HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Refinement of Stopping Rules During Treatment of Hepatitis C Genotype 1 Infection With Boceprevir and Peginterferon/Ribavirin

Ira M. Jacobson,[1] Patrick Marcellin,[2] Stefan Zeuzem,[3] Mark S. Sulkowski,[4] Rafael Esteban,[5] Fred Poordad,[6] Savino Bruno,[7] Margaret H. Burroughs,[8] Lisa D. Pedicone,[8] Navdeep Boparai,[8] Weiping Deng,[8] Mark J. DiNubile,[8] Keith M. Gottesdiener,[8] Clifford A. Brass,[8] Janice K. Albrecht,[8] and Jean-Pierre Bronowicki[9]

In comparison with peginterferon/ribavirin alone, boceprevir with peginterferon/ribavirin significantly improves sustained virological response (SVR) rates in patients with chronic hepatitis C virus (HCV) genotype 1 infections, but treatment failure remains a significant problem. Using phase 3 trial databases, we sought to develop stopping rules for patients destined to fail boceprevir-based combination therapy in order to minimize drug toxicity, resistance, and costs in the face of ultimate futility. Exploratory post hoc analyses using data from the Serine Protease Inhibitor Therapy 2 (SPRINT-2) study (treatment-naive patients) and the Retreatment With HCV Serine Protease Inhibitor Boceprevir and Peginterferon/Rebetol 2 (RESPOND-2) study (treatment-experienced patients) were undertaken to determine whether protocol-specified stopping rules (detectable HCV RNA at week 24 for SPRINT-2 and at week 12 for RESPOND-2) could be refined and harmonized. In SPRINT-2, a week 12 rule with an HCV RNA cutoff of ≥100 IU/mL would have discontinued therapy in 65 of 195 failures (sensitivity = 33%) without sacrificing a single SVR among 475 successes (specificity = 100%). Viral variants emerged after week 12 in 36 of the 49 evaluable patients (73%) who would have discontinued at week 12 using a ≥100 IU/mL stopping rule. In RESPOND-2, five of six patients with week 12 HCV RNA levels between the lower limit of detection (9.3 IU/mL) and the lower limit of quantification (25 IU/mL) who continued therapy despite the protocol-stipulated futility rule achieved SVR; one additional patient with a week 12 HCV RNA level of 148 IU/mL also continued therapy, had undetectable HCV RNA at week 16, and attained SVR. *Conclusion:* Although a stopping rule of detectable HCV RNA at week 12 would have forfeited some SVR cases, week 12 HCV RNA levels ≥100 IU/mL almost universally predicted a failure to achieve SVR in both treatment-naive and treatment-experienced patients. In boceprevir recipients, the combination of 2 stopping rules—an HCV RNA level ≥100 IU/mL at week 12 and detectable HCV RNA at week 24—maximized the early discontinuation of futile therapy and minimized premature treatment discontinuation. (HEPATOLOGY 2012;56:567-575)

Combination therapy with peginterferon alfa/ribavirin (P/R) has been the standard approach to the management of chronic hepatitis C virus (HCV) infections for the last decade. Sustained virological response (SVR) rates of 54% to 56% were achieved in the pivotal trials of

Abbreviations: HCV, hepatitis C virus; LLD, lower limit of detection; LLQ, lower limit of quantification; P/R, pegintron alfa/ribavirin; RESPOND-2, Retreatment With HCV Serine Protease Inhibitor Boceprevir and Pegintron/Rebetol 2; SPRINT-2, Serine Protease Inhibitor Therapy 2; SVR, sustained virological response.

From the [1]Center for the Study of Hepatitis C, Weill Cornell Medical College, New York, NY; [2]Bichat-Beaujon Biomedical Research Center, National Institute of Health and Medical Research/Hepatology Service, Beaujon Hospital, University Paris-Diderot, Clichy, France; [3]J. W. Goethe University Hospital, Frankfurt, Germany; [4]Johns Hopkins University School of Medicine, Baltimore, MD; [5]Vall d'Hebron University Hospital, Barcelona, Spain; [6]Cedars-Sinai Medical Center, Los Angeles, CA; [7]Internal Medicine and Liver Unit, Fatebenefratelli e Oftalmico Hospital, Milan, Italy; [8]Merck Sharp & Dohme, Whitehouse Station, NJ; and [9]National Institute of Health and Medical Research Unit 954, University Hospital of Nancy, Henri Poincaré University, Vandoeuvre-lès-Nancy, France.

Received March 14, 2012; accepted May 16, 2012.

Navdeep Boparai is currently affiliated with Bristol-Myers Squibb (Hopewell, NJ); Keith M. Gottesdiener is currently affiliated with Rhythm Pharmaceuticals (Boston, MA); and Clifford A. Brass is currently affiliated with Novartis (Summit, NJ).

peginterferon alfa-2a and peginterferon alfa-2b with ribavirin.[1,2] Patients with genotype 1 HCV infections had lower SVR rates (approximately 40%) and required 48 weeks of therapy, whereas higher SVR rates were attained by patients with genotype 2 or 3 infections despite shorter treatment durations.[1-5] The troublesome array of toxicities associated with interferon-based therapy led to retrospective analyses of the pivotal trial databases, and these analyses culminated in the identification of robust early stopping rules for futility. It was consistently observed for genotype 1 infections that a failure to attain a $\geq$2-log reduction in the baseline HCV RNA level by week 12 of therapy was associated with a negative predictive value for SVR of 97% to 100%,[1,6] and this observation was incorporated into routine clinical practice early in the era of peginterferon-based therapy.[7] This response-guided paradigm has spared many patients destined to fail P/R therapy the futile prolongation of treatment with its attendant side effects and additional costs. Furthermore, the retreatment of interferon-nonresponders has demonstrated that patients with detectable HCV RNA at week 12 of P/R therapy rarely achieve SVR.[8]

The recently licensed nonstructural 3/4A serine protease inhibitors [boceprevir (Victrelis, Merck, Whitehouse Station, NJ) and telaprevir (Incivek, Vertex Pharmaceuticals, Cambridge, MA)] must be given with P/R because of their low barrier to viral resistance when they are used as monotherapy.[9,10] In contrast to conventional P/R therapy, virological failure with protease inhibitor–based combination therapy is often attended by the selection of viral variants with resistance to protease inhibitors. This resistance may emerge early during treatment before impending failure becomes apparent by standard monitoring.[9-15]

The pivotal trials of boceprevir included a 4-week P/R lead-in period for all patients followed by the addition of boceprevir at the beginning of the fifth week. The duration of treatment varied among the different arms of each study. The Serine Protease Inhibitor Therapy 2 (SPRINT-2) study demonstrated that the addition of boceprevir to standard P/R therapy significantly improved SVR rates in previously untreated patients.[11] The Retreatment With HCV Serine Protease Inhibitor Boceprevir and Pegintron/Rebetol 2 (RESPOND-2) study likewise demonstrated superior response rates with boceprevir plus P/R in patients who had partially responded to or relapsed after a standard course of P/R alone.[14]

Beyond the potentially increased drug toxicity and unnecessary costs for patients continuing treatment without a realistic chance of SVR, the risk of emerging resistance provides an additional incentive to define early stopping rules for protease-inhibitor regimens. In this study, we retrospectively analyzed data from the pivotal boceprevir trials with two related aims: (1) to establish the earliest possible stopping rules for boceprevir therapy in treatment-naive and treatment-experienced patients and (2) to determine whether uniform

Address reprint requests to: Ira M. Jacobson, M.D., Center for the Study of Hepatitis C, Weill Cornell Medical College, 1305 York Avenue, New York, NY 10021. E-mail: imj2001@med.cornell.edu; fax: 646 962 0433.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.25865

Potential conflict of interest: The Serine Protease Inhibitor Therapy 2 study (ClinicalTrials.gov identifier NCT00705432) and the Retreatment With HCV Serine Protease Inhibitor Boceprevir and Pegintron/Rebetol 2 study (ClinicalTrials.gov identifier NCT00708500) were funded by Schering-Plough/Merck. The trials were designed, managed, and analyzed by employees of the sponsor in conjunction with external academic investigators. Every coauthor of this article had full access to all pertinent data upon request. A penultimate version of this article was reviewed by the sponsor. Each coauthor approved an essentially final version of this article. The opinions expressed in this report represent the consensus of the authors and do not necessarily reflect the formal positions of Merck or the other institutions listed as investigator affiliations. Present and former employees of Merck may own stock or stock options in the company. All academic authors have been investigators for Schering-Plough/Merck. In addition, Ira M. Jacobson has received research support from Schering-Plough/Merck, Tibotec, Roche/Genentech, Pharmasset, Anadys, Boehringer-Ingelheim, Novartis, Gilead, Vertex, GlobeImmune, Idenix, Abbott, Zymogenetics, and Human Genome Sciences and has served as a consultant and/or speaker for Bristol-Myers Squibb, Novartis, Gilead, Schering-Plough/Merck, Pfizer, Vertex, GlobeImmune, Human Genome Sciences, Boehringer-Ingelheim, Pharmasset, Zymogenetics, Tibotec, Abbott, Roche/Genentech, Anadys, and Sanofi-Aventis. Patrick Marcellin has received grant support from Abbott, Bristol-Myers Squibb, Boehringer-Ingelheim, Echosens, Gilead, Janssen-Tibotec, Schering-Plough/Merck, Novartis, Roche, Pfizer, Pharmasset, GlaxoSmithKline and Vertex and has served as a consultant and/or speaker for Abbott, Bristol-Myers Squibb, Gilead, Janssen-Tibotec, Schering-Plough/Merck, Novartis, Roche, Pharmasset, and Vertex. Stefan Zeuzem has served as a consultant and/or speaker for Abbott, Achillion, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead, iTherX, Janssen-Cilag, Schering-Plough/Merck, Novartis, Roche, Santaris, Taussen-Tibotec, and Vertex. Mark S. Sulkowski has been a consultant for Schering-Plough/Merck, Abbott, Anadys, Boehringer Ingelheim Pharmaceuticals, Gilead, Pfizer, Human Genome Sciences, Roche, Taussen-Tibotec, and Vertex and has received grant support from Schering-Plough/Merck, Abbott, Boehringer Ingelheim Pharmaceuticals, Gilead, Bristol-Myers Squibb, Roche, Vertex, Tibotec, and Pharmasset. Rafael Esteban has served as a consultant and/or speaker for Schering-Plough/Merck. Fred Poordad has received research grants from Schering-Plough/Merck, Vertex, Genentech, Bristol-Myers Squibb, Gilead, Pfizer, Abbott, Tibotec, Idenix and Pharmasset, is a member of the speaker's bureau for Genentech and Gilead, and is an advisor/consultant for Schering-Plough/Merck, Vertex, Gilead, Genentech, and Abbott. Savino Bruno has served as a consultant and/or speaker for Schering-Plough/Merck, Bristol-Myers Squibb, and Roche. Jean-Pierre Bronowicki has served as a consultant and/or speaker for Schering-Plough/Merck, Roche, Gilead, Bristol-Myers-Squibb, Janssen, Boehringer-Ingelheim, Novartis, and Bayer and has received payments from Roche for expenses incurred by meeting attendance.

Additional Supporting Information may be found in the online version of this article.

stopping rules could be applied to both patient populations. The overarching goal was to formulate straightforward and practical criteria enabling the discontinuation of therapy as early as possible in the maximum proportion of patients destined to fail without the premature discontinuation of treatment in patients who might still attain SVR. In large part, these previously unpublished analyses formed the basis for the recommendations addressing the early discontinuation of boceprevir-based therapy due to futility that are included in the US and European Union product labels and are reflected in the updated guidelines from the American Association for the Study of Liver Diseases.[7]

Patients and Methods

Objectives. Hypothesis-generating analyses were retrospectively performed with the SPRINT-2 and RESPOND-2 databases to determine whether early stopping rules based on the absolute HCV RNA level or its decline from the baseline level could be identified for boceprevir-containing regimens in order to minimize the toxicities and costs associated with continuing ineffective treatment, ensure that very few (if any) patients would be deprived of SVR by premature discontinuation, prevent the emergence of resistant HCV variants in the face of ultimately futile therapy, and harmonize (and thereby simplify) stopping rules across patient populations.

Study Designs. SPRINT-2 and RESPOND-2 were phase 3 randomized, placebo-controlled studies conducted with HCV genotype 1–infected treatment-naive and treatment-experienced patients, respectively; they compared standard therapy with peginterferon alfa-2b and ribavirin to two treatment regimens that added boceprevir after an initial 4-week lead-in period with peginterferon/ribavirin alone (Supporting Figs. 1 and 2).[11,14] The protocols were approved by the appropriate review committees prior to the enrollment of any patients. Participants were assigned to a control P/R arm or one of two boceprevir-containing arms. In SPRINT-2, patients entered either a nonblack cohort or black cohort according to self-identified race. In RESPOND-2, patients were stratified by their previous response to P/R therapy into partial responder and relapser groups; null responders by history were excluded. Further details are presented in the supporting information.

Plasma HCV RNA levels were measured with the TaqMan 2.0 assay (Roche Diagnostics, Branchburg, NJ) with a lower limit of quantification (LLQ) of 25 IU/mL and a lower limit of detection (LLD) of 9.3 IU/mL. Samples were obtained at screening, at baseline, every 2 weeks through week 12, and at weeks 16, 20, 24, 28, 34, 40, 48, 52, 60, and 72 (depending on the treatment duration). Specimens were to be obtained within a period of 1 or 2 weeks before or after the designated time point. In both studies, genotypic resistance testing was at minimum to be performed at entry and at the time of failure.

Stopping Rules. Futility rules were specified by protocol as detectable HCV RNA at week 24 (SPRINT-2) or at week 12 (RESPOND-2). Patients whose study therapy was stopped for futility per protocol were considered treatment failures. In this retrospective analysis, the impact of alternative stopping rules using different HCV RNA thresholds [cutoffs of $\geq$9.3 (LLD), $\geq$25 (LLQ), $\geq$50, $\geq$100, or $\geq$1000 IU/mL] as well as $<$2-log and $<$3-log reductions of HCV RNA levels from the baseline level was assessed at week 8 (SPRINT-2 and RESPOND-2), at week 12 (SPRINT-2), and at week 16 (SPRINT-2).

Patient Selection and Analytical Approach. Only patients treated with one or more doses of boceprevir were eligible for these analyses. For each proposed stopping rule, patients were excluded if an HCV RNA measurement at the specified time point was not available within the designated window. When more than one HCV RNA measurement was available during a designated window, the highest value was used in the analyses. Evaluable patients were divided into SVR and non-SVR groups. We assumed that all patients who discontinued therapy because of protocol-specified stopping rules would not have achieved SVR. In deriving stopping rules, our analyses did not distinguish between specific boceprevir regimens or differentiate between the reasons for failing to attain SVR (e.g., virological failure, missing outcome data, or discontinuations unrelated to virological failure). The operating characteristics of each cutoff value for HCV RNA were compared at the various time points. In selecting stopping rules, we imposed essentially zero tolerance for discontinuing therapy in patients who would go on to achieve SVR while trying to maximize discontinuations in patients not attaining SVR as early as possible. Simplicity, convenience, and compatibility with standard clinical practice were also considered.

After identifying a robust stopping rule earlier than the rule specified by the protocol in SPRINT-2, we reviewed the population sequencing data for viruses isolated from the 65 boceprevir recipients with week 12 HCV RNA levels $\geq$100 IU/mL who would have discontinued therapy according to the proposed rule. The emergence of resistance-associated variants was

considered possibly preventable by the week 12 stopping rule if a new variant was first detected by polymerase chain reaction genotyping any time after day 84.

Results

Patient Accounting and Baseline Characteristics. In SPRINT-2, 938 nonblack and 159 black treatment-naive patients were independently randomized and treated with one or more doses of any study medication. Overall, 704 treatment-naive patients who received one or more doses of boceprevir in SPRINT-2 were eligible for the current analysis. SVR was achieved in 475 boceprevir recipients (67%); 9 and 0 of these patients were missing HCV RNA measurements at weeks 8 and 12, respectively. SVR was not achieved in 229 boceprevir recipients (33%); 23 and 34 were missing HCV RNA measurements at weeks 8 and 12, respectively.

After stratification in RESPOND-2, 144 partial responders and 259 relapsers were randomized and treated with one or more doses of the study medication. Overall, 316 treatment-experienced patients who received one or more doses of boceprevir in RESPOND-2 were eligible for this analysis; this number included 111 partial responders and 205 relapsers. SVR was achieved in 202 boceprevir recipients (64%); 5 were missing HCV RNA measurements at week 8. SVR was not achieved in 114 boceprevir recipients (36%); 11 were missing HCV RNA measurements at week 8.

Stopping Rules in Treatment-Naive Patients. Figure 1 displays scatter plots of HCV RNA levels in 672 and 670 evaluable boceprevir recipients at weeks 8 and 12, respectively, from SPRINT-2. The recipients were divided into SVR and non-SVR groups. No absolute threshold could be established at week 8 (after 4 weeks of boceprevir) that would have allowed the early discontinuation of failing therapy in patients without the loss of some SVRs (Table 1).

All 65 patients with HCV RNA levels $\geq$100 IU/mL at week 12 failed to achieve SVR; only 3 of these patients (all of whom had week 12 levels <300 IU/mL) reached undetectable levels by the end of treatment but subsequently relapsed. Viral variants first identified after week 12 were found in 36 of the 49 patients (73%) with resistance data who would have stopped therapy at week 12 with the $\geq$100 IU/mL rule. In 49 of the 79 patients with detectable HCV RNA levels (<100 IU/mL) at week 12, HCV RNA became undetectable between weeks 12 and 24. Ultimately, 21 of these 49 patients achieved SVR.

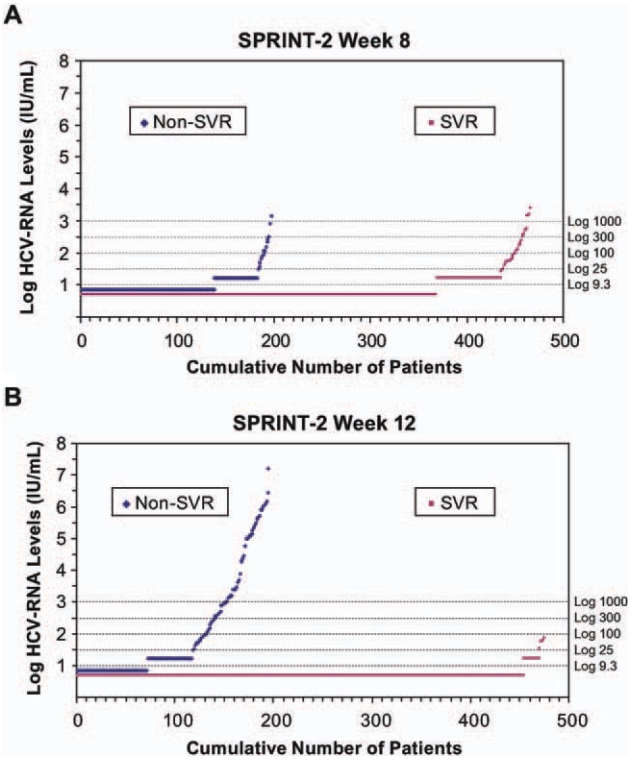

Fig. 1. Two-dimensional scatter plots of HCV RNA levels in evaluable boceprevir recipients from SPRINT-2 at (A) week 8 and (B) week 12. The recipients were divided into SVR and non-SVR groups. After stratification by the HCV RNA level at screening ($\leq$400,000 versus >400,000 IU/mL) and by the infecting genotype 1 subtype (1a versus 1b), patients were randomized to one of three arms. Arm 1 (the standard-of-care arm) received peginterferon alfa-2b subcutaneously once per week (1.5 μg/kg) for 48 weeks plus oral ribavirin twice daily [600-1400 mg/day (weight-based dosing)] and a placebo capsule 3 times per day (beginning in week 5). Patients randomized to arm 3 (the fixed-duration therapy arm) received peginterferon/ribavirin for a 4-week lead-in period, followed by the addition of 800 mg of oral boceprevir 3 times per day to peginterferon/ribavirin for 44 weeks. Patients randomized to arm 2 (the response-guided therapy arm) were treated for a total duration of 28 or 48 weeks; the length of therapy depended on whether or not their HCV RNA levels were undetectable from week 8 to week 24. Patients with detectable HCV RNA at any visit between weeks 8 and 24 continued therapy with peginterferon/ribavirin plus a placebo until week 48. Therapy was discontinued for patients in all arms for futility if HCV RNA was detectable at the week 24 visit. Boceprevir was given for a total duration of 44 weeks to continuing patients in arm 3 and for a total duration of 24 weeks to continuing patients in arm 2 (regardless of the rapidity of response). The *x* axes show the cumulative number of patients with HCV RNA levels up to the corresponding values on the *y* axes. The dotted horizontal lines across the graphs indicate the HCV RNA thresholds studied as stopping rules in the current analysis.

These data indicate that a stopping rule with an HCV RNA cutoff of $\geq$100 IU/mL at week 12 would have allowed the early discontinuation of failing therapy in 65 of 195 possible failures (sensitivity = 33%) without sacrificing a single SVR among 475 successes (specificity = 100%). A more stringent stopping rule of detectable HCV RNA at week 12 would have

Table 1. Application of Stopping Rules With Different Thresholds at Different Time Points in Evaluable Treatment-Naive Patients From SPRINT-2

	Week 8 Stopping Rule (n = 672)*				Week 12 Stopping Rule (n = 670)†			
Threshold HCV RNA Level	Patients Stopped by Week 8 Rule (n)	Additional Patients Stopped by Week 24 Rule (n)	Total Patients Stopped (n)	SVR Missed With Week 8 Rule (n)	Patients Stopped by Week 12 Rule (n)	Additional Patients Stopped by Week 24 Rule (n)	Total Patients Stopped (n)	SVR Missed With Week 12 Rule (n)
≥9.3 IU/mL (LLD)	260	11	271	98	144	20	164	21
≥25 IU/mL (LLQ)	155	25	180	31	83	41	124	5
≥50 IU/mL	147	26	173	26	78	43	121	4
≥100 IU/mL	120	32	152	16	65	49	114	0
≥1000 IU/mL	61	57	118	4	43	61	104	0
<2-log decline from the baseline	13	74	87	0	24	71	95	0
<3-log decline from the baseline	34	66	100	1	34	66	100	0

SVR was operationally defined as undetectable levels of HCV RNA 24 weeks after the completion of therapy.

*There were 466 patients (69%) with SVR and 206 patients (31%) without SVR. Because of the 4-week lead-in period with P/R alone, these patients had received only 4 weeks of boceprevir by treatment week 8.

†There were 475 patients (71%) with SVR and 195 patients (29%) without SVR. Because of the 4-week lead-in period with P/R alone, these patients had received only 8 weeks of boceprevir by treatment week 12.

sacrificed 21 SVRs. A less stringent stopping rule at week 12 (≥1000 IU/mL) would also have prevented the premature discontinuation of therapy but would have enabled appropriate discontinuation in only 43 patients. Similar results were found with the week 16 stopping rules (Supporting Table 1).

In contrast to an absolute HCV RNA threshold level, the degree of the decline from the baseline HCV RNA level was generally a less discriminative predictor of outcomes at most time points. Notably, 24 of 83 patients (29%) with a <0.5-log decline in HCV RNA levels from baseline to week 4 (the end of the lead-in P/R phase) still achieved SVR when boceprevir was added. In contrast, <2-log and <3-log declines in the HCV RNA levels from baseline to week 8 accurately identified modest numbers of therapeutic failures with only 1 misclassification of a patient eventually achieving SVR, but this strategy would require testing at an additional time point.

Stopping Rules in Treatment-Experienced Patients. Figure 2 displays a scatter plot of HCV RNA levels in 300 evaluable boceprevir recipients at week 8 from RESPOND-2. The recipients were divided into SVR and non-SVR groups. No robust futility rule was evident at week 8 that would have completely prevented missed SVRs (Table 2). However, a week 8 HCV RNA cutoff of ≥1000 IU/mL would have allowed appropriate early discontinuation in 27 patients at the cost of 1 SVR.

Per protocol, 72 patients were to be discontinued for futility because of detectable HCV RNA at week 12 (Table 3). In this group, 39 patients had week 12 levels <100 IU/mL; these patients included 31 with

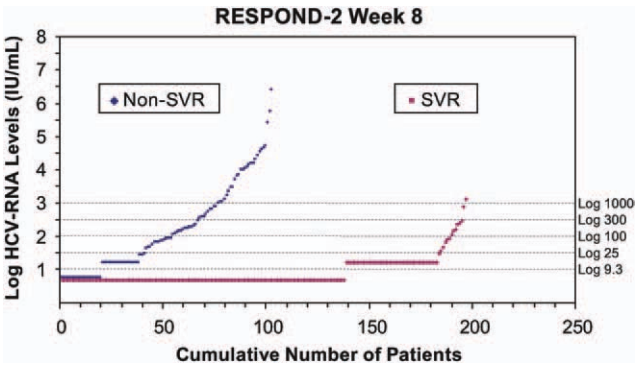

Fig. 2. Two-dimensional scatter plots of HCV RNA levels in evaluable boceprevir recipients from RESPOND-2 at week 8. The recipients were divided into SVR and non-SVR groups. After stratification by the previous treatment response history (partial response versus relapse) and by the infecting genotype 1 subtype (1a versus 1b), patients were randomized to one of three arms. Arm 1 (the standard-of-care arm) received peginterferon alfa-2b subcutaneously once per week (1.5 μg/kg) for 48 weeks plus oral ribavirin twice daily [600-1400 mg/day (weight-based dosing)] and a placebo capsule 3 times per day (beginning in week 5). Patients randomized to arm 3 (the fixed-duration therapy arm) received peginterferon/ribavirin for a 4-week lead-in period, followed by the addition of 800 mg of oral boceprevir 3 times per day to peginterferon/ribavirin for 44 weeks. Patients randomized to arm 2 (the response-guided therapy arm) were treated for a total duration of 36 or 48 weeks; the length of therapy depended on whether or not their HCV RNA levels were undetectable at week 8. Patients with detectable HCV RNA at week 8 continued therapy with peginterferon/ribavirin plus a placebo until week 48. Therapy was discontinued for patients in all arms for futility if HCV RNA was detectable at the week 12 visit. Boceprevir was given for a total duration of 44 weeks to continuing patients in arm 3 and for a total duration of 32 weeks to continuing patients in arm 2 (regardless of the rapidity of response). The *x* axis shows the cumulative number of patients with HCV RNA levels up to the corresponding values on the *y* axis. The dotted horizontal lines across the graph indicate the HCV RNA thresholds studied as stopping rules in the current analysis.

Table 2. Application of Stopping Rules With Different Thresholds at Week 8 in Evaluable Treatment-Experienced Patients From RESPOND-2

	Week 8 Stopping Rule (n = 300)*			
Threshold HCV RNA Level	Patients Stopped by Week 8 Rule (n)	Additional Patients Stopped by Week 12 Rule (n)	Total Patients Stopped (n)	SVR Missed With Week 8 Rule (n)
≥9.3 IU/mL (LLD)	142	7	149	59
≥25 IU/mL (LLQ)	79	14	93	14
≥50 IU/mL	70	15	85	11
≥100 IU/mL	57	24	81	8
≥1000 IU/mL	27	45	72	1
<2-log decline from the baseline	3	69	72	0
<3-log decline from the baseline	19	54	73	1

SVR was operationally defined as undetectable levels of HCV RNA 24 weeks after the completion of therapy.

*There were 197 patients (67%) with SVR and 103 patients (33%) without SVR. Because of the 4-week lead-in period with P/R alone, these patients had received only 4 weeks of boceprevir by treatment week 8.

HCV RNA levels between the LLQ (25 IU/mL) and the LLD (9.3 IU/mL). Six of these 31 patients completed the treatment despite the protocol stipulation that such patients discontinue therapy. All six patients had >5.5-log declines from the baseline HCV RNA levels by week 12. Five of the six patients (both patients with a previous partial response and three of the four patients with a previous relapse with P/R) were treated for 48 weeks (including 44 weeks of boceprevir) and achieved SVR; the other patient received 36 weeks of treatment and did not attain SVR. Although detectable HCV RNA levels (<100 IU/mL) at week 12 did not preclude SVR, only one of the eight patients with week 12 levels between 25 and 100 IU/mL continued therapy and achieved HCV RNA undetectability by the end of treatment; this patient relapsed during follow-up. Among the 33 patients with detectable HCV RNA levels (≥100 IU/mL) at week 12, therapy was continued in 1 patient who achieved SVR; the HCV RNA levels in this successfully treated patient were 14,813,507 IU/mL at baseline; detectable (<25 IU/mL) at week 10 (day 71); 103, 125, and 148 IU/mL in a single specimen (run in triplicate) at week 12 (day 85); and undetectable by week 16 (day 113) and thereafter.

Five of the 21 patients (24%) with a <0.5-log decline in the baseline HCV RNA levels at week 4 achieved SVR after the addition of boceprevir. At week 8, a <2-log decline was the only rule with which no SVR was missed, but therapy would have been discontinued in just three patients with this criterion. In all, 195 of the 277 evaluable patients (70%) with a ≥4-log decline at week 12 in their baseline HCV RNA levels achieved SVR; this number includes 6 patients with HCV RNA detectable at week 12 (as described previously).

Discussion

With conventional P/R therapy, generally accepted stopping rules include a <2-log viral load decline at week 12 and/or detectable HCV RNA at week 24. Early treatment discontinuation can help to prevent unnecessarily prolonged therapy with its attendant toxicity and additional costs in patients who are very unlikely to achieve SVR. With regimens containing a protease inhibitor along with P/R, stopping rules are also used to preempt the emergence of resistance-associated variants in patients destined to fail. According to our analysis of the SPRINT-2 sequencing data, the

Table 3. Disposition of Evaluable Treatment-Experienced Patients From RESPOND-2 With Detectable HCV RNA at Week 12

Week 12 HCV RNA Level	Description	Total Patients (n)	Patients Continued on Treatment (n)	Patients With SVR (n)	SVR Rate in Patients Continued on Therapy Despite Protocol Stopping Rule (%)
≥9.3 to <25 IU/mL	Between LLD and LLQ	31	6	5	–
≥25 to <100 IU/mL	From LLQ to 100 IU/mL	8	1	0	–
≥100 IU/mL	Satisfied proposed week 12 stopping rule	33	1	1	–
≥9.3 IU/mL	Total detectable	72	8	6	75

emergence of resistance-associated variants potentially could have been avoided in up to 73% of the 49 evaluable cases satisfying the week 12 stopping rule of an HCV RNA level ≥100 IU/mL.

Our exploratory analyses suggest that a robust stopping rule can be uniformly applied to treatment-naive and treatment-experienced patients who receive boceprevir combination therapy as early as week 12 with an HCV RNA cutoff of 100 IU/mL. The week 12 stopping rule would be added to (and not replace) the week 24 criterion of undetectable HCV RNA levels and fit conveniently into standard practice. The application of these stopping rules would be expected to result in virtually no patients with a realistic chance of attaining SVR being deprived of this opportunity by the premature discontinuation of therapy. Less stringent stopping rules at week 12 (e.g., an HCV RNA level ≥1000 IU/mL or a <3-log or <2-log decline from the baseline) similarly would have minimized missed SVR opportunities but would have resulted in the appropriate cessation of therapy in fewer patients and thereby exposed more patients unnecessarily to drug toxicity and increased the potential for the emergence of resistance-associated variants in the face of ultimate futility. Conversely, earlier stopping rules (a <0.5-log decline from the baseline at week 4) and more stringent stopping rules (detectability at week 12) would have led to premature discontinuation in some patients who could have achieved SVR.

Accurate week 8 stopping rules (which would reflect only 4 weeks of boceprevir treatment) could interrupt failing therapy even earlier than the proposed week 12 rule. Using a <3-log HCV RNA decline at week 8 as a stopping rule, one SVR would have been missed in each of the treatment-naive and treatment-experienced populations. A <3-log decline in the HCV RNA level by week 8 might reasonably be incorporated into a decision to terminate therapy, especially in the face of significant drug toxicity. Likewise, HCV RNA levels that remained ≥1000 IU/mL at week 8 predicted a failure to attain SVR in 27 of 28 treatment-experienced patients (96%) from RESPOND-2. A logistical drawback to a week 8 stopping rule is the need for testing at an additional time point.

The per-protocol stopping rules for futility were detectable HCV RNA at week 24 in SPRINT-2 and detectable HCV RNA at week 12 in RESPOND-2.[11,14,16] We could not systematically test the accuracy of the prespecified futility rules, but protocol violations proved informative. The actual choice of a detectable HCV RNA level at week 12 (the protocol-specified stopping rule in RESPOND-2) was based on earlier observations in patients with advanced fibrosis for whom previous therapy had failed.[8] However, even in that study, 12% of the patients with low but detectable HCV RNA levels at week 12 still attained SVR after 48 weeks of P/R therapy. In the RESPOND-2 study, HCV RNA undetectability turned out in retrospect to be too stringent a requirement for continuing triple therapy at week 12. Although patients continuing on therapy despite protocol futility rules potentially represent a select subgroup treated by site investigators because of other favorable prognostic characteristics, sufficient numbers of these patients attained SVR for us to be confident that insistence on HCV RNA undetectability at week 12 to justify continued therapy would deny some patients a chance for SVR.

The sole exception to the proposed week 12 stopping rule in our analysis of both pivotal boceprevir trials was a treatment-experienced patient with HCV RNA measurements in triplicate ranging from 103 to 148 IU/mL at week 12 who continued therapy and attained SVR. The apparent differences among these measured values (obtained from the same sample) and the threshold value of 100 IU/mL largely reflect assay variability. This patient had a high baseline viral load that had decreased by 4 logs at week 12 and became persistently undetectable by week 16. Thresholds should be interpreted considering the full clinical context,[17] and decisions to stop therapy are best individualized. Accordingly, a patient with a week 12 HCV RNA level just greater than the cutoff of 100 IU/mL after a precipitous decline from a high baseline level may be appropriately continued on therapy with follow-up monitoring within a few weeks to assess whether the HCV RNA levels have become undetectable before a final decision to stop therapy is made.

A widely accepted criterion for stopping a second course of P/R therapy in patients for whom previous P/R therapy had failed is detectable HCV RNA at week 12.[8] Our data indicate that this standard futility rule may be too strict when such patients are being retreated with P/R plus boceprevir and would sacrifice a nontrivial number of SVRs. Because five of the six patients with week 12 HCV RNA levels between the LLD (9.3 IU/mL) and the LLQ (25 IU/mL) and one patient with a week 12 HCV RNA level just greater than 100 IU/mL attained SVR with ongoing therapy in RESPOND-2, it can be reasonably inferred that an appropriate stopping threshold would be approximately 100 IU/mL for treatment-experienced patients.[16] Using a week 12 threshold of 100 IU/mL in RESPOND-2 would have salvaged at least 5 SVRs missed by the cutoff of detectable HCV RNA at a

cost of prolonging therapy (and potentially selecting resistance-associated variants) in 39 patients. All six patients with detectable HCV RNA at week 12 who achieved SVR had at least a 4-log decline in HCV RNA levels from baseline to week 12, probably explaining why therapy was continued despite the protocol stopping rule. A cutoff of 100 IU/mL for boceprevir recipients harmonizes the stopping rules at week 12 in all patient populations, and this should simplify decision making for busy clinicians. Patients with levels modestly above the week 12 HCV RNA cutoff of 100 IU/mL who have a $\geq$4-log decline from their baseline viral loads may deserve a longer therapeutic trial. Admittedly, the proposed week 12 stopping rule of $\geq$100 IU/mL for treatment-experienced patients could not be rigorously tested because of the futility rule prespecified in RESPOND-2.

Our hypothesis-generating analyses have several limitations. These stopping rules were derived exclusively from patients treated in rigorously controlled clinical trials with boceprevir and P/R that already had protocol-stipulated futility rules.[11,14] Black patients and patients with cirrhosis were underrepresented in the derivation set, whereas historical null responders and human immunodeficiency virus–coinfected patients were excluded from the pivotal trials. Stopping rules may be regimen-dependent to some degree.[18,19] However, because the numbers were too small for adequate subgroup analyses, our results did not make distinctions between the different boceprevir regimens studied in the phase 3 program or the specific reasons for failure. The proposed rules have not yet been validated in other settings or populations. Different assays for HCV RNA may have varying operating characteristics, and decision thresholds may need to be adjusted accordingly. Combination rules using both the absolute level of HCV RNA and the decline from baseline[17] were not systematically assessed in our analyses. Although we decided to sacrifice sensitivity for specificity, the premature discontinuation (false-positive) rate with any stopping rule is unlikely to ever be exactly zero. Furthermore, there is no explicit consensus about what constitutes an unacceptably high risk of misclassifying futility. Although the enforced protocol-specified futility rules were accepted as 100% accurate in our analyses, their overall false-positive rate in the literature may be as high as 3%.[1,2,6,8,18-20] Stopping rules should be applied with particular caution when the HCV RNA values fall within the assay variability range of the decision thresholds.[19,20] Whether these boceprevir-derived stopping rules can be generalized to other HCV protease inhibitors or newer classes of directly acting antiviral agents is not addressed by our study.

Despite the inherent limitations of the analyses, our report illuminates the rationale underlying the futility rules in the approved labels for boceprevir. Importantly, the provision of the actual data to clinicians should make them confident that the application of these rules will not deprive appropriate patients of a meaningful chance of SVR. Of course, decisions should be individualized to account for each patient's circumstances. Antiviral therapy is becoming increasingly complex, and stopping criteria will undoubtedly change again with the emergence of new therapeutic options for chronic HCV infections (as seen here after the licensing of the first two protease inhibitors). During this auspicious time for patients and practitioners alike, futility rules can be applied most effectively when their basis is transparent and understood.

Our recommendations are consistent with the US Food and Drug Administration position and the 2011 practice guidelines from the American Association for the Study of Liver Diseases.[7] In addition to detectable HCV RNA at week 24, an earlier and robust week 12 stopping rule of an HCV RNA level $\geq$100 IU/mL can conveniently be incorporated into the routine care of both treatment-naive and treatment-experienced patients treated with boceprevir combined with peginterferon/ribavirin. In particular, our findings challenge the common practice of discontinuing P/R therapy in treatment-experienced patients with detectable HCV RNA at week 12 in favor of using a week 12 futility threshold of 100 IU/mL in all patients receiving boceprevir-containing regimens. The sequential application of stopping rules at weeks 12 and 24 appears to maximize the early discontinuation of futile therapy while minimizing premature treatment discontinuation in patients who might achieve SVR. These rules merit validation in larger and varied patient populations in the future.

Acknowledgment: The authors thank all the patients, health care providers, and investigators involved in these studies. They are also indebted to Richard Barnard for providing the resistance data from SPRINT-2; to Ruiyun Jiang for quality-checking the input used for these analyses; and to Jon Stek, Joann DiLullo, Kathleen Newcomb, and Karyn Davis for providing indispensable advice and support in the preparation of this article.

References

1. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958-965.

2. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975-982.
3. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346-355.
4. Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Solá R, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med 2007;357:124-134.
5. Mangia A, Dalgard O, Minerva N, Verbaan H, Bacca D, Ring-Larsen H, et al. Ribavirin dosage in patients with HCV genotypes 2 and 3 who completed short therapy with peg-interferon alpha-2b and ribavirin. Aliment Pharmacol Ther 2010;31:1346-1353.
6. Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alpha-2b plus ribavirin in patients with chronic hepatitis C. HEPATOLOGY 2003;38:645-652.
7. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. HEPATOLOGY 2011;54:1433-1444.
8. Poynard T, Colombo M, Bruix J, Schiff E, Terg R, Flamm S, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology 2009;136:1618-1628.
9. Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. Gastroenterology 2010;138:447-462.
10. Gambarin-Gelwan M, Jacobson IM. Resistance-associated variants in chronic hepatitis C patients treated with protease inhibitors. Curr Gastroenterol Rep 2012;14:47-54.
11. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-1206.
12. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-2416.
13. Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med 2011;365:1014-1024.
14. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1207-1217.
15. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417-2428.
16. Harrington PR, Zeng W, Naeger LK. Clinical relevance of detectable but not quantifiable hepatitis C virus RNA during boceprevir or telaprevir treatment. HEPATOLOGY 2012;55:1048-1057.
17. Neumann AU, Pianko S, Zeuzem S, Yoshida EM, Benhamou Y, Mishan M, et al. Positive and negative prediction of sustained virologic response at weeks 2 and 4 of treatment with albinterferon alfa-2b or peginterferon alfa-2a in treatment-naïve patients with genotype 1, chronic hepatitis C. J Hepatol 2009;51:21-28.
18. Sánchez-Tapias JM, Diago M, Enríquez J, Romero-Gómez M, Bárcena R, Crespo J, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. Gastroenterology 2006;131:451-460.
19. Buti M, Lurie Y, Zakharova NG, Blokhina NP, Horban A, Teuber G, et al. Randomized trial of peginterferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response. HEPATOLOGY 2010;52:1201-1207.
20. de Leuw P, Sarrazin C, Zeuzem, S. How to use virological tools for the optimal management of chronic hepatitis C. Liver Int 2011;31:3-12.