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EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Efficacy and safety of boceprevir plus peginterferon–ribavirin in patients with HCV G1 infection and advanced fibrosis/cirrhosis

Savino Bruno[1,*], John M. Vierling[2], Rafael Esteban[3], Lisa M. Nyberg[4], Hugo Tanno[5], Zachary Goodman[6], Fred Poordad[7,†], Bruce Bacon[8], Keith Gottesdiener[9], Lisa D. Pedicone[9,‡], Janice K. Albrecht[9], Clifford A. Brass[9,§], Seth Thompson[9], Margaret H. Burroughs[9]

[1]*Department of Internal Medicine, A.O. Fatebenefratelli e Oftalmico, Milan, Italy;* [2]*Gastroenterology and Hepatology Section, Baylor College of Medicine, Houston, TX, United States;* [3]*Internal Medicine and Liver Unit, Vall d'Hebron Hospital, Barcelona, Spain;* [4]*Kaiser Permanente, San Diego, CA, United States;* [5]*Gastroenterology and Hepatology Service, Hospital Provincial del Centenario, Rosario, Argentina;* [6]*Center for Liver Diseases, Inova Fairfax Hospital and the Betty and Guy Beatty Center for Integrated Research, Falls Church, VA, United States;* [7]*Center for Liver Disease and Transplantation, Cedars-Sinai Medical Center, Los Angeles, CA, United States;* [8]*Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, St. Louis, MO, United States;* [9]*Merck Sharp & Dohme Corp., Whitehouse Station, NJ, United States*

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Background & Aims: We assessed the safety and efficacy of boceprevir (BOC) plus peginterferon–ribavirin (PR) in patients with HCV-G1 infection and advanced fibrosis/cirrhosis (Metavir F3/F4).
Methods: In two randomized controlled studies of previously untreated and previous treatment failures, patients received a 4-week lead-in of PR followed by PR plus placebo for 44 weeks (PR48); PR plus BOC using response guided therapy (BOC/RGT); or PR plus BOC for 44 weeks (BOC/PR48).
Results: The trials enrolled 178 patients with F3/4. HCV RNA levels at week 4 and 8 were highly predictive of response. No patient with F3/4 in the PR48 arm with a <1 $\log_{10}$ decline in HCV RNA at week 4 achieved SVR, whereas those randomized to BOC/RGT or BOC/PR48 had SVR rates of 11–33% (F3) and 10–14% (F4). In these latter groups, patients with high baseline viral load (>2 $\times$ 10^6 IU/ml) had an overall SVR rate of 6% (2/33). For patients with a $\geqslant$1 $\log_{10}$ decline at week 4, SVR rates in the BOC/PR48 arm of SPRINT-2 and RESPOND-2, respectively, were 77% and 87% *vs.* 18% and 50% for PR48; SVR rates in early responders (undetectable HCV RNA at week 8) were 90–93% in the BOC/PR48 arm. Neutropenia and thrombocytopenia were more common in cirrhotics than non-cirrhotics.
Conclusions: BOC improves SVR rates in patients with F3/4, and longer treatment duration provides the most benefit. With triple therapy, SVR rates are modest in F4 patients with a <1 $\log_{10}$ decline at week 4, thus the 4-week PR lead-in aids in the assessment of early futility.

Introduction

It is well known that advanced fibrosis and cirrhosis impact the chance of sustained virologic response (SVR) using combination therapy with peginterferon–ribavirin [1,2]. While there are increased risks in treating these patients, survival rates are significantly higher in patients with cirrhosis who attain an SVR than non-responders, with respect to liver failure and hepatocellular carcinoma (HCC); thus, the primary goal of treating these patients is viral eradication [3–5].

Standard-of-care therapy for HCV genotype-1 patients has evolved from the combination of peginterferon–ribavirin to triple therapy with a direct-acting antiviral agent (DAA) that targets the HCV non-specific protein 3/4a (NS3/4A) protease combined with a peginterferon–ribavirin backbone [6–9]. Two large phase 3 trials assessed the safety and efficacy of the DAA boceprevir (BOC) in previously untreated patients (SPRINT-2) and previous treatment-failure patients (RESPOND-2) with chronic hepatitis C genotype-1 [6,7]. These studies demonstrated that the rate of SVR was significantly improved with BOC plus peginterferon–ribavirin compared to peginterferon–ribavirin alone. Common predictors of SVR in both studies included treatment with BOC,

Keywords: HCV-G1 infection; Advanced fibrosis; Cirrhosis; Boceprevir; Triple therapy.
Received 16 August 2012; received in revised form 5 November 2012; accepted 6 November 2012; available online 23 November 2012
☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2012.12.007.
* Corresponding author. Address: A.O. Fatebenefratelli e Oftalmico, Corso di Porta Nuova, 23, Milano, Italy. Tel.: +39 0263632421; fax: +39 0263632714.
E-mail address: savino.bruno@fbf.milano.it (S. Bruno).
† Present address: Texas Liver Institute/Alamo Medical Research, University of Texas, San Antonio, TX, United States.
‡ Present address: Focus Medical Communications, Parsippany, NJ, United States.
§ Present address: Novartis, East Hanover, NJ, United States.
Abbreviations: BOC, boceprevir; PR, peginterferon–ribavirin; HCV-G1, hepatitis C virus, genotype-1; RGT, response guided therapy; SVR, sustained virologic response; HCC, hepatocellular carcinoma; NS3/4A, non-specific protein 3/4a.

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low baseline viral load, and absence of cirrhosis. In addition, recent analyses demonstrated the relationship and utility of baseline factors, including *IL-28B* genotype, and their association with SVR and early viral kinetics. In these analyses, a $\geqslant 1\ \log_{10}$ decline in HCV RNA at week 4 (i.e., after the four-week lead-in period with peginterferon–ribavirin) was shown to be the strongest overall predictor of SVR [10].

The impact of advanced fibrosis/cirrhosis on SVR rates was examined in SPRINT-2 and RESPOND-2 [6,7]. Interestingly, in the peginterferon–ribavirin control arm of SPRINT-2, SVR rates were numerically higher in patients with cirrhosis (46%; 6/13) *vs.* those without cirrhosis (37%; 126/339) and were considerably higher than the 20–30% SVR rates observed in cirrhotic patients in other studies [11,12]. Patients with cirrhosis, who were randomized to a BOC-containing regimen, achieved SVR rates of 31% (5/16; BOC/RGT) to 42% (10/24; BOC/PR48). In the RESPOND-2 trial, no patients in the control arm with cirrhosis achieved SVR (0/10), whereas those in the BOC arms had SVR rates of 35% (6/17; BOC/RGT) and 77% (17/22; BOC/PR48).

Here we further explore the efficacy and safety of triple therapy in patients with cirrhosis and/or advanced fibrosis who participated in the SPRINT-2 and RESPOND-2 studies. We retrospectively analyzed data from the pivotal BOC trials to determine the relationship between on-treatment viral kinetics and SVR, and we assessed baseline characteristics to identify early futility time points in patients with advanced fibrosis/cirrhosis.

Materials and methods

SPRINT-2 (NCT00705432) and RESPOND-2 (NCT00708500) were phase III, international, randomized, double-blind, placebo-controlled studies of adult patients with chronic HCV genotype-1 infection [6,7]. The study protocols and data analysis plans are available at http://www.nejm.org. In both studies, standard therapy with peginterferon alfa-2b and ribavirin (PegIntron and Rebetol, respectively; Merck) was compared with two treatment regimens in which BOC was added after a lead-in period of peginterferon–ribavirin alone (Supplementary Fig. 1). SPRINT-2 involved 1097 previously untreated patients. RESPOND-2 involved 403 patients who had failed to attain an SVR after an adequate course of previous peginterferon–ribavirin therapy, defined as either a non-response (i.e., a decrease in the HCV RNA level of $>2\ \log_{10}$ by week 12 but with a detectable HCV RNA level during the therapy period) or relapse (i.e., an undetectable HCV RNA level at the end of treatment, without subsequent attainment of an SVR). Exclusion criteria for both studies were as previously described.

Non-cirrhotic patients were required to have a liver biopsy performed within 3 years of study entry. A biopsy demonstrating cirrhosis was acceptable regardless of the length of time since biopsy. All liver-biopsy specimens from both studies were assessed for Metavir fibrosis scores by the same pathologist (author ZG) who was unaware of treatment assignment. Possible Metavir scores were as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis.

Peginterferon alfa-2b and BOC were administered as previously described. Patients were randomly assigned to one of three treatment groups. In all groups, peginterferon alfa-2b and ribavirin (PR) were administered for 4 weeks (the lead-in period). Subsequently, the first group received placebo plus PR for 44 weeks (abbreviated as PR48); the second group received BOC plus PR using response-guided therapy (abbreviated as BOC/RGT); and the third group received BOC plus PR for 44 weeks (abbreviated as BOC/PR48). In the BOC/RGT of both studies, the duration of therapy was based on a prespecified decision point, whereby those with undetectable HCV RNA at week 8 were eligible for shorter therapy (Supplementary Fig. 1).

Plasma HCV RNA levels were measured with the use of the TaqMan 2.0 assay (Roche Diagnostics), which has lower limits of quantification and detection of 25 and 9.3 IU/ml, respectively; the lower limit of detection was used for the definition of undetectable at all time points. Both studies prospectively consented patients for pharmacogenomic testing and collected samples for biomarker identification, as described previously [10]. Population sequencing was used to detect resistance-associated amino acid variants (RAVs), previously identified to confer reduced susceptibility to BOC [13–16].

Efficacy analyses

In both studies, the primary end point was SVR, which was defined as undetectable HCV RNA at follow-up week 24. If data were missing at follow-up week 24, then follow-up week 12 data was carried forward, if available. Analysis of SVR by fibrosis score subgroups, formed by categorizing as F0/1/2/3 (non-cirrhosis) *vs.* F4 (cirrhosis) and F0/1/2 (non-advanced fibrosis) *vs.* F3/4 (advanced fibrosis), was pre-specified in the Data Analysis Plan and has been previously reported [6,7].

For the current report, we performed *post hoc* analyses which assessed SVR rates by Metavir score for patient subgroups determined by (1) the week 4 response to interferon (poor response [$<1\ \log_{10}$ decline] *vs.* good response [$\geqslant 1\ \log_{10}$ decline]), (2) the treatment week 8 response (undetectable [early responder] *vs.* detectable [late responder]), (3) the historical response to treatment (prior non-response *vs.* prior relapse) for patients in RESPOND-2, and (4) the *IL-28B* rs12979860 genotype (CC, CT, or TT). For the analysis of the week 4 response, further stratification by baseline HCV viral load and HCV genotype was also performed. These analyses were based on a modified intent-to-treat population, which included all patients who completed the lead-in period of treatment, received at least one dose of boceprevir or placebo, and had a baseline Metavir score available. No imputations were done for subgroups where covariate information (e.g., fibrosis score) was missing. No inferential statistics were planned for these subgroups; statistical comparisons on baseline characteristics, using the Chi-square test for categorical variables, and independent samples *t*-test for continuous variables, should be considered exploratory.

Safety analyses

Adverse events (AE) were graded by the investigators according to a modified World Health Organization grading system. Non-life-threatening hematologic AEs were managed by means of dose reduction or administration of hematopoietic growth factors (or both). Data for AEs and hematologic events by WHO grade include a phase 2 study in previously untreated patients (SPRINT-1; NCT00423670) where patients were stratified by cirrhosis *vs.* no cirrhosis [17].

Results

Patient characteristics

Of the 1500 patients enrolled in SPRINT-2 and RESPOND-2, 1435 (96%) had non-missing data for baseline Metavir fibrosis score; 178 (12%) had advanced fibrosis/cirrhosis (Metavir score F3/4) and 102 of these patients (7%) had cirrhosis (Metavir score F4). In SPRINT-2, patients with advanced fibrosis/cirrhosis were older and more patients with advanced fibrosis/cirrhosis were male (Table 1). There was also a higher proportion of patients with advanced fibrosis/cirrhosis from Latin America and North America, compared to Europe, although Latin Americans represented only 2% of the study population. In RESPOND-2, patients with advanced fibrosis/cirrhosis had a higher mean BMI and lower baseline viral load than patients without advanced fibrosis/cirrhosis. Baseline characteristics of patients with cirrhosis showed similar trends (Supplementary Table 1). *IL-28B* genotype data at the rs12979860 locus were available for 631 (60%) and 243 (65%) of SPRINT-2 and RESPOND-2 patients, respectively (Table 1). In SPRINT-2, the CC, CT, and TT genotypes were equally distributed between those with and without advanced fibrosis/cirrhosis. In RESPOND-2, the CC genotype was present in 32% of patients with advanced fibrosis/cirrhosis *vs.* 22% of those without advanced fibrosis/cirrhosis.

Table 1. Baseline patient characteristics, by Metavir score.

	SPRINT-2		RESPOND-2	
	F0/1/2	F3/4	F0/1/2	F3/4
	N = 960	N = 100	N = 297	N = 78
	n/m[a] (%)	n/m[a] (%)	n/m[a] (%)	n/m[a] (%)
Sex				
Male	561/632 (89)	71/632 (11)	192/249 (77)	57/249 (23)
Female	399/428 (93)	29/428 (7)	105/126 (83)	21/126 (17)
p value	0.01		0.16	
Race				
Black	139/154 (90)	15/154 (10)	42/47 (89)	5/47 (11)
Non-Black	821/906 (91)	85/906 (9)	255/328 (78)	73/328 (22)
p value	0.88		0.07	
Age (yr), mean ± SD	48.9 ± 9.5	52.1 ± 7.7	52.6 ± 7.7	53.7 ± 7.5
p value	<0.001		0.28	
BMI, mean ± SD	27.5 ± 5.0	28.4 ± 5.2	28.0 ± 4.3	29.8 ± 5.2
p value	0.11		0.001	
Region				
North America	689/773 (89)	84/773 (11)	207/264 (78)	57/264 (22)
Europe	243/255 (95)	12/255 (5)	89/110 (81)	21/110 (19)
Latin America	28/32 (87)	4/32 (13)	1/1 (100)	0/1 (0)
p value	0.01		0.76	
HCV subtype[b]				
1a	596/667 (89)	71/667 (11)	172/219 (79)	47/219 (21)
1b	330/356 (93)	26/356 (7)	124/154 (81)	30/154 (19)
p value	0.21		0.53	
Viral load				
>800,000 IU/ml	820/906 (91)	86/906 (9)	264/326 (81)	62/326 (19)
≤800,000 IU/ml	140/154 (91)	14/154 (9)	33/49 (67)	16/49 (33)
p value	0.87		0.03	
Prior response, n/N[c] (%)			N = 297	N = 78
Non-response	n.a.	n.a.	103 (35)	28 (36)
Relapse	n.a.	n.a.	194 (65)	50 (64)
IL28B rs12979860 genotype[d], n/N (%)	N = 577	N = 54	N = 190	N = 53
CC	176 (31)	15 (28)	41 (22)	17 (32)
CT	296 (51)	27 (50)	123 (65)	26 (49)
TT	105 (18)	12 (22)	26 (14)	10 (19)

n.a., not available.
[a]n, patients with indicated fibrosis score; m, patients with indicated characteristics.
[b]NS5B sequencing by Virco. Data missing for 37 patients in SPRINT-2 and 2 in RESPOND-2.
[c]n, patients with indicated characteristic; N, patients with indicated fibrosis score.
[d]Includes patients who consented to genomic testing and completed the lead-in phase.

Baseline and on-treatment predictors of SVR

The $\log_{10}$ decline in HCV RNA at week 4, the end of the lead-in period, was highly predictive of response, in patients with advanced fibrosis/cirrhosis. In both studies, none of the patients with advanced fibrosis/cirrhosis in the PR48 control arm with <1 $\log_{10}$ decline in HCV RNA at week 4 achieved SVR (Fig. 1A). Those randomized to a BOC-containing regimen had SVR rates ranging from 13% (2/16) to 25% (3/12). Patients with ⩾1 $\log_{10}$ decline in HCV RNA at week 4 had substantially higher SVR rates than those with <1 $\log_{10}$ decline (Fig. 1B). In both studies, F3 patients who received PR had SVR rates of 40–50%; however in RESPOND-2, none of the patients with cirrhosis who received PR achieved SVR (0/6). Patients with advanced fibrosis/cirrhosis in the BOC/PR48 arm had higher SVR rates (77% (920/26) in SPRINT-2; 87% (20/23) in RESPOND-2) than patients in the BOC/RGT arm (52% (11/21) and 55% (11/20), respectively).

Baseline viral load appeared to impact rates of SVR in patients who received BOC and who had a <1 $\log_{10}$ HCV RNA decline at week 4. In SPRINT-2, patients who had a viral load >2,000,000 IU/ml had SVR rates of 5% (1/19); the corresponding SVR rate in RESPOND-2 was 7% (1/14). Combining both studies, SVR was attained in 6% (2/33) of these patients, 4% (1/26) with HCV genotype-1a and 14% (1/7) with genotype-1b, respectively, corresponding to a negative predictive value of 94%. Conversely, for those patients with a <1 $\log_{10}$ HCV RNA decline at week 4 but baseline viral load ⩽ 2,000,000 IU/ml, SVR rates were 43% (3/7) in SPRINT-2 and 60% (3/5) in RESPOND-2. Of the 6 patients

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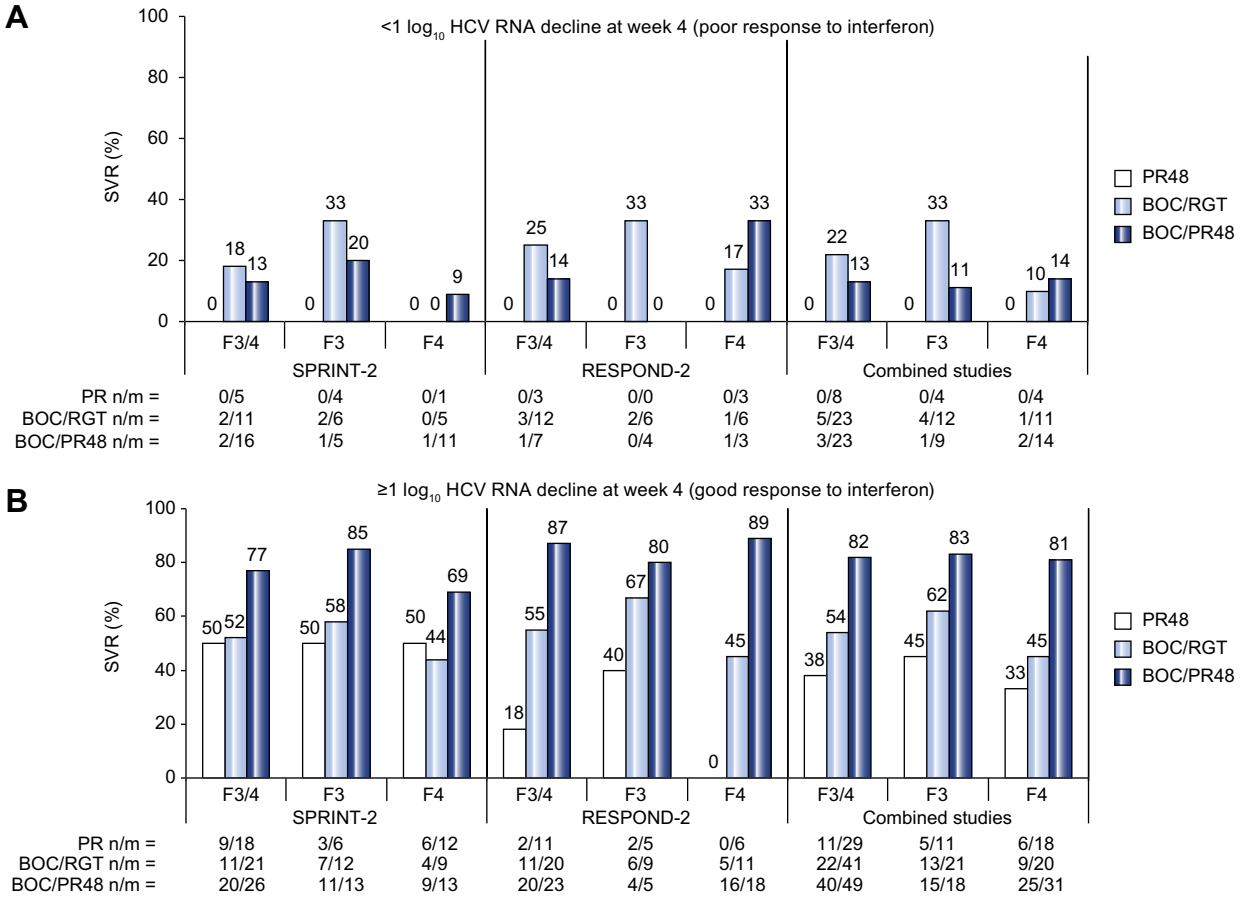

Fig. 1. Sustained virologic response (SVR) in patients with advanced fibrosis/cirrhosis with (A) poor response *vs.* (B) good response to interferon.

who achieved SVR, 2 were HCV genotype-1a (both in SPRINT-2) and 4 were genotype-1b (1 in SPRINT-2; 3 in RESPOND-2).

In the response-guided-therapy groups of both studies (BOC/RGT), the duration of therapy was based on a prespecified decision point whereby those patients with undetectable HCV RNA at week 8 were eligible for shorter therapy. For patients with advanced fibrosis/cirrhosis, we utilized treatment week 8 to define 'early responders' (HCV RNA undetectable at week 8) and 'late responders' (HCV RNA detectable at week 8). In both studies, for patients with advanced fibrosis/cirrhosis, SVR rates in early responders were more than three times higher than in late responders (Fig. 2) and were comparable to SVR rates in patients without advanced liver disease (Supplementary Fig. 2).

For patients in RESPOND-2, we also examined SVR rates based on historical response to treatment (i.e., prior non-response *vs.* prior relapse). Among patients with advanced fibrosis/cirrhosis, those with prior non-response had SVR rates of 0% (0/5), 30% (3/10), and 46% (6/13) in the PR48, BOC/RGT, and BOC/PR48 arms, respectively (Supplementary Fig. 3). The corresponding SVR rates for those with prior relapse were 20% (2/10), 50% (11/22), and 83% (15/18) in the PR48, BOC/RGT, and BOC/PR48 arms, respectively.

An analysis of SVR rates by *IL-28* genotype was limited due to the small number of patients (Supplementary Table 2). In SPRINT-2, only 5 cirrhotic patients had the favorable CC genotype (2 PR, 1 BOC/RGT, and 2 BOC/PR48) and each of these patients achieved SVR. The CT genotype was the most common, and SVR rates were 17% (PR48, 1/6), 33% (BOC/RGT, 2/6) and 0% (BOC/PR48, 0/4). Eight patients had the less favorable TT genotype (1 PR, 3 BOC/RGT, and 4 BOC/PR48) and the corresponding SVR rates were 100% (1/1), 0% (0/3), and 50% (2/4). In RESPOND-2, 8 cirrhotic patients had the CC genotype (0 PR, 4 BOC/RGT, and 4 BOC/PR48) and the SVR rate was 75% in each of the BOC arms. SVR rates for cirrhotic patients with the CT genotype were 0% (PR48, 0/5), 33% (BOC/RGT, 2/6), and 86% (BOC/PR48, 6/7). Ten patients had the less favorable TT genotype (2 PR; 2 BOC/RGT; 6 BOC/PR48) and the corresponding SVR rates were 0% (0/2), 50% (1/2), and 67% (2/6).

Resistance

Among patients in SPRINT-2 who did not achieve SVR and had post-baseline samples sequenced, RAVs were detected in 56% of patients (52/94) who received BOC/RGT and 53% of those (50/94) who received BOC/PR48. Among patients in RESPOND-2 who did not achieve SVR and had post-baseline samples sequenced, RAVs were detected in 43% (20/46) of those who received BOC/RGT and 48% (19/40) who received BOC/PR48. The proportion of patients with advanced fibrosis/cirrhosis who developed RAVs, stratified by the week 4 response (<1 log *vs.* $\geqslant$1 $\log_{10}$ decline), is shown in Fig. 3. In SPRINT-2, RAVs were more frequently detected in patients with poor response to interferon (86%; 18/21) *vs.* those with good response to interferon (50%; 7/14). In RESPOND-2, RAVs

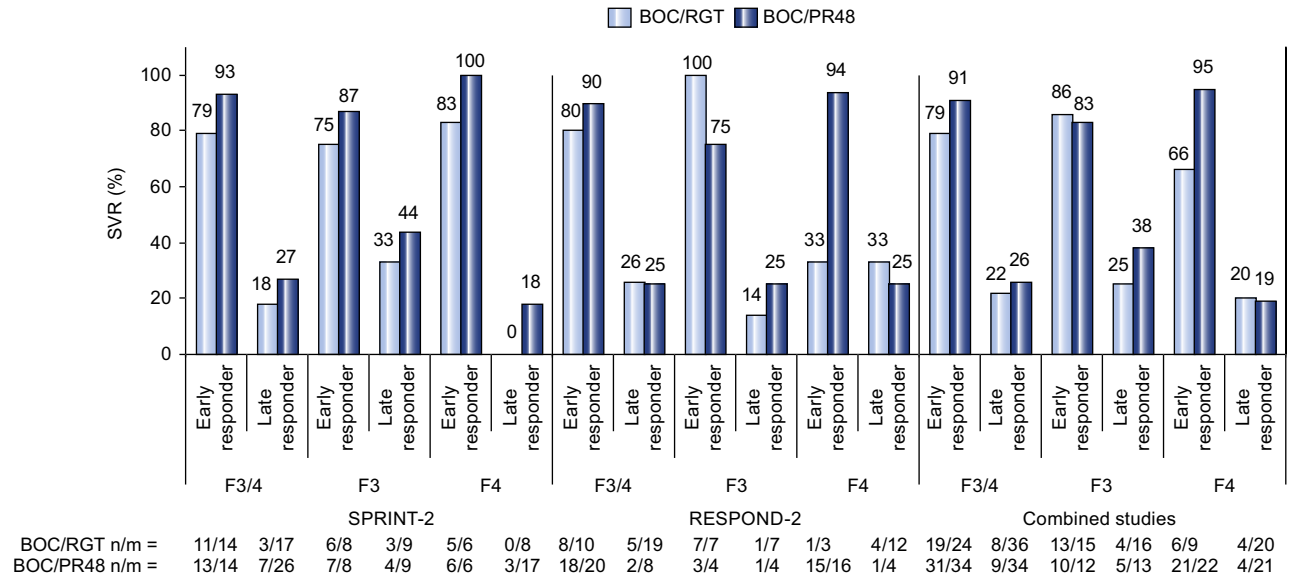

Fig. 2. Sustained virologic response (SVR) by Metavir score in early responders (undetectable HCV RNA at week 8) *vs.* late responders (detectable HCV RNA at week 8).

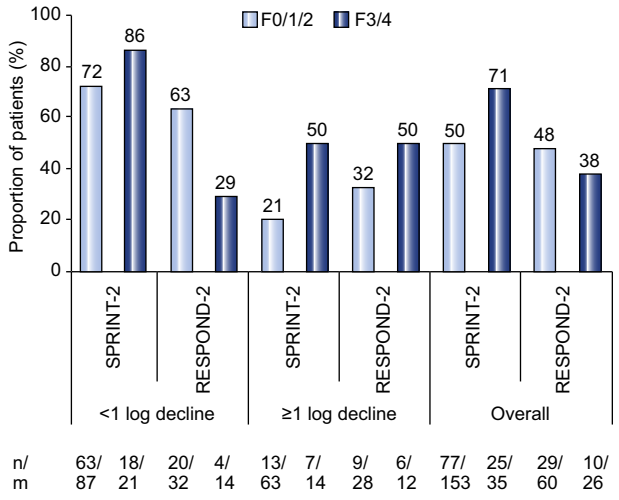

Fig. 3. Resistance-associated variants among patients randomized to boceprevir who did not achieve SVR, by Metavir score and week 4 response (<1 log_{10} *vs.* ⩾1 log_{10} decline).

were detected in 29% (4/14), and 50% (6/12) of patients with poor *vs.* good response to interferon.

Safety

Clinical manifestations of liver disease were more frequently reported in patients with cirrhosis than in patients without cirrhosis; however, few events relating to the clinical progression of liver disease (ascites, esophageal varices, portal hypertension, and hepatocellular carcinoma) were reported. In the BOC arms (combined studies), serious AEs occurred in 16% of patients with cirrhosis (and in 11% of those without cirrhosis) and in most cases were associated with advancing CHC (e.g., HCC, esophageal variceal hemorrhage) or have been reported with PR backbone therapy (e.g., anemia, gastritis, pancreatitis, hyperglycemia, diarrhea, dehydration). Regardless of the degree of fibrosis/cirrhosis, the most common AEs were fatigue, anemia, nausea, and headache (Table 2). Notable treatment-related events, that occurred more frequently in the BOC/PR group than the PR group (>10% difference), were anemia and dysgeusia.

The median treatment duration in cirrhotic patients was 175 days in the PR control arms and 239 days in the BOC/PR arms. There was a clear shift to lower hemoglobin concentration with BOC/PR *vs.* PR control (Fig. 4A). To a lesser extent, there were also shifts in neutrophils and platelets when comparing BOC/PR arms to PR control (Fig. 4B and C). Other laboratory results (including lymphocytes, see Fig. 4D) were similar for cirrhotic and non-cirrhotic patients. Of the 143 patients with cirrhosis in SPRINT-1, SPRINT-2 and RESPOND-2, 42% (60/143) received erythropoietin for the management of anemia compared with 38% of patients without cirrhosis (719/1887); 4% (6/143) of patients with cirrhosis received a transfusion compared with 2% (30/1887) of patients without cirrhosis.

Discussion

Several studies of PR therapy have reported that achievement of an SVR in patients with cirrhosis was associated with reversal of fibrosis and a reduction in the incidence of hepatic decompensation and liver-related death compared with patients who did not achieve SVR [12,18,19]. In SPRINT-2 and RESPOND-2, pretreatment liver biopsy specimens were scored by a single pathologist using Metavir criteria, allowing a robust analysis of safety and efficacy in well-characterized patients with compensated advanced liver disease. Interferon responsiveness, as demonstrated by the week 4 lead-in response, was an important predictor of SVR in these patients. As was found in the overall study population, SVR was more likely in patients with advanced

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Table 2. Adverse event (AE) summary by Metavir score, SPRINT-2 and RESPOND-2 combined, boceprevir treatment groups combined.

	Metavir score					
	F0/1/2		F3/4		F4†	
	Control N = 389	BOC N = 868	Control N = 39	BOC N = 139	Control N = 31	BOC N = 112
Any AE – No. (%)	380 (98)	862 (99)	39 (100)	138 (99)	31 (100)	112 (100)
Serious AE[a]	32 (8)	99 (11)	3 (8)	21 (15)	3 (10)	18 (16)
Death	4 (1)	3 (<1)	0	0	0	0
Study drug discontinuation due to AE	56 (14)	116 (13)	2 (5)	17 (12)	3 (10)	16 (14)
Dose modification due to AE[b]	83 (21)	301 (35)	16 (42)	57 (41)	13 (42)	44 (39)
Most common AEs (incidence ≥30% in any arm)						
Fatigue	224 (58)	475 (55)	22 (56)	78 (56)	17 (55)	67 (60)
Headache	172 (44)	386 (44)	13 (33)	59 (42)	10 (32)	42 (38)
Nausea	158 (41)	396 (46)	18 (46)	53 (38)	15 (48)	45 (40)
Insomnia	120 (31)	282 (32)	11 (28)	42 (30)	9 (29)	36 (32)
Pyrexia	123 (32)	269 (31)	12 (31)	47 (34)	9 (29)	35 (31)
Anemia	107 (28)	411 (47)	10 (26)	73 (53)	7 (23)	60 (54)
Chills	109 (28)	293 (34)	10 (26)	51 (37)	9 (29)	45 (40)
Diarrhea	81 (21)	207 (24)	7 (18)	39 (28)	6 (19)	35 (31)
Dysgeusia	64 (16)	352 (41)	7 (18)	61 (44)	3 (10)	48 (43)

†Includes patients who participated in SPRINT-1.
[a]Deaths are also included in Serious AE count.
[b]If a subject had both a dose modification and study drug discontinuation due to AE, then the subject was counted only in the study drug discontinuation due to AE category.

fibrosis/cirrhosis who had $\geqslant 1.0\ \log_{10}$ decline in HCV RNA at week 4 (the end of the PR lead-in phase), and in those with undetectable HCV RNA at week 8 (early responders).

As previously reported, the clearest benefit of adding BOC to PR therapy was seen in patients with previous treatment failure, where SVR rates in patients with cirrhosis who received BOC in addition to PR were 35–77%, compared to 0% for PR alone [7]. In previously untreated patients with cirrhosis, SVR rates were not substantially different between the three treatment groups, partly because of the high response rate in the control group [6]. The high SVR rate in the PR control patients of SPRINT-2 could have been due, in part, to differences in *IL-28B* genotype across the three arms; however, only 29 of the 53 (55%) patients with cirrhosis in SPRINT-2 consented to genomic testing, so we cannot determine whether the 13 patients who received PR control had a higher proportion of the favorable CC genotype compared with the BOC/RGT and BOC/PR48 arms, as 4 patients had missing data for *IL-28B*. Nonetheless, our study provides important new information regarding predictors of SVR in this patient population. SVR rates, in patients with advanced fibrosis/cirrhosis with $\geqslant 1\ \log_{10}$ decline in HCV RNA after the 4-week lead-in, were 77–87% after completion of 44 weeks of triple therapy, compared with 50% for 48 weeks of PR therapy alone. Those with undetectable HCV RNA at week 8 (corresponding to 4 weeks of triple therapy) had SVR rates of 79–80% (BOC/RGT) and 90–93% (BOC/PR48). Thus, early viral kinetics can be used to predict the response to treatment in patients with cirrhosis.

Unlike PR therapy, virologic failure on protease inhibitor-based combination therapy may result in selection of viral variants with resistance to protease inhibitors. Such resistance may emerge early during treatment, thus it is important to identify which patients have little chance of achieving SVR. Among patients in SPRINT-2 and RESPOND-2 with advanced fibrosis/cirrhosis, who did not achieve SVR and had post-baseline samples sequenced, RAVs were detected in approximately 50% of the cases. In SPRINT-2, RAVs were more frequently detected in patients with $<1\ \log_{10}$ HCV RNA decline at week 4. In patients with cirrhosis, none of the patients with $<1\ \log_{10}$ decline at week 4 who received PR alone achieved SVR, whereas those who received triple therapy achieved SVR rates of 10–14%. Thus with triple therapy, the 4-week lead-in helps define patients in whom the addition of DAA is less effective; however, the week 4 HCV RNA level alone may not be sufficient to determine which patients should stop therapy early. In our study, among patients with advanced fibrosis/cirrhosis, who had $<1\ \log_{10}$ decline in HCV RNA at week 4 and baseline viral load >2,000,000 IU/ml, only 6% (2/33) achieved SVR (combined studies). However, the reliability of this parameter for stopping therapy by week 4 in cirrhotic patients should be confirmed in other studies before it can be adopted in clinical practice.

The present analysis suggests that patients with cirrhosis tolerated a three-drug regimen, albeit with a higher frequency of anemia, neutropenia, and thrombocytopenia than those treated with PR alone. Anemia in cirrhotics was managed with somewhat more erythropoietin use (42% *vs.* 38%) and transfusions (4% *vs.* 2%) than in patients without cirrhosis. Patients with cirrhosis who received BOC/PR had more serious AEs and discontinuation of study medication due to AEs than those who received PR, but the majority of patients were able to complete treatment. Dose modifications due to AE occurred with similar frequency in BOC/PR-treated and PR-treated subjects with cirrhosis.

There are several limitations to our analyses. The analyses were exploratory, using data from studies that were not designed to compare treatment effects based on cirrhosis/fibrosis status. Furthermore, it is well-recognized that rare and potentially serious AEs may not emerge during clinical trials, and the number of

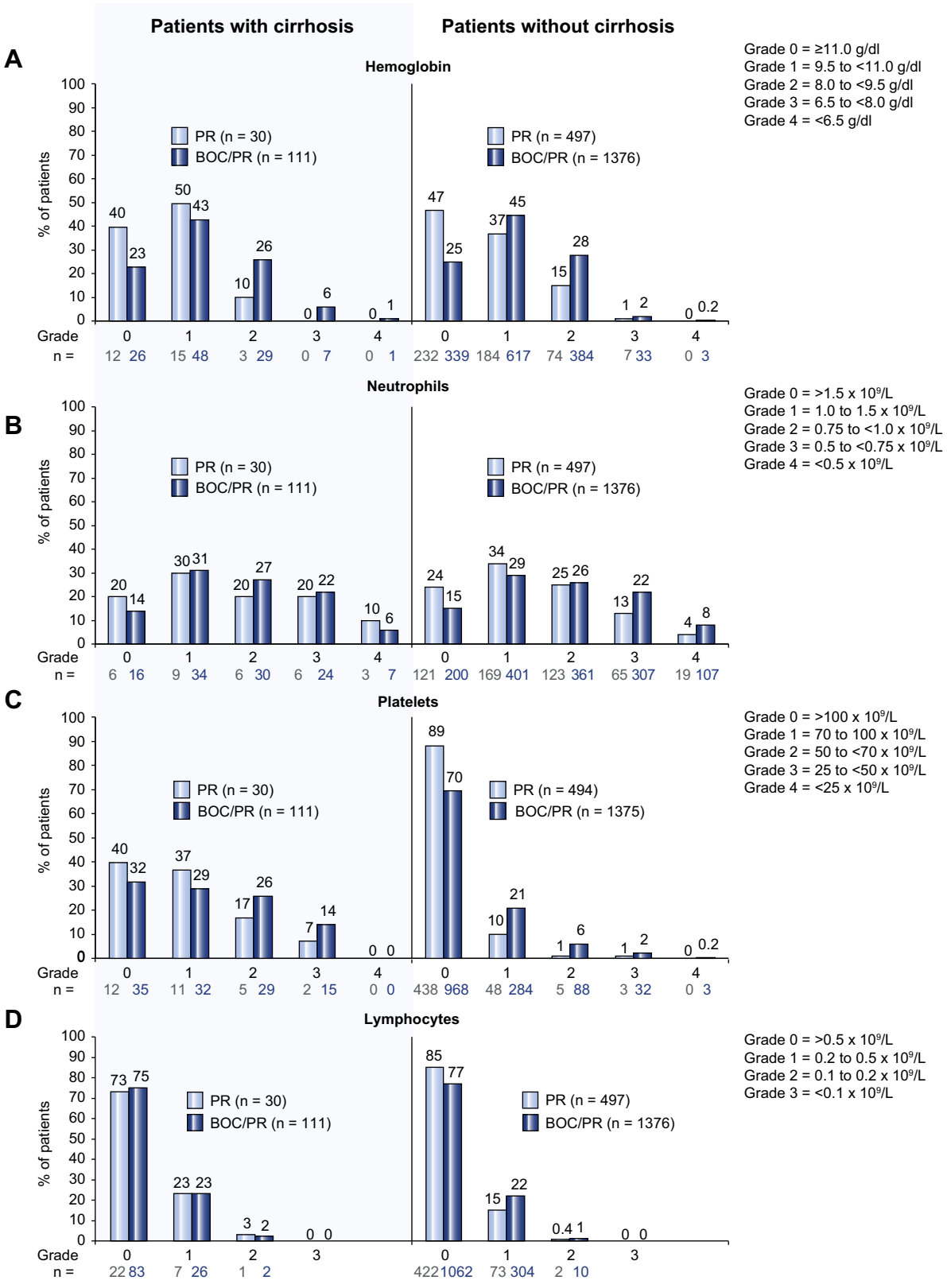

Fig. 4. Nadir values for hematologic parameters during treatment, by cirrhosis status (with *vs.* without), including patients who participated in SPRINT-1.

patients with cirrhosis and/or advanced fibrosis in the SPRINT-2 and RESPOND-2 studies was small, limiting the certainty of our conclusions. Nonetheless, the data from these trials provide important information to clinicians when treating these patients, and complement other safety and efficacy studies in patients with compensated cirrhosis. For example, the Compassionate Use of Protease Inhibitors in Viral C Cirrhosis (CUPIC) was established prior to the licensing of telaprevir (TVR) and BOC in France, in order to provide early access to the new drugs in patients with hepatitis C, judged to be in urgent need of treatment [20]. Early access was provided to TVR or BOC for patients with compensated cirrhosis, HCV genotype-1 infection and prior relapse or partial response to PR. It is likely that many patients treated in CUPIC would not have met inclusion criteria for TVR or BOC pivotal trials; for example, 20% of patients in CUPIC had platelet counts below the inclusion criteria for BOC trials. In *interim* analyses of the CUPIC patient cohort, who received at least 16 weeks of BOC or TLV, rates of virologic response after 16 weeks of treatment were high, but triple therapy was associated with increased rates of SAEs (30–51%) compared to those reported in phase 3 trials. These findings, along with our subgroup analysis, which exclusively focused on the hardest-to-treat CHC patient population, may represent reference standards in the evaluation of future DAAs.

In summary, the results of these subgroup analyses suggest that BOC improves SVR rates in patients with advanced fibrosis/cirrhosis and that the longer treatment duration (4 weeks of PR plus 44 weeks of BOC plus PR) provides the greatest benefit to these patients. In this very difficult-to-treat subset of patients receiving triple therapy with BOC, the 4-week lead-in defines those in whom the addition of BOC results in low SVR rates. Discontinuing therapy in these patients would avoid the risk of potential AEs associated with first generation PIs, as well as those associated with continued exposure to interferon. Although the risk of AEs should be balanced with the known increased survival rates of cirrhotic patients who attain an SVR, the use of a 4-week lead-in (per the current recommendations for BOC treatment) to characterize IFN sensitivity is a powerful prognostic tool. The degree of HCV RNA log decline after a 4-week lead-in provides important information for determining whether the benefits of initiating first generation PI therapy outweigh the risks for each individual patient.

Financial support

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., provided all funding for this study.

Conflicts of interest

S. Bruno: grants and research support from Merck and Roche; advisory committees for Merck; speaking and teaching for Roche, Merck, and Bristol Myers Squibb.

J. Vierling: research grants, consulting fees or honorarium, and support for travel to meetings for the study or other purposes from Merck; consultancy fees from Bristol Myers Squibb, Gilead, Vertex and Roche; expert testimony for the FDA and CDC; grants/grants pending from Excalenz, Hyperion, Ocera, Ikaria, Intercept, Mochida, Sundise, Abbott, Conatus, Gilead, GlobeImmune, Hyperion, Idenix–Novartis, Novartis, Pharmasset, Pfitzer, Roche, Vertex, Zymogenetics, Bristol Myers Squibb, and Johnson and Johnson; payment for CME lectures including service on speakers bureaus from Chronic Liver Diseases Foundation; patents (planned, pending, or issued) for HCV riboprobes and S.C.I.D mouse model; royalties from Liver Immunology 2nd Edition, Gershwin, Vierling and Manns, eds.; travel/accommodations/meeting expenses from NIH, NIDDK; is the Digestive Diseases Week Secretary–Treasurer, and is a member of Clinical Research Centers of America.

R. Esteban: member of speakeŕs bureau or advisor for Schering-Plough (now part of Merck), Gilead, Novartis, Bristol-Myers-Squibb, and GlaxoSmithKline.

L. Nyberg: research grants from Merck, Gilead, Abbott, Pharmasset, Roche/Genentech/Anadys, Vertex, Bristol-Myers-Squibb, Human Genome Sciences, and Idenix/Novartis; Speakers Bureau for Merck.

H. Tanno: advisory fees from Merck Sharp & Dohme Corp.

Z. Goodman: consultation fees from Merck and Pfizer; grants/grants pending from Merck, Gilead Sciences and Fibrogen.

F. Poordad: consultancy fees from Merck, Vertex, Abbott, Gilead, Achillion, Genentech, and Tibotec; grants/grants pending from Merck; payment for development of educational presentations and speaker fees from Merck, Genentech, Salix and Gilead.

B. Bacon: consultancy fees from Gilead, Three Rivers Pharmaceuticals, Valeant, Vertex, and Human Genome Sciences; grants/grants pending from Roche, Gilead, Bristol Myers Squibb, Three Rivers Pharmaceuticals, Valeant, Vertex, Human Genome Sciences, Wyeth, and Romark Laboratories; payment for lectures including service on speaker's bureaus for Three Rivers Pharmaceuticals, Gilead, and Merck; and served on Data and Safety Monitoring Boards for Novartis, ISIS, Vertex and Gilead.

K. Gottesdiener, L. Pedicone, J. Albrecht, C. Brass, S. Thompson, and M. Burroughs are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and may own stock or stock options in the company.

Authors' contributions

Margaret Burroughs, Clifford Brass, and Janice Albrecht designed the original study. Seth Thompson was responsible for statistical analysis. Zachary Goodman assessed all liver biopsy specimens for Metavir fibrosis scoring. Savino Bruno, John Vierling, Rafael Esteban, Lisa Nyberg, Hugo Tanno, Fred Poordad, and Bruce Bacon enrolled patients and/or contributed to data collection for the original study. Savino Bruno, Keith Gottesdiener, Lisa Pedicone, and Margaret Burroughs drafted the paper. All authors provided critical input to the draft. All authors reviewed the final draft and agree with its content.

Acknowledgements

We thank all study participants and investigators. We also thank Kim M. Strohmaier and Heather L Sings (Merck) for writing support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2012.11.020.

Appendix Addendum: RESPOND-2 Investigators

Belgium – J. Delwaide, Y. Horsmans, H. Van Vlierberghe; Canada – F. Anderson, S.V. Feinman, J. Heathcote, P. Marotta, A. Ramji, F. Wong, K. Peltakian and K. Kaita; France – L. Alric, S. Ben Ali, M.-A. Bigard, M. Bourliere, N. Boyer-Darrigrand, J.-P. Bronowicki, V. De Ledinghen, C. Hezode, P. Lebray, P. Marcellin, M. Maynard–Muet, S. Pol, T. Poynard, A. Tran, C. Trepo, R. Truchi, A. Vallet-Pichard; Germany – T. Berg, R. Guenther, A.W. Lohse, M.P. Manns, C. Niederau, W.E. Schmidt, U. Spengler, H. Wedemeyer, S. Zeuzem; Italy – G. Carosi, M. Colombo, A. Craxì, M. Rizzetto, A.L. Zignego, M. Zuin; Puerto Rico – A. Reymunde; Spain – M. Buti Ferret, R. Esteban; USA – N. Afdhal, B. Bacon, L. Balart, M. Bennett, T. Box, T. Boyer, M. Davis, S. Flamm, B. Freilich, J. Galati, G. Galler, A. Gibas, E. Godofsky, S. Gordon, J. Herrera, S. Herrine, I. Jacobson, J. King, P. Kwo, E. Lawitz, W. Lee, J. Levin, V. Luketic, J. McCone, J. McHutchison, K. Mullen, T. Morgan, A. Muir, F. Nunes, A. Nyberg, L. Nyberg, M.P. Pauly, C. Peine, F. Poordad, N. Ravendhran, R. Reindollar, T. Riley, L. Rossaro, R. Rubin, M. Ryan, E. Schiff, K. Sherman, M. Shiffman, R. Strauss, J. Vierling, R. Yapp. Study Pathologist – Dr. Zachary Goodman.

Appendix Addendum: SPRINT-2 Investigators

Argentina – L. Colombato, J. Curciarello, M. Silva, H. Tanno, R. Terg; Belgium – M. Adler, P. Langlet, L. Lasser, F. Nevens; Canada – F. Anderson, R. Bailey, M. Bilodeau, C. Cooper, S.V. Feinman, J. Heathcote, M. Levstik, A. Ramji, M. Sherman, S. Shafran, E. Yoshida; France – A. Achim, S. Ben Ali, M.-A. Bigard, C. Bonny, M. Bourliere, N. Boyer-Darrigrand, J.-P. Bronowicki, V. Canva, P. Couzigou, V. De Ledinghen, D. Guyader, C. Hezode, D. Larrey, M. Latournerie, P. Marcellin, P. Mathurin, M. Maynard–Muet, J. Moussalli, R. Poupon, T. Poynard, L. Serfaty, A. Tran, C. Trepo, R. Truchi, J.-P. Zarski; Germany – T. Berg, N. Dikopoulos, C. Eisenbach, P.R. Galle, G. Gerken, T. Goeser, M. Gregor, D. Klass, M.R. Kraus, C. Niederau, J.F. Schlaak, R. Schmid, P. Thies, K. Schmidt, R. Thimme, H. Weidenbach, S. Zeuzem; Italy – M. Angelico, S. Bruno, G. Carosi, A. Craxì, A. Mangia, M. Pirisi, M. Rizzetto, G. Taliani, A.L. Zignego; Netherlands – H.W. Reesink; Portugal – F. Serejo; Puerto Rico – A. Reymunde¸ B. Rosado, E. Torres; Spain – R. Barcena Marugan, M. De La Mata, J.L. Calleja, G. Castellano, M. Diago, R. Esteban, C. Fernandez, J. Sanchez Tapias, M.A. Serra Desfilis; USA – N. Afdhal, A. Al-Osaimi, B. Bacon, L. Balart, M. Bennett, D. Bernstein, M. Black, C. Bowlus, T. Boyer, D. Dalke, C. Davis, G. Davis, M. Davis, G. Everson, F. Felizarta, S. Flamm, B. Freilich, J. Galati, G. Galler, R. Ghalib, A. Gibas, E. Godofsky, F. Gordon, S. Gordon, J. Gross, S. Harrison, J. Herrera, S. Herrine, K.-Q. Hu, J. Imperial, I. Jacobson, D. Jones, A. Kilby, J. King, A. Koch, K. Kowdley, E. Krawitt, P. Kwo, L. Lambiase, E. Lawitz, W. Lee, J. Levin, R. Levine, X. Li, A. Lok, V. Luketic, M. Mailliard, J. McCone, J. McHutchison, D. Mikolich, T. Morgan, A. Muir, Don Nelson, F. Nunes, A. Nyberg, L. Nyberg, P. Pandya, M.P. Pauly, C. Peine, G. Poleynard, F. Poordad, D. Pound, J. Poulos, M. Rabinovitz, N. Ravendhran, J. Ready, K. Reddy, R. Reindollar, A. Reuben, T. Riley, L. Rossaro, R. Rubin, M. Ryan, J. Santoro, E. Schiff, T. Sepe, K. Sherman, M. Shiffman, M. Sjogren, R. Sjogren, C. Smith, L. Stein, R. Strauss, M. Sulkowski, R. Szyjkowski, H. Vargas, J. Vierling, D. Witt, R. Yapp, Z. Younes.

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