The treatment paradigm for hepatitis C virus (HCV) is changing very rapidly. In the short time since the publication of our CME/CE-certified activity, Exploring Emerging Treatment Options in the Context of Holistic HCV Treat-Or-Defer Decisions, the Food and Drug Administration (FDA) antiviral drug advisory committees reviewed data on two emerging direct-acting antiviral agents for the treatment of HCV; additionally, the American Association for the Study of Liver Diseases (AASLD) held its annual conference, at which a substantial volume of new data was presented. Because new therapies have recently become available and others may become available in the near future, much of these recently reported data are immediately relevant. In this focused update, we explore recently reported data that are anticipated to influence HCV treatment decisions in 2014.

Patients With HCV Genotype 1

In October 2013, the FDA antiviral advisory panel met on two consecutive days to review the new drug applications for two direct-acting antiviral agents: simeprevir and sofosbuvir. Both agents have now been approved for patients with genotype 1 in combination with peginterferon alfa (PegIFN) and ribavirin (RBV).\(^1,2\) Sofosbuvir was also approved for use in genotypes 2 and 3 (discussed in more detail below) and genotype 4 (not included in this focused update).

Simeprevir

Simeprevir is an NS3/4a protease inhibitor that has been studied in several large trials. In our CME/CE-certified activity, we discussed the results of QUEST 1 and QUEST 2, which evaluated simeprevir in only treatment-naïve patients. At the November 2013 annual meeting of the AASLD in Washington, DC, data were presented from the phase 3 PROMISE trial, which evaluated simeprevir in relapers.\(^3\) Key characteristics of this trial include:

- N = 393 patients
- 150 mg simeprevir once daily with PegIFN/RBV backbone
- Treatment duration: 24 or 48 weeks based on response-guided therapy
- Included treatment-experienced patients and those with cirrhosis

Rates of sustained virologic response at 12 weeks post-treatment (SVR12) stratified by level of fibrosis are shown in Figure 1. Simeprevir was well tolerated, and discontinuation rates due to adverse events were low (3%). As previously seen with simeprevir, transient

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**FIGURE 1. PROMISE: SVR12 by Level of Fibrosis**

increases in bilirubin were observed, and some patients experienced increased photosensitivity.1,4

Recently, it has become clear that a critical factor in patient response to simeprevir is the presence of the Q80K polymorphism at baseline; presence of this mutation translates to reduced efficacy of simeprevir in combination with PegIFN/RBV. Results from a pooled analysis of QUEST 1 and 2 reported at the November 2013 AASLD meeting suggest that the Q80K polymorphism appears to be much more prevalent in patients with genotype 1a than in those with genotype 1b.4 In addition, a regional analysis showed geographic variability in the presence of this polymorphism, with a higher frequency among genotype 1a patients in North America (about 48%) than in Europe (19.4%) or South America (9.1%).5 Based on the high prevalence of the Q80K polymorphism in North American patients with HCV genotype 1a infection, the prescribing label for simeprevir includes a strong recommendation for screening patients for the presence of the NS3 Q80K polymorphism at baseline. Patients with genotype 1a who are Q80K positive should not be treated with PegIFN/RBV and simeprevir; other regimens should be considered.1

**Simeprevir/Sofosbuvir**

The presentation of the first data set from the COSMOS study was a much-anticipated highlight of the 2013 AASLD annual meeting. This trial combines simeprevir with sofosbuvir (the NS5B polymerase inhibitor) in genotype 1 patients for 12 or 24 weeks. Key tenets of this trial design include6:

- Two cohorts:
  - Cohort 1: n = 80; null responders to PegIFN/RBV with METAVIR fibrosis stage 0 to 2
  - Cohort 2: n = 87; treatment-naive patients and null responders with METAVIR fibrosis stage 3 or 4 (cirrhosis)
- Sofosbuvir 400 mg PO QD + simeprevir 150 mg PO QD with or without RBV
- Treatment duration: 12 or 24 weeks

In the cohort 1 data presented in Washington, DC, the SVR12 rates were greater than 95% in prior null responders treated for 12 or 24 weeks; the addition of RBV did not affect the SVR12 rate (Figure 2). Additionally, the Q80K polymorphism was detected in 50% of patients with genotype 1a in cohort 1 and appeared to influence the SVR12 rate.6,7 No virologic failures were observed in patients with HCV genotype 1a without the Q80K polymorphism or in patients with genotype 1b. However, 3 patients with genotype 1a and the Q80K polymorphism experienced viral relapse; still, the SVR12 rate among this subgroup was 89%, and most patients with the Q80K polymorphism achieved SVR.6,7 Early data from cohort 2 (treatment-naïve patients and null responders with METAVIR fibrosis stage 3 or 4) also show encouraging results with SVR4 rates between 93.3% and 100%.

**Sofosbuvir**

At the AASLD meeting, researchers presented exciting data for the traditionally hard-to-treat HCV population of patients who are coinfected with HIV. The genotype 1 results from the PHOTON-1 trial evaluating 24 weeks of sofosbuvir with RBV in patients naïve to HCV treatment showed encouraging results; SVR12 rates were 76% in this group (Figure 3).8,9
Patients With Genotypes 2 and 3

Sofosbuvir/PegIFN/RBV

Although genotypes 2 and 3 have often been studied as a single group, it is becoming clear that efficacy rates vary between these genotypes. Results from the LONESTAR-2 study were reported at the AASLD meeting (Figure 4); this trial evaluated 12 weeks of sofosbuvir/PegIFN/RBV in patients with genotype 2 or 3 with and without cirrhosis who had failed to respond to prior treatment with PegIFN/RBV.\textsuperscript{10} Important considerations when evaluating these data include:

- \( N = 47 \)
- Sofosbuvir with PegIFN/RBV backbone
- Treatment duration: 24 weeks
- All treatment-experienced patients, about 50\% with compensated cirrhosis

Among genotype 3 patients, SVR\textsubscript{12} rates did not differ between those with or without cirrhosis, as shown in Figure 4.\textsuperscript{10} In addition, the SVR\textsubscript{12} rates for sofosbuvir/PegIFN/RBV are higher than those reported with the 16-week course of sofosbuvir/RBV.\textsuperscript{10,11}

Sofosbuvir/RBV Without PegIFN

Results from the VALENCE trial, which evaluated sofosbuvir/RBV without PegIFN, also show some important outcomes. Key characteristics of this study include\textsuperscript{12,13}:

- Genotype 2, \( n = 73 \); genotype 3, \( n = 250 \)
- Sofosbuvir with RBV

Among genotype 3 patients, the results of this trial showed high rates of SVR\textsubscript{12} in treatment-naïve patients regardless of the presence of cirrhosis, as well as high rates of SVR\textsubscript{12} in treatment-experienced patients without cirrhosis (Figure 5). However, the SVR\textsubscript{12} rate was lower for treatment-experienced patients with cirrhosis despite 24 weeks of sofosbuvir plus RBV.\textsuperscript{12,13}

A Pooled Analysis

To evaluate the question about duration of treatment for patients with genotype 3, the FDA performed a pooled analysis of the registration trials FISSION, POSITRON, FUSION, and VALENCE, as shown in Figure 6.\textsuperscript{13}

Sofosbuvir was approved for use in combination with RBV for patients with genotype 2 (12 weeks) or genotype 3 (24 weeks) by the FDA in December of 2013.\textsuperscript{2}

A Glimpse Into the Future

Another protease inhibitor, faldaprevir, has been studied in several phase 3 clinical trials. The earlier reported phase 3 studies STARTVerso1 and STARTVerso2 were discussed in our CME/CE-certified activity, Exploring Emerging Treatment Options in the Context of Holistic HCV Treat-Or-Defer Decisions. New information from these data sets, which were reported at the 2013 AASLD annual meeting, showed
some geographic variation in response to faldaprevir. Jensen and colleagues showed regional variation in SVR12 rates, with higher cure rates reported in trials completed in Europe and Asia than in those completed in North America. In STARTVerso3, results of which were also reported at AASLD, faldaprevir plus PegIFN/RBV in treatment-experienced patients showed SVR rates of 70% for relapsed patients but 33% for null responders.

Faldaprevir has also been studied with a non-nucleoside polymerase inhibitor (deleobuvir) in a phase 2 trial, which showed a lack of response in genotype 1a patients (SVR12 = 17%) but encouraging response in genotype 1b patients (SVR12 = 95%). Phase 3 trials in patients with genotype 1b are underway based on these data. In addition, researchers are evaluating the impact of the addition of an NS5A inhibitor (PPI-668) to faldaprevir and deleobuvir. Very early results presented at AASLD show encouraging changes in viral kinetics, and more data are expected in the future.

Sofosbuvir plus an NS5A inhibitor is being studied in fixed-dose combinations in several trials. Phase 2 data from the ELECTRON trial of sofosbuvir + ledipasvir with/without RBV or GS-9669 (a non-nucleoside polymerase inhibitor) were reported at the 2013 AASLD meeting. Among genotype 1 treatment-experienced patients in this study, SVR12 rates increased from 70% with sofosbuvir/ledipasvir to 100% with the addition of either RBV or GS-9669. Another noteworthy trial, the LONESTAR trial, evaluated sofosbuvir/ledipasvir with/without RBV in patients who were treatment naïve or had virologic failure following previous protease inhibitor therapy (boceprevir or telaprevir) for 8 or 12 weeks. This single-center study involved 100 patients in two cohorts. In cohort A, 60 non-cirrhotic treatment-naïve patients were randomized 1:1:1 to sofosbuvir plus ledipasvir (8 weeks), sofosbuvir plus ledipasvir and RBV (8 weeks), or sofosbuvir plus ledipasvir and RBV (12 weeks). In cohort B, 40 patients with virologic failure following boceprevir or telaprevir were randomized 1:1 to sofosbuvir plus ledipasvir (12 weeks) or sofosbuvir plus ledipasvir and RBV (12 weeks); in this cohort, 55% of patients had compensated cirrhosis. In cohort A, the SVR12 rate for patients...
treated with sofosbuvir plus ledipasvir (8 weeks) was 95% without the addition of RBV and 100% in patients with the addition of RBV. Among those in cohort A (treatment naïve) who received 12 weeks of sofosbuvir plus ledipasvir and RBV, the SVR12 rate was 95%. Within the previously treated cohort (cohort B), the SVR12 rate was 95% among patients treated with sofosbuvir plus ledipasvir for 12 weeks and 100% among those who received sofosbuvir plus ledipasvir and RBV for 12 weeks.\textsuperscript{20}

In Exploring Emerging Treatment Options in the Context of Holistic HCV Treat-Or-Defer Decisions, we discussed the AVIATOR trial, which suggested that regimens for patients with genotype 1b might show similar results with a more simplified regimen. At the 2013 AASLD meeting, Lawitz and colleagues presented the data from PEARL-1, which evaluated ABT-450/ritonavir/ABT-267 in treatment-naïve and null-responder patients with genotype 1b. These results showed high SVR rates (90% to 95.2%).\textsuperscript{21,22}

Finally, a new combination was presented for the first time at the 2013 AASLD meeting: a second-generation protease inhibitor with an NS5A inhibitor (MK-5172 + MK-8742) with and without RBV. Data from this study (C-WORTHY) showed SVR12 rates between 89% and 100%, and more studies are planned.\textsuperscript{23}

These are just a few of the exciting developments in the field of HCV management. Recently there have also been important studies demonstrating the impact of many other developments, including expanding screening and the use of noninvasive strategies to evaluate fibrosis. Although these data are beyond the scope of this discussion, it is clear that clinicians caring for patients with HCV are now better armed and can expect even more advances in the future.
References