Clinical Roundtable Monograph

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New Developments in the Treatment of Hepatitis C Virus (HCV): A Roadmap for the Diagnosis, Treatment, and Management of Patients with HCV

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Abstract

Chronic hepatitis C virus (HCV) infection represents a major public health concern, as this condition can cause a number of serious consequences and its incidence is rising in the United States. For many years, the standard-of-care therapy for patients with genotype 1 HCV infection was a combination of pegylated interferon and ribavirin. While effective in many patients with genotype 1 HCV infection, this regimen is not universally effective: A number of patients either fail to respond to this treatment or relapse after treatment. The introduction of 2 novel agents—telaprevir and boceprevir—promises to change the treatment paradigm for patients with genotype 1 HCV infection, as these new agents can boost rates of sustained virologic response when combined with pegylated interferon and ribavirin. In this roundtable, several experts discuss HCV screening and assessment; review data from the clinical trials that led to the US Food and Drug Administration's approval of telaprevir and boceprevir; and describe some of the issues associated with these new agents, including their unique adverse events. In addition, treatment algorithms in this monograph illustrate the dosing schedule and stopping rules for both agents.

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists, hepatologists, and other healthcare professionals involved in the treatment of patients with hepatitis C virus (HCV) infection.

Statement of Need/Program Overview: The diagnosis and treatment of HCV continues to experience enormous advancements affecting many elements of managing HCV. The gastroenterology clinician must remain on top of these advancements, since hepatologists are operating at capacity, and much of the care for these patients will be in gastroenterology clinics. Both hepatologists and gastroenterologists must be knowledgeable about all diagnostic and treatment options that are available for managing HCV-infected patients, as well as learn, understand, and effectively utilize these advancements. Most busy hepatologists and gastroenterologists are unable to attend all of the meetings during the year where these data are presented. However, repetitive exposure to clinical results appears to increase awareness and allows clinicians to incorporate this new information into practice. Further, providing a roadmap and tools for diagnosis, treatment, and management will increase integration of this information.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Explain the latest developments in the treatment of HCV, including screening, diagnosis, and assessment.
2. Differentiate emerging investigational compounds from existing agents used in the treatment of patients with HCV.
3. Assess the potential clinical implications, including improving treatment response and outcomes, of new anti-HCV agents in patients with chronic HCV infection using findings from clinical trials evaluating these agents.
4. Effectively apply the results of pivotal clinical research to the clinical management of patients with HCV infection.
5. Discuss how this new information can be integrated into the care of HCV-infected patients.

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New Developments in HCV Screening, Diagnosis, and Assessment

Bruce R. Bacon, MD

In order to benefit from new hepatitis C virus (HCV) treatments, patients first must be diagnosed. Currently, HCV screening employs a risk-based approach, but age-based screening has also been considered and may prove beneficial. Patients who are selected for screening can undergo testing via either serologic or molecular assays. If patients test positive for HCV infection, several factors should then be assessed, including HCV genotype, liver enzyme levels, disease severity, the presence of co-infections or other comorbidities, and the patient's interleukin-28B (*IL-28B*) genotype, all of which can help to guide the selection of appropriate therapy. See Table 1 for a summary of key points related to HCV screening, diagnosis, and assessment.

Current Screening Recommendations

Current screening recommendations for HCV employ a risk-based approach, in which the primary care physician or general internist queries patients regarding their risk factors. These recommendations are largely based on practice guidelines published by the Centers for Disease Control and Prevention (CDC) and the American Association for the Study of Liver Diseases (AASLD).[1,2]

The CDC practice guidelines state that individuals should be routinely tested for HCV infection based on their risk for infection. In addition, the CDC recognizes that screening should be performed for anyone who wishes to know or is concerned about his or her HCV infection status. According to practice guidelines produced by the AASLD, all persons should be screened for behaviors that place them at high risk for HCV infection. Those who are at risk based on these criteria should then be tested for the presence of HCV infection. Neither the CDC nor the AASLD guidelines recommend routine HCV infection screening in the general population.

The AASLD and CDC guidelines identify several at-risk groups; patients in these groups are most likely to be infected with HCV and should be routinely tested. These groups are listed in Table 2. These risk factors were validated among a group of 1,000 randomly selected patients who attended an inner-city primary care clinic.[3] This study confirmed that patients were more likely to be HCV-infected if they had risk factors in their medical history (blood transfusions, dialysis, abnormal liver enzymes), exposure history

Table 1. Screening, Diagnosis, and Assessment of Patients with Hepatitis C Virus (HCV) Infection

- **Screening**
  - Current screening approach is based on assessment of risk factors
  - Age-based screening is also being considered
- **Diagnosis**
  - Serologic assays detect the presence of anti-HCV antibodies
    - Both laboratory-based and point-of-care assays are available
  - Molecular assays detect HCV RNA
    - Can be qualitative or quantitative
    - Quantitative assays have sensitivities as low as 10–50 IU/mL
- **Assessment**
  - HCV genotype should be determined
    - Genotype 1 is most common in the United States
    - Genotypes 2 and 3 are traditionally easier to treat
  - Liver biopsy can be beneficial in some patients
    - Can help to determine the extent of a patient's liver disease
    - Use of biopsy is limited by associated risks, potential for sampling error, need for expert interpretation, and cost
  - Measure liver enzyme levels
    - Up to 30% of HCV-infected patients exhibit persistently normal liver enzyme levels
    - Natural history of HCV infection is much milder in patients with persistently normal alanine aminotransferase levels
  - Check for co-infection
    - Hepatitis B virus
    - HIV
  - Check for potential comorbidities
    - Autoimmune liver disease
    - Hemochromatosis
    - α1 antitrypsin deficiency
    - Wilson disease
  - Consider assessment of patient's genotype (ie, interleukin-28B status)
    - Can predict natural viral clearance ability and response to treatment
    - In patients with genotype 1 HCV infection, CC genotype is associated with higher rates of sustained virologic response

Table 2. Individuals at Higher Risk for Hepatitis C Virus (HCV) Infection

- Persons who have ever injected illegal drugs, either in the recent or remote past. This group includes individuals who injected only 1 time and who do not identify as drug users.
- Persons with conditions associated with a high prevalence of HCV infection. These may include individuals with hemophilia who received clotting factor concentrates produced prior to 1987; individuals who have ever been on hemodialysis; HIV-infected individuals; and individuals with unexplained abnormal liver enzyme findings.
- Persons who received a transfusion of blood or a blood component or who underwent organ transplantation prior to July 1992.
- Healthcare personnel, emergency medical workers, and public safety employees who are exposed to HCV-positive blood via needle sticks, sharps, or mucosal exposure.
- Children born to HCV-positive mothers.
- Current sexual partners of HCV-infected persons.

(any blood contact), and/or social history (previous or current illicit drug use, incarceration, past or current sexual activity). Multivariate analysis showed that each of these domains was significantly associated with increased odds of HCV infection. The medical history odds ratio (OR) was 1.9 (95% confidence interval [CI], 1.1–3.6; *P*=.03), exposure history OR was 3.4 (95% CI, 2.0–5.9; *P*<.01), and social history OR was 6.1 (95% CI, 3.7–10.3; *P*<.01).

In 2004, the US Preventive Services Task Force (USPSTF) released recommendations for HCV screening that differed in many ways from the recommendations already developed by the CDC and the AASLD.[4] In some regards, the USPSTF guidelines align with current CDC and AASLD guidelines; for example, the USPSTF guidelines state that HCV testing is not recommended for patients with no specific risk factors for infection and no symptoms of liver disease, as there is insufficient scientific evidence to prove that HCV screening during routine healthcare is associated with improved patient outcomes. However, diverging markedly from the current CDC and AASLD guidelines, the USPSTF guidelines neither recommend nor recommend against routine HCV testing in patients with specific HCV-infection risk factors.

Overcoming Barriers to Optimal Screening

Unfortunately, a large number of HCV-infected individuals are not diagnosed when a risk-based screening approach is used. Indeed, estimates suggest that up to 80% of the HCV-infected population has not yet been identified.[5] Several barriers prevent diagnosis of HCV-infected persons under a risk-based screening paradigm. For example, individuals who used intravenous drugs many years earlier, especially those who did so sparingly, may not consider themselves to be at risk for HCV infection, and therefore they may hesitate to volunteer information about their prior drug use. In a qualitative study conducted among intravenous drug users, several barriers to HCV testing were identified, including perceptions of HCV infection as being relatively benign, fear of investigations and treatment, and feeling well.[6] Likewise, some patients who underwent surgery several years earlier may not remember or may not know whether they were given a blood transfusion. These factors represent significant barriers that can limit the effectiveness of risk-based screening policies.

Another major barrier to optimal utilization of risk-based HCV screening was demonstrated in a national survey of 1,412 primary care physicians in the United States.[7] The results of this survey showed that while the vast majority of respondents (>90%) were able to correctly identify the most common risk factors for HCV infection, only 59% reported that they asked all of their patients about these risk factors. Additionally, only 70% of respondents stated that they conducted HCV screening in all patients with a risk factor.

One potential alternative to current HCV screening practices is age-based screening. This screening strategy recognizes that the majority (75%) of the HCV-infected population was born between 1946 and 1964 (the so-called "Baby Boomers").[8,9] In the first study to examine age-based screening outcomes for HCV, McGarry and colleagues developed a Markov model to evaluate the effects of an age-based screening strategy; these data were presented during the 2011 Digestive Disease Week conference held May 7–10 in Chicago, Illinois.[10,11] In this study, a Markov model of the natural history of HCV and related liver disease was developed, and this model was used to calculate a lifetime estimate of HCV-related outcomes under 2 screening strategies: risk-based screening and age-based screening. In the age-based strategy, targeted screening was performed among adults born between 1946 and 1964. This detailed Markov model included several factors: the number of people screened, diagnosed, treated, and achieving sustained virologic response (SVR); the total number of cases of liver disease; and the total number of liver disease–related deaths. Notably, the potential impact of new antiviral therapies was not considered in this study.

A comparison of this model's age-based and risk-based screening strategies led to several significant conclusions. Approximately 1.3 million of the 102 million Americans between the ages of 40 and 64 years were estimated to be HCV-positive yet unaware of their condition. Importantly, approximately one third of these HCV-infected individuals

will have stage F3 or F4 fibrosis, which is consistent with the long-term duration of their infection. While 78.7 million of these individuals would be tested under an age-based screening strategy, only 8 million would be tested under the current risk-based screening strategy. Furthermore, while age-based screening could lead to the diagnosis of 1.3 million people with HCV infection, only 427,000 people would receive an HCV diagnosis under a risk-based screening strategy. Diagnosis of this many individuals under age-based or risk-based screening strategies would correspond to treatment of 742,000 and 235,000 HCV-positive individuals, respectively.

Thus, the model presented by McGarry and colleagues predicts that age-based screening with subsequent treatment could potentially prevent 113,000 cases of compensated cirrhosis, 53,000 cases of decompensated cirrhosis, 28,000 cases of hepatocellular carcinoma (HCC), 6,000 new liver transplantations, and 48,000 HCV-related deaths. While age-based screening was expected to incur higher costs nationally compared to risk-based screening ($45.1 billion vs $32 billion), costs related to advanced liver disease were expected to be lower ($21.7 billion vs $25.8 billion). Importantly, extending the lives of the affected individuals would cost $25,279 per quality adjusted life-year gained, which is lower than the willingness-to-pay threshold of most Americans.

The CDC is currently assessing the practicality and feasibility of routine, age-based HCV screening.[12] This strategy is being tested in the BEST-C study, which is being supported by a public-private partnership called the Viral Hepatitis Action Coalition. In the BEST-C study, collaborating medical centers will use a birth year–based approach in which onetime HCV screening will be recommended for all individuals born between 1945 and 1965. This study will assess the cost of this approach, the proportion of individuals who test positive for HCV, and the burden this approach places on medical staff and systems. The cost-benefit ratio of this age-based screening approach will be compared to the cost-benefit ratio of the current risk-based screening strategy in order to determine the effectiveness of each approach. Based on these results, the CDC expects to update its guidelines in 2012 to reflect new recommendations for HCV screening.

Current Methods for Diagnosis

If patients have been selected for HCV screening—whether via a risk-based or age-based approach—then a blood test is typically performed to look for signs of HCV infection. Two types of blood tests are available for diagnosis of HCV infection: serologic assays and molecular assays. Serologic assays are enzyme immunoassays designed to detect the presence of anti-HCV antibodies in the serum or plasma. Third-generation serologic assays have been shown to have a specificity of at least 99% in patients with chronic liver disease.[13] False positives are more prevalent in populations with a relatively low incidence of HCV, while false negatives are more likely in the setting of severe immunosuppression, as can occur in HIV-infected individuals or organ transplant recipients.[14-16]

Molecular assays are designed to measure the presence of viral nucleic acids (ie, HCV RNA) and can provide results that are either qualitative (detection only) or quantitative. While qualitative assays were historically considered to be more sensitive, their use has recently become more limited, as today's quantitative real-time polymerase chain reaction–based assays offer sensitivities down to 10–50 IU/mL.[1] The specificity of these assays is also high, ranging from 98% to 99%.[1]

In addition to laboratory-based assays, the first rapid HCV test recently gained approval from the US Food and Drug Administration (FDA); this test can detect HCV antibodies in whole blood obtained via a fingerstick or venipuncture. Designed for use in point-of-care settings such as doctors' offices or emergency rooms, this test provides results in 20 minutes. This test was evaluated in a multicenter, prospective study of individuals with signs and/or symptoms of HCV infection and individuals who were at risk for HCV infection, and the results of this test were compared with established laboratory-based tests for HCV detection.[17] The specificity of this test was found to be 99.6–99.9% in a number of specimen types (including venous blood, fingerstick blood, serum, plasma, or oral fluid), and the sensitivities were also very high (99.7–99.9% for venous blood, fingerstick blood, serum, and plasma; 98.1% for oral fluid).

According to the AASLD guidelines, diagnosis of HCV infection requires serum testing for both anti-HCV antibodies and HCV RNA.[1] Because the amount of HCV RNA present at baseline can be useful for patient management, the guidelines also suggest that a quantitative molecular assay be used when making the diagnosis. Once an HCV diagnosis is confirmed, patients should usually be referred to a specialist with experience in the management of HCV—typically a hepatologist, gastroenterologist, or infectious disease specialist. This need for specialist care is primarily due to the complex nature of the disease and the myriad of treatment options that are currently available.

Consequences of Delayed Diagnosis

Data from natural history studies indicate that over half (55–85%) of individuals who develop acute HCV infection will go on to develop chronic HCV infection.[18-20] Chronic HCV infection markedly increases the risk for progression to cirrhosis and HCC. Over a period of 3 decades, the risk of developing cirrhosis can be as high as 25% among

chronically HCV-infected individuals, and this risk may be accelerated among obese persons, those who are immunosuppressed (ie, patients who are co-infected with HIV), and patients who abuse alcohol.[21,22] Among individuals with HCV-related cirrhosis, there are also significant risks for development of hepatic decompensation (30% over 10 years) and progression to HCC (1–3%).[23] Ultimately, these patients face an increased risk of needing liver transplantation and/or dying of liver disease–related causes.

A number of medical consequences can arise when HCV infection goes undiagnosed, and the silent nature of HCV infection–related complications means that these complications tend to progress undetected over the course of years. Fortunately, many of these risks can be reduced with treatment. The reduction in viral load achieved with the use of antiviral therapy can help patients feel healthier—even those with mild disease—and if HCV-infected patients are diagnosed and treated before they begin to develop liver damage, such as fibrosis and early cirrhosis, then antiviral therapy may be able to alter the natural history of the disease and reduce the likelihood of developing more advanced liver disease such as HCC. Thus, early diagnosis can potentially have a marked impact on healthcare costs and quality of life.

The effect of viral control on health-related quality of life among HCV-infected individuals has been demonstrated in several studies. Arora and colleagues conducted a study in which 491 patients with persistently normal alanine transaminase (ALT) levels were randomized to receive either treatment with peginterferon α-2a plus ribavirin for 24 or 48 weeks, or no treatment for 72 weeks.[24] Health-related quality of life was assessed with the self-administered Short Form-36 Health Survey and Fatigue Severity Scale. Patients in both treatment arms (24-week therapy or 48-week therapy) who achieved SVR with treatment had a significantly better quality of life, as well as less fatigue, compared to patients who did not achieve SVR. In a second study, HCV-infected individuals (46 with persistently normal ALT levels and 92 matched subjects with elevated ALT levels) were treated with interferon α-2b plus ribavirin for up to 48 weeks.[25] In this study, the Hepatitis Quality of Life Questionnaire was used to assess health-related quality of life. This assessment found that antiviral therapy was associated with significant improvements from baseline in nearly all domains of health-related quality of life, both among patients with normal ALT levels and those with elevated ALT levels.

Factors to Assess Upon Diagnosis

Once a patient is diagnosed with HCV, the genotype of the particular HCV strain needs to be determined, as HCV genotype can predict the likelihood of response to a particular therapy and determine the optimal duration of treatment. An international consensus has recognized at least 6 unique HCV genotypes (1–6), with genotypes 1, 2, and 3 being the most frequently encountered in the United States.[26-28] Genotype 1 HCV is the most common genotype, occurring in approximately 75% of HCV-infected Americans; genotypes 2 and 3 comprise 10–20% of cases.[29] Importantly, a randomized trial of 1,311 patients demonstrated that the optimal duration and dosage of therapy should be based on the patient's HCV genotype.[30] While patients with genotype 1 HCV infection require 48 weeks of treatment with peginterferon α (2a or 2b) and a standard dose of ribavirin, patients with genotype 2 or 3 HCV infection can be treated with just 24 weeks of peginterferon and a lower dose of ribavirin.

In addition to determining a patient's HCV genotype, a liver biopsy may need to be performed as part of a patient's initial work-up. As noted in the AASLD guidelines, the 3 main reasons for performing a liver biopsy in an HCV-infected individual are to provide information regarding the current status of liver injury, to identify features useful for guiding therapy, and to reveal the existence of advanced fibrosis or cirrhosis that would require closer HCC surveillance.[1] While liver biopsies are a gold standard assessment for defining the extent of liver disease, they are limited by their associated risks, potential for sampling error, need for expert interpretation, and cost. Liver biopsies are not routinely performed in patients with genotype 2 or 3 HCV infection, as the likelihood of a successful response to antiviral therapy is already very high in this population. In contrast, patients with genotype 1 HCV infection may benefit from a liver biopsy, as it can provide information that may help to guide later treatment decisions. However, liver biopsies may become less necessary for patients with genotype 1 HCV infection as newer therapeutic agents improve treatment efficacy in this population.

The patient's liver enzyme levels should also be assessed upon diagnosis in order to determine whether any elevations or abnormalities are present. However, physicians should recognize that up to 30% of HCV-infected patients exhibit persistently normal liver enzyme levels. Studies show that the natural history of HCV infection is much milder in patients with persistently normal ALT levels, with long-term disease stability and slower (or no) progression of disease to cirrhosis.[31] One study reported that HCV-infected patients with persistently normal ALT levels were significantly more likely to be women, to have lower HCV RNA titers, and to have lower liver inflammation and fibrosis scores.[32] However, these patients are not immune from developing significant liver disease, and thus they should still be monitored carefully.

Another important factor to consider in newly diagnosed HCV patients is the presence of co-infections, such as hepatitis A virus, hepatitis B virus, or HIV. It is also neces-

sary to determine the presence of potential comorbidities, such as autoimmune liver disease or metabolic or inherited disorders (ie, hemochromatosis, α1 antitrypsin deficiency, or Wilson disease).

Finally, the patient's *IL-28B* genotype may need to be considered, as 2 single nucleotide polymorphisms on chromosome 19 have been shown to play a significant role in response to HCV treatment; the 3 variations are CC, CT, and TT.[33] These polymorphisms are located upstream of the *IL-28B* gene, which encodes the antiviral cytokine interferon λ. Studies have shown that *IL-28B* polymorphisms are associated with a patient's ability to achieve SVR, with the presence of a favorable *IL-28B* polymorphism being associated with a 2-fold increase in response to treatment with peginterferon plus ribavirin.[34-36] Additionally, *IL-28B* polymorphisms appear with different frequencies among different ethnic groups, providing a potential explanation for the observed differences in SVR rates among these groups.

Interestingly, *IL-28B* polymorphisms may also dictate an individual's natural viral clearance ability.[37] Among treatment-naïve patients with genotype 1 HCV infection, a CC genotype is associated with a greater likelihood of rapid virologic response (RVR) compared to patients with the CT or TT genotype (28% vs 5% and 5%; *P*<.0001), a higher rate of complete early virologic response (87% vs 38% and 28%; *P*<.0001), and SVR (69% vs 33% and 27%; *P*<.0001).[38] In patients with genotype 2 or 3 HCV infection, *IL-28B* polymorphisms are associated with SVR rates among those individuals who do not achieve RVR (OR, 1.76; 95% CI, 1.16–2.7).[39]

The effect of *IL-28B* polymorphisms on the new anti-HCV protease inhibitors (PIs) has also been examined. A substudy of the ADVANCE trial suggested that the addition of telaprevir to peginterferon and ribavirin yielded benefit across all *IL-28B* genotype subgroups.[40,41] In ADVANCE, patients were randomized to receive either 8 or 12 weeks of telaprevir (or no telaprevir) combined with peginterferon and ribavirin, followed by additional peginterferon plus ribavirin for a total treatment duration of 24 or 48 weeks. Among the 454 patients for whom *IL-28B* genotype data were available, the CT genotype was most common, followed by CC and then TT (49%, 33%, and 18%, respectively). Overall SVR rates were 78% and 65% for the 12-week and 8-week telaprevir treatment arms, respectively, versus 38% for the control arm. Patients with the CC genotype were the most likely to achieve SVR (90% with the 12-week telaprevir regimen); in comparison, the SVR rate among patients with the CC genotype who received only peginterferon and ribavirin was 68%. Among patients treated with the 12-week telaprevir regimen, SVR rates were 71% for patients with the CT genotype and 73% for patients with the TT genotype; among those receiving only peginterferon and ribavirin, SVR rates were 25% and 23%, respectively.

In studies of patients with genotype 1 HCV infection who were treated with boceprevir combination therapy, *IL-28B* polymorphisms have been reported to predict virologic response. *IL-28B* polymorphisms were evaluated as a predictor of SVR in the SPRINT-2 trial, which studied treatment-naïve patients, and in the RESPOND-2 trial, which evaluated previously treated patients.[42] Among the 2 trials, the distribution of *IL-28B* genotypes was 54% CT, 28% CC, and 18% TT. The CC polymorphism was found to predict Week 8 treatment response with boceprevir in both the SPRINT-2 trial (89.4% SVR with CC vs 52.0% SVR with CT/TT) and in the RESPOND-2 trial (82.0% vs 51.3%, respectively).

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New Agents for the Treatment of HCV

Mark S. Sulkowski, MD

The primary goal of HCV treatment is to achieve SVR, which is defined as undetectable levels of HCV RNA more than 24 weeks after the discontinuation of therapy. In long-term follow-up studies, SVR has been shown to be durable in more than 99% of patients followed for approximately 5 years.[1-4] More importantly, compared to HCV-infected persons who are not treated or are nonresponsive to therapy, patients who achieve SVR have improved liver histology and decreased risks of end-stage liver disease, HCC, and death. These data support the growing consensus among researchers that viral eradication, or cure, is possible with HCV antiviral therapy.

Until very recently, the standard-of-care treatment for chronic HCV infection was peginterferon □-2a or □-2b and ribavirin. Using this regimen, SVR was achieved in 40–50% of persons infected with genotype 1 HCV. Pretreatment patient and virus factors are predictive of the likelihood of SVR. For example, SVR rates are generally higher in patients with minimal hepatic fibrosis, favorable *IL-28B* genotype (CC vs CT or TT), and nonblack race. In addition, on-treatment virologic response provides an accurate assessment of the efficacy of therapy. HCV RNA levels determined at Weeks 4, 12, and 24 are used to determine interferon responsiveness and the optimal duration of treatment, as well as to define stopping rules for virologic futility. Thus, the application of viral kinetics has become a key tool for assessing treatment response.

The AASLD practice guidelines outlined a number of patient characteristics that can be used to identify HCV-infected patients in whom treatment is widely accepted, is contraindicated, or should be individualized (Table 3).[5] Overall, however, the rates of HCV treatment with peginterferon and ribavirin are relatively low in the United States compared to other countries, such as France. Thus,

Table 3. Groups in Which Hepatitis C Virus (HCV) Treatment is Widely Accepted, Should be Individualized, or is Contraindicated*

Characteristics of Patients in Whom…		
Treatment is Widely Accepted	**Treatment Should be Individualized**	**Treatment is Contraindicated**
• ≥18 years of age, *and* • HCV RNA positive in serum, *and* • Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher), *and* • Compensated liver disease,† *and* • Acceptable hematologic *and* biochemical indices,†† *and* • Willing to be treated and adhere to treatment requirements, *and* • No contraindications	• Failed previous treatment (nonresponders and relapsers) to either interferon □ with or without ribavirin, or peginterferon □ monotherapy • Current users of illicit drugs or alcohol who are willing to participate in a substance abuse program (such as a methadone program) or alcohol support program • Liver biopsy shows no fibrosis or only mild fibrosis • Acute HCV infection • Co-infection with HIV • 2–17 years of age • Chronic renal disease (either requiring or not requiring hemodialysis) • Decompensated cirrhosis • Liver transplant recipients	• Major uncontrolled depressive illness • Most solid organ transplant (kidney, heart, or lung) recipients • Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin • Untreated thyroid disease • Pregnant or unwilling to comply with adequate contraception • Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, or chronic obstructive pulmonary disease • <2 years of age • Known hypersensitivity to drugs used to treat HCV

*Adapted from Ghany MG, Strader DB, Thomas DL, et al; American Association for the Study of Liver Diseases.[5]

†Total serum bilirubin <1.5 g/dL; international normalized ratio <1.5; serum albumin >3.4 g/dL; platelet count=75,000/mm^3; and no evidence of hepatic decompensation (hepatic encephalopathy or ascites).

††Hemoglobin >13 g/dL for men and >12 g/dL for women; neutrophil count >1,500/mm^3; and serum creatinine <1.5 mg/dL.

it is important for clinicians to recognize that treatment should be considered in the context of the individual patient's potential for benefit and risk of therapy. Recent advances in HCV treatment will clearly change the assessment of the potential for benefit, since these therapies have been associated with higher SVR rates.

In May 2011, the FDA approved the first new drugs for the treatment of chronic HCV infection in nearly a decade. Both telaprevir and boceprevir are NS3/4A PIs that act directly to inhibit HCV replication; as such, they are the first direct-acting antiviral (DAA) agents to reach the clinic. These drugs are approved for use in combination with peginterferon and ribavirin for the treatment of chronic HCV genotype 1 infection in persons who have never been previously treated (treatment-naïve) and those who are treatment-experienced (nonresponders and relapsers). Based on markedly higher SVR rates compared to standard therapy with peginterferon and ribavirin in these populations, triple therapy with an HCV PI has already become the standard-of-care therapy for the treatment of HCV genotype 1 infection. Of note, these agents are not approved for use in patients with genotype 2 or 3 HCV infection, for whom peginterferon and ribavirin continue to offer a high likelihood of SVR. While these HCV PIs offer the promise of improved SVR rates, they also represent a paradigm shift for both patients and clinicians; indeed, clinicians should rapidly learn to use these new tools to improve clinical outcomes.

Telaprevir

Telaprevir is approved for use in combination with peginterferon and ribavirin to treat genotype 1 chronic HCV infection. This approval was based on successful results from 3 phase III trials that evaluated telaprevir plus peginterferon and ribavirin in both treatment-naïve and previously treated patients with genotype 1 HCV infection.

The ADVANCE study was a randomized, double-blind, placebo-controlled phase III trial, the results of which were recently published in *The New England Journal of Medicine*.[6] This study included 1,088 treatment-naïve patients with genotype 1 HCV infection who were randomized to 1 of 3 treatment arms: The first arm received 12 weeks of telaprevir (750 mg every 7–9 hours) plus peginterferon α-2a (180 µg weekly) and ribavirin (1,000–1,200 mg daily), followed by peginterferon α-2a plus ribavirin for an additional 12 or 24 weeks based on the virologic response at Weeks 4 and 12 (response-guided therapy); the second arm received 8 weeks of telaprevir plus peginterferon α-2a and ribavirin (patients received placebo in place of telaprevir during Weeks 8–12), followed by response-guided peginterferon and ribavirin for an additional 12 or 36 weeks; and the third arm received 12 weeks of placebo plus peginterferon α-2a and ribavirin, followed by peginterferon α-2a and ribavirin through Week 48. For the telaprevir groups, the decision to assign patients to an additional 12 or 36 weeks of peginterferon and ribavirin was based on the HCV RNA response at Weeks 4 and 12; patients with undetectable levels of HCV RNA at these time points (defined as extended RVR) received an additional 12 weeks of therapy (for a total duration of 24 weeks). In contrast, patients who did not achieve an undetectable level of HCV RNA after 4 weeks were treated with an additional 36 weeks of peginterferon and ribavirin (for a total duration of 48 weeks).

Most of the patients enrolled in the ADVANCE trial were white males, approximately three fourths (77%) of patients in each arm had baseline HCV RNA levels at or above 800,000 IU/mL, and 20–23% of patients in each group had bridging fibrosis or cirrhosis at baseline. This study demonstrated that patients treated with telaprevir for either 12 or 8 weeks achieved significantly higher SVR rates than patients who received only peginterferon and ribavirin (75% and 69% vs 44%; $P<.001$ for both comparisons). Similarly, the 2 groups treated with telaprevir achieved higher rates of RVR (defined as undetectable levels of HCV RNA at Week 4) compared to placebo (68% and 66% vs 9%), as well as higher rates of extended RVR (58% and 57% vs 8%). Thus, nearly 60% of patients treated with telaprevir achieved extended RVR and qualified for the shorter duration of therapy, potentially resulting in a substantial reduction in overall treatment-related morbidity. A majority of patients who achieved extended RVR also subsequently achieved SVR (89%, 83%, and 97% in the 12-week telaprevir, 8-week telaprevir, and placebo arms, respectively). Importantly, SVR rates were higher for telaprevir-treated patients across many hard-to-treat patient groups: blacks, patients with advanced fibrosis or cirrhosis, and patients with high baseline HCV RNA levels. While the difference between the 8-week telaprevir regimen and the 12-week telaprevir regimen was relatively small, the analysis clearly favored 12 weeks of telaprevir plus peginterferon and ribavirin. For example, the rate of virologic failure during the treatment period was somewhat lower among patients who received the longer duration of telaprevir (8% with 12 weeks of telaprevir vs 13% with 8 weeks of telaprevir).

A second telaprevir study—the ILLUMINATE study—was a confirmatory, randomized, open-label, phase III trial, the final results of which were presented by Sherman and colleagues at the 2010 AASLD Annual Meeting.[7] This study used a noninferiority design to compare 2 durations of telaprevir-based triple therapy in treatment-naïve patients with genotype 1 HCV infection who achieved extended RVR. A total of 540 patients received 12 weeks of telaprevir (750 mg every 8 hours) plus peginterferon α-2a (180 µg weekly) and ribavirin (1,000–1,200 mg daily), followed by additional peginterferon α-2a and ribavirin through

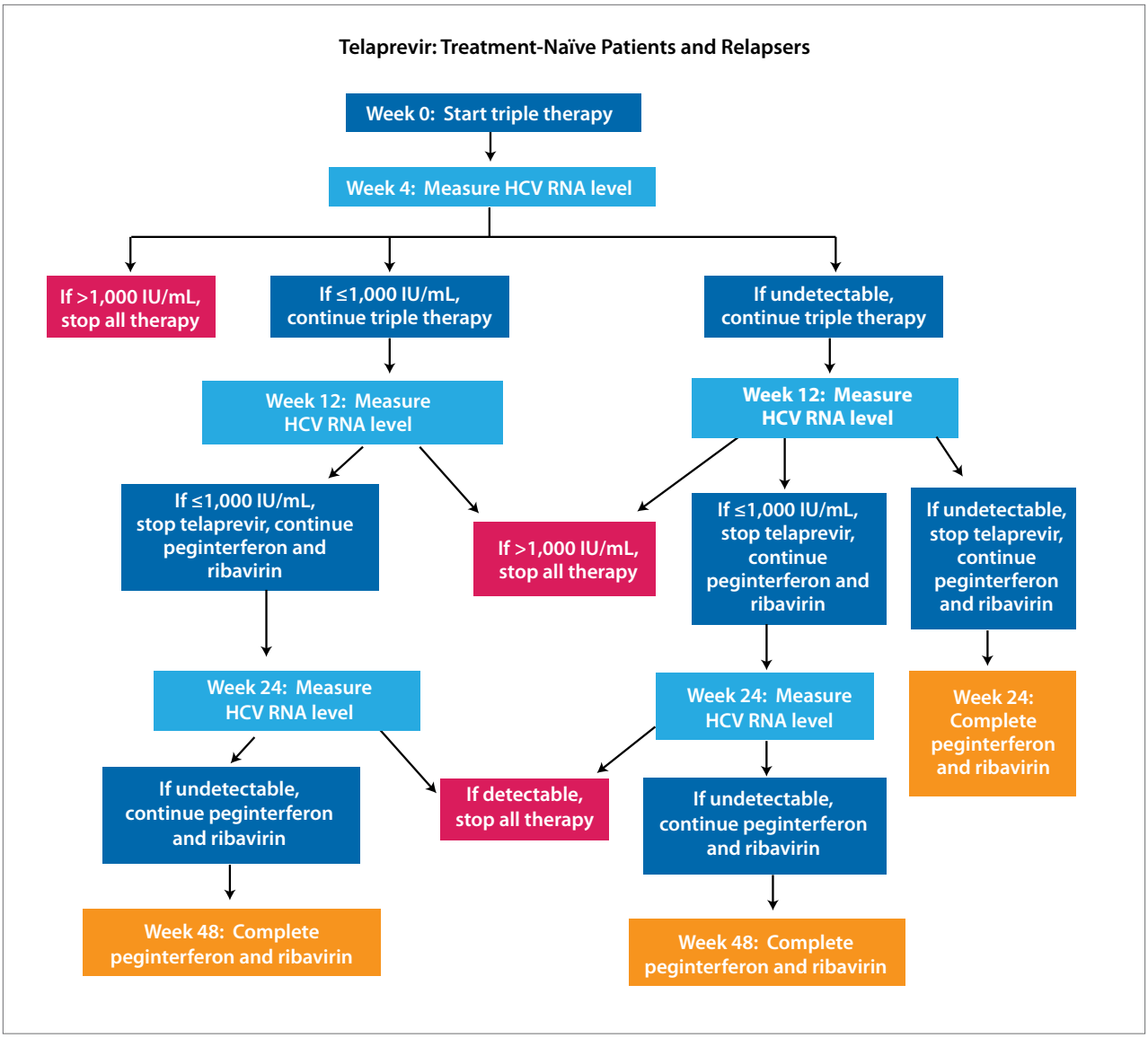

Figure 1. Telaprevir-based treatment algorithm for treatment-naïve patients and patients who relapsed after prior treatment with peginterferon and ribavirin. See the manufacturer's prescribing information for full details.

HCV=hepatitis C virus.

Week 20. At Week 20, patients who had not achieved extended RVR (defined as undetectable levels of HCV RNA at Weeks 4 and 20) continued treatment with peginterferon -2a and ribavirin through Week 48; patients who had achieved extended RVR by Week 20 were randomized to receive peginterferon -2a and ribavirin through either Week 24 or Week 48. Overall, this analysis compared 12 weeks of telaprevir and 24 weeks of peginterferon -2a and ribavirin versus 12 weeks of telaprevir and 48 weeks of peginterferon -2a and ribavirin.

The patient population was comprised mainly of white males with high (≥800,000 IU/mL) HCV RNA levels at baseline. Bridging fibrosis or cirrhosis was observed at baseline in 21–23% of patients in each treatment group. The 24-week duration of peginterferon -2a and ribavirin treatment yielded a noninferior SVR rate compared to the 48-week regimen among patients who achieved extended RVR (4.5% difference in favor of the shorter therapy). Although SVR rates were markedly higher among patients who achieved extended RVR (92% vs 87.5% for patients in the 24-week and 48-week treatment groups, respectively), SVR was also achieved by 64% of patients who did not achieve extended RVR. High SVR rates were maintained regardless of patients' race or extent of liver fibrosis.

A number of adverse events were reported in the telaprevir studies discussed above; however, the ADVANCE trial was the only study that contained a control arm of treatment-naïve patients who did not receive telaprevir. In the ADVANCE study, fewer patients in the telaprevir arms discontinued treatment compared to patients in the placebo arm (26–29% vs 44%).[6] However, a number of adverse events were reported at rates that were at least 10% higher in the telaprevir arms compared to the placebo arm, including pruritus, nausea, rash, anemia, and diarrhea. Adverse events associated with telaprevir will be discussed in detail in the next section.

Finally, results from the REALIZE study were presented by Zeuzem and colleagues at the 2011 annual meeting of the European Association for the Study of the Liver.[8] This international, multicenter, double-blind, phase III trial evaluated patients with genotype 1 HCV infection who had previously failed peginterferon -2a and ribavirin therapy; patients in this study received 12 weeks of telaprevir plus peginterferon -2a and ribavirin followed by 32–36 weeks of peginterferon -2a and ribavirin. A total of 662 patients were randomized to 1 of 3 treatment arms, and patients were stratified by their HCV RNA level and prior response to therapy (null response, partial response, or relapse). Patients in the first treatment arm received 12 weeks of telaprevir (750 mg every 8 hours) plus peginterferon -2a (180 µg weekly) and ribavirin (1,000–1,200 mg daily), followed by 4 weeks of placebo plus peginterferon -2a and ribavirin; patients in the second arm received placebo plus peginterferon -2a and ribavirin for the initial 4 weeks of treatment, followed by 12 weeks of telaprevir plus peginterferon -2a and ribavirin; and patients in the third arm received placebo plus peginterferon -2a and ribavirin for 16 weeks. All patients then received peginterferon -2a and ribavirin during Weeks 16–48.

Patients' baseline characteristics were well balanced between the treatment arms; the patient population was mostly white males with high (≥800,000 IU/mL) baseline HCV RNA levels. Compared to the ADVANCE and ILLUMINATE studies—which involved treatment-naïve patients—the treatment-experienced patients in the REALIZE study were more likely to have either bridging fibrosis or cirrhosis (45–50%).

The study results showed that telaprevir-based treatment produced early and robust virologic suppression even among patients who had previously failed peginterferon -2a and ribavirin therapy. The SVR rates achieved by patients in either of the telaprevir-containing treatment arms were significantly higher than the SVR rate for the placebo arm, regardless of patients' prior response to therapy. For example, among patients who relapsed following prior treatment with peginterferon -2a and ribavirin, SVR rates were 83% in the group that received initial telaprevir treatment and 88% in the delayed telaprevir treatment group, compared to 24% in the placebo arm (P<.001 for both comparisons). These trends were maintained regardless of baseline fibrosis stage. The rates were similarly significant among previous nonresponders (41% and 41% vs 9%), previous partial responders (59% and 54% vs 15%), and previous null responders (29% and 33% vs 5%; P<.001 for all comparisons vs placebo), but SVR rates decreased according to the magnitude of prior response. Thus, prior

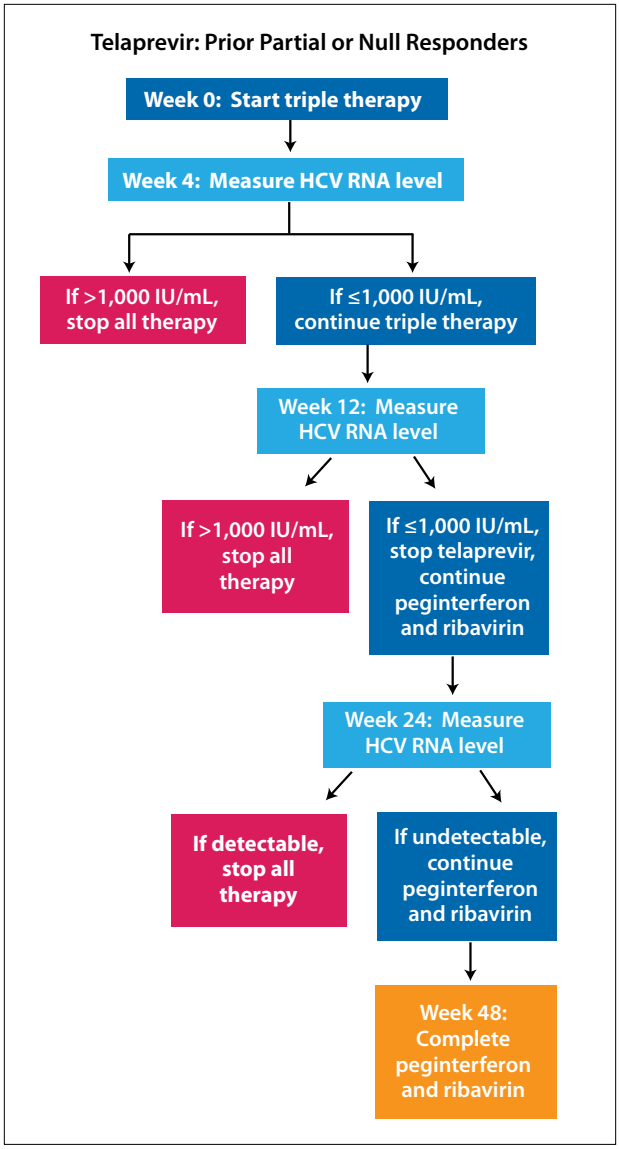

Figure 2. Telaprevir-based treatment algorithm for patients who had a partial or null response following previous treatment with peginterferon and ribavirin. See the manufacturer's prescribing information for full details.

HCV=hepatitis C virus.

response to treatment should be considered when administering telaprevir to treatment-experienced patients. Prior relapsers have an outstanding probability of response and, according to FDA approval for telaprevir, they may be considered for a shortened duration of therapy per the same response-guided therapy criteria used for treatment-naïve patients; in contrast, partial and null responders should receive 12 weeks of telaprevir-based triple therapy followed by an additional 36 weeks of peginterferon and ribavirin. The adverse events associated with telaprevir in this population were similar to those observed in the treatment-naïve studies.

Based on these data, telaprevir is indicated as part of a triple therapy regimen for genotype 1 chronic HCV infection in both treatment-naïve patients and patients who failed previous therapy. For treatment-naïve patients and prior virologic relapsers, the approved regimen is 12 weeks of telaprevir in combination with peginterferon and ribavirin, followed by an additional 12 or 24 weeks of peginterferon and ribavirin (Figure 1). If the patient achieves extended RVR (undetectable levels of HCV RNA at Weeks 4 and 12), treatment can be limited to a total of 24 weeks. If extended RVR is not achieved, treatment is continued for a total of 48 weeks. For persons with prior partial or null response, treatment must be extended to a total of 48 weeks (Figure 2). Importantly, the triple therapy regimen with telaprevir has stopping rules for virologic futility: Patients who have an HCV RNA level above 1,000 IU/mL after 4 or 12 weeks of triple therapy should discontinue all medications, as the likelihood of their achieving SVR is very low. In addition, all patients with a detectable level of HCV RNA after 24 weeks of therapy should discontinue therapy at that time.

Boceprevir

The other new DAA agent for treatment of chronic HCV infection is boceprevir, a potent inhibitor of the HCV NS3 protease. Like telaprevir, boceprevir is approved for use in combination with peginterferon α and ribavirin to treat genotype 1 chronic HCV infection. This approval was based on successful results from 2 phase III trials that evaluated boceprevir in treatment-naïve and treatment-experienced patients with genotype 1 HCV infection.

The SPRINT-2 study, conducted by Poordad and colleagues, was an international, double-blind, randomized, phase III trial that compared the standard therapy of peginterferon α-2b plus ribavirin versus 2 boceprevir-containing treatment regimens.[9] A total of 1,097 genotype 1 HCV–infected patients with previously untreated disease (938 nonblack and 159 black) were treated with peginterferon α-2b (1.5 µg/kg weekly) and ribavirin (600–1,400 mg daily) for 4 weeks. Following this lead-in period, patients received 1 of 3 treatment regimens: placebo plus peginterferon α-2b and ribavirin for an additional 44 weeks; response-guided therapy with boceprevir (800 mg 3 times daily) plus peginterferon α-2b and ribavirin for at least 24 weeks (patients with undetectable HCV RNA levels at Weeks 8–24 stopped all therapy after Week 28; patients with detectable HCV RNA levels at Weeks 8–24 received placebo plus peginterferon α-2b and ribavirin for an additional 20 weeks); or boceprevir plus peginterferon α-2b and ribavirin for 44 weeks.

Among nonblack patients, SVR was achieved by significantly more patients in the 24-week and 44-week boceprevir treatment arms than the placebo arm (67% and 68% vs 40%; $P<.001$ for both comparisons). A similar trend was observed among black patients, although SVR rates were lower in this group (42% and 53% vs 23%; $P=.04$ and $P=.004$ for 24-week and 44-week boceprevir treatment vs placebo, respectively). Among patients in the 24-week boceprevir treatment arm, 44% of patients had undetectable HCV RNA levels between Weeks 8 and 24 and were able to discontinue treatment after a total treatment duration of 28 weeks. In terms of safety, anemia led to dose reductions in 21% of patients treated with boceprevir versus 13% of patients treated with placebo.

A second boceprevir study, the RESPOND-2 trial by Bacon and colleagues, was a similarly designed, randomized, phase III trial that also compared standard treatment (peginterferon α-2b plus ribavirin) with 2 boceprevir-containing treatment regimens.[10] The primary difference in this study was the patient population: In contrast to the treatment-naïve patients in the SPRINT-2 study, all 403 patients in the RESPOND-2 trial had received previous treatment for genotype 1 chronic HCV infection. Patients who had relapsed or showed a partial response to prior therapy were enrolled in RESPOND-2, but prior null responders were excluded from this trial. In this study, all 3 treatment arms included a 4-week lead-in period during which patients received peginterferon α-2b (1.5 µg/kg weekly) plus ribavirin (600–1,400 mg daily). After this lead-in period, patients received 1 of 3 treatments: Patients in the control arm received placebo plus peginterferon α-2b and ribavirin for an additional 44 weeks; patients in the response-guided therapy arm received boceprevir (800 mg 3 times daily) plus peginterferon α-2b and ribavirin for at least 32 weeks (if patients' HCV RNA level was undetectable after Week 8, they stopped therapy at Week 32; if their HCV RNA levels were detectable after Week 8, patients received placebo plus peginterferon α-2b and ribavirin for an additional 12 weeks); and patients in the third arm received boceprevir plus peginterferon α-2b and ribavirin for 44 weeks. Significantly, SVR rates were much higher among patients in the 32-week and 44-week boceprevir treatment arms compared to the placebo arm (59% and 66% vs 21%; $P<.001$ for both

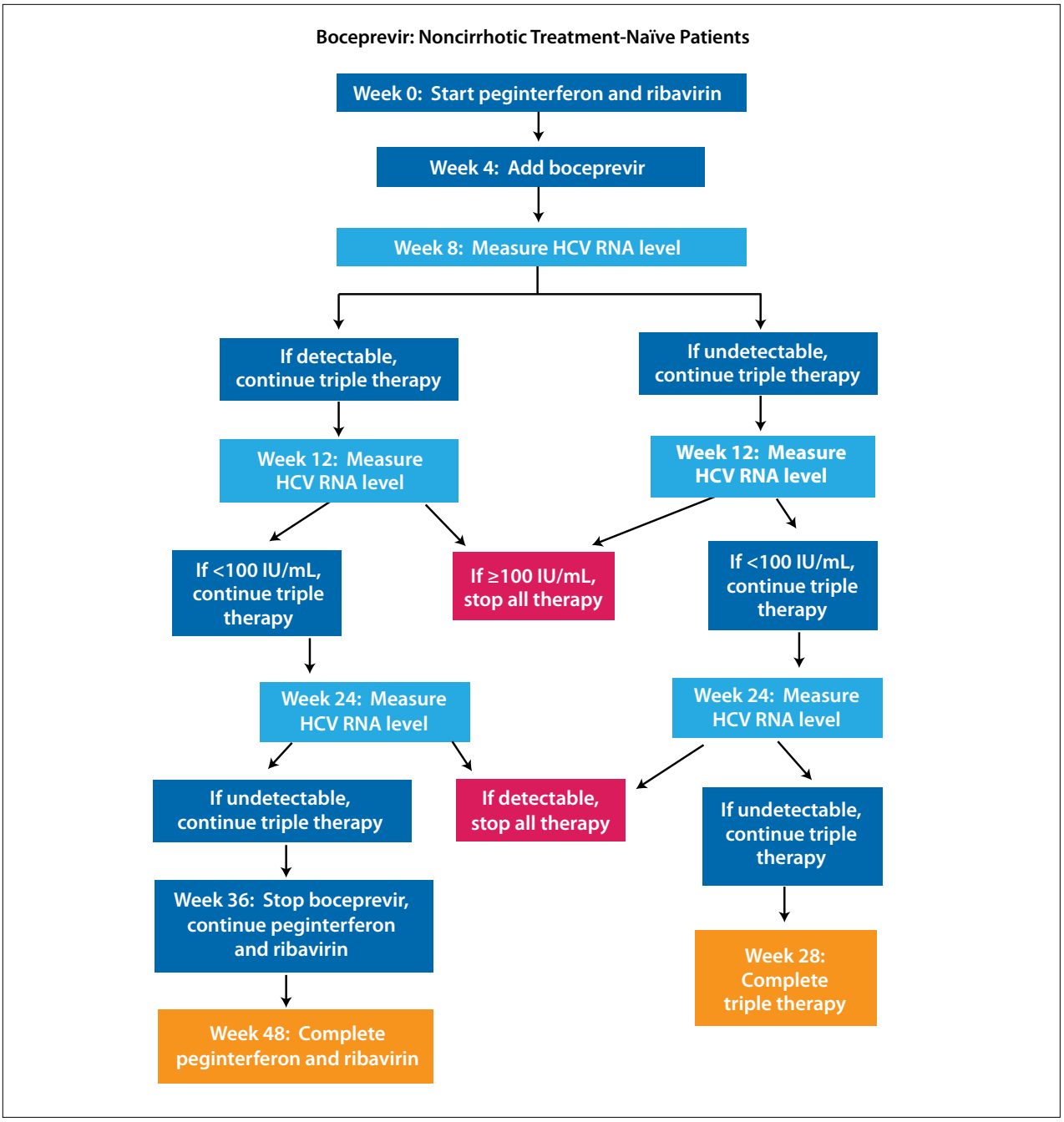

Figure 3. Boceprevir-based treatment algorithm for noncirrhotic treatment-naïve patients. See the manufacturer's prescribing information for full details.

HCV=hepatitis C virus.

comparisons). For patients who achieved undetectable levels of HCV RNA at Week 8, SVR rates were 86% after 32 weeks of boceprevir-based triple therapy and 88% after 44 weeks of boceprevir-based triple therapy.

In both boceprevir studies, anemia was the most notable adverse event associated with boceprevir, with a higher rate of erythropoietin administration among boceprevir-treated patients compared to placebo-treated patients (41–46% vs 21%). In these registration trials, anemia (hemoglobin <10 g/dL) was managed by dose reduction of ribavirin and/or administration of erythropoietin; overall, approximately 42% of treatment-naïve patients were treated with erythropoietin. SVR rates were not reduced in patients with anemia, however, suggesting that dose reduction of

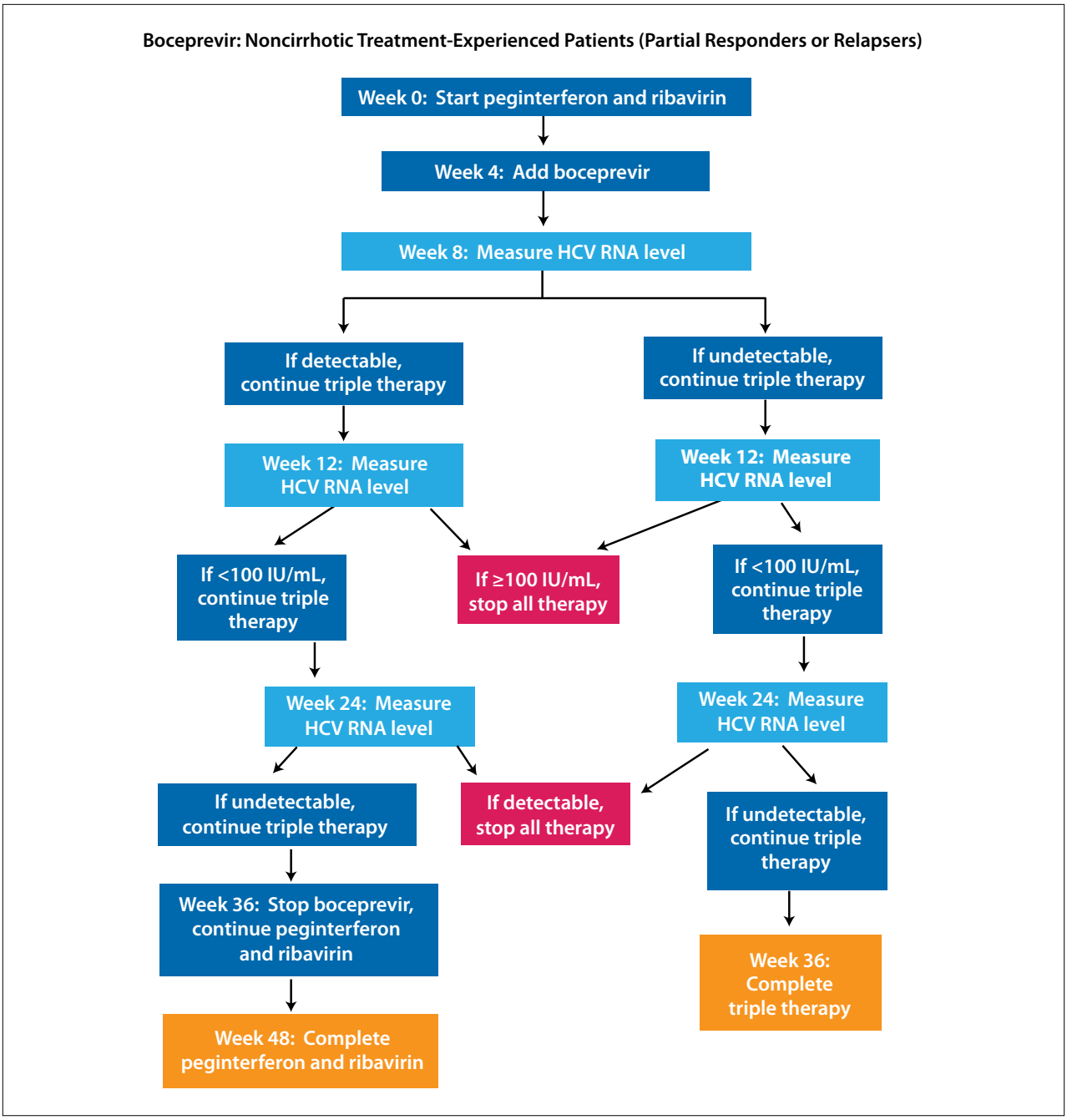

Figure 4. Boceprevir-based treatment algorithm for noncirrhotic patients who showed a partial response to previous treatment with peginterferon and ribavirin or who relapsed following previous treatment with peginterferon and ribavirin. See the manufacturer's prescribing information for full details.

HCV=hepatitis C virus.

ribavirin—with or without erythropoietin—was effective. Adverse events associated with boceprevir will be discussed in more detail in the next section.

Given these studies, boceprevir is recommended for both treatment-naïve and treatment-experienced patients with genotype 1 HCV infection. For treatment-naïve patients whose HCV RNA levels are undetectable at the end of Week 8 (after a 4-week lead-in period of peginterferon and ribavirin, followed by 4 weeks of boceprevir-based triple therapy) and Week 24, the total treatment duration is 28 weeks (4 weeks of lead-in followed by 24 weeks of triple therapy); otherwise, therapy should be continued

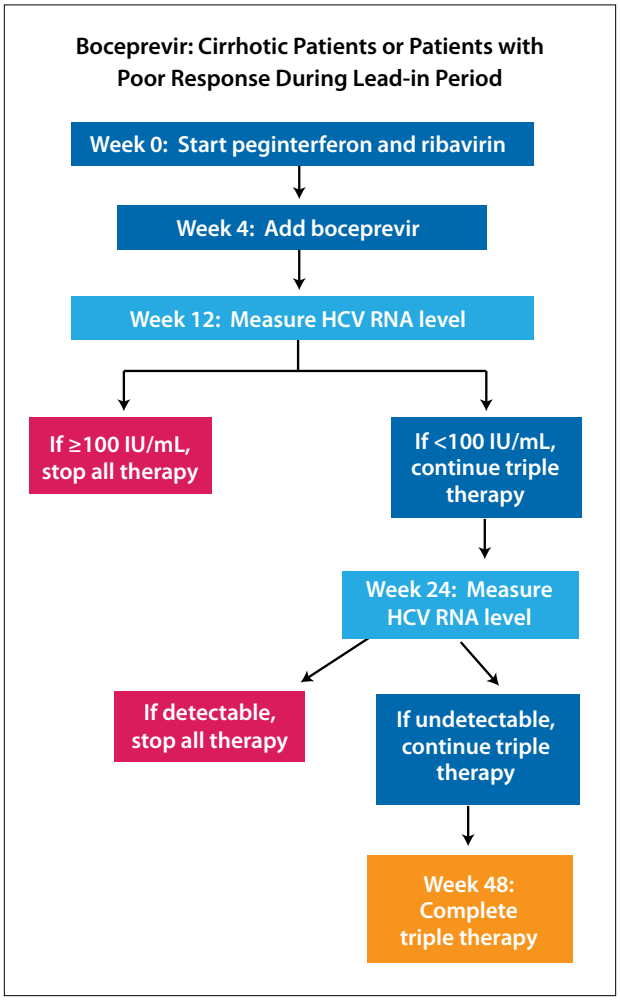

Figure 5. Boceprevir-based treatment algorithm for cirrhotic patients or patients who show a less-than-0.5 $\log_{10}$ decline in hepatitis C virus (HCV) RNA level during the 4-week lead-in period. See the manufacturer's prescribing information for full details.

through Week 48 (for a total triple-therapy duration of 36 weeks; Figure 3). A similar treatment regimen is recommended for previous partial responders or relapsers, except that patients in this population who achieve HCV RNA undetectability at Weeks 8 and 24 should receive a total of 36 weeks of treatment (Figure 4). It is recommended that cirrhotic patients and patients who show a less-than-0.5 $\log_{10}$ decline in HCV RNA level during the 4-week lead-in period be treated with 4 weeks of peginterferon and ribavirin followed by 44 weeks of boceprevir plus peginterferon and ribavirin (Figure 5). Importantly, the boceprevir-based triple therapy regimen has stopping rules for virologic futility: All treatment should be discontinued if a patient's HCV RNA level is greater than 100 IU/mL after 12 weeks of therapy (4 weeks of lead-in therapy followed by 8 weeks of triple therapy) or if the viral load is detectable at Week 24.

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Integrating New Agents Into Patient Care

Fred Poordad, MD

Given the promising efficacy data discussed in the previous section, many clinicians are eager to begin incorporating telaprevir and boceprevir into clinical practice. When doing so, clinicians need to consider the clinical endpoints they aim to achieve, as well as the appropriate duration of therapy for each patient. In addition, clinicians need to remain alert to the side effects that have been associated with these new drugs.

SVR as a Clinical Endpoint

The use of SVR as a clinical endpoint has been validated in multiple studies investigating HCV therapies. Based on evidence from 19 cohort studies, each of which compared the outcomes of patients achieving SVR to the outcomes of nonresponders, SVR has been shown to be associated with consistent improvements in patient outcomes, including decreased incidences of HCC and diabetes, as well as decreased rates of decompensated liver disease, liver disease–related mortality, and overall mortality.[1] For example, the Veterans Affairs Cohort study, which evaluated data from 12,166 genotype 1 HCV–infected patients who were treated with peginterferon and ribavirin, found a 30% reduction in the risk of overall mortality among patients who achieved SVR versus patients who were null responders (hazard ratio, 0.70; $P<.0001$).[2]

Multiple factors influence whether an HCV-infected individual will achieve SVR with therapy. Patient-related factors include race, extent and degree of fibrosis or cirrhosis, presence of co-infections, *IL-28B* polymorphisms, and patients' ability to adhere to their prescribed regimen. Disease-related factors include prior response to therapy, early response during therapy (at Weeks 4 and 12), and baseline HCV RNA level. Treatment-related factors include the duration of treatment.

New Strategies to Guide Treatment Decisions

The FDA defines pharmacometric analysis as a novel concept that could allow improved determination of the optimal duration of therapy in different populations. Specifically, pharmacometrics is "an emerging science … that quantifies drug, disease and trial information to aid efficient drug development and/or regulatory decisions."[3] This concept relies on the idea that any treatment-naïve population of HCV-infected individuals contains within it all of the possible subpopulations of patients with a particular response to peginterferon and ribavirin therapy (early responders, null responders, etc.).

Response-guided therapy, a treatment approach in which agent administration is individualized based on a patient's virologic response, is an example of how this theory can be used in practice.[4] When used appropriately in patients with favorable viral kinetics, response-guided therapy can shorten the amount of time during which a patient is exposed to potentially toxic agents. This strategy can also facilitate earlier identification of patients who are unlikely to respond to a particular agent; discontinuing therapy before these patients have completed a full course of treatment reduces costs and prevents patients from unnecessarily experiencing treatment-related toxicities. Clinicians can consider all patients as candidates for response-guided therapy, but not all patients will meet the criteria for abbreviated therapy. If a patient does not exhibit the early response required by the response-guided therapy regimen, then patients are simply treated for the longer duration, or therapy is discontinued if a futility endpoint is met.

Management of Adverse Events Associated with Telaprevir

In the 3 phase III trials of telaprevir discussed in the previous section (ADVANCE, ILLUMINATE, and REALIZE), the most clinically relevant adverse events associated with telaprevir were rash/pruritus, anemia, and anorectal disorders.[5-7] Clinicians should be aware of these side effects, as some of them may require that the drug regimen be adjusted or even that all therapy be stopped.

Rash and pruritus, first identified as important telaprevir-associated toxicities in phase II trials, were carefully monitored in the phase III trials of telaprevir. This detailed monitoring and management plan was 3-pronged, consisting of Rash Special Search Criteria (SSC), Events of Special Interest (ESI), and a Dermatology Expert Panel (DEP) to retrospectively adjudicate controversial cases.

Of the 1,797 patients with any telaprevir exposure in the phase III trials, over half (56%) experienced rash SSC events; in comparison, only one third (34%) of the 493 control patients (those treated with peginterferon and ribavirin alone) developed rash SSC events. Of the rashes observed

with telaprevir, the majority were mild or moderate; severe (grade ≥3) rash and pruritus occurred in only 4% of telaprevir-treated patients and less than 1% of control patients. By ESI, the incidence of rash was 7% of telaprevir-treated patients and less than 1% of control patients. A similar trend was observed for the incidence of rash and/or pruritus (73% vs 48%). Of note, 11 telaprevir-treated patients had a suspected diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome and another 3 patients had a suspected diagnosis of Stevens-Johnson syndrome, both of which are life-threatening conditions. Clinicians must be aware of these conditions and know how to diagnose and manage them.

In most cases, no specific management of rash or pruritus was required: 5% of telaprevir-treated patients initiated oral antihistamine therapy, compared to 2% of control patients; 4% of telaprevir-treated patients used topical steroids versus 2% of control patients; and 3% of telaprevir-treated patients used systemic steroids versus 1% of patients in the control group. Telaprevir was discontinued in 7% of patients due to rash or pruritus.

The DEP found that the cases of rash and/or pruritus in telaprevir-treated patients were histologically and clinically similar to those occurring in patients who received peginterferon and ribavirin alone. However, telaprevir-associated rashes were generally more extensive and severe. Importantly, the DEP was more likely than the study investigators to diagnose a case as a severe cutaneous adverse reaction (SCAR), which has greater implications for morbidity and mortality than typical rash and/or pruritus. The detection of a few SCAR cases in these trials is notable, as investigators were not trained to identify this entity.

Anemia was another important adverse event that occurred at a greater frequency among telaprevir-treated patients versus control patients (36% vs 17%). The majority of anemia cases involved hemoglobin levels at or below 10 g/dL (37% of telaprevir-treated patients vs 15% of control patients), although some patients had hemoglobin levels at or below 8.5 g/dL (10% vs 3%, respectively). Anemia occurred more frequently in females, patients over the age of 45 years, individuals with a lower body mass index, and patients with cirrhosis. Clinical events that were identified as being potentially associated with anemia included fatigue, angina, dizziness, dyspnea, and syncope. In the ADVANCE, ILLUMINATE, and REALIZE studies, use of erythropoiesis-stimulating agents (ESAs) was not permitted. Instead, anemia was managed by either blood transfusions (6% of telaprevir-treated patients vs 1% of control patients) or changes to the treatment regimen, including ribavirin dose reduction (23% vs 10%, respectively), ribavirin interruption (6% vs 1%, respectively), or discontinuation of telaprevir (4%).

Anorectal disorders were also reported at a greater frequency among telaprevir-treated patients versus control patients (29% vs 7%). The majority of these cases involved hemorrhoids, anorectal discomfort, and/or anal pruritus. These events were generally mild or moderate in severity (less than 1% were grade ≥3), and only 7 patients discontinued telaprevir due to anorectal disorders.

Management of Adverse Events Associated with Boceprevir

In phase III trials of boceprevir, hematologic adverse events emerged as important treatment-related toxicities. The most notable of these events is anemia, with boceprevir-treated patients showing greater magnitude decreases in hemoglobin levels compared to patients who received standard therapy. In addition, boceprevir-treated patients experienced higher rates of neutropenia and thrombocytopenia. Based on these data, boceprevir appears to have a suppressive effect on bone marrow, which should be closely monitored in clinical practice. The following data regarding hematologic toxicities associated with boceprevir were collected during the 2 phase III clinical trials discussed in the previous section (SPRINT-2 and RESPOND-2).[8,9]

In these studies, clinical anemia was present in 52% of the 1,057 patients treated with boceprevir plus peginterferon and ribavirin, compared to only 30% of the 443 patients treated with peginterferon and ribavirin alone. Possible clinical manifestations of anemia included fatigue, dyspnea, asthenia, dizziness, chest pain, chest discomfort, malaise, and syncope. Many patients had hemoglobin levels at or below 10 g/dL (52% of boceprevir-treated patients vs 32% of control patients), and some patients had more dramatic decreases; hemoglobin levels at or below 8.5 g/dL were observed in 9% of boceprevir-treated patients versus 4% of control patients. Notably, anemia events occurred at a greater frequency in females compared to males: 65% versus 43%, respectively, in the boceprevir-treated group and 42% versus 20%, respectively, in the control group.

The average decline in hemoglobin levels was approximately 1 g/dL greater in boceprevir-treated patients compared to control patients. However, anemia was considered to be a serious adverse event in approximately the same proportion of patients in each group (1% of boceprevir-treated patients vs <1% of control patients). In approximately half of all cases of anemia observed in these studies, this side effect resulted in a dose reduction of at least 1 of the drugs being administered (25% of boceprevir-treated patients vs 13% of control patients); more rarely, anemia resulted in a dose interruption (3% vs 2%, respectively) or dose discontinuation (2% vs 1%, respectively). Notably, assessment of hemoglobin levels during these studies was confounded by patients' hemoglobin levels at baseline. Patients with lower baseline hemoglobin levels generally exhibited a higher likelihood of experiencing anemia and requiring management of their anemia during the study; however, the

magnitude of hemoglobin level declines also tended to be smaller in these patients.

Both SPRINT-2 and RESPOND-2 allowed the use of ESAs as a supportive measure for treatment-related anemia. Overall, patients in the boceprevir-treated group required a longer ESA treatment duration than control patients (ESA therapy longer than 100 days: 24% vs 11%; longer than 150 days: 16% vs 7%; longer than 200 days: 10% vs 5%). Importantly, patients who received boceprevir as part of a response-guided therapy regimen were able to discontinue ESA therapy earlier than patients who received the full 48 weeks of boceprevir-based treatment (ESA therapy longer than 100 days: 21% vs 27%; longer than 150 days: 11% vs 20%; longer than 200 days: 5% vs 15%). However, clinicians should remember that ESAs do not currently carry an indication for the treatment of anemia in patients with chronic HCV infection, and these agents themselves are associated with potential toxicities.

In addition to anemia, neutropenia was another hematologic adverse event experienced more frequently in patients whose treatment included boceprevir: grade 3 neutropenia occurred in 23% of boceprevir-treated patients versus 13% of control patients; grade 4 neutropenia occurred in 7% and 4%, respectively. In the control group, none of the neutropenia events was considered serious or life-threatening and none resulted in drug discontinuation; in the boceprevir-treated group, serious or life-threatening events occurred in less than 1% of patients (3 individuals) and drug discontinuation due to neutropenia occurred in less than 1% of patients (8 individuals).

Finally, thrombocytopenia, while much more infrequent, also occurred at a higher rate in boceprevir-treated patients compared to control patients (grade 3: 4% vs 1%; grade 4: <1% vs 0%). Thrombocytopenia was considered serious in less than 1% of patients (3 individuals) and resulted in drug discontinuation in less than 1% of patients (4 individuals), all of whom received boceprevir as part of their treatment regimen.

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Question-and-Answer Forum

How will the availability of telaprevir and boceprevir change the management of patients with chronic HCV infection?

Bruce R. Bacon, MD The introduction of these agents into routine clinical practice is going to complicate patient management. The complex stopping rules and virologic decision points that need to be followed when using these agents will make it increasingly necessary that clinicians follow patients closely over the course of treatment. Furthermore, these drugs are associated with their own unique adverse events that clinicians will need to watch for and mitigate against as necessary. However, the impressive response rates that can be achieved when these new agents are added to standard therapy make the extra work worthwhile.

Mark S. Sulkowski, MD The high response rates that have been demonstrated with these newer agents, combined with their ability to potentially shorten the overall duration of treatment in a large number of patients, will prompt greater enthusiasm among physicians regarding treatment of patients with genotype 1 HCV infection. Concomitantly, we will likely see an increase in the number of patients asking for therapy.

What practical tips can you offer for improving HCV management in the era of DAA therapy?

BRB It is critical that physicians understand all of the various decision points involved in the administration of these new agents. Clinicians can achieve this goal by carefully reviewing the data from critical studies evaluating these agents—some of which are described in this monograph—as well as becoming familiar with the treatment algorithms supplied by the drug manufacturers.

MSS Physicians need to carefully discuss these new options with their genotype 1 HCV–infected patients. Until now these patients have only been familiar with the relatively poor responses and high toxicities associated with peginterferon plus ribavirin, and they should be made aware of the potential for higher SVR rates when telaprevir or boceprevir are incorporated into the treatment regimen. However, they should also be informed about the greater complexity of triple therapy regimens, as well as the toxicity profiles associated with these new drugs. During this discussion, the patient should be provided with a strategy for reporting and managing adverse events. For example, if a patient on telaprevir develops a rash, the physician should have a strategy in place to manage this side effect—perhaps by having the patient come to the office for a quick visit, or by collaborating with a dermatologist in the community to help manage this case. Finally, the importance of treatment adherence should be emphasized with patients, especially as these new drugs require oral administration 3 times daily.

What do you consider to be the major unmet needs in the diagnosis and treatment of HCV infection?

BRB Regarding diagnosis, the major issue currently facing this field is the vast proportion of HCV-infected individuals thought to be undiagnosed. Continued effort is needed to reinforce awareness of this issue and help physicians recognize the importance of earlier HCV diagnosis. Once patients are diagnosed, the long-term treatments required to manage chronic HCV infection are often very expensive. Thus, patients will need to have either public or private health insurance benefits that allow for the purchase of these medications and will cover the specialist visits needed to monitor treatment response.

What future clinical studies will be important for improving HCV-infected patient management?

BRB Important questions that will need to be explored in the future include what role these new agents will have in the post-transplantation setting and what role they may have in patients with advanced liver cirrhosis. Additionally, questions remain regarding the efficacy of these drugs in patients with HIV or hepatitis B virus co-infection. It will also be important to further study the potential for drug-drug interactions with these novel agents.

MSS One exciting aspect of future trends in HCV management is elimination of peginterferon from the treatment regimen. This particular agent is associated with a number of adverse events, and many patients would prefer not to receive it. One potential alternative is pegylated interferon □, a type of interferon that appears to have a more favorable toxicity profile.

Another important topic to explore in future studies is how to improve response rates among patients who experienced prior treatment failure. Approximately 30% of HCV-infected patients are null responders, and cirrhotic patients are even more likely to have a null response to peginterferon and ribavirin therapy. There is hope that novel combinations involving DAA agents will help to improve the SVR rates in these null responders, but further study of this population is needed.

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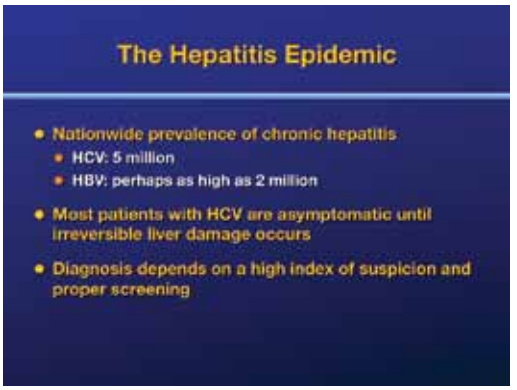
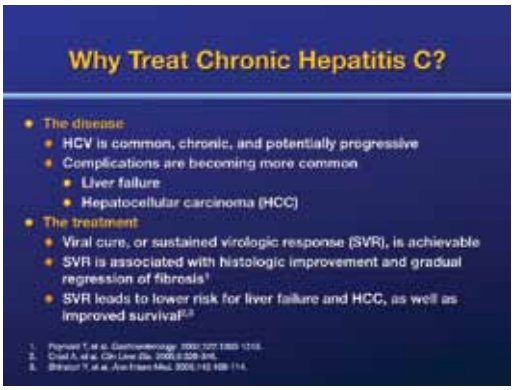
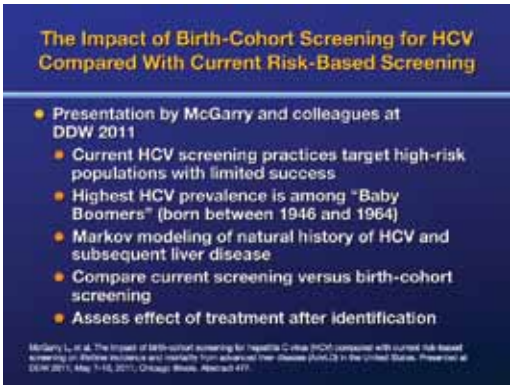
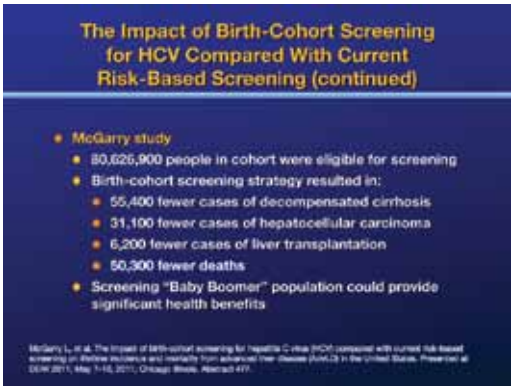
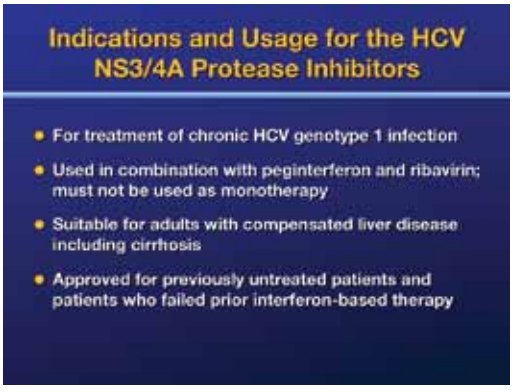
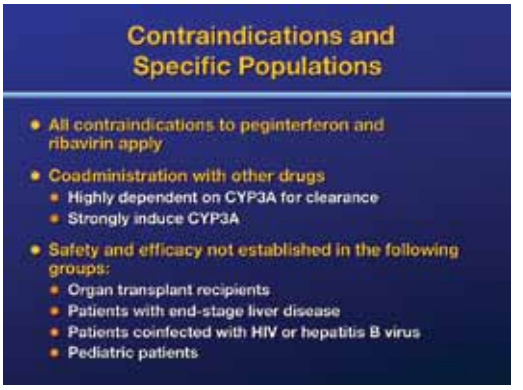




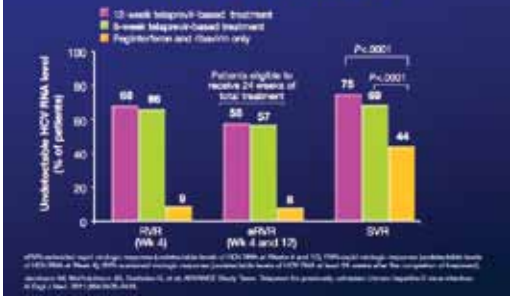




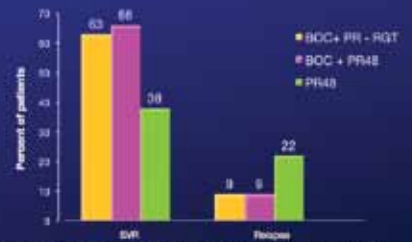




Telaprevir in Treatment-Naïve Patients: ADVANCE Study Results



Boceprevir in Treatment-Naïve Patients: SPRINT-2 Study Results



Telaprevir Rash Management

Symptom	Management Strategy
Serious skin reaction	• All components of treatment discontinued • Refer patient for urgent medical care
Mild-to-moderate rash	• Follow for progression • Oral antihistamines and/or topical corticosteroids can be used • Systemic corticosteroids are not recommended
Mild-to-moderate rash that progresses	• Discontinue (do not dose reduce) telaprevir and do not restart • Can continue peginterferon and ribavirin, but sequential/simultaneous interruption/discontinuation is necessary if rash is not improved within 7 days • Monitor until resolved

Anemia is Common With Both Boceprevir and Telaprevir But Duration of Exposure is Different

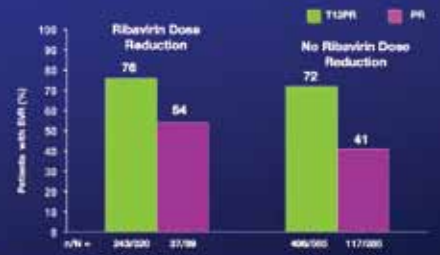
Boceprevir (24–32 weeks or 44 weeks)

- ESA allowed
- ~30% had Hb <10g/dL
- 43% received ESA; dose modification of peginterferon and/or ribavirin in 26%
- ~3% of anemic patients required blood transfusion

Telaprevir (12 weeks)

- ESA generally prohibited
- ~40% had Hb <10g/dL
- Dose modification of ribavirin for anemia (26%)
- ~12% of anemic patients required blood transfusion

Telaprevir SVR Rates According to Ribavirin Dose Reduction in ADVANCE and ILLUMINATE Studies



Boceprevir SVR in Patients With Hemoglobin <10 g/dL by EPO and/or Ribavirin Dose Reduction

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