study Design



- RBV DR by increments of 200 mg at the discretion of the investigator (first increment of 400 mg if initial dose was 1,400 mg/day)
- EPO was started at 40,000 units/wk and could be modified at the investigator's discretion to doses of 20,000 to 60,000 units/wk
- If Hb≤7.5 g/dL, all study drugs were discontinued

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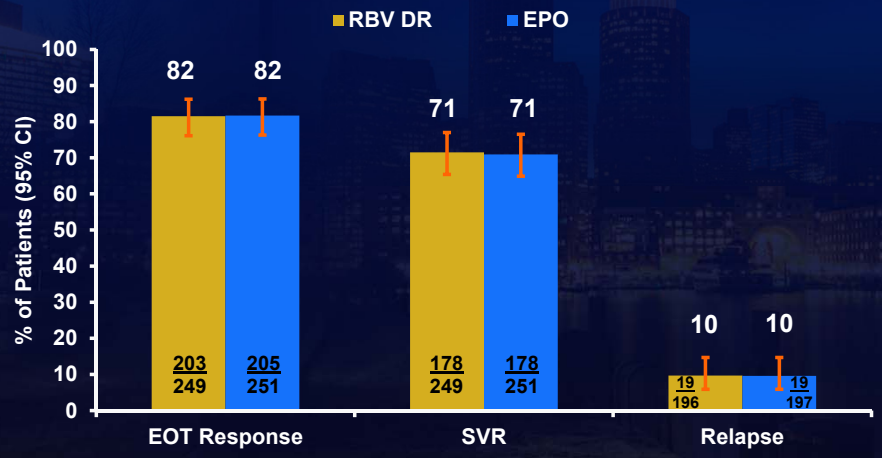
Primary Efficacy Results



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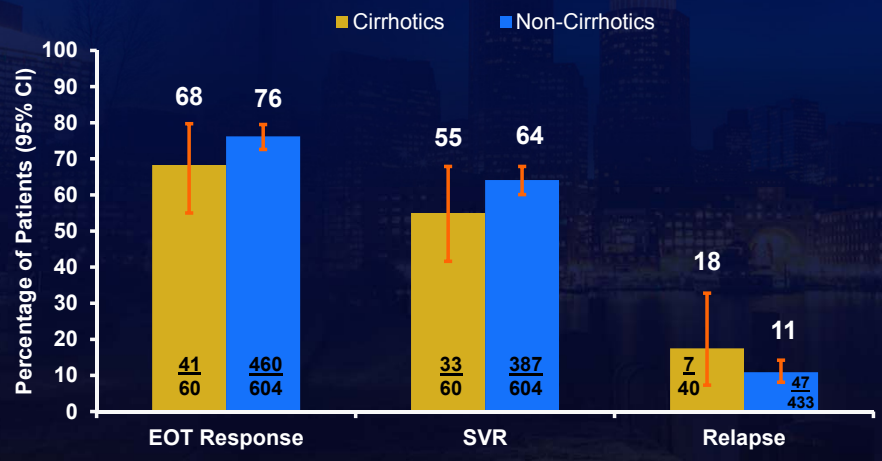
Efficacy Results in Cirrhotics and Non-Cirrhotics



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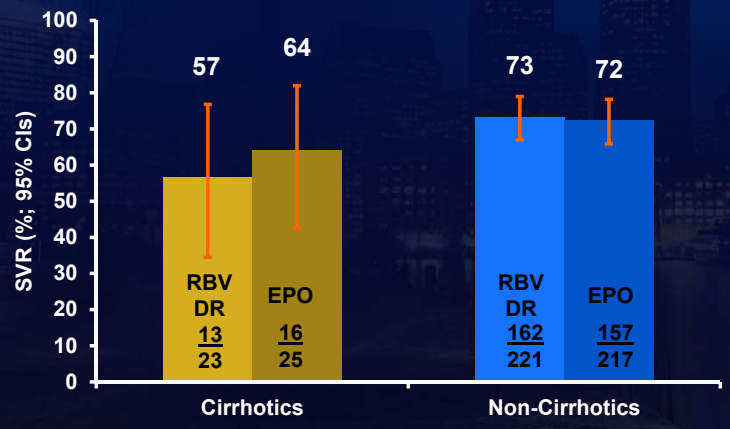
SVRs in Cirrhotics Were Similar with RBV Dose Reduction or EPO



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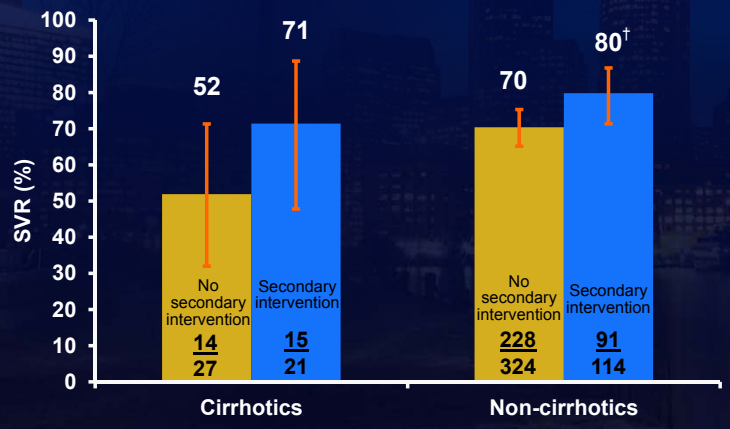
SVRs in Patients* Who Did or Did Not Receive Secondary Interventions for Anemia



†Chi-square p-value=0.051 for difference between 80% and 70%
*Excludes patients who were treated and not randomized to anemia management

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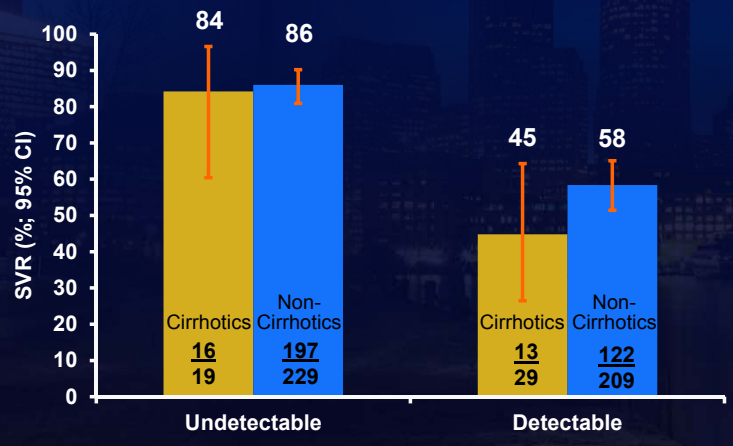
Timing and Magnitude of Ribavirin Dose Reduction do not impact SVR with Boceprevir + Peginterferon / Ribavirin in the Anemia Management Study in HCV G1 Patients

Fred Poordad, Eric Lawitz, K. Rajender Reddy, Nezam Afdhal, Christophe Hézode, Stefan Zeuzem, Samuel S. Lee, Jose Luis Calleja, Robert S. Brown, Jr, Antonio Craxi, Heiner Wedemeyer, Bruce R. Bacon, Steven L. Flamm, Weiping Deng, Kenneth Koury, Frank Dutko, Margaret Burroughs, Katia Alves, Janice Wahl, Lisa D. Pedicone, Clifford Brass, Janice Albrecht, Mark S. Sulkowski

Abstract 154

Higher SVR Rates if Undetectable HCV RNA Levels at Start Time of Primary Anemia Management



Excludes patients who were treated and not randomized to anemia management

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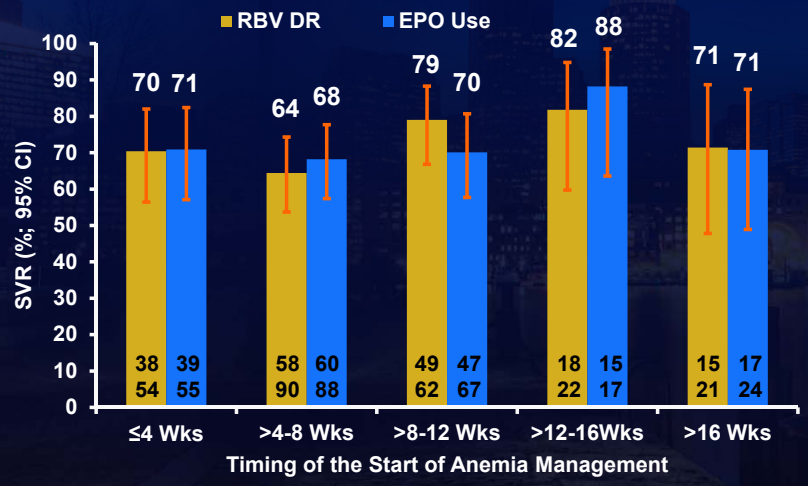
SVR Rates Did Not Vary with the Start Time of Anemia Management



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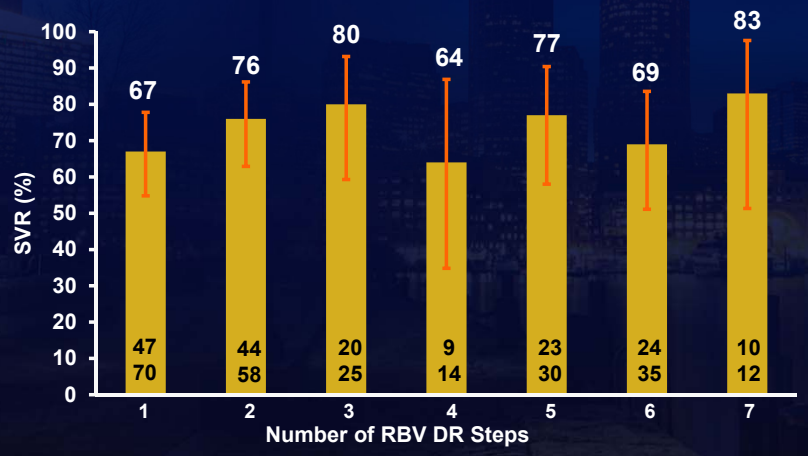
SVR Did Not Vary by Number of Steps of RBV Dose Reduction



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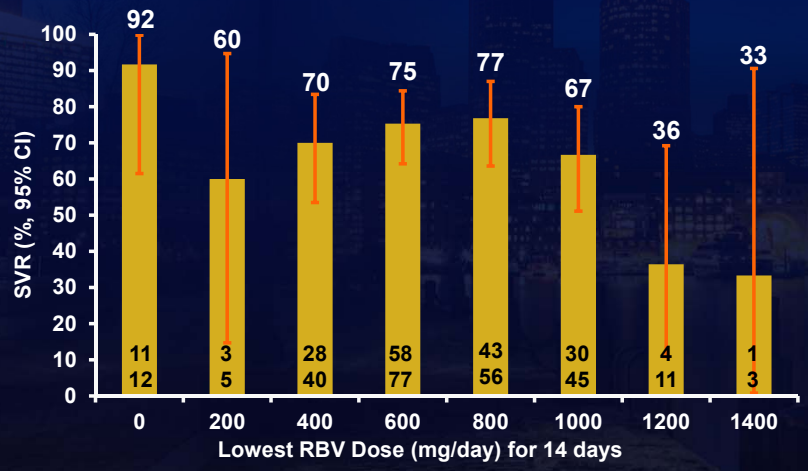
SVR Rates by Lowest RBV Dose Received for 14 days*



Poordad F, et al. 63rd AASLD; Boston, MA; November 9-13, 2012; Abst. 154.

Effectiveness of HCV Triple Therapy with Telaprevir in New York City

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Abstract

Background: Efficacy and safety in RCTs often differ from effectiveness during pragmatic use. To optimize treatment, real-life experience with telaprevir/peg-interferon/ribavirin (triple therapy) is needed.

Results: The group was 65% caucasian. Median age was 57 years. Median log_{10} HCV viral load was 6.4, 36% had advanced fibrosis/cirrhosis, 19% were treatment naïve, 24% were relapsers, 49% were non-responders (partial, null, breakthrough), and 7% were intolerant to prior treatment. An RVR occurred in 44%, an EVR in 71% and an eRVR in 38%. Two HCV RNA positive patients discontinued treatment due to rashes. By week-4, 85% had anemia, and 23% had severe anemia. Hemoglobin continued to drop, where at week 12 98% had anemia, and 38% had severe anemia. Calcium and platelets decreased significantly compared to baseline. Creatinine increased above normal in 9 patients.

Conclusions: Adverse events were surprisingly common and severe. By week-4, 23% of patients developed severe anemia, 10% had creatinine above normal, and 2% discontinued treatment due to severe rash.

Aim

To determine safety and effectiveness of triple therapy in a real-life setting.

Method

Baseline and week-4 data were retrospectively analyzed from medical records of 98 genotype 1 patients receiving care at Mount Sinai, with IRB approval. Viral load was measure with Roche Ampliprep test with a lower limit of quantification (LLOQ) of 43 IU/mL.

Undetectable HCV RNA was defined as a viral load lower than the limit of detection (LLOD). A rapid virological response (RVR) was defined as undetectable HCV RNA at 4-weeks, and an early virological response (EVR) as undetectable HCV RNA at 12-weeks. An extended rapid virological response eRVR was defined as undetectable HCV RNA at both weeks 4 and 12. RCT RVR rates were obtained from published data. Non-responders (NR) included patients with a history of being partial responders, null responders, breakthrough

FIB-4 values were calculated and values ≥3.25 indicated advanced fibrosis/cirrhosis. Anemia was hemoglobin < 13.5 g/dL (men) and < 12 g/dL (women). Severe anemia was hemoglobin < 9 g/dL and/or a decrease ≥4.5 g/dL.

Data were analyzed in SPSS. Paired t-tests, Wilcoxon signed rank tests, and Fisher's exact test were used. A p-value of 0.05 and below was considered significant. A forward selection multivariable model (p<0.1) was conducted to determine variables independently associated with virologic failure.

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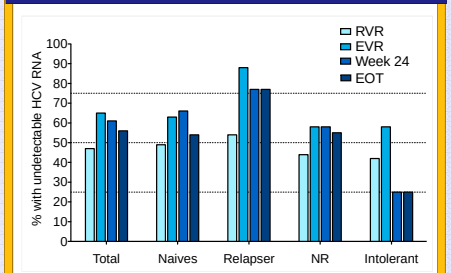
Baseline characteristics (N = 135)

Characteristic	Baseline
Median Age (IQR)	56 (51-61)
Sex- males (% of total)	92 (68%)
Race – n (% of total)	
White	91 (67%)
Black	23 (17%)
Others/Unknown	21 (16%)
Previous treatment history – n (% of total)	
Naive	35 (26%)
Relapser	26 (19%)
Non-responders	62 (46%)
Intolerant	12 (9%)
Advanced fibrosis or cirrhosis – n (% of total)	45 (33%)
HIV co-infection	16 (12%)
Diabetes	21 (16%)
Median baseline log10 HCV viral load	6.44 (5.88 – 6.86)
Median Hemoglobin (IQR) [g/dL]	14.1 (13.2 – 15.0)
Median platelets (IQR) [count/uL]	160 (121 – 202)
Median creatinine (IQR) [mg/dL]	0.94 (0.82 – 1.08)

Virologic response to triple therapy were highest among relapsers



N=135	Total%	Naïve (35)	Relapser (26)	NR (62)	Intolerant (12)
Virologic failures	36 (27%)	7 (19%)	2 (8%)	23 (37%)	4 (33%)
Discontinuations related to AE's	19 (14%)	7 (20%)	3 (12%)	5 (8%)	4 (33%)

Compared to virologic response rates in the registration trials (ADVANCE and REALIZE) RVR rates were significantly lower in naives at MSSM than patients in the ADVANCE trial (49% vs. 68%, p = 0.03), but not different in relapsers (54% vs. 70%, p = 0.13).

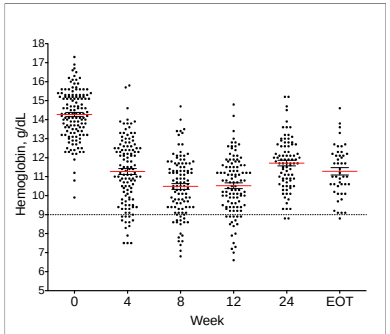
Race was independently associated with developing virologic failure within the first 48 weeks of treatment

Outcome: Virologic Failure	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Age, years	0.97	0.94 - 1.01	0.19			
Sex, Female	1.1	0.49 - 2.47	0.82			
Race, Black	4.97	1.94 - 12.78	<0.01	4.06	1.52 – 10.86	<0.01
Previously treated, Naïve	1.63	0.64 - 4.15	0.303			
APRI Score	1.03	0.85 - 1.24	0.78			
HIV co-infection	0.91	0.28 - 3.02	0.87			
Diabetes	1.12	0.40 - 3.15	0.83			
HCV RNA copies/mL ≥ 800,000	4.41	1.25 - 15.59	0.02	3.24	0.89 – 11.79	0.08

Blacks were more likely to develop virologic failure during triple therapy treatment. In a forward selection model, race was controlled by HCV RNA viral load above 800,000 copies/mL. Black race is an extremely strong predictor of developing a virologic failure. Blacks were more likely to develop virologic failure while on treatment.

Side effects including severe anemia were common during triple therapy treatment

Characteristic (units) Median (IQR)	Week 4	Week 12	Week 24	EOT
Hemoglobin (g/dL)	11.3 (9.9 – 12.5)	10.6 (9.4 – 11.6)	11.7 (10.8 – 12.7)	11.1 (10.4-12.2)
Severe anemia	33 (24%)	67 (49%)	68 (50%)	69 (51%)
Blood Transfusions	5 (4%)	12 (9%)	13 (10%)	13 (10%)
Hospitalizations	1 (1%)	8 (6%)	16 (12%)	19 (14%)
Rash	28 (21%)	59 (44%)	61 (45%)	61 (45%)
Rectal Symptoms	45 (33%)	52 (39%)	52 (39%)	53 (39%)



The red line represent median hemoglobin level at each week. The nadir for hemoglobin for the entire group occurred at week 12.

Conclusion

- The RVR rate for patients at MSSM was 47%, the EVR rate was 65%.
- The RVR rate for naives and relapsers at MSSM was significantly lower than those found in RCT's.
- Adverse events were surprisingly common and severe.
- By week-4, 24% of patients developed severe anemia, many requiring tranfusion, 10% had creatinine above normal, and 2% discontinued treatment due to severe rash.
- Differences in RCT and real life virologic response could in part be due to the differences in proportion of race.

References

1. Sherman KE, Flamm SL, Afdhal NH, *et al.* Response-Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection, *NEJM*, 2011; 365:1014-24.
2. Zeuzem S, Andreone P, Pol S, *et al.* Telaprevir for Retreatment of HCV Infection, *NEJM*, 2011;364:2417-28.