As a result, early identification of infections and continued research on cure strategies—particularly using regimens that do not include interferon (IFN)—are vital to this patient population. This review will highlight advances in HCV care from the past year, including research presented at recent gastroenterology and hepatology meetings. Although the incidence of HCV infection continues to decline, cases of cirrhosis and hepatocellular carcinoma remain steady.¹

Screening and Diagnostics
In August 2012, the Centers for Disease Control and Prevention (CDC) recommended a one-time HCV screening for all Americans born between 1945 and 1965 (aka baby boomers).² According to the CDC report, 75% of HCV-infected individuals in the United States were born during that period, but the overwhelming majority—as many as 75%—are unaware of their HCV status. The CDC said screening baby boomers could lead to the detection of more than 800,000 HCV infections, and avert cases of advanced liver disease and as many as 120,000 deaths.

But the CDC’s recommendation received a lukewarm response from the US Preventive Services Task Force (USPSTF). In its November 2012 draft opinion, the task force said screening should be offered to adults at high risk, such as those with a history of IV drug use and those who received blood transfusions before 1992. For baby boomers, the task force said clinicians may
“consider offering” HCV screening. However, in June 2013, the USPSTF changed its stance and gave a “B” recommendation to screening for this population. The Affordable Care Act requires private insurers to cover any preventative screening that carries an A or B recommendation from the USPSTF.

Also in June 2013, the FDA approved a test that identifies HCV genotypes (GTs) in infected patients, the Abbott RealTime HCV Genotype II test (Abbott Molecular, Inc.). This test can differentiate between HCV GTs 1, 1a, 1b, 2, 3, 4, and 5 using a sample of blood plasma or serum. This knowledge can aid physicians in determining the appropriate approach to treatment: Because HCV GTs respond differently to various drugs, this information can result in better patient outcomes.

The FDA based its approval of the Abbott RealTime HCV Genotype II in part on an assessment of the test’s accuracy in differentiating specific HCV GTs compared with a validated gene-sequencing method. The FDA also reviewed data demonstrating the relationship between HCV GT and effectiveness of drug therapy.

In February 2013, the FDA approved a next-generation viral-load test from Roche to accurately quantitate HCV RNA levels in order to assess a patient’s response to antiviral therapy. The COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test (version 2.0) is intended for use in the management of patients with chronic HCV infection, in conjunction with clinical and laboratory markers of infection. It is an in vitro nucleic acid amplification test for the quantitation of HCV RNA GTs 1 to 6 in human plasma or serum. The test can be used to predict the probability of sustained virologic response (SVR) early during a course of antiviral therapy, and to assess response to antiviral treatment as measured by changes in HCV RNA level.

This real-time polymerase chain reaction–based HCV test is designed for use with Roche’s fully automated COBAS AmpliPrep/COBAS TaqMan system, an established platform for viral-load monitoring of multiple infectious diseases that improves workflow in testing laboratories. The system can be combined with the COBAS P630 instrument that provides an integrated, preanalytical primary tube-handling solution.

**Table. Adverse Events in Patients Receiving PEG-IFN Lambda Compared With PEG-Interferon Alfa**

<table>
<thead>
<tr>
<th></th>
<th>PEG-IFN Lambda (180 mcg)</th>
<th>PEG-IFN Alfa (180 mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any serious AEs, n</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Patients with any AEs, %</td>
<td>88.2</td>
<td>97.1</td>
</tr>
<tr>
<td>Patients with IFN dose modifications, %</td>
<td>7.8</td>
<td>28.2</td>
</tr>
<tr>
<td>Patients with ribavirin dose modifications, %</td>
<td>10.8</td>
<td>33</td>
</tr>
</tbody>
</table>

AEs, adverse events; IFN, interferon; PEG-IFN, pegylated interferon

Based on reference 6.

**Treatment Options**

**THE LIVER MEETING 2012**

At the 2012 meeting of the American Association for the Study of Liver Diseases (AASLD), a plethora of research was unveiled on the treatment of HCV infection. According to preliminary results from the EMERGE trial, the use of a novel IFN, pegylated (PEG)-IFN lambda-1a (Lambda, Bristol-Myers Squibb), may improve the treatment of patients with HCV infection. Treatment of HCV infection with PEG-IFN alfa-2a, a type I IFN, can be effective, but it also causes frequent adverse events (AEs), including hematologic toxicity. PEG-IFN lambda is a type III IFN that uses a different signaling pathway and has demonstrated robust antiviral activity. Because it uses a receptor present on fewer types of cells, it has a more favorable tolerability profile than PEG-IFN alfa.

The EMERGE study is a Phase IIb, multicenter, single-arm, open-label trial that enrolled 526 noncirrhotic, treatment-naive adults infected with chronic HCV GT 1, 2, 3, or 4. Patients were randomized 1:1:1 to receive PEG-IFN alfa 180 mcg, or 1 of 3 dosages of PEG-IFN lambda (120, 180, or 240 mcg) administered weekly in combination with daily oral ribavirin (RBV), which was administered in accordance with the prescribing information.

Patients and providers were blinded throughout the study, and a pharmacist who was not blinded prepared the drug at each study site. The IFN dose could be held and reduced in cases of moderate or severe depression in study participants or for other significant grade 3 or 4 AEs related to the study drug. SVR was defined as an HCV RNA level less than the lower limit of quantification (25 IU/mL).

Results were presented through week 72 for 407 patients with HCV GT 1 or 4. Overall, AEs were similar for both treatments (Table). Several AEs of any grade were markedly higher in patients who received PEG-IFN lambda, including myalgia (33% vs 5.9%), pyrexia (33% vs 7.8%), chills (21.4% vs 3.9%), and arthralgia (20.4% vs 5.9%). All cases of hyperbilirubinemia resolved following discontinuation of the study drug.

Elsewhere at the 2012 AASLD Meeting, late-breaking
abstracts and a slew of other studies discussed new oral regimens that can be used to achieve high SVR rates in a variety of HCV patient cohorts, including null responders.

The AVIATOR trial tested 8-, 12-, and 24-week regimens of a combination of RBV plus 3 direct-acting antiviral agents (DAAs) being developed by Abbott Laboratories: ABT-450, ABT-267, and ABT-333. ABT-450, an NS3/4A protease inhibitor (PI), is coadministered with ritonavir (ABT-450/r) in a once-daily dose.7 ABT-267, an NS5A inhibitor, also is a once-daily therapy. ABT-333, a non-nucleoside polymerase inhibitor, is used twice daily.

In exploratory studies,7 combinations containing ABT-450/r have achieved SVR rates greater than 90% in HCV GT 1–infected patients. In the current study, researchers set out to identify the optimal drug combination for HCV GT 1–infected patients who were either treatment-naive or null responders to previous treatment with PEG-IFN and RBV. To be eligible, participants could not have cirrhosis or HIV infection. Seven arms of the study, which included 571 patients, were evaluated for different drug combinations and regimen durations, up to 24 weeks.

SVR rates at week 12 were 97.5% in the treatment-naive group and 93.3% in null responders. Relapses primarily occurred in patients who received 8 weeks of therapy compared with those who received 12 weeks. Ninety-six percent of HCV GT 1a–infected treatment-naive patients and 89% of HCV GT 1a–infected null responders achieved an SVR at week 12. No AEs were observed, and only 2 of the 448 patients discontinued treatment due to an AE attributed to the study drug.

The SOUND-C2 trial tested a combination of 2 drugs developed by Boehringer Ingelheim—faldaprevir and BI 207127—with or without RBV in treatment-naive patients with HCV GT 1 infection.8 Faldaprevir is an NS3/4A PI, and BI 207127 is a non-nucleoside NS5B inhibitor.

The study included 362 patients (33 with cirrhosis) and had 5 arms, which tested different dosing schemes and treatment durations, from 16 to 40 weeks. The 28-week regimen, using a twice-daily dosing scheme performed best, resulting in a 69% SVR overall at week 12 and an 85% SVR at week 12 in HCV GT 1b patients. Patients with cirrhosis achieved an SVR of 67%.

The most common AEs were asthenia, pruritus, rash, photosensitivity, jaundice, nausea, vomiting, diarrhea, and transient indirect hyperbilirubinemia. Overall, 36% of patients experienced AEs: 12% were considered severe, and 8% led to discontinuation of treatment.

Mark Sulkowski, MD, medical director of the Viral Hepatitis Center in the Divisions of Infectious Diseases and Gastroenterology & Hepatology at Johns Hopkins School of Medicine in Baltimore, presented results of a study that tested an all-oral combination of daclatasvir (Bristol-Myers Squibb), an NS5A inhibitor, and sofosbuvir, with or without RBV.9 The combination—tested in treatment-naive patients—was given for 24 weeks to patients infected with HCV GT 1a, 1b, 2, or 3, and for 12 weeks to patients with HCV GT 1a or GT 1b. All patients were noncirrhotic.

Researchers randomized 44 patients with HCV GT 2/3 to 1 of 3 treatment groups: daclatasvir 60 mg daily plus sofosbuvir 400 mg daily with or without RBV for 24 weeks, or sofosbuvir daily for 7 days. Researchers also randomized 44 patients with HCV GT 1a/1b to receive sofosbuvir every day for 7 days followed by daclatasvir and sofosbuvir daily for a total of 24 weeks, or daclatasvir plus sofosbuvir daily, with or without RBV, for 24 weeks. During a second stage of the study, 82 patients with HCV GT 1a or 1b were randomized to receive 12 weeks of daclatasvir plus sofosbuvir, with or without RBV.

Overall, more than 93% of patients with HCV GT 1, 2, or 3 achieved an SVR with the drug combinations. Among the 44 patients with HCV GT 2 or 3 infection, 93% achieved an SVR at week 24, with 1 patient having a confirmed relapse. Among the 126 patients with HCV GT 1 infection, 96% of those who had reached the 12 weeks post-treatment stage had an SVR at week 12; this included 3 patients who did not have an SVR at week 4. The SVR rate at week 24 in this group was 98%. The drug combination was well tolerated.

Gregory Everson, MD, director of the Section of Hepatology at the University of Colorado Denver, in Aurora, presented results from a Phase IIa open-label study of AI443-014, which tested a 12-week regimen of 3 drugs developed by Bristol-Myers Squibb: daclatasvir, asunaprevir, and BMS-791325.10 The 4-arm study included treatment-naive, noncirrhotic patients with HCV GT 1 infection. Results were presented only for the 2 arms of the study that included BMS-791325 75 mg plus daclatasvir and asunaprevir. One group of patients was treated for 12 weeks (n=16) and the other was treated for 24 weeks (n=16). Patients (mean age, 48 years) had a high viral load and 75% were infected with HCV GT 1a. (The other 2 arms received 150 mg of the investigational agent.)

In the group receiving treatment for 24 weeks, researchers only had complete data for SVR at week 4 (94%). Two patients assigned to this arm discontinued treatment before completing the 24-week phase: One patient, who withdrew consent at week 9 of treatment, was lost to follow-up (HCV RNA was undetectable at week 8), and the other patient, who stopped treatment at week 14 due to poor venous access, achieved SVR at week 4. In the group that received 12 weeks of treatment, SVR was 94% at weeks 4 and 12. Two patients assigned to this arm discontinued treatment before completing the full 12-week phase: One patient stopped treatment at week 11 but still achieved SVR at week 12, and the other completed the 12 weeks of treatment but did not return for post-treatment follow-up (HCV RNA
was undetectable at end of treatment). These high SVR rates were achieved despite the more difficult-to-treat characteristics of HCV GT 1a infection and non-IL28B CC GTs of the patients. Although 4 patients in the study discontinued treatment prematurely, there were no discontinuations because of AEs.

**EASL 2013**

The 2013 Annual Meeting of the European Association for the Study of the Liver (EASL) also provided a forum for researchers to present significant advances in HCV care. The NEUTRINO study, a Phase III, open-label trial, investigated a combination of sofosbuvir, PEG-IFN, and RBV for 12 weeks in 292 treatment-naive patients with chronic HCV GT 1; 28 patients with HCV GT 4; and 7 patients with HCV GT 5/6. The combination regimen led to an SVR rate of 90% 12 weeks after completing treatment, a rate significantly higher than that reported in historical controls (60%).

All patients received daily 400-mg sofosbuvir, a pan-genomic NS5B HCV polymerase inhibitor, along with RBV 1,000 to 1,200 mg daily, and PEG-IFN 180 mcg weekly, for 12 weeks. Seventeen percent of patients had compensated cirrhosis and 29% had IL28B CC GTs. At baseline, patients had platelet counts greater than 90,000/mL, none had neutropenia, and the mean HCV RNA viral load was 6.4 log IU/mL.

All of the patients who did not achieve SVR at week 12 relapsed following an initial response to treatment. None of these patients were found to have NS5B S282T resistance after relapse. Subgroup-specific SVR rates at week 12 were 80% in patients with cirrhosis, 89% in cirrhotic and noncirrhotic patients with HCV GT 1, 96% in HCV GT 4 patients, and 100% in HCV GT 5/6 patients.

Common AEs of treatment included fatigue (59%), headache (36%), nausea (34%), and insomnia (25%); 2% of patients discontinued treatment. Serious AEs occurred in 1% of patients.

Results from the FUSION trial also were unveiled at the 2013 EASL Meeting. FUSION was a randomized, placebo-controlled, double-blind Phase III study of dual therapy with sofosbuvir 400 mg daily and RBV 1,000 to 1,200 mg daily, and included 201 treatment-experienced patients with HCV GT 2/3. Most of the patients were white men, with a mean age of 54 years. Thirty percent of patients had the IL28B CC GT, 34% had compensated cirrhosis, 63% had HCV GT 3, 75% had relapsed following previous treatment, and 25% were prior null responders. Patients were randomized to receive either 12 weeks of treatment with sofosbuvir and RBV followed by 4 weeks of placebo, or 16 weeks of treatment with sofosbuvir and RBV.

In the 16-week treatment group, 78% of HCV GT 2 patients with cirrhosis and 100% of HCV GT 2 patients without cirrhosis achieved SVR compared with 60% and 96%, respectively, of patients in the 12-week treatment group. SVR rates in HCV GT 3 patients in the 16-week treatment group were 61% and 63% for patients with or without cirrhosis, respectively, compared with 19% and 37%, respectively, of patients in the 12-week treatment group.

Serious AEs occurred in 3% and 5% of patients in the 16- and 12-week treatment groups, respectively, but no patients discontinued treatment because of drug-related AEs. Of patients in the 16- and 12-week groups, 10% and 5%, respectively, experienced a drop in hemoglobin greater than 10 g/dL, and 2% of patients in the 12-week treatment group had hemoglobin less than 8.5 g/dL. Common AEs in both treatment groups included fatigue, headache, insomnia, nausea, irritability, cough, and diarrhea.

Results also were presented from the ELECTRON trial, in which investigators set out to determine whether combining sofosbuvir, a uridine nucleotide analog HCV polymerase inhibitor, and a second DAA agent with a different mechanism of action could improve SVR rates when administered with RBV in patients with HCV GT 1. To this end, they evaluated sofosbuvir 400 mg once daily plus RBV 1,000 to 1,200 mg in 25 treatment-naive patients and 10 prior null responders with HCV GT 1; 2 other groups of similar numbers of patients received the same treatment regimen plus either ledipasvir (GS-5885), an HCV NS5A inhibitor, 90 mg daily, or GS-9669, a non-nucleoside NS5B inhibitor, 500 mg daily. Treatment duration in all groups was 12 weeks. Mean baseline HCV RNA levels ranged from 5.9 log10 to 6.9 log10. None of the patients had cirrhosis, and most had HCV GT 1a.

In the control group, 84% and 10% of treatment-naive and null responders, respectively, achieved an SVR at week 12. In the ledipasvir treatment group, 100% of patients achieved SVR at week 12. In the GS-9669 group, 92% of treatment-naive patients achieved an SVR at week 12, and among 3 prior null responders with data available at week 12 post-treatment, all achieved an SVR. Serious AEs occurred in 1 treatment-naive patient in the control group and in 2 treatment-naive patients who received ledipasvir.

Researchers from the CUPIC (Compassionate Use of Protease Inhibitors in Cirrhotics) trial also were in attendance to report their findings at EASL 2013. As part of the French Early Access Program, 485 treatment-experienced HCV GT 1a/b patients with cirrhosis were offered treatment with a first-generation HCV PI in combination with PEG-IFN and RBV in an open-label fashion. The treating physicians decided whether to prescribe boceprevir-or telaprevir-based triple therapy:
190 individuals received the standard boceprevir-based regimen, and 295 patients underwent standard telaprevir-based treatment. The majority of patients were prior relapers. All patients had cirrhosis; nearly all were Child-Pugh class A; and patients had a mean Model for End-stage Liver Disease score of 8.1.

Findings of the intent-to-treat analysis showed that 79% of telaprevir recipients had a virologic response at week 8, and 40% continued with SVR at week 12: This included 53% of prior relapers, 32% of partial responders, and 29% of null responders. Among those who discontinued treatment early, approximately 19% did so because of detectable HCV RNA, 27% relapsed, 41% experienced viral breakthrough, and 14% experienced AEs.

In the boceprevir treatment group, 51% had a virologic response at week 8, and 41% continued with SVR at week 12, including 51% of prior relapers, 40% of partial responders, and 11% of null responders. Premature treatment discontinuation in this group was due to detectable HCV RNA in approximately 36% of patients, relapse in 27%, viral breakthrough in 26%, and AEs in 11%.

Serious AEs occurred in 54% and 51% of telaprevir and boceprevir recipients, respectively, and included a 2.4% and 1.6% mortality rate, respectively. Grade 3/4 infections occurred in 9.1% and 4.2% of telaprevir and boceprevir recipients, respectively; grade 3/4 hepatic decompensation occurred in 5.1% and 4.7%, respectively; grade 3 rash occurred in 5.4% and 1%, respectively; and grade 3/4 anemia occurred in 12.9% and 10%, respectively.

Following preliminary results presented at the Liver Meeting 2012, subanalysis data from the AVIATOR study was presented at EASL 2013. The population included 247 noncirrhotic patients with HCV GT 1 who received a 4-drug treatment regimen for 12 or 24 weeks in a randomized open-label fashion. Treatment included 100 or 150 mg once daily of ABT-450, a potent HCV NS5A inhibitor, 400 mg twice daily of ABT-333, a non-nucleoside HCV polymerase inhibitor, and 1,000 to 1,200 mg daily of RBV, administered in 2 doses. The 12-week treatment group included 79 treatment-naive patients and 45 prior null responders; the 24-week group had 80 treatment-naive patients and 43 prior null responders.

Results showed that 99% of treatment-naive patients and 93% of null responders in the 12-week treatment arm achieved SVR at week 12, and 96% and 93% of the 2 groups, respectively, achieved an SVR at week 24. In the 24-week treatment group, SVR at week 12 occurred in 93% and 98% of treatment-naive patients and null responders, respectively, whereas 90% and 95% had an SVR at week 24.

One treatment-naive patient in the 12-week treatment group and 2 in the 24-week group experienced relapse. Additionally, 3 prior null responders in the 12-week group and one in the 24-week group experienced viral breakthrough. Six patients discontinued treatment due to AEs, but researchers considered only 4 of these related to treatment. Four serious AEs were reported, but only 1—a case of arthralgia—was believed to be treatment-related.

Finally, researchers described a study in which they randomized 41 HCV GT 1 patients without cirrhosis who had failed prior treatment with telaprevir or boceprevir in combination with PEG-IFN and RBV to 1 of 2 treatment regimens: 21 patients received 60 mg daily of daclatasvir, an HCV NS5A replication complex inhibitor, along with sofosbuvir 400 mg daily, and 20 patients received the same regimen plus RBV, both for 24 weeks.

Most patients had received telaprevir previously, most were white, and approximately 60% were men. The majority of patients had HCV GT 1a and IL28B TT or TT GTs. More than 80% had META VIR scores of F2 or higher. Mean HCV RNA for both groups was 6.3 log_{10} IU/mL. None of the participants had discontinued prior treatment with telaprevir or boceprevir because of an AE.

Findings showed that 91% and 80% of the RBV-free and RBV-containing treatment groups, respectively, experienced a virologic response 2 weeks after treatment initiation, and 100% had a virologic response by the end of treatment. All participants also experienced an SVR at weeks 4 and 12. Common mild or moderate AEs in both groups included fatigue, headache, alopecia, and arthralgia. Constipation and diarrhea each occurred in 5% of non-RBV recipients and in 20% of RBV recipients. No severe AEs occurred in the RBV-free group.

Conclusion

Important advances pertaining to treatment efficacy, SVRs, and targeted therapy through the use of genotyping and viral-load monitoring continue to occur. The clinical landscape is also moving toward IFN-free therapy, an important development for reducing treatment-related AEs. Research continues to inform the ideal uses for the recently approved DAAs, telaprevir and boceprevir. Moreover, several new agents are currently being investigated in clinical trials; 2 of these agents, sofosbuvir and simeprevir, have shown exciting results and are now under FDA review for use in HCV combination regimens. All of these new therapies will require continued research to inform their role within specific HCV GTs, but all told, these advances ensure that patients will not have to suffer the long treatment durations and related morbidity of old, with the potential for curing their infection.
References


