

A Review of Standard and Newer Treatment Strategies in Hepatitis C

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Abstract

Chronic infection with hepatitis C virus (HCV) is common, but underdiagnosed and undertreated worldwide. The most important treatment outcome in HCV is sustained virological response (SVR), due to its impact on reducing the risks of liver-related mortality, hepatocellular carcinoma, and hepatic decompensation. The degree of baseline liver disease, IL28B genotype, and HCV genotype are important determinants of response to treatment, and SVR rates less than 50% can be expected for persons with genotype 1 receiving standard peginterferon with ribavirin. The rates are even lower when cirrhosis is present. There is little evidence supporting improved outcomes with peginterferon and ribavirin retreatment, and escalation of ribavirin dosage leads to an increased risk of adverse events. Introduction of the protease inhibitors, boceprevir and telaprevir, has resulted in SVR rates between 67% and 79% when used as part of a triple therapy regimen, which has become the standard of care for those with genotype 1 HCV. More work is needed to develop strategies to further improve treatment outcomes, and ideally to develop a vaccine to prevent the development of chronic HCV.

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For author information and disclosures, see end of text.

Estimates suggest that if 1998 treatment practices were in place from 2005 to 2025, then 196,000 (confidence interval [CI], 178,000-214,000) hepatitis C virus (HCV)-related deaths would occur during this period in the United States. If 15% of patients were treated and sustained virological response (SVR) were achieved in 80%, then 182,000 (CI, 165,000-198,000) HCV-related deaths would occur during that period. If 50% of patients were treated and 60% SVR were achieved, the death rate would be decreased to 160,000 (CI, 145,000-175,000). If 100% of patients were treated and 60% SVR were achieved, the mortality would be decreased to 124,000 (CI, 111,000-136,000).¹ In a recent meta-analysis, SVR was associated with a 77% reduction in liver-related mortality, a 79% reduction in hepatocellular carcinoma (HCC), and an 84% reduction in hepatic decompensation, compared with treatment failure.² These data highlight the importance of HCV treatment from a patient and public health perspective. This article, the second in a series of 3 articles focused on hepatitis C, will highlight the standard and newer treatment options in the context of guidelines and provide suggestions for incorporating newer options into treatment algorithms.

Rationale for Early and Effective Treatment

The goals of treatment are to prevent complications and death related to HCV. Since these outcomes are not easily measured due to the insidious progression of HCV complications over decades, the treatment of HCV centers around improving virological outcomes associated with quantitative polymerase chain reaction (PCR) HCV assays.³ The most important outcome is SVR, because it has been linked to a reduction in mortality.^{2,3} SVR is defined as a negative HCV ribonucleic acid (RNA) test 24 weeks after cessation of treatment, and is generally referred to as a virological cure. A rapid virological response (RVR) is defined as the clearance of HCV from serum by week 4 using a sensitive PCR-based assay with a lower limit of detection of 50 international units (IUs)/mL, although this may change with increased sensitivity of newer assays. Achieving an RVR is a strong predictor of achieving an SVR with therapy. An early virological response (EVR) is defined as a reduction of 2 log or more in HCV RNA level compared with baseline

HCV RNA level or negative HCV RNA at treatment week 12. Failure to achieve an EVR is a powerful predictor of failure to achieve an SVR. If an EVR or RVR is achieved, an end-of-treatment response (ETR) refers to undetectable virus at the end of a 24- or 48-week course. ETR does not predict SVR, but is a necessary predecessor. A relapse is said to occur when there is a reappearance of HCV RNA in serum after therapy is discontinued, but after an ETR is documented.³

When patients are still receiving treatment, several virological outcomes suggest poor response to treatment. A nonresponder refers to a patient who fails to clear HCV RNA from serum after 24 weeks of therapy, while a partial nonresponder exhibits a decrease of 2 log or less in HCV RNA, but a positive HCV RNA test result at week 24. A null nonresponder demonstrates failure to decrease HCV RNA by 2 logs or more after 24 week of therapy. A virological breakthrough occurs when there is reappearance of HCV RNA while still on therapy.³ These adverse virological events while on therapy are associated with a need for treatment regimen discontinuation or modification to optimize outcomes.

Historical Standard of Care Treatment Options

Historically, interferon-based therapies were the standard antiviral strategy for the initial management of HCV. The addition of ribavirin to interferon alfa-2b was found to be effective in improving SVR at 24 to 48 weeks of treatment compared with placebo (31%-38% vs 6%-13%; $P < .001$, respectively).⁴ Ribavirin plus interferon alfa-2b also improved SVR relative to interferon alfa-2b alone in relapsed patients (49% vs 5%, $P < .001$).⁵ Meta-analyses demonstrated that ribavirin plus interferon also improved SVR in patients who were non-responsive to initial interferon monotherapy, but this older regimen was only associated with a 14% to 15% success rate.^{6,7}

As peginterferon was introduced, it was compared with interferon-based treatment.^{8,9} Peginterferon has a polyethylene glycol molecule added to the interferon, which increases the half-life of the interferon molecule and allows for convenient dosing.⁸ Peginterferon alfa-2b plus ribavirin was compared with interferon alfa-2b for the initial treatment of HCV,⁸ with the dosing regimen being subcutaneous peginterferon 1.5 mcg/kg each week plus oral ribavirin 800 mg per day for 48 weeks, or peginterferon 1.5 mcg/kg each week subcutaneously for 4 weeks followed by 0.5 mcg/kg per week for 44 weeks plus ribavirin 1000 to 1200 mg per day. Interferon was dosed as 3 million units subcutaneously 3 times per week plus ribavirin 1000 to 1200 mg per day for

48 weeks. Ribavirin was dosed based on weight and the total daily dose was divided into 2 doses per day. In that trial, the SVR for the high-dose peginterferon alfa-2b regimen was 54%, which was higher than the rate for the low-dose peginterferon (47%, $P = .01$) or interferon (47%, $P = .01$) regimens. Among patients with genotype 1, the respective SVR rates were 42%, 34%, and 33%, while in patients with genotypes 2 and 3, SVR was achieved in approximately 80% of patients in all 3 treatment groups. In multivariate modeling, SVR was independently associated with non-genotype 1 patients, lower baseline viral load, lighter patient weight, and younger age. Presence or absence of cirrhosis in association with SVR could not be adequately assessed due to its low prevalence (5% to 7%) in the baseline population. Adverse effect profiles were similar among groups.⁸ Another study compared subcutaneous peginterferon alfa-2a 180 mcg once weekly plus ribavirin 1000 to 1200 mg daily, subcutaneous peginterferon alfa-2a 180 mcg once weekly plus placebo, and interferon alfa-2b 3 times weekly plus ribavirin 1000 to 1200 mg daily for 48 weeks. The rate of SVR was greater with peginterferon alfa-2a plus ribavirin (56%) than interferon alfa-2b plus ribavirin (44%, $P < .001$) or peginterferon alfa-2a alone (29%, $P < .001$). Among patients with genotype 1, the respective SVR rates were 46%, 36%, and 21%. The incidence of influenza-like symptoms ($P = .02$) and depression ($P = .01$) was lower in the peginterferon groups.⁹ These studies indirectly suggested similar efficacy of the peginterferon products when combined with ribavirin, and improvement in SVR relative to interferon with ribavirin.^{8,9}

A head-to-head study of the peginterferon products was conducted to determine the therapy of choice for HCV.¹⁰ In the study, patients with HCV genotype 1 who were previously untreated were randomized to undergo 48 weeks of peginterferon alfa-2b 1.5 mcg/kg per week plus ribavirin 800 to 1400 mg per day, or a low dose of 1 mcg/kg per week plus ribavirin 800 to 1400 mg per day, or peginterferon alfa-2a 180 mcg per week plus ribavirin 1000 to 1200 mg per day. SVR was achieved in 39.8% of the standard-dose peginterferon alfa-2b group, 38% of the low-dose peginterferon alfa-2b group, and 40.9% of the peginterferon alfa-2a group ($P = NS$ for all comparisons). Relapse occurred in 23.5%, 20%, and 31.5% of patients, respectively (P value not assessed). However, when HCV RNA was undetectable at week 4, 86.2% achieved an SVR, and when the virus was undetected at week 12, SVR was achieved in 78.7% of patients. The adverse effect profile was similar among all 3 regimens, with more serious adverse events occurring among patients in the peginterferon alfa-2a group (11.7%) than among patients in the standard dose peginterferon

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alfa-2b group (8.6%, $P = .02$). Common adverse effects included discontinuation for any reason (low-dose peginterferon alfa-2b, 51.5%; standard-dose peginterferon alfa-2b, 47%; peginterferon alfa-2a, 40%), discontinuation for virological non-response (low-dose peginterferon alfa-2b, 35.1%; standard-dose peginterferon alfa-2b, 25.7%; peginterferon alfa-2a, 20.4%), neutrophil count less than 750 per mm^3 (14.6%-27%), hemoglobin less than 10 g/dL (25.3%-30.7%), use of an erythrocyte-stimulating agent (14.2%-16.6%), fatigue (64.4%-66.5%), headache (42.3%-49.9%), nausea (36.4%-42.5%), insomnia (38.3%-41.4%), pyrexia (22.9%-34.9%), anemia (28.8%-33.9%), myalgia (22.5%-26.9%), neutropenia (18.5%-31.5%), depression (19.4%-25.5%), irritability (25.1%-25.8%), and rash (21.9%-28%). Dose modification was necessary in 33.3% of patients in the low-dose peginterferon alfa-2b group, 43.3% of patients in the standard-dose peginterferon alfa-2b group, and 42.9% of patients in the peginterferon alfa-2a group; the majority of these involved modification of the ribavirin component of the regimen.¹⁰

Peginterferon and ribavirin regimens have also been utilized for other clinical scenarios, including patients with hepatitis C and cirrhosis, patients experiencing treatment failure, and patients co-infected with HIV.¹¹⁻¹⁶ Studies have demonstrated that higher-risk patients had lower SVR rates, ranging from 18% to 35%, and that high-dose ribavirin increased efficacy, but also increased adverse effects, such as anemia. The studies also demonstrated that non-Hispanic white patients had a higher rate of SVR with peginterferon alfa plus ribavirin (52%) than black patients (19%, $P < .001$), primarily in patients with genotype 1 (98%).¹⁶ The results highlight the differential response to treatment based on patient demographic characteristics, and suggest that in most situations, an SVR rate of less than 50% may be expected with standard doses of peginterferon with ribavirin.

Evidence-Based Treatment Guidelines and Limitations of Current Treatment Options

Treatment guidelines focused on standard therapies suggest that treatment decisions should be based on the severity of liver disease, potential for serious adverse effects, likelihood of treatment response, presence of comorbid conditions, and patient acceptance of treatment.³ Although treatment with peginterferon with ribavirin is no longer the standard of care for genotype 1 HCV, it is the foundational regimen for current triple drug regimens, so clinicians should understand the standard approach to treatment.

For patients with genotype 1 and 4, historical guidelines suggested that peginterferon plus ribavirin should be planned

for 48 weeks, using peginterferon alfa-2a 180 mcg subcutaneously per week with oral ribavirin 1000 mg for patients weighing 75 kg or less, and ribavirin 1200 mg for patients over 75 kg, or peginterferon alfa-2b 1.5 mcg/kg subcutaneously per week with ribavirin 800 mg for patients up to 65 kg, 1000 mg for patients 65 kg to 85 kg, 1200 mg for patients 85 kg to 105 kg, and 1400 mg for patients over 105 kg. Follow-up HCV RNA testing should occur at week 12 for assessment of EVR, and treatment should be discontinued in patients who do not achieve an EVR. If a complete EVR is obtained, treatment may continue for a total of 48 weeks. For patients with a partial EVR, a 24-week HCV RNA assessment should be conducted, and if negative, treatment should be continued to 48 weeks, and if positive, therapy should be discontinued. In patients with genotype 1 who have delayed virus clearance, therapy may be extended to 72 weeks. Patients who achieve negative HCV RNA should be assessed 24 weeks after treatment for SVR. In patients with genotype 2 or 3, treatment with standard dose peginterferon and ribavirin 800 mg for 24 weeks is recommended. Genotype 2 or 3 patients who achieve negative HCV RNA at 24 weeks should be assessed 24 weeks after treatment for SVR.

Patients with cirrhosis who achieve SVR should be monitored at 6-month intervals for HCC regardless of genotype. Retreatment of patients who fail to achieve SVR after a full course of peginterferon and ribavirin is not recommended. Retreatment (with triple therapy, which is discussed later) may be considered for non-responders, partial responders, and relapsers who have been previously treated with non-pegylated interferon-based therapy or with peginterferon monotherapy. Careful assessment is needed and retreatment risks and benefits must be discussed with patients who were cirrhotic null responders to previous therapy, as these patients appear to have low response rates and high resistance rates to triple therapy. Maintenance with pegylated interferon alone is not recommended for bridging fibrosis or cirrhosis in patients who experienced treatment failure with peginterferon and ribavirin.³

SVR attainment is independently associated with improvements in mortality rate and adverse liver-related outcomes.¹⁻³ Patients with genotype 1 and/or high-risk features (eg, bridging fibrosis, cirrhosis) also exhibit reduced response to conventional interferon-based treatments.¹¹⁻¹⁶ New guidelines from the American Association for the Study of Liver Diseases published in 2011 include triple therapy antiviral regimens due to the introduction of newer agents.¹⁷ The guidelines provide an update on treatment strategy and indicate that triple therapy with peginterferon alfa, ribavirin, and boceprevir or telaprevir is currently the optimal strategy.

Standard doses from the cited trials are recommended.¹⁸⁻²⁴ Treatment decisions are based on treatment experience (treatment naïve vs treatment experienced) and on disease severity (without cirrhosis vs with cirrhosis).¹⁷ The guidelines for HCV genotype 1 provide the same level of recommendation for both boceprevir or telaprevir, and advise against their use without both peginterferon and ribavirin.¹⁷ One treatment strategy was mapped into 2 algorithms, as shown in **Figures 1** and **2**.²⁵ For treatment-naïve patients, the telaprevir dose is 750 mg orally (with food, 3 times per day) with peginterferon and ribavirin for 12 weeks, followed by 12 to 36 weeks of peginterferon and ribavirin. In patients without cirrhosis and an undetectable HCV RNA at weeks 4 and 12, the total duration may be shortened to 24 weeks. Patients with cirrhosis should receive a total of 48 weeks of therapy. All 3 drugs should be stopped if HCV RNA is greater than 1000 IU/mL at weeks 4 or 12, or is detectable at week 24. For treatment-naïve patients who will be treated with boceprevir, 800 mg is administered orally with food 3 times per day along with peginterferon and ribavirin for 24 to 44 weeks, following a 4-week peginterferon and ribavirin lead-in phase. In patients without cirrhosis and an undetectable HCV RNA at weeks 8 and 24, therapy may be stopped at week 28 after a 4-week lead-in phase with peginterferon and ribavirin, and a 24-week course of triple therapy. If HCV RNA is greater than 100 IU/mL at week 12 or detectable at week 24, triple therapy should be stopped.^{17,25}

New Options and Opportunities in HCV

The limitations of standard therapies have led to the development of medications directed at improving outcomes associated with HCV.¹⁷ Medications from 1 class of direct-acting agents (DAAs), the NS3/4A serine protease inhibitors (PIs), are available on the market. These agents inhibit enzymatic activity by mimicking the cleavage end product of the proteolytic reaction in HCV. Within this class of agents, telaprevir and boceprevir are currently available.²⁶⁻²⁸

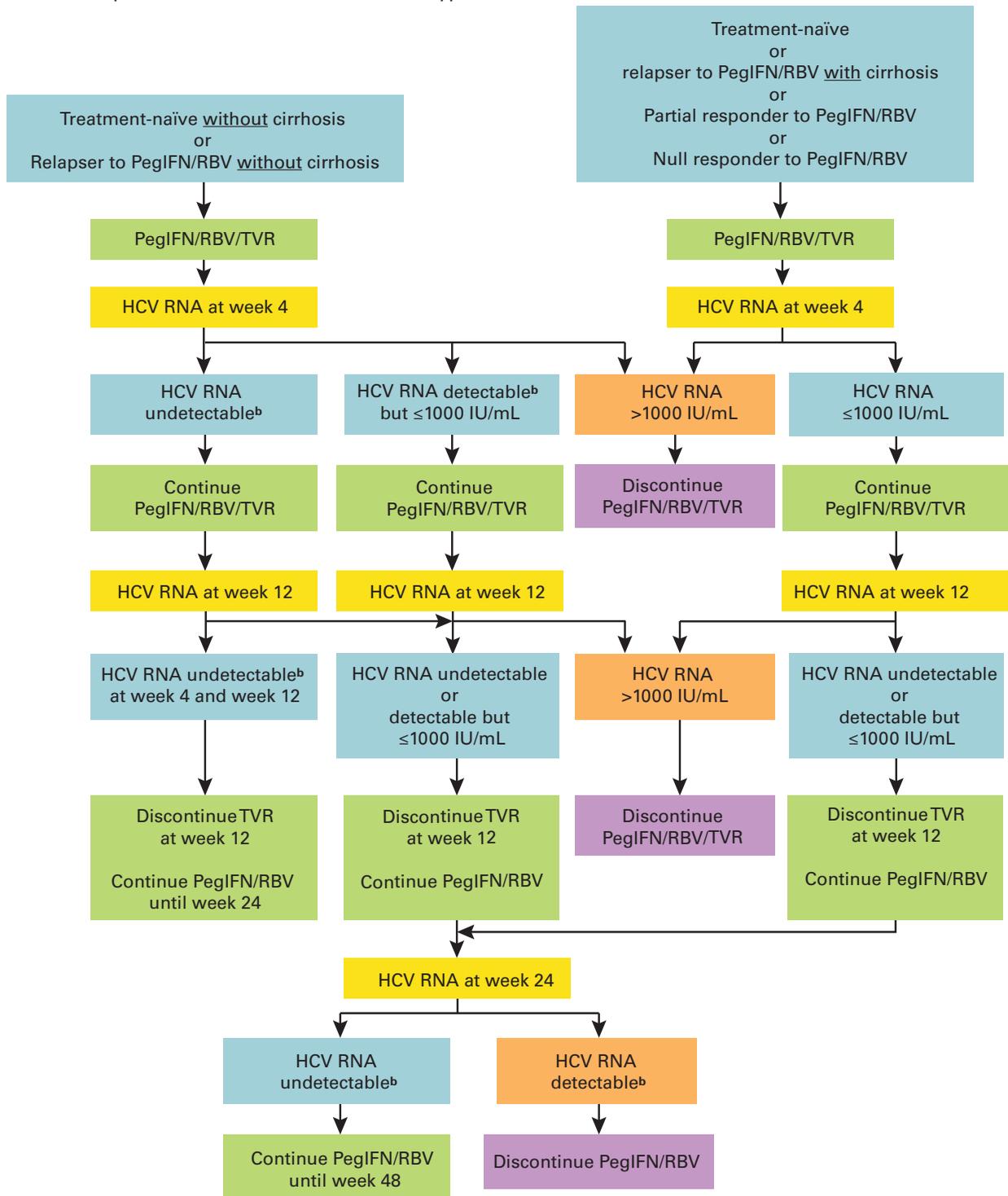
Telaprevir was studied with peginterferon alfa-2a 180 mcg per week subcutaneously and ribavirin 1000 mg to 1200 mg per day for 48 weeks in patients with HCV genotype 1 in the PROVE1 study.¹⁸ Telaprevir was given as 1250 mg on day 1 and 750 mg every 8 hours for 12 weeks, 24 weeks, or 48 weeks. Telaprevir was compared with placebo for 48 weeks. The rates of SVR were 41% (placebo), 35% (12 weeks), 61% (24 weeks; $P = .02$ vs placebo), and 67% (48 weeks; $P = .002$ vs placebo). Viral breakthrough occurred in 7% of telaprevir-treated patients, but discontinuation due to adverse effects occurred in 21% of the telaprevir groups and 11% of the placebo group, with rash being the most common

reason for discontinuation.¹⁸ In another study (PROVE2), telaprevir and peginterferon alfa-2a were evaluated with or without ribavirin in patients with chronic hepatitis C genotype 1.¹⁹ Telaprevir was given as 1250 mg on day 1 and 750 mg every 8 hours for 12 weeks with peginterferon alfa-2a 180 mcg weekly and ribavirin dosed according to body weight for 24 weeks, or telaprevir, ribavirin, and peginterferon for 12 weeks, or telaprevir and peginterferon without ribavirin for 12 weeks, or peginterferon with ribavirin and placebo for 48 weeks. The respective rates for SVR were 69%, 60% ($P = .12$ vs placebo), 36% ($P = \text{NS}$ vs telaprevir, ribavirin, and peginterferon for 12 weeks), and 46% ($P = .004$ vs telaprevir with peginterferon and ribavirin). Telaprevir-related adverse events included rectal side effects, rash, and anemia.¹⁹ These results demonstrated that telaprevir improved SVR compared with standard therapy.

In patients who had received previous treatment, telaprevir in combination with peginterferon alfa-2a plus ribavirin was compared with peginterferon alfa-2a plus ribavirin in 2 studies.^{23,24} In 1 of those studies, patients with genotype 1 who had not developed an SVR on peginterferon alfa plus ribavirin received a telaprevir 1125-mg loading dose, then 750 mg 3 times daily for 12 weeks with peginterferon alfa plus ribavirin for 24 weeks, telaprevir for 12 weeks with 48 weeks of peginterferon alfa plus ribavirin, telaprevir for 24 weeks with peginterferon alfa plus ribavirin for 24 weeks, or peginterferon plus ribavirin for 24 weeks. SVR occurred in 51%, 53%, 24%, and 14% of patients, respectively. All active comparators had statistically improved outcomes relative to peginterferon alfa plus ribavirin.²³ In another study (REALIZE), patients with genotype 1 who had no response, partial response, or relapse on peginterferon plus ribavirin were randomized to receive telaprevir for 12 weeks with 48 weeks of peginterferon alfa-2a plus ribavirin, peginterferon alfa plus ribavirin for 4 weeks followed by 12 weeks of telaprevir plus peginterferon alfa and ribavirin with an additional 32 weeks of peginterferon alfa and ribavirin, or 48 weeks of peginterferon alfa plus ribavirin. In patients with a previous relapse, SVR rates were 83%, 88%, and 24%, respectively. Patients with a previous partial response had SVR rates of 59%, 54%, and 15%, respectively, and patients with no previous response had respective SVR rates of 29%, 33%, and 5%. Anemia, neutropenia, and leukopenia were more common in the telaprevir groups. These results highlight the beneficial effect of telaprevir in patients with previous inadequate response to dual therapy with peginterferon plus ribavirin, regardless of whether or not a telaprevir lead-in phase was used.^{23,24}

In the SPRINT-1 study, boceprevir was given in combination with peginterferon alfa-2b and ribavirin to patients with

■ Figure 1. Telaprevir (TVR)/Peginterferon (PegIFN)/ribavirin (RBV) Algorithm for Both Treatment-Naïve and Treatment-Experienced Patients With HCV Genotype 1^{25,a}



HCV indicates hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; RNA, ribonucleic acid; TVR, telaprevir.

^aPegIFN alfa-2a 180 mcg per week or PegIFN alfa-2b 1.5 mcg/kg per week. RBV (in 2 divided doses) with food: <75 kg: 1000 mg per day or ≥75 kg: 1200 mg per day; alternative weight-based RBV dosing: <65 kg: 800 mg/d, 65-85 kg: 1000 mg/d, >85-105 kg: 1200 mg/d, >105 kg: 1400 mg per day. TVR 750 mg (two 375 mg tablets) orally every 8 h with food (20 g fat).

^bA sensitive real-time quantitative HCV RNA assay with a lower limit of detection of <10-15 IU/mL should be used for decision making to determine treatment duration with response-guided therapy.

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hepatitis C genotype 1 to assess SVR.²⁰ Patients were randomized to peginterferon alfa-2b 1.5 mcg/kg weekly plus ribavirin 800 to 1400 mg daily for 48 weeks (control group), or peginterferon alfa-2b and daily ribavirin for 4 weeks followed by peginterferon alfa-2b, daily ribavirin, and boceprevir 800 mg 3 times daily for 24 weeks or 44 weeks, or peginterferon alfa-2b, daily ribavirin, and boceprevir 800 mg 3 times daily for 28 weeks or 48 weeks. An additional part of the study assessed patients randomly assigned to peginterferon alfa-2b, daily ribavirin, and boceprevir 800 mg 3 times daily for 48 weeks versus peginterferon alfa-2b, boceprevir 800 mg 3 times daily, and low-dose ribavirin (400-1000 mg) for 48 weeks. The rate of SVR was 38% in the control group, 54% in the 28-week group ($P = .013$ vs control), 56% in the in the 4-week lead-in plus 24-week treatment group ($P = .005$ vs control), 67% in the 48-week group ($P < .0001$ vs control), and 75% in the 4-week lead-in plus 44-week treatment group ($P < .001$ vs control). Low-dose ribavirin was associated with breakthrough (27%) and relapse (22%), which was similar to control (24%). Patients in the boceprevir groups had higher rates of anemia (55% vs 34%) and dysgeusia (27% vs 9%) than patients in the control group. These results suggested that boceprevir after a 4-week lead-in phase with peginterferon alfa-2b and ribavirin improved SVR compared with standard treatment.²⁰

Boceprevir was also studied in patients with prior non-response to peginterferon-ribavirin.²¹ In RESPOND-2, all patients received peginterferon alfa-2b and ribavirin at standard doses for 4 weeks, followed by peginterferon alfa-2b and ribavirin at standard doses plus placebo for 44 weeks (control), peginterferon alfa-2b and ribavirin at standard doses plus boceprevir for 32 weeks, or peginterferon alfa-2b and ribavirin at standard doses plus boceprevir for 44 weeks. Respective SVR rates were 21%, 59% ($P < .001$ vs control), and 66% ($P < .001$ vs control).²¹ The most common adverse effect of boceprevir and telaprevir was anemia. Skin disorders (eg, rash, pruritis) occurred more frequently in the telaprevir-based regimens. In most cases, these adverse effects are manageable and do not require discontinuation, but approximately 5% of rashes are severe and do require discontinuation.²²

For treatment-experienced patients, retreatment with either telaprevir or boceprevir with peginterferon and weight-based ribavirin is recommended for patients with virological relapse or those who were partial responders to interferon alfa or peginterferon alfa and/or ribavirin.¹⁷ Retreatment with telaprevir, peginterferon, and ribavirin may be considered for prior null responders to interferon alfa or peginterferon alfa and/or ribavirin. Response-guided

retreatment is summarized in the algorithms in Figures 1 and 2. Based on available evidence, and in the absence of head-to-head comparisons, response rates to telaprevir-based regimens appear superior.^{21,23,24}

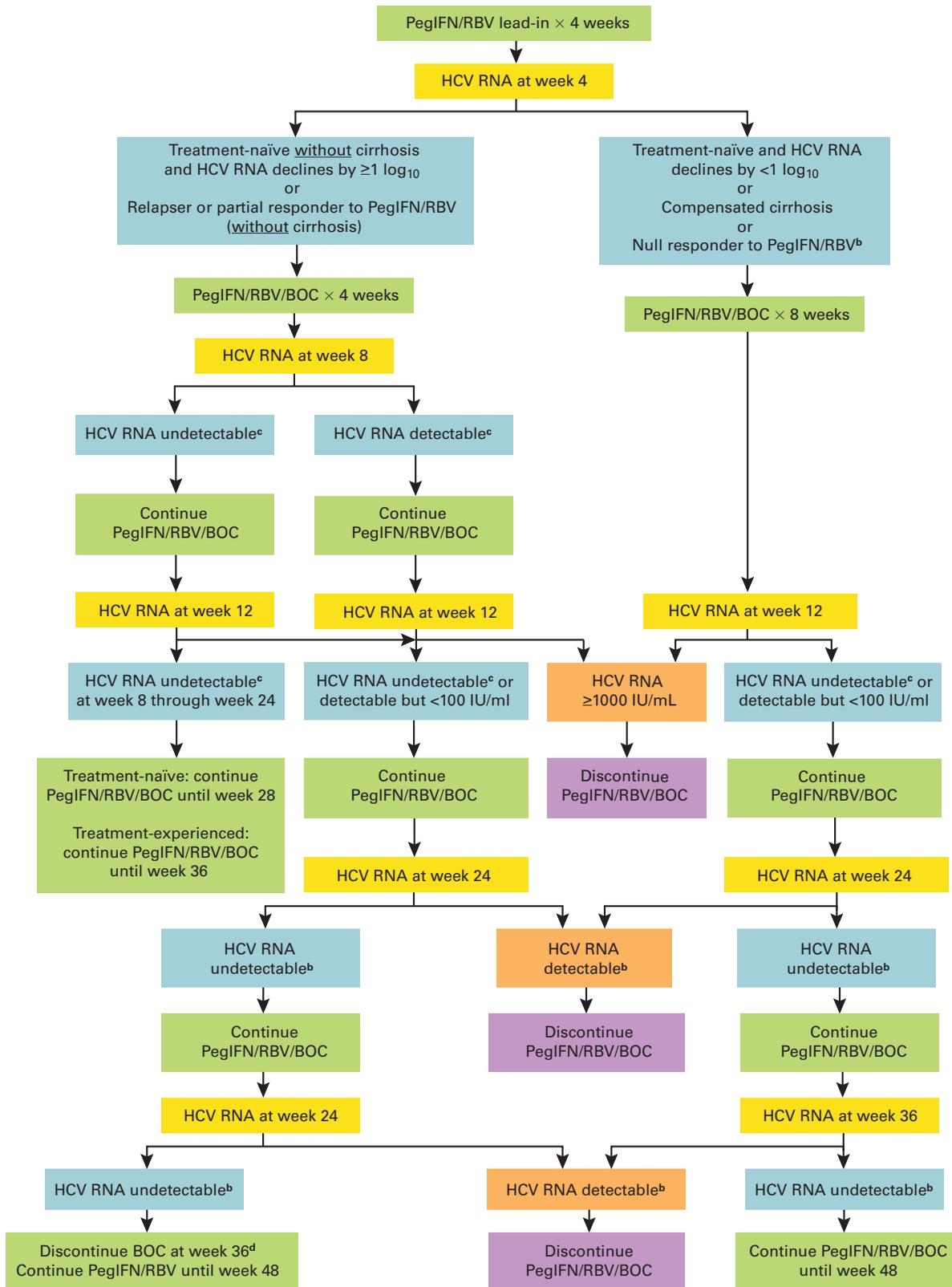
Predictors of Treatment Outcomes

As discussed previously, SVR is the most powerful predictor of improved clinical outcomes in HCV. RVR on therapy is important, because it is an accurate predictor of whether an SVR is likely to be achieved, and is measurable earlier in the treatment course.³ Before treatment is initiated, the presence of genotype 1 is associated with an increased risk of treatment failure to standard antiviral therapies.^{29,30} Non-response to peginterferon with ribavirin has been associated with interleukin (IL)28 gene single nucleotide polymorphisms.³¹ SVR rates with the favorable C/C genotype range from 60% to 80%, and less than 30% for the less favorable C/T or T/T genotypes.³² The IL28B genotype is so important that its assessment has been endorsed by the US Food and Drug Administration for stratification in trials of agents for HCV.³² The importance of IL28 genotype appears to be lessened for patients on triple drug regimens, but it is still an important clinical consideration (Table).³³ The Table also highlights the importance of other factors such as liver disease, genetic background, and HCV viral load.³³ Response rates are lower in non-Caucasian populations. Additionally, higher viral loads and/or more extensive liver disease (extensive fibrosis or cirrhosis) are associated with a lower response to treatment. During treatment (with triple therapy), higher response rates may be observed in patients developing anemia or a more significant hemoglobin decline. Virological response rates may also be used to tailor the duration of therapy if a positive outcome is achieved.³³ One study in patients with HCV genotype 1 on telaprevir with peginterferon and ribavirin who were non-responders to peginterferon and ribavirin characterized the determinants of response.³⁴ In the study, SVR on triple therapy was predicted by Arg70 substitution in the core protein of HCV-1b (66.7% vs 0% Gln70[His70]; $P = .015$), by partial response to previous treatment (50% vs 0% null response; $P = .077$), and especially by Arg70 plus a partial response (80% vs 0% without both findings; $P = .004$). ETR was higher in patients with low-level (<10 mcg/L) alpha-fetoprotein (81.8% vs 0% with higher levels; $P = .011$), in addition to previous partial response ($P = .041$).³⁴

Emerging Therapeutic Options

The pharmacologic pipeline for agents targeting HCV is immense.²⁶ Agents similar in mechanism to telaprevir

Figure 2. Boceprevir (BOC)/Peginterferon (PegIFN)/Ribavirin (RBV) Algorithm for Both Treatment-Naïve and Treatment-Experienced Patients With HCV Genotype 1^{25,a}



(Figure 2 footnotes are at bottom of adjacent page.)

■ **Table. Factors Associated With SVR to Triple Therapy With Peginterferon/Ribavirin/HCV Protease Inhibitors³³**

Pretreatment response factors	
Host factors	
IL28B genotype	Lower response rates in patients carrying the T allele of the rs12979860 SNP; less important in triple therapy than in PEG-IFN α /RBV therapy
Stage of liver disease	Lower response rates in patients with advanced fibrosis/cirrhosis
LDL levels	Higher SVR in patients with high LDL levels (only telaprevir studies)
Genetic background	Lower response rates in non-white (Caucasian) populations, higher responses in Asian patients
Viral factors	
HCV genotype 1a vs 1b	Lower response rates in patients with HCV genotype 1a. Becomes more important in patients with other poor response factors
Baseline viral load	Slightly lower SVR rates in patients with very high baseline HCV RNA levels (>2 x 10 ⁶ IU/mL)
On-treatment response factors	
Virological response during PEG-IFN α /RBV "lead-in" phase	Response to PEG-IFN α /RBV after 4 weeks is associated with SVR both in treatment-naïve and in treatment-experienced patients May identify patients that do not need PI-containing treatment
Virological response during triple therapy	Response-guided therapy (24 [28] vs 48 weeks of treatment) is based on the response after 4 weeks of PI treatment. Stopping rules based on week 4-8-12 response during PI therapy
Anemia/hemoglobin decline	Higher response rates in patients developing anemia or a >3 g/dL hemoglobin decline
<p>HCV indicates hepatitis C virus; LDL, low density lipoprotein; PEG-IFN, pegylated interferon; PI, protease inhibitor; RBV, ribavirin; SNP, single nucleotide polymorphism; SVR, sustained virological response. Reprinted with permission from Dusheiko G, Wedemeyer H. New protease inhibitors and direct-acting antivirals for hepatitis C: interferon's long goodbye. <i>Gut</i>. In press.</p>	

and boceprevir are in development, as are agents that differ in mechanism. The NS3/4A PIs telaprevir and boceprevir represent linear (covalent) ketoamide derivatives, but non-covalent macrocyclic PIs are also in development. Among the noncovalent molecules, danoprevir and vaniprevir are emerging.²⁶ In addition, NS5B RNA-dependent RNA polymerase inhibitors, nucleoside inhibitors of HCV polymerase, non-nucleoside inhibitors of HCV polymerase, NS5A inhibitors, NS4B inhibitors, host cofactor inhibitors of cyclophilin A, and HMG CoA reductase inhibitors are being studied.^{26,28} A majority of these agents are in various phases of research. A site 3 and 4 non-nucleoside inhibitor, tegobuvir, is being studied alone and in a ritonavir-boosted formulation for use with peginterferon plus ribavirin, but SVR rates were similar to peginterferon-ribavirin dual therapy, ~56%. Another mol-

ecule targeting NS5A, BMS-790052, is administered once per day and has demonstrated promising results (36% SVR) in combination with peginterferon-ribavirin in previous null responders.²⁶

In addition, quadruple drug regimens and all-oral regimens are being developed, with promising results.^{35,36} In one open-label phase 2a study, patients with HCV genotype 1 infection who had not experienced a response to previous therapy (ie, had not had ≥ 2 log decline in HCV RNA after ≥ 12 weeks of treatment with peginterferon and ribavirin) were randomly assigned to receive the NS5A replication complex inhibitor daclatasvir (60 mg once daily) and the NS3 protease inhibitor asunaprevir (600 mg twice daily) alone (group A) or in combination with peginterferon alfa-2a and ribavirin (group B) for 24 weeks.³⁷ In group A, 36% of patients achieved SVR

⇐ HCV indicates hepatitis C virus; PegIFN, peginterferon; RBV, ribavirin; RNA, ribonucleic acid; TVR, telaprevir.

^aPegIFN alfa-2a 180 mcg per week or alfa-2b 1.5 mcg/kg/wk. RBV (in 2 divided doses) with food: less than 75 kg: 1000 mg per day or 75 kg and over: 1200 mg per day; alternative weight-based RBV dosing: less than 65 kg: 800 mg per day, 65 to 85 kg: 1000 mg per day, 86 to 105 kg: 1200 mg per day, over 105 kg: 1400 mg per day. BOC 800 mg (four 200 mg capsules) orally every 8 h with food.

^bA sensitive real-time quantitative HCV RNA assay with a lower limit of detection of <10-15 IU/mL should be used for decision making to determine treatment duration with response-guided therapy.

^cBOC was not studied in null responders; this population was excluded from the Phase 3 study of patients who had previously failed treatment. Efficacy data and US Food and Drug Administration labeling for this population is based solely on mathematical modeling.

^dDiscontinuation of BOC at week 36 is supported by modeling, but was not directly studied in the clinical trials. Following a 4-week lead-in with PegIFN-RBV, the addition of BOC to Peg-RBV for 44 weeks achieved higher sustained virologic response compared with 24 weeks in late responders (detectable HCV RNA at week 8) in the registration trials.

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at 12 weeks and 24 weeks after treatment, establishing feasibility of achieving a response with only DAAs. All patients in group B had an SVR at 12 weeks after treatment, and 90% had an SVR at 24 weeks after treatment. Diarrhea was the most common adverse event in both groups; transient elevations of alanine aminotransferase levels to more than 3 times the upper limit of the normal range also occurred.

A vaccine is needed due to the urgent public health issues associated with HCV; however, the high degree of mutability of the HCV genome and limited knowledge of the protective immune response following infection has hindered progress in vaccine development.^{38,39}

Summary

SVR is the most important treatment outcome of HCV, because it is associated with a reduction in liver-related mortality, HCC, and hepatic decompensation. The protease inhibitors, boceprevir and telaprevir, have demonstrated SVR rates of up to 79% when used as part of a triple therapy regimen, and are now considered the standard of care. Currently, RVR is the best predictor of SVR. Response rates in patients considered to have experienced prior treatment failure have been very promising with triple therapy regimens. More work is needed to develop strategies to further improve treatment outcomes, and to develop a vaccine to prevent the development of HCV.

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