Poster 1582

Response-Guided Therapy for Boceprevir Combination Treatment? Results from HCV SPRINT-1

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Abstract

Background: HCV SPRINT-1 investigated a 4-week lead-in of PegIntron (P;1.5 µg/kg/QW) plus Ribavirin (R;800-1400 mg/day) prior to the addition of Boc (800 mg TID) for 24 or 44 weeks. Analysis of this data may lead to RGT paradigms.

Methods: Viral response was assessed by Roche TaqMan (LLD=15 IU/mL) at multiple time points including treatment weeks 4, 8, 12, 24, and 24 weeks post-treatment (sustained virologic response; SVR).

Results: Patients were all G1 (1a>1b) with 15% African-Americans, 7% cirrhotics, and 90% high viral load. W8 virology was available for all 103 patients in each arm. The majority of patients (64%) became negative by week 8 and SVR rates were similar for the long (94%) and short (82%) treatment arms (p=NS). In contrast, patients who first became negative between week 8 and 16, benefited from longer therapy (SVR 79% vs 21%; p=0.004) but represented only 18% of the population. A third group never achieved undetectable HCV RNA by W16; this group primarily comprises null responders (11/18 in 48W arm) at week 4.

	28-Week Treatment			48-Week Treatment		
Time to First Negative (wk)	Pt distribution n	%	SVR%	Pt distribution n	%	SVR%
≤8	66	64%	82% (54/66)	66	64%	94% (62/66)
>8 - ≤16	19	18%	21% (4/19)	19	18%	79% (15/19)
>16 - never	18	17%	0% (0/18)	18	17%	0% (0/18)

Conclusions: The majority of patients (64%) had undetectable HCV RNA after 4 weeks of triple therapy following the lead-in and had a high rate of SVR (82%) following a shortened 28-week treatment duration. Only 18% of patients first achieving undetectable HCV RNA after week 8 and before week 16 of therapy benefited from a longer treatment regimen of 48 weeks. These data suggest that only a minority of treatment-naïve G1 patients will require more than 28 weeks of therapy, and response-guided therapy based on week-8 viral response may be a powerful predictive tool to individualize therapy. The SPRINT-2 trial is designed to prospectively confirm this treatment paradigm.

Background

- Response-guided therapy
  - Enables clinicians to tailor duration of peginterferon + ribavirin therapy
  - Applies to all genotypes
  - Depends on viral response at various time points during treatment
  - Rapid virologic response (RVR) and complete early virologic response (cEVR) timepoints (weeks 4 and 12) guide treatment decisions in hepatitis C (HCV) patients.
- Boceprevir is an HCV NS3 protease inhibitor
- Addition of boceprevir to peginterferon + ribavirin significantly improves SVR in genotype 1 HCV-infected individuals over standard of care regardless of treatment duration (28 or 48 weeks)

Background (cont'd)

- Higher viral clearance rates observed at week 4 and 12 after addition of boceprevir to peginterferon alfa-2b + ribavirin
- Preliminary data suggests that the use of a 4-week lead-in with peginterferon + ribavirin allows
  - Achievement of steady-state drug levels
  - Alfa interferon-mediated immune system activation
  - Lower HCV burden
  - May reduce the emergence of viral resistance

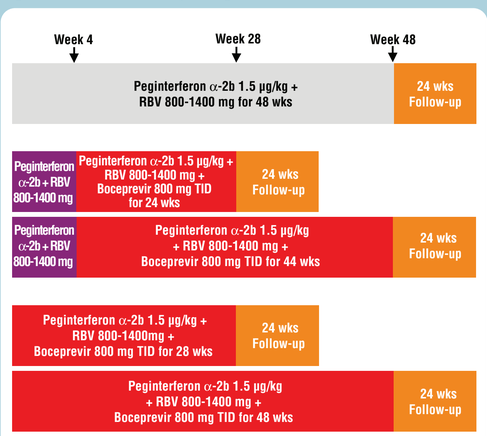
Aims

- To evaluate early viral responses (time to first undetectable HCV RNA) as predictors of duration of therapy (28 or 48 weeks) with boceprevir combination therapy
  - 4 weeks of peginterferon alfa-2b + ribavirin lead-in followed by addition of boceprevir 800 mg TID
- To explore whether the 4-week lead-in with peginterferon alfa-2b + ribavirin will predict treatment duration

Methods

- This open-label randomized trial enrolled previously untreated adults with genotype 1 HCV
- Viral response was assessed with Roche COBAS TaqMan (LLD=15 IU/mL)
- Virology assessed at multiple time points including:
  - Treatment weeks 0, 4, 8, 12, 24, and 48 weeks of boceprevir therapy
  - 24 weeks post-treatment
- Subtype assessed by Trugene assay

Figure 1. SPRINT-1 Study Design*



*Part 1.

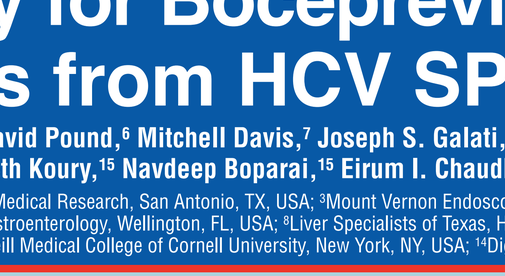
Results

Table 1. Baseline Characteristics were Similar Between Treatment Arms

	P/R 48 Control 48 wks (N=104)	P/R/B 28 wks (N=107)	P/R 4 wks → P/R/B 24 wks* (N=103)	P/R/B 48 wks (N=103)	P/R 4 wks → P/R/B 44 wks* (N=103)
Gender, %					
Male	67	59	50	61	56
Race, %					
Caucasian	80	80	83	84	83
Black	15	17	15	14	15
Mean age, yrs	48.3	46.4	47.7	46.7	47.6
Mean weight, kg	83.4	83.4	79.9	80.0	78.4
HCV subtype, %					
1a	51	63	51	53	58
1b	40	28	36	35	34
1 (no sub-type)	9	9	13	12	8
Viral load mean, log_{10} IU/mL	6.53	6.64	6.53	6.54	6.53
HCV RNA >600,000 IU/mL, %	90	92	87	91	90
Cirrhosis, %	8	7	7	9	6

*Boceprevir added to treatment regimen after 4-week lead-in of peginterferon alfa-2b = ribavirin. Source (A-3.1: Summary of Baseline Characteristics).

Figure 2. SVR by Treatment Arm



HCV RNA measured by Roche COBAS TaqMan LLD <15 IU/mL.
*p-values compared with P/R control.
†One late relapser after follow-up Week 24, not included in SVR.

- Significantly more patients in the four boceprevir groups achieved SVR than those in the control group (Figure 2)

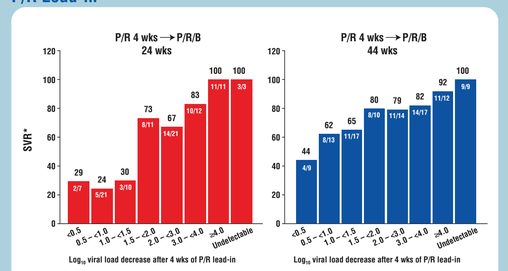
Table 2. SVR by Time to First Undetectable HCV RNA and 28 vs 48 Weeks Overall Treatment Duration

Time to first undetectable HCV RNA*	P/R Control 48 wks % (n/N)	P/R 4 wks → P/R/B 24 wks % (n/N)	P/R 4 wks →P/R/B 44 wks % (n/N)
≤4 wks	100 (8/8)	82 (54/66)	94† (62/66)
>4 wks to ≤12 wks	83 (24/29)	21 (4/19)	79‡ (15/19)
>12 wks	30 (7/23)	0 (0/1)	0 (0/1)
Never negative	0 (0/44)	0 (0/17)	0 (0/17)

*Time after peginterferon alfa-2b + RBV in control; time after boceprevir dosing in treatment arms.
†p= NS vs 28-week lead-in arm.
‡p<0.004 vs 28-week lead-in arm.

- Eighteen percent of patients first achieved viral negativity between week 4 and 12 of boceprevir triple therapy (TW8-16). These patients benefited from longer duration of therapy of 48 weeks

Figure 3. Predictability of SVR Based on Response During 4-Week P/R Lead-in

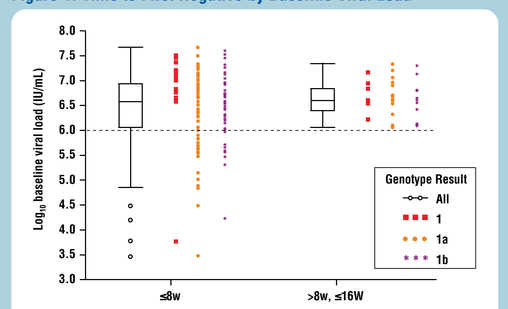


*Undetectable HCV RNA using Roche COBAS TaqMan with LLD <15 IU/mL;
7 and 2 patients were missing week 4 virology in 28 and 48 wk groups, respectively.

Table 3. Baseline Characteristics: Early vs Late Responders (28 and 48 Week Arms)

	≤4 weeks Boc	>4 wks to ≤12 weeks Boc
Gender, % (n/N)		
Female	48 (63/132)	42 (16/38)
Male	52 (69/132)	58 (22/38)
Race, % (n/N)		
White	85 (112/132)	87 (33/38)
Non-white	15 (20/132)	13 (5/38)
Mean age, yrs	47	49
Mean weight, kg	77	79
BMI	27	27
Baseline Viral Load, IU/mL		
Mean	2,893, 348	4,367, 458
Median	3,977, 855	4,221, 374
Viral Load, % (n/N)		
Low (≤600,000)	17 (22/132)	0
High (>600,000)	83 (110/132)	100 (38/38)
Genotype, % (n/N)		
1a	52 (69/132)	45 (17/38)
1b	39 (51/132)	39 (15/38)
1	9 (12/132)	16 (6/38)
Cirrhosis, % (n/N)		
Cirrhotic	5 (6/132)	5 (2/38)
Non-cirrhotic	95 (126/132)	95 (36/38)

Figure 4. Time to First Negative by Baseline Viral Load



- All patients with low viral load at baseline (≤600,000 IU/mL) who became undetectable did so by TW8

Summary

- The majority of patients achieved undetectable HCV RNA after 4 weeks of triple therapy with boceprevir (TW8)
  - These patients have high SVR rates with 28 weeks (82%) or 48 weeks (94%) of therapy
- Eighteen percent of patients first achieved viral negativity between week 4 and 12 of boceprevir triple therapy (TW8-16)
  - These late responders benefited from 48 weeks of therapy (79%) with low SVR rates with 28 weeks therapy of 21%
- All patients achieving SVR were viral negative by week 12 of triple therapy (TW16)
- Responses after the 4-week lead-in period (>1.5 log drop) may also define, less precisely, a population only needing short triple therapy
- Baseline characteristics could not define the minority of patients requiring longer therapy. However, all patients with low viral load at baseline (≤600,000 IU/mL) who became undetectable did so by TW8 and required only 28 weeks of therapy

Conclusions

- **Boceprevir significantly improves SVR**
- **Although baseline characteristics cannot predict which patients will benefit from longer therapy, in-treatment virologic responses appear likely to do so (response-guided therapy)**
- **Data from the larger phase 3 trial, HCV SPRINT-2, will more precisely define appropriate RGT for boceprevir triple therapy**

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