Update on the Diagnosis and Treatment of Hepatitis C

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Editor’s Note: This article went to press in advance of the International Liver Congress 2012/47th annual meeting of the European Association for the Study of Liver Disease, held April 18-22, 2012. New research from this meeting and from the 2012 Digestive Disease Week meeting will be included in an updated version of this review, scheduled for publication in October 2012.

Hepatitis C virus (HCV) infection is a national and global public health concern, affecting up to 4 million individuals in the United States and 200 million individuals worldwide. Despite a declining incidence of new HCV infections in the United States, the prevalence of advanced liver disease secondary to chronic HCV infection, including cirrhosis and hepatocellular carcinoma (HCC), is expected to rise in the coming years.

Diagnostic Considerations

Ideally, testing for HCV is performed in asymptomatic patients who are determined to be at increased risk for HCV infection. Various societies have implemented guidelines pertaining to medical history and behaviors that constitute an increased risk for HCV. The American Association for the Study of Liver Diseases published guidelines on the diagnosis, management, and treatment of HCV in 2009. Criteria for individuals who should be screened for HCV include:

- Children born to HCV-infected mothers
- Hemodialysis
- Hemophilia (recipients of clotting factor concentrates prior to 1987)
- HCV-infected sexual partner(s)
- HIV infection
- Needlestick injury or mucosal exposure to HCV-positive blood
- Recipients of blood product transfusions or organ transplants prior to July 1992
- Use of illicit IV drugs in the remote past
- Unexplained elevated serum aminotransferase levels

Initial testing for HCV infection involves a screening assay to detect anti-HCV antibodies. The most widely used test is the enzyme immunoassay (EIA), marketed under several trade names. The newest “third-generation” EIAs are highly specific (>99%). Recently, an over-the-counter antibody test with comparable accuracy, called Hepatitis C Check (Home Access Health Corporation), was approved by the FDA. For this test, a blood sample is collected via a finger stick and mailed to the manufacturer. Results are reported within 10 business days, and post-test counseling and provider referral are offered. Additionally, a newly FDA-approved rapid test for HCV called OraQuick (OraSure Technologies, Inc.) has comparable accuracy to EIAs. This test uses a finger stick or venipuncture blood sample, and yields a result within 20 minutes.

For confirmatory testing for HCV infection, direct detection of HCV RNA has largely replaced recombinant immunoblot assay, which previously had been used to identify false-positive anti-HCV results. Testing for HCV RNA also is indicated for patients in whom anti-HCV antibody might be falsely negative, including immunocompromised patients such as those infected with HIV, organ transplant recipients, and patients on hemodialysis, as well as patients in whom there is suspicion of acute HCV infection. Molecular testing for HCV RNA traditionally has fallen into 2 categories: qualitative assays and quantitative assays. Qualitative assays, which yield a positive or negative result for detection of HCV RNA, have been supplanted by real-time polymerase chain reaction (PCR) assays. These PCR assays have a high sensitivity (25-43 international units (IU)/mL HCV RNA) and have the ability to quantify viral load simultaneously. Quantitative PCR for HCV RNA is indicated at initiation of HCV therapy and at defined intervals during therapy to evaluate treatment response. It should be noted that viral load does not correlate with disease severity.
General Treatment Considerations

Chronic HCV infection places patients at risk for developing progression of hepatic fibrosis to cirrhosis and HCC. The overall goal of HCV therapy is to prevent these complications through viral eradication. Viral eradication in response to treatment is predicted by sustained virologic response (SVR), which is defined as undetectable serum HCV RNA at 24 weeks after discontinuation of treatment. This response portends a 99% likelihood of remaining HCV RNA-negative in long-term follow-up.8

Both viral and host characteristics influence the likelihood of response to treatment. Host factors include race, obesity, insulin resistance, and severity of hepatic fibrosis.9-11 Viral characteristics include viral genotype and viral load at initiation of therapy.12 There are six major genotypes of HCV:13 in the United States, HCV genotype 1 is the most common, comprising 60% to 70% of HCV isolates, followed by HCV genotypes 2 and 3.14 The remaining HCV genotypes are uncommon in the Western world. Response to treatment is highly dependent on viral genotype; therapy with pegylated interferon-alpha (PEG-IFNα) and ribavirin (RBV) yields SVR rates of 70% to 80% in patients with HCV genotypes 2 and 3, and significantly lower rates in patients with HCV genotype 1.15

Advances in Treatment of HCV Genotype 1

Until very recently, standard therapy for chronic HCV genotype 1 infection consisted of a combination of PEG-IFNα and RBV. Despite advances in the understanding of the relationship between viral kinetics and treatment response and the importance of weight-based dosing of RBV in patients with HCV genotype 1, viral eradication rates remain suboptimal with PEG-IFNα/RBV therapy. SVR rates for HCV genotype 1 are approximately 40% following 48 weeks of PEG-IFNα/RBV therapy and even lower in black patients and in patients with high viral load or advanced fibrosis.6-18

The treatment of patients with chronic HCV genotype 1 infection was bolstered by the recent discovery of a group of single nucleotide polymorphisms (SNPs) in the region of the interleukin 28B (IL28B) gene (encoding interferon-λ-3) through genome-wide association
for genotype). For this reason, testing to 30% in patients with the CT or TT IL28B patients with the favorable CC predict SVR by a range of more IL28B test confers the ability to treated with PEG-IFN SVR in HCV genotype 1 patients the most powerful predictor of in both treatment-naive patients improve SVR rates dramatically, therapy has been demonstrated to life cycle. The addition of these new inhibit enzymes involved in the viral replication and are targeted to nonspecific, DAAs are the product commercially available members of with the approval of telaprevir genotype 1 occurred in May 2011 patient about treatment for HCV. These landmark trials established the role of RGT in previously untreated subjects with chronic hepatitis C. Genotype 1: SVR, sustained virologic response; T8, telaprevir; 8 weeks; T12, telaprevir; 12 weeks See text for complete dosing regimen details.

### Table 1. Regimens for HCV Treatment-Naive Patients

<table>
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<tr>
<th>Trial</th>
<th>Treatment Regimen</th>
<th>SVR Rate, %</th>
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ADVANCE, A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir; BOC, boceprevir; PR48, pegylated interferon-α/ribavirin for 48 weeks; RGT, response-guided therapy; SPRINT-2, Safety and Efficacy of Boceprevir in Previously Untreated Subjects With Chronic Hepatitis C; Genotype 1: SVR, sustained virologic response; T8, telaprevir; 8 weeks; T12, telaprevir; 12 weeks

### Telaprevir

Telaprevir is a selective peptidomimetic NS3 protease inhibitor that forms a covalent, reversible enzyme–inhibitor complex. An early study demonstrated potent in vitro antiviral activity in HCV replicon systems. The efficacy of telaprevir in combination with PEG-IFN/RBV, in both treatment-naive and treatment-experienced patients with HCV genotype 1, was demonstrated in the Phase 2b PROVE 1, 2, and 3 (Protease Inhibition for Viral Evaluation 1, 2, and 3) trials. These landmark trials established the superior efficacy of telaprevir in combination with PEG-IFN/RBV over PEG-IFN/RBV alone, showed that RBV is an essential component of the regimen, and laid the foundation for the concept of response-guided therapy (RGT), in which treatment duration is determined by viral response early in the course of therapy.

The pivotal Phase 3 ADVANCE (A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir) trial, compared telaprevir-based RGT with standard of care in 1,088 patients with chronic HCV genotype 1 infection. Patients were randomized to 1 of 3 treatment arms: telaprevir plus PEG-IFN/RBV for 8 weeks followed by additional weeks of PEG-IFN/RBV (T8PR), telaprevir plus PEG-IFN/RBV for 12 weeks followed by additional weeks of PEG-IFN/RBV (T12PR), or standard of care with PEG-IFN/RBV for 48 weeks (PR48). Patients in the telaprevir treatment arms who achieved undetectable HCV RNA at weeks 4 and 12 (extended rapid viral response [eRVR]) were treated for a total of 24 weeks, whereas those who did not achieve eRVR were treated for 48 weeks.

Treatment with telaprevir led to significantly higher SVR rates, at 75% and 69% in the T12 and T8 groups, respectively, compared with 44% in the PR48 (control) group (P<0.0001 for both comparisons). It should be noted that a reanalysis using revised criteria led to different SVR rates—79%, 72%, and 46%, respectively—which are published in the telaprevir package insert.) Relapse rates were 9% in both telaprevir groups compared with 28% in the control group. In the T12PR treatment arm, which received the subsequently approved treatment regimen, 58% of patients achieved eRVR, of whom 89% achieved SVR. Discontinuation of therapy for adverse events (AEs) during treatment was more common in the telaprevir groups: 10% of patients in both telaprevir groups discontinued therapy versus 7% of patients in the control group. Grade 3 rash occurred in 6% of patients in the T12PR group versus 4% in the T8PR group. As suggested in earlier studies, telaprevir was associated with an incremental decline in hemoglobin concentration of 1.0 to 1.5 g/dL compared with patients in the control group during the period of telaprevir dosing. Notably, anorectal complaints were more prevalent in telaprevir-treated patients. The overall discontinuation rate secondary to AEs was lower in the ADVANCE trial than in the PROVE trials. This was partly attributable to a strategy of sequential instead of “all-at-once” discontinuation of the study drugs when severe rash occurred in patients in the ADVANCE trial, with telaprevir being stopped first, unlike the case in earlier studies of telaprevir.

The Phase 3 REALIZE trial (Re-treatment of Patients with telaprevir-based Regimens to Optimize Outcomes) evaluated treatment-experienced patients. In this prospective trial, 662 HCV genotype 1 relapers, partial responders, and null responders (<2 log decrease in HCV RNA at week 12 on prior therapy) were randomized to 3 groups: telaprevir plus PEG-IFN/RBV for 12 weeks followed by PEG-IFN/RBV for 36 weeks (simultaneous-start arm); a lead-in phase of PEG-IFN/RBV for 4 weeks followed by telaprevir plus PEG-IFN/RBV for 12 weeks followed by PEG-IFN/RBV for an additional 32 weeks (delayed-start arm); or 12 weeks of placebo plus PEG-IFN/RBV followed by 36 weeks of PEG-IFN/RBV alone. The delayed-start arm was the only arm with a lead-in phase of PEG-IFN/RBV in the entire development program for telaprevir. Among relapers, the SVR rate was 83% in the simultaneous-start arm, 88% in the delayed-start arm, and 24% in the control group. For prior partial responders, SVR rates were 59% and 54% in the simultaneous- and delayed-start arms, respectively, versus 15% in the control group. Finally, 29% and 33% of null responders achieved SVR in the simultaneous and delayed-start arms, respectively, versus 5% in the control group. The authors concluded that although both telaprevir-based regimens were superior to the control treatment regimen, the lead-in phase did not significantly improve SVR rates compared with a simultaneous start.

An analysis of the impact of hepatic fibrosis on SVR rates in the REALIZE trial demonstrated that among relapers, SVR was minimally affected, even if cirrhosis was present, but that cirrhosis did result
in decreased SVR rates in partial and null responders. The effect was most dramatic in the latter group, of whom about 40% achieved SVR if mild or bridging fibrosis was present compared with 14% of patients with cirrhosis. HCV genotype also had an impact on SVR: Rates were 10% to 15% in prior nonresponders with HCV genotype 1a versus 1b.

Yet another analysis of the lead-in arm from the REALIZE trial examined the association between the degree of HCV RNA decline after 4 weeks of PEG-IFN/RBV and the subsequent chance of achieving SVR: If HCV RNA declined by less than 1 log_{10} at week 4, relapsers had an SVR rate of 62% compared with 94% for those with a 1 log_{10} or greater decline in HCV RNA at week 4. For partial responders, SVR rates were 56% and 59% for those groups, respectively. The greatest effect of HCV RNA at week 4 occurred in null responders, with SVR rates of 15% and 54% for those with a less than 1 log_{10} and 1 log_{10} or greater decline, respectively.29

Further subgroup analyses of SVR rates by IL28B genotype were performed for the ADVANCE and REALIZE trials.10,31 In the ADVANCE trial, 42% of patients, all of whom were white, underwent IL28B testing. Of these, 33% had the CC polymorphism, 49% had the CT polymorphism, and 18% had the TT polymorphism. Telaprevir improved SVR rates for all IL28B subtypes, with the largest increase in efficacy occurring in patients with the CT and TT polymorphisms but the highest overall SVR rate observed in the CC group. An eRVR, and concomitant eligibility for a shortened course of therapy, were more common in the CC group. In the REALIZE study, 80% of patients underwent genetic testing. Of these, 18% had the CC polymorphism; 61%, the CT polymorphism; and 21%, the TT polymorphism. The authors concluded that the IL28B genotype was not predictive of response to treatment in this patient population, and that it appears to be of limited use in assessing patients who underwent prior treatment and will be re-treated with a telaprevir-based regimen.

Based on results from these studies, telaprevir is approved for the treatment of chronic HCV genotype 1 infection. The medication is available in oral tablet form and is indicated at a dose of 750 mg to be taken 3 times daily in combination with PEG-IFN/RBV.32 Package instructions state that patients must receive the 3-drug regimen for 12 weeks, followed by RGT of either 12 or 36 additional weeks of PEG-IFN/RBV, depending on viral response and prior response. For treatment-naive patients and prior relapsers, those with undetectable HCV RNA at weeks 4 and 12 should undergo therapy with 12 additional weeks of PEG-IFN/RBV. The exception to this guideline is for treatment-naive patients with cirrhosis and undetectable HCV RNA at weeks 4 and 12: 36 additional weeks of PEG-IFN/RBV is suggested for these patients. For prior partial and null responders, all patients should receive 12 weeks of the 3-drug regimen, followed by 36 weeks of PEG-IFN/RBV. Discontinuation is recommended for patients with HCV RNA greater than 1,000 IU/mL at week 4 or 12, or detectable HCV RNA at week 24.

Because telaprevir is a potent inhibitor of the cytochrome enzyme CYP3A, it is contraindicated for concurrent use with medications that are highly dependent on CYP3A for clearance. Noteworthy medications include lovastatin, simvastatin, and atorvastatin. Similarly, concurrent use of medications that strongly induce CYP3A, and can thereby lead to reduced efficacy, should be avoided. Because exposure to ethinyl estradiol may be reduced when telaprevir is coadministered, hormonal contraceptives should not be used as 1 of the 2 required methods of contraception for PEG-IFN/RBV therapy while telaprevir is being given and for 2 weeks after telaprevir is discontinued. Clinicians should consult the list of contraindicated drugs and the more extensive list of drugs with potential interactions available in the telaprevir package insert. Dose reduction and telaprevir monotherapy are strictly prohibited in order to minimize the emergence of viral resistance.

**Boceprevir**

Boceprevir is another selective peptidomimetic NS3 protease inhibitor that forms a covalent but reversible enzyme-inhibitor complex. Early studies established potent in vivo antiviral activity in the HCV replicon system and benefit in HCV genotype 1 patients treated with IFN. As with telaprevir, RBV is an essential component of boceprevir-containing treatment regimens.33,34 The multicenter Phase 2 SPRINT-1 (Serine Protease Inhibitor Therapy-1) trial demonstrated improved viral eradication rates with the addition of boceprevir to standard therapy, and also suggested the potential role of a 4-week lead-in period of PEG-IFN/RBV before the initiation of boceprevir therapy to achieve optimal SVR rates and minimize the rates of virologic resistance with the 3-drug regimen.35

The Phase 3 SPRINT-2 trial (Safety and Efficacy of Boceprevir in Previously Untreated Subjects With Chronic Hepatitis C Genotype 1) studied boceprevir in combination with PEG-IFNα2b/RBV in 1,097 treatment-naive HCV genotype 1 patients (938 non-black, 159 black).36 All patients received a 4-week lead-in PEG-IFN/weight-based RBV (600-1,400 mg daily), and were randomized to the following treatment arms: placebo plus PEG-IFN/RBV for an additional 44 weeks; boceprevir plus PEG-IFN/RBV for an additional 44 weeks; or an RGT arm with boceprevir plus PEG-IFN/RBV for an additional 24 weeks, followed by 20 more weeks of PEG-IFN/RBV if serum HCV RNA was detectable at any time during weeks 8 through 24. In all 3 groups, treatment was discontinued for patients with detectable HCV RNA at week 24, according to a standard futility rule. The non-black and black patient cohorts were analyzed separately.

In the non-black cohort, the SVR rate in the standard-of-care group (placebo plus PEG-IFN/RBV) was 40%. Rates were significantly higher in both boceprevir groups: 68% in the 48-week treatment group (P<0.0001 vs control) and 67% in the RGT group (P<0.0001 vs control). As expected, SVR rates in black patients were lower (23%) than in non-black patients in the standard-of-care arm. The addition of boceprevir significantly improved SVR rates in black patients, to 53% in the 48-week treatment group (P=0.004 vs control) and 42% in the RGT group (P=0.04 vs control). A modified intention-to-treat analysis, which included only patients who received at least a single dose of boceprevir, demonstrated SVR rates of 53% and 47%, respectively, in the same cohort.

SVR rates were also assessed based on viral response during the 4-week lead-in phase. In the non-black cohort, high responsiveness to PEG-IFN/RBV, as shown by a 1 log_{10} or greater decline in HCV RNA, was strongly predictive of SVR for all groups compared with a less than 1 log_{10} decline (82% vs 39% in the 48-week treatment group, respectively; 82% vs 29% in the RGT group, respectively; and 52% vs 5% in the control group, respectively). Relapse rates were lower in non-black patients who received boceprevir (8% in the 48-week treatment group, 9% in the RGT group, and 23% in the control group); however, this was not the case in black patients (17%, 12%, and 14%, respectively). The authors noted that the number of events in the smaller black cohort was too low to allow comparison between treatment groups.

Discontinuation of therapy secondary to AEs in the SPRINT-2 trial was similar for all 3 groups: 16%, 16%, and 12% for the control, 48-week, and RGT groups, respectively. As first observed in the SPRINT-1 trial, anemia was more common in patients treated with boceprevir, at 49%, than in control patients, at 29%. Although dose reduction secondary to anemia was required more often in patients on boceprevir than in those in the control group (21% vs 13%, respectively), treatment discontinuation was rare (2% vs 1%). Unlike the telaprevir regimen, erythropoietin use was permitted in the boceprevir study and was more frequent in both boceprevir arms. A modest incidence of neutropenia of unclear clinical significance was noted with boceprevir use, as was an increased incidence of dysgeusia.

The Phase 3 HCV-RESPOND-2 (Retreatment with HCV Serine Protease Inhibitor boceprevir and Peginteron/Rebetol 2) trial evaluated boceprevir-based regimens in treatment-experienced patients.37 The prior nonresponders were “partial” responders—they had experienced a 2 log_{10} or greater reduction in HCV RNA by week 12 of prior therapy—but they had persistent viremia at week 24 or they were patients who relapsed, having attained undetectable HCV RNA at the end of treatment but not having achieved SVR. Patients were randomized to receive a 4-week lead-in with PEG-IFN/RBV followed by PEG-IFN/RBV for 48 weeks (control group); a 4-week lead-in with PEG-IFN/RBV followed by boceprevir plus PEG-IFN/RBV for 44 weeks; or a 4-week lead-in with PEG-IFN/RBV followed by RGT. Patients in the RGT arm received boceprevir plus PEG-IFN/RBV for 32 weeks if serum HCV RNA was undetectable at week 8, or an additional 12 weeks of PEG-IFN/RBV for patients with detectable
HCV RNA at week 8. Patients with detectable HCV RNA at week 12 discontinued all treatment and were advanced to follow-up.

SVR rates in the control group were low (21%) compared with the 48-week treatment group (66%; P<0.001) and the RGT group (59%; P<0.001). As expected, prior responders had higher SVR rates than prior non-responders in all 3 groups. The authors noted that patients with a 1 log_{10} or greater decline in HCV RNA at the end of the 4-week lead-in period (good response to IFN) had the highest SVR rates (79% and 73% in the 48-week and RGT groups, respectively). Patients in the boceprevir treatment groups with a less than 1 log_{10} decline in HCV RNA during the lead-in period (poor response to IFN) had significantly higher SVR rates than corresponding patients in the control group (34% and 33% vs 0%, respectively). Discontinuation secondary to AEs was reported at 2%, 12%, and 8% in the 3 study arms, respectively. Anemia was more common in the boceprevir groups (43% and 46%) than in the control group (20%), although overall treatment discontinuation secondary to anemia was rare in all groups (0%, 3%, and 0% in the control, 48-week, and RGT groups, respectively).

An analysis of SVR rates based on IL28B subtype was performed for approximately two-thirds of patients in the SPRINT-2 and RESPOND-2 trials for whom the results of genetic testing were available. Overall, 29% of patients had the CC polymorphism; 54%, the CT polymorphism; and 18%, the TT polymorphism in the 2 boceprevir studies. In the control group in the SPRINT-2 trial, SVR rates were approximately 50% higher in patients with the favorable CC genotype than in those with the CT or TT genotype. The patients with the CC genotype in the boceprevir treatment groups had SVR rates that were 9% to 27% higher than patients with the CT or TT genotype, but the proportional increase in SVR was much greater in the CT and TT genotype patients. In prior treatment failure patients in the RESPOND-2 trial, SVR rates in the control group were not clearly affected by IL28B genotype. Boceprevir significantly increased SVR rates across all IL28B genotypes. Viral response at the end of the 4-week lead-in period superseded the predictive value of IL28B for SVR in both treatment-naive and treatment-experienced patients.

Boceprevir is approved for the treatment of chronic HCV genotype 1 infection administered in oral tablets at a dosage of 800 mg 3 times daily in combination with PEG-IFN/RBV. Per the package instructions, patients should receive a 4-week lead-in with PEG-IFN/RBV, followed by the addition of boceprevir 3 times per day in combination with PEG-IFN/RBV. Duration of treatment is determined by response, which is based on HCV RNA level at treatment weeks 8, 12, and 24. For treatment-naive patients with undetectable HCV RNA at weeks 8 and 24, 3-drug therapy is terminated at week 28. For treatment-naive patients with detectable HCV RNA at week 8 and undetectable HCV RNA at week 24, the 3-drug regimen is completed through week 36, followed by PEG-IFN/RBV alone through week 48. In previously partial responders or relapsers with undetectable HCV RNA at week 8 and detectable HCV RNA at week 24, the 3-drug regimen is continued through week 36. Patients with detectable HCV RNA at week 8 and undetectable HCV RNA at week 24 are treated with the extended course of the 3-drug regimen through week 36, followed by PEG-IFN/RBV alone through week 48. Treatment is deemed futile if HCV RNA is 100 IU/mL or greater at week 12 or if HCV RNA is detectable at week 24, at which points the 3-drug regimen should be discontinued. Package instructions state that RGT was not studied in patients who had less than 2 log_{10} reduction in HCV RNA during prior PEG-IFN/RBV therapy. Physicians are encouraged to treat these patients for the longer duration of therapy. This longer 48-week duration of therapy also is suggested for patients with a poor response to IFN at week 4 or those with compensated cirrhosis.

Like telaprevir, boceprevir is a potent inhibitor of CYP3A, although its major metabolic pathway is aldol-keto reductase. It is contraindicated for concurrent use with medications that are highly dependent on CYP3A clearance. It is also contraindicated for concurrent use with medications that strongly induce CYP3A. Familiarity with the drugs listed as contraindicated or capable of potential interactions with boceprevir, which overlap considerably with those for telaprevir, is essential. Dose reduction and monotherapy are strictly prohibited.

### Future Directions

In addition to telaprevir and boceprevir, numerous other DAAIs from several classes are being studied. These include novel HCV protease inhibitors, as well as medications that target the NS5A replication complex protein and the NS5B RNA-dependent RNA polymerase. Additionally, drugs that inhibit host factors that can augment viral replication, such as cyclophilin antagonists, are being evaluated.

A novel NS3/4a protease inhibitor given once daily, TMC455, in combination with PEG-IFN/RBV has shown promising results in early trials. The PILLAR study is a dose- and duration-ranging study incorporating RGT. In a preliminary report, 79% to 86% of patients in the TMC435 treatment arms were able to cease therapy at week 24, and SVR rates in these patients ranged from 88% to 97%. Viral response was enhanced with the addition of TMC435 compared with standard of care in all IL28B genotypes. There was no significant difference in AEs between TMC435-treated patients and patients in the placebo arm, with discontinuation of therapy secondary to AEs occurring in 7.1% and 7.8% of study participants, respectively. In a contemporaneous study in treatment-experienced patients,

### Table 2. Regimens for HCV Treatment-Experienced Patients

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<tr>
<th>Trial</th>
<th>Treatment Regimen*</th>
<th>SVR Rate, %</th>
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BOC, boceprevir; PR48, pegylated interferon-α/ribavirin for 48 weeks; REALIZE, Re-treatment of Patients with telaprevir-Based Regimens to Optimize Outcomes; RESPOND-2, Retreatment with HCV Serine Protease Inhibitor boceprevir and PegIntron/Rebetol; RGT, response-guided therapy; SVR, sustained virologic response; T8, telaprevir, 8 weeks; T12, telaprevir, 12 weeks

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* See text for complete dosing regimen details.
called ASPIRE, TMC435 combined with PEG-IFN/RBV yielded higher rates of on-treatment response than PEG-IFN/RBV alone, including response rates at week 24 of higher than 70% in prior null responders.\textsuperscript{41} Other protease inhibitors that have demonstrated incremental increases in SVR or on-treatment response rates in treatment-naive patients and/or prior nonresponders include BI201335, danoprevir (which is being studied with ritonavir boosting), and BM5650032, among others.\textsuperscript{42-45}

Inhibitors of the HCV NS5A protein, which is active within the viral replication complex, appear extremely promising. The first data on SVR rates in patients treated with a drug from this class, BMS790052, were presented in early 2011. Patients were given BMS790052 at 3, 10, or 60 mg once daily in combination with PEG-IFN/RBV for 48 weeks or PEG-IFN/RBV alone. SVR rates in patients who received the 2 higher doses of BMS790052 were 92% and 83% compared with 25% in the control group; the drug also was well tolerated.\textsuperscript{46}

Favorable rates of HCV suppression have been shown with use of RG7128, a potent nucleoside analog polymerase inhibitor of HCV. In the PROPEL study, patients in 4 treatment arms received different doses and/or duration of treatment with RG7128 in combination with PEG-IFN/RBV, and were compared with a fifth group of patients who received PEG-IFN/RBV alone.\textsuperscript{47} The combination of RG7128 with PEG-IFN/RBV was safe and well tolerated, yielding rapid virologic response (RVR) rates of 39% to 63% and complete early virologic response (cEVR, defined as undetectable HCV RNA at week 12) rates of 68% to 87% in patients with HCV genotypes 1 and 4, 20% of whom had cirrhosis. Preliminary results from a second study of RG7128, the JUMP-C trial, were presented recently.\textsuperscript{48} Of patients treated with RG7128 at the now established dose of 1,000 mg twice daily plus PEG-IFN/RBV who achieved eRVR, 76% went on to achieve SVR at 12 weeks after cessation of therapy. However, a recent study\textsuperscript{49} in this cohort raised questions about whether 24 weeks represents an optimal treatment duration with this drug.

Another nucleoside polymerase inhibitor, PSI-7977, has shown promising SVR rates in treatment-naive HCV genotype 1 patients in a Phase 2 study.\textsuperscript{50} In the PROTON study, 121 patients were randomized to receive PSI-7977 200 or 400 mg or placebo once daily plus PEG-IFN/RBV. Overall, 98% of patients in the PSI-7977 treatment groups achieved RVR, with 100% of patients reaching week 12 with undetectable HCV RNA. There were no observed viral breakthroughs. In a smaller cohort of patients with HCV genotypes 2 and 3, 100% of patients treated with PSI-7977 plus PEG-IFN/RBV for 12 weeks achieved SVR, except for 1 patient who was lost to follow-up. These data reinforce the prevailing evidence that nucleoside analogs are distinct for their much higher barrier to viral resistance than HCV protease inhibitors or HCV NS5A inhibitors, and as outlined below, they may be an attractive option for DAA combination regimens.

As with several DAA agents, a cyclophilin inhibitor, alisporivir, has demonstrated favorable SVR rates in combination with PEG-IFN/RBV.\textsuperscript{51} In a recent trial, treatment-naïve HCV genotype 1 patients were randomized to receive alisporivir plus PEG-IFN/RBV for 48 weeks, alisporivir plus PEG-IFN/RBV for 24 weeks, alisporivir plus PEG-IFN/RBV in an RGT fashion (24 weeks for those achieving RVR and 48 weeks for those not doing so), or placebo plus PEG-IFN/RBV for 48 weeks. SVR rates were 76%, 53%, and 69% in each of the alisporivir treatment groups, respectively, compared with 55% in the control group.

Another recent development is the potential use of PEG-IFNα, with favorable safety and tolerability than with PEG-IFNα.\textsuperscript{52} In a study of 526 treatment-naïve patients with chronic HCV infection who were randomized to receive ribavirin plus PEG-IFNα, 240, 180, or 120 mcg or ribavirin plus PEG-IFNα, cEVR rates were significantly higher for all PEG-IFNα doses than for standard of care (56.3%, 55.9%, and 55.0% vs 37.9%, respectively) in patients with HCV genotypes 1 and 4. Treatment with PEG-IFNα also was associated with fewer hematologic toxicities and flu-like and musculoskeletal symptoms than PEG-IFNα. This recent data appear to require that at least one component be a drug with a high barrier to HCV resistance, such as a nucleoside analog. Barring this component, RBV appears to be a potentially viable adjunctive third drug. This was illustrated in a trial of an HCV protease inhibitor and a non-nucleoside polymerase inhibitor in the presence or absence of RBV: virologic breakthroughs in the absence of RBV and a protective effect was observed in the presence of RBV.\textsuperscript{53} Breakthroughs also occurred in a combination therapy trial involving telaprevir and a non-nucleoside drug, VX-222.\textsuperscript{54} In contrast, another study of a protease inhibitor and a non-nucleoside polymerase inhibitor, RBV appeared to prevent virologic breakthroughs.\textsuperscript{55}

The past year was historic not only for the approval of the first 2 protease inhibitors, but for the demonstration of the eagerly awaited proof of concept that HCV infection can be cured without interferon. At least 4 such studies have appeared in various forms, ranging from press releases to published papers. A small but highly influential study examined the combination of asunaprevir (previously known as BMS650032), a protease inhibitor, and daclatasvir (previously known as BMS790052), a potent NS5A inhibitor that is believed to act via inhibition of cell entry or translation of 240 nucleotides in infected cells, in 11 HCV genotype 1 null responders. Seven of 11 patients (63.6%) achieved RVR when treated with the 2-drug combination for 24 weeks.\textsuperscript{56} Additionally, 5 patients had undetectable HCV RNA at 24 weeks, and 4 patients achieved SVR at week 12–2 of 2 patients with HCV genotype 1b and 2 of 9 patients with HCV genotype 1a. Most of the remaining patients had virologic breakthrough, with detection of resistant variants to both drugs. Intriguingly, all of 10 null responders who received a quadruple regimen containing PEG-IFN/RBV and the 2 DAs achieved an SVR, fueling intense interest in further investigation of quadruple therapy. Studies on both IFN-free therapy and quadruple therapy with PEG-IFN/RBV and 2 DAs have been initiated or are being planned.

The high response rate of HCV genotype 1b to a dual DAA regimen was demonstrated in another IFN-free trial combining asunaprevir and daclatasvir in genotype 1b null responders.\textsuperscript{57} Out of 10 enrolled patients, 9 patients completed 24 weeks of treatment, all of whom achieved SVR at weeks 12 and 24. The ELECTRON trial examined the previously mentioned nucleoside polymerase inhibitor, PSI-7977 (now known as GS-7977). In this trial, an SVR rate of 100% was observed in 40 treatment-naive patients with HCV genotypes 2 and 3 in all study arms, including 12-week regimens of PSI-7977 plus PEG-IFN/RBV (the latter given for 4, 8, or 12 weeks) and an IFN-free arm of PSI-7977 plus RBV for 12 weeks.\textsuperscript{58,59} In a 10-patient cohort of PSI-7977 monotherapy, all patients had undetectable HCV RNA at end of treatment, but four patients had relapsed at the time the initial data were presented. However, in HCV genotype 1 null-responders treated with a 12-week regimen of PSI-7977 and RBV, promising early viral suppression with 100% undetectable HCV RNA at the end of treatment did not prevent virologic relapse, with nearly all patients relapsing within 4 weeks of the end of treatment.\textsuperscript{60} This and other observations have raised the question of whether intrinsic IFN responsiveness might still influence the response to IFN-free antiviral regimens, perhaps depending on the subtype of HCV genotype 1 and on components of the antiviral regimen (eg, HCV genotype 1a becomes resistant more readily, at least to protease inhibitors, than HCV genotype 1b). Data from an HCV genotype 1b treatment naïve cohort are eagerly awaited.

Conclusion

The exciting developments described here mandate education of all physicians who treat patients with HCV in the proper use of the new agents, including management
of side effects. Individualization of treatment decisions, both in treatment-naive and treatment-experienced patients, remains of paramount importance. We can expect studies in patients for whom the role of the already approved agents has not been clearly defined, such as HIV-coinfected patients (studies are in progress with protease inhibitors), transplant recipients, and patients with decompensated liver disease. Trials involving DAAIs of several classes, as well as drugs with other mechanisms of action, either with or without PEG-IFN/RBV, are proceeding at a remarkable pace. Ultimately, it would appear that the field of HCV therapy is moving inexorably toward the development of interferon-free therapy for many if not most or even all patients.

References


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