Hepatitis C therapy: Looking toward interferon-sparing regimens
Trang H. Au, Christopher J. Destache, and Renuga Vivekanandan

Abstract

Objective: To describe chronic hepatitis C virus (HCV) infection, including its epidemiology and pathophysiology; review current treatment options for HCV infection; recognize investigational agents being studied as part of interferon-free therapy; and summarize clinical trials for the new agents.

Data sources: PubMed for 2004 through August 2014 using search terms hepatitis C, American Association for the Study of Liver Diseases, sofosbuvir, simeprevir, and as needed specific names of other agents in development during this time; news articles and news releases about company actions with regard to clinical trials and filings for marketing approval in the United States.

Study selection: At the discretion of the author based on clinical relevance of study and relevance to national guidelines for HCV therapy.

Results: HCV infection is an important medical and public health problem in the United States and worldwide that can cause cirrhosis, hepatocellular carcinoma, and liver failure. The advent of newly developed targeted therapies is changing the treatment paradigm for this disease. Although traditional therapy with pegylated interferon and ribavirin remain therapeutic options, direct-acting agents such as sofosbuvir (Sov 알알—and Gilead) and simeprevir (Olysi—to Janssen) are producing faster, earlier, and improved treatment response with fewer adverse effects. The combination of anti-HCV agents and the duration of treatment are based on genotype, patient treatment status, and patient risk factors. The dramatic and sustained clearance of the virus with these drugs makes sustained virologic response a reality for patients who are unable to tolerate pegylated interferon. The downside is their high cost, which may make them economically unsustainable. However, for patients infected with HCV, the potential for a cure and improved quality of life may now be a reality.

Conclusion: HCV, a well-known blood-borne disease associated with significant morbidity and mortality worldwide, can be effectively and safely treated with new anti-HCV agents such as SOF. While these new medications are in their early filings for marketing approval in the United States.

www.pharmacist.com FEBRUARY 2015

Trang H. Au, PharmD, MPH, PGY2 Hematology/Oncology Resident, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Christopher J. Destache, PharmD, FCCP, Professor of Pharmacy Practice, School of Pharmacy and Health Professions, Creighton University, Omaha, NE

Renuga Vivekanandan, MD, Assistant Professor of Internal Medicine, Division of Infectious Diseases, School of Medicine, Creighton University, Omaha, NE

Disclosures: Christopher J. Destache, PharmD, FCCP, has served as a speaker for and has received grant support from Cubist Pharmaceuticals and has received grant support from Durata Therapeutics and Cexera. Trang H. Au, PharmD, MPH; Renuga Vivekanandan, MD; and APHA’s editorial staff declare no conflicts of interest or financial interests in any product or service mentioned in this activity, including grants, employment, gifts, stock holdings, and honoraria. For complete staff disclosures, please see the APHA Accreditation Information section at www.pharmacist.com/education.

Reprinted from the Journal of the American Pharmacists Association (www.japha.org) and available for continuing pharmacy education credits at www.pharmacist.com/education.


Learning objectives
At the conclusion of this knowledge-based activity, the pharmacist will be able to:

- Describe chronic hepatitis C virus (HCV) infection, including its epidemiology and pathophysiology.
- Review current treatment options for HCV infection.
- Recognize investigational agents being studied as part of interferon-free therapy.
- Summarize clinical trials for the new agents.
Hepatitis C virus (HCV) is a contagious, blood-borne viral pathogen associated with significant morbidity and mortality. HCV infections can cause liver inflammation and progress to cirrhosis, hepatocellular carcinoma, and liver failure. Since the 1988 discovery of viral antigens specific for HCV (previously called non-A, non-B hepatitis), substantial advances in molecular biology and sequence data have enabled identification and isolation of the virus. More recently, targeted therapies with a favorable efficacy and safety profile compared with other therapies are becoming available. These direct-acting agents (DAAs) and their inclusion in current treatment guidelines are transforming the treatment and management of HCV infections.

Table 1 lists current common abbreviations and acronyms used in the literature for HCV.

### Objectives
The purpose of this article is to describe chronic HCV infection, including its epidemiology and pathophysiology; review current treatment options; recognize investigational agents being studied as part of interferon-free therapy; and summarize clinical trials for the new agents.

### Search methodology
To identify relevant literature, PubMed was searched for the years 2004 through August 2014 using the terms hepatitis C, American Association for the Study of Liver Diseases, sofosbuvir, simeprevir, and other specific agents as needed. Landmark clinical trials were identified and reviewed, with attention to those cited in nationally recommended guidelines for management of HCV infections. News articles, news releases, and other sources of current information were used to determine actions of companies such as filings with the Food and Drug Administration (FDA) for approval of agents used in treating HCV infections.

### Epidemiology
HCV causes acute and chronic infection primarily affecting the liver. Approximately 130 million to 150 million people worldwide have a diagnosis of chronic HCV. In the United States, HCV is the most common blood-borne viral infection; an estimated 4.1 million U.S. persons have been exposed to HCV, and 3.2 million have chronic disease. HCV has an annual age-adjusted mortality rate of 4.58 per 100,000 deaths and is the leading cause of liver transplantation in the United States. Other complications include coinfection with human immunodeficiency virus (HIV), steatosis, insulin resistance, diabetes, and renal disease. Concomitant HIV infection exacerbates HCV disease and makes spontaneous clearance of HCV less likely.

Despite the decline in HCV incidence in the last decade, chronic HCV infection accounts for more disease burden and death than infections of hepatitis B virus or HIV. Evaluation of long-term morbidity and mortality in patients with HCV has demonstrated that risk of death is reduced by 45% and risk of liver complications by 27% among patients who achieve viral load suppression, defined as the absence of HCV ribonucleic acid (RNA) in serum by a sensitive test at the end of treatment. Sustained virologic response (SVR) is defined as viral load suppression at the end of treatment and again at 6 months.

Chronic HCV infections are caused by six major genotypes and more than 40 subtypes. Genotypes 1, 2, and 3 are common in Western countries; genotypes 1, 4, and 5 are common in Africa; and genotype 6 predominates in Asia. Genotypes 1a and 1b are generally considered more difficult to treat, which may be explained by the absence of the favorable-treatment polymorphism associated with interleukin-28B (IL-28B). The favorable genetic variant shown to be the most important predictor of SVR is the CC variant (a genetic
subset of IL-28B). In the United States, genotype 1 represents 73% of infections, although the prevalence of genotypes 4 to 6 is increasing because of the growth in cultural diversity.

Among persons in the United States who are chronically infected with HCV, an estimated 45% to 85% are unaware of their infection. This presents a challenge for appropriate identification of HCV cases and highlights the importance of recognizing risk factors for infection. The single most important risk factor for HCV infection is injection drug use, which accounts for more than 60% of acute infections. Intranasal illicit drug use is another risk factor for HCV infection. Other risk factors include long-term hemodialysis; tattoos inked in an unregulated setting; exposure to HCV-infected blood from needlestick, sharps, or mucosal injury; children born to HCV-positive women; and prior blood transfusions or organ transplants. HIV infection and unexplained chronic liver disease with elevated liver enzymes can also increase risk for HCV infection.

In addition to significant mortality and morbidity, HCV disease is associated with a significant economic burden. Analysis of a data pool of 30 U.S. managed care organizations showed that patients with HCV have higher all-cause costs, mean inpatient costs, and prescription drug costs. In addition, hospitalization rates of HCV patients are significantly higher than those of people without HCV (24% vs. 7%, respectively).

Transmission
The primary mode of HCV transmission is by percutaneous exposure to infected blood. The virus is not transmitted by hugging, kissing, sharing utensils, or breastfeeding. Blood, tissue, and organ donation account for many of the chronic HCV infections among those born between 1945 and 1965, commonly called the “baby boomer” generation. However, this source of infection has been of less concern since improved interviewing techniques and laboratory screening tests became available in 1992. According to current estimates, 1 in 1 million blood products may transmit HCV. Although injection drug use is at the center of the present HCV epidemic, it remains difficult to study. A new group of injection drug users is attracting attention for characteristics unseen in previous cohorts: 24 years of age or younger, white, nonminority, nonurban, and prior use of opioids.

Among women with HCV, approximately 5% transmit the virus to their child. Perinatal transmission has the highest risk at the time of birth. The risk of mother-to-infant transmission is twice as high among women coinfected with HCV and HIV compared with women who have HCV infection alone.

Epidemiologic studies have identified HIV infection as an independent risk factor for HCV infection. Because people with HIV and HCV coinfection appear to be less likely to clear the HCV virus, they may be more infectious than those who have HCV infection alone. On the whole, sexual transmission of HCV occurs less commonly than perceived, but the incidence of acute HCV infection is increasing in the HIV-positive cohort of men who have sex with men.

Highly active antiretroviral therapy has successfully extended the life expectancy of HIV-infected individuals, but it may also contribute to the misperception that unprotected sex is less risky in the setting of controlled HIV infection. The practice of decision-making about sexual behavior according to same HIV status is also known as serosorting. Serosorting is associated with increased incidence of sexually transmitted diseases such as herpes and syphilis, which increases susceptibility to HCV infection.

Pathophysiology
HCV is a single-stranded, enveloped RNA virus of the Flaviviridae family that replicates at a rate of 1010–1012 virions per day. The genetic diversity of HCV is attributed to its rapid replication rate and the poor fidelity of its RNA polymerase. The lack of proofreading by RNA-dependent RNA polymerase leads to mutant viruses with genetic heterogeneity. A high rate of genetic substitutions occurs during acute infection and decreases with continuous infection. The main reason for these high rates of genetic substitution is the selective pressure exerted by antibodies and activated T cells during acute infection. This mechanism may also explain why HCV infection resolves spontaneously in some patients. The HCV genome includes 3,000 amino acids. Host and viral proteases are involved in producing components of the capsid, envelope, and viral enzymes required for replication and virion assembly.

Although HCV was discovered approximately 15 years ago, its life cycle is not fully understood because small animal models do not exist and the virus does not replicate in cell culture. Researchers have hypothesized that the complex, multistep pathway of viral entry into hepatocyte involves lipid metabolism and host factors. Glycoproteins on the viral envelope bind to the cellular receptor proteins on the cell surface, among which the CD81 molecule has been the most studied. Internalization occurs by endocytosis in a low pH-dependent manner. The exact mechanism by which the viral genome is released from the nucleocapsid into the host cell is unknown. After replication and assembly, the virions that carry the viral genome are released into the extracellular space. Overall, the replication process is similar to that of HIV.

HCV-induced chronic inflammation of the liver involves a host of immune cells, including T and B lymphocytes, macrophages (Kuffer cells), natural killer cells, pro-inflammatory cytokines, and neutrophils. Tumor necrosis factor can cause liver damage by apoptosis-mediated death of hepatocytes and fibrosis formation. With prolonged infection, antibody-mediated cytotoxicity further contributes to fibrosis progression. The exact mechanism by which HCV causes hepatic cell carcinoma is unknown. Although HCV is not thought to be oncogenic per se, an HCV-associated oncogenic effect cannot be ruled out. The proliferative potential of HCV proteins in vitro, including the core, NS3, NS5A, and NS5B proteins, is hypothesized to possess oncogenic potential. More specifically, HCV viral proteins may interfere with cellular proteins,
such as cyclin and cyclin-dependent kinase, which regulate cell cycle control. Cell cycle dysregulation produces an imbalance of tumor suppressor genes and oncogene activity.15

Screening
Current guidelines recommend comprehensive screening for patients who have increased risk for HCV infection, with risk factors grouped by behaviors, exposures, and comorbid medical conditions. One-time testing for HCV is recommended in persons who meet the following criteria:

1. Behaviors—history of injection or intranasal illicit drug use regardless of frequency or duration
2. Exposures—long-term hemodialysis, tattoos received in an unregulated setting, health care workers who have had needlestick injury or mucosal exposure to HCV-positive blood, children born to HCV-infected mothers, receipt of blood or blood product transfusion or organ transplant before July 1992, and history of incarceration
3. Comorbid medical conditions—HIV infection, unexplained chronic liver disease, or chronic hepatitis (including elevated alanine aminotransferase levels)3

In addition, the Centers for Disease Control and Prevention recommends HCV testing at least once in the lifetime of persons born between 1945 and 1965.17 All testing should be done using one of the seven tests approved by FDA, which include manual and automated laboratory assays or a point-of-care assay.

Serologic and molecular assays are used to diagnose and manage HCV infection. A positive serologic HCV test result may be interpreted in three different ways: current and active infection that may be acute or chronic, prior infection that is now resolved, or a false-positive result. The delay of several months between exposure to HCV and development of detectable antibodies to the virus can lead to a false-reacting screening test that does not discriminate between resolved and chronic infection.

To confirm test results, an HCV nucleic acid test is performed. Molecular qualitative assays with real-time polymerase chain reaction and transcription-mediated amplification are used to detect viral nucleic acid. Presence of viremia confirms a current and active infection. False-positive results are more likely in patients who have low risk for HCV infection.17

A second test may be performed with a different FDA-approved test for a questionable false-negative serologic test result. Absence of laboratory evidence for active HCV infection is defined as a positive serologic test and negative molecular test, such as an HCV RNA test. For patients who have negative laboratory evidence despite the presence of risk factors for HCV, repeating the HCV RNA test may be considered.

Clinical presentation
The majority of patients with acute HCV are asymptomatic, and researchers have estimated that as many as 85% of patients with chronic HCV are unaware of their infection.3 Table 2 lists common patient categories and their usual response to therapy.

Symptomatic patients with HCV infections may present with fatigue, appetite loss, jaundice, dark urine, clay-colored stool, nausea, and abdominal pain, particularly right upper quadrant pain. Symptoms may appear 2 weeks to 6 months after exposure. With chronic HCV infections, most people do not have symptoms until liver damage has developed. Elevated liver function enzymes are often found inadvertently during routine blood tests, leading to further testing. However, liver enzyme levels can and often do fluctuate between normal or near normal and high. Thus, liver enzyme tests are sometimes needed several times as part of the diagnostic work-up.

Because HCV is often asymptomatic, identifying patients and diagnosing infection is particularly challenging. Among the patients found to have acute infection, 60% to 70% progress to chronic infection. Among patients with chronic infection, up to 20% develop cirrhosis over several decades, and up to 5% die of cirrhosis or hepatocellular carcinoma.

The inherent difficulty in identifying patients with HCV infection underscores the importance of recognizing patients with risk factors that warrant screening for antibodies to the virus. Approximately 20% to 25% of patients with acute infection clear the virus spontaneously and do not progress to chronic status. The reason for this spontaneous clearance remains unknown.17,18 Characteristics that favor spontaneous clearance are being female, younger than 40 years of age, and symptomatic.

Diagnosis
An accurate diagnosis of HCV requires both serologic and molecular assays to determine the degree of viremia in the circulating blood. The appearance of viral RNA may occur as early as 1 month after exposure, and antibodies to the virus may be detected approximately 2 months after exposure. A quantitative HCV RNA test to establish baseline viremia is necessary before treatment is initiated. The relative decline of subsequent measures of viremia is compared to the baseline viral load to assess efficacy of treatment. In addition, severity of liver damage is evaluated, usually by liver biopsy to assess degree of fibrosis.

In patients for whom liver biopsy is not possible, imaging by ultrasound, computer tomography, and liver elastography and use of noninvasive clinical markers, such as ami-

Table 2. Definitions of types of patients with hepatitis C virus

<table>
<thead>
<tr>
<th>Patient types</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive</td>
<td>Has never been treated with anti-HCV</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>Has a reduced response to anti-HCV therapy</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>Nonresponder who does not have a 2 log 10 IU/mL reduction of hepatitis C RNA by week 12</td>
</tr>
<tr>
<td>Null responder</td>
<td>Nonresponder who has a 2 log 10 IU/mL reduction of hepatitis C RNA by week 12</td>
</tr>
<tr>
<td>Partial responder</td>
<td>Has a reduced response to anti-HCV therapy</td>
</tr>
</tbody>
</table>

Abbreviation used: HCV, hepatitis C virus; RNA, ribonucleic acid.
notransferase enzymes, albumin, bilirubin, international normalized ratio, Model for End-Stage Liver Disease score, and Child–Pugh score, may be used. In addition, aspartate aminotransferase-to-platelet ratio index or fibrosis-4 index (FIB-4) can identify HCV patients most likely to have a more severe degree of fibrosis.19

Liver biopsy is an invasive procedure that can provide objective information about the degree of hepatic scar tissue, liver inflammation, and steatosis. The Metavir assessment is commonly used to stage fibrosis (scored from F0 to F4).3 Although liver biopsy is considered the gold standard diagnostic tool, it is not without complications, of which bleeding is the most common. Additional risks include puncture of other internal organs and underdiagnosis of cirrhosis due to sampling error.20 Furthermore, liver biopsy is expensive, and the interpretation of histopathology samples requires expert analysis.

Determination of HCV genotype is important because treatment regimens are based on genotype. HCV genotypes respond differently to therapy, and certain regimens have been effective for particular genotypes. Historically, combination therapy with pegylated interferon (IFN) and ribavirin (RBV) was initiated. The advent of specifically targeted antiviral therapy (STAT-C) compounds has broadened therapeutic options.21 Therefore, patients are not necessarily restricted to the RBV–IFN regimen, which is associated with an extensive adverse effect profile that can be so intolerable that it limits treatment.

Patients who have a confirmed diagnosis of HCV should be given comprehensive counseling about preventing further liver damage and spreading the disease. Most importantly, patients should be educated about cessation of alcohol intake and, if necessary, provided with support to achieve abstinence. Alcohol consumption in the setting of HCV infection can accelerate liver fibrosis, progress to cirrhosis, and contribute to higher incidence of hepatocellular cancer. Patients with HCV who abuse alcohol have decreased survival compared with patients who are HCV-positive without alcohol intake or those who are HCV-negative and abuse alcohol.22 The deterioration of HCV status secondary to alcohol abuse is hypothesized to occur by increased oxidative stress, cytotoxicity, immune system dysfunction, and enhanced viral replication. Abstinence may help reverse these effects.23

In addition to intensive, complete education about alcohol cessation, medical conditions that may exacerbate liver fibrosis, such as hepatitis B and HIV infection, should be evaluated. Vaccination against hepatitis A and hepatitis B is also recommended, as well as patient education about how to avoid transmitting HCV. More specifically, patients should be advised on the following: do not share dental or shaving equipment; cover bleeding wounds; cease illicit drug use, but if this is continued do not share drug paraphernalia; do not donate blood or fluid products; use barrier precautions to prevent sexual transmission; and clean any blood spills at home with diluted bleach and water (1:9 ratio) while wearing gloves.

### Treatment

Several agents are FDA-approved for treatment of HCV (Table 3). In the following sections we discuss IFN, RBV, boceprevir (BOC; Victrelis—Merck), telaprevir (TVR; Incivek—Vertex), sofosbuvir (SOF; Sovaldi—Gilead), and simeprevir (SMV; Olysio—Janssen), with a focus on information that is relevant to real-world practice. Current American Association for the Study of Liver Diseases (AASLD) guidelines state that treatment should be given to patients with advanced fibrosis (Metavir F3), patients with compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C. Table 4 reviews the criteria for patient types in whom HCV therapy should be initiated.3

**Pegylated interferon**

Treatment with IFN is a mainstay of HCV therapy.24,25 Two IFN products, IFN alpha-2a and IFN alpha-2b, are currently available in the United States. As its name indicates, interferon interferes with viral replication. The polyethylene glycol moiety that was added to interferon beginning in the 1980s has improved the tolerability of IFN therapy and increased its half-life. As a result, the drug remains in the body for a longer time and requires less frequent dosing. IFN alpha-2a is dosed according to weight, whereas IFN alpha-2b is given as a fixed dose. When used to treat HCV, both products are administered as weekly subcutaneous injections.

Despite the improved adverse effect profile of IFN, tolerance can still be a barrier to treatment. Influenza-like symptoms can be treatment limiting. Bone marrow suppression resulting in anemia, neutropenia, and thrombocytopenia, as well as psychiatric problems such as depression, irritability, insomnia, and moodiness, may occur and could halt treatment. Because IFN is a subcutaneous injection that must be self-administered, some patients are not interested in receiving this therapy.

**Ribavirin**

RBV is a nucleoside analog drug that inhibits the ability of HCV to replicate.26,27 It is not as effective as monotherapy but appears to boost cure rates and reduce risk of relapse when added to HCV treatment regimens. A twice-daily oral medication available in tablet, capsule, or solution formulation, RBV is dosed according to weight, with a 75-kg threshold for dose adjustment. Its major adverse effect is dose-dependent anemia, which may be managed successfully by either lowering the dose or supplementing it with red blood cell growth factors. Other adverse effects reported include cardiac problems, depression, skin rash, fatigue, diarrhea, dizziness, and gastrointestinal disturbances such as nausea and vomiting.

Overall, combination RBV–IFN produced an average SVR of 35% to 40% in most clinical trials. Given the overwhelming number of patients requiring HCV therapy, this response rate was too low, and a search for molecular therapies that produce higher SVRs began.
<table>
<thead>
<tr>
<th>Product labeling sections</th>
<th>IFN</th>
<th>RBV</th>
<th>SMV</th>
<th>TVR</th>
<th>SOF</th>
<th>BOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug class</td>
<td>Interferon</td>
<td>Nucleoside analog</td>
<td>Nucleoside analog</td>
<td>Protease inhibitor</td>
<td>Protease inhibitor</td>
<td>Protease inhibitor</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Interferes with viral replication</td>
<td>Inhibits viral replication</td>
<td>Inhibits viral replication</td>
<td>Inhibits NS3A/4</td>
<td>Inhibits NS3A/4</td>
<td>Inhibits NS3A/4</td>
</tr>
<tr>
<td>Dose or dose range</td>
<td>IFN alpha-2a: 180 mcg weekly</td>
<td>IFN alpha-2b: 6 mcg/kg weekly</td>
<td>&lt;75 kg: 1,000 mg twice daily</td>
<td>800 mg three times daily</td>
<td>1,200 mg once daily</td>
<td>1,200 mg twice daily</td>
</tr>
<tr>
<td>Renal adjustment</td>
<td>Combined with RBV, IFN</td>
<td>Tablets: Alternate 200 mg and 400 mg EOD when CrCl is 30–50 mL/min (or not recommended when CrCl &lt; 50 mL/min; see package insert); capsule/solution: contraindicated for CrCl &lt; 30 mL/min</td>
<td>Capsule/solution: contraindicated for CrCl &lt; 30 mL/min</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hepatic adjustment</td>
<td>IFN alpha-2a: 135 mcg if LFTs are rising</td>
<td>IFN alpha-2b: Discontinue if SOCl &gt; 2 mg/dL</td>
<td>IFN alpha-2b: Discontinue if hepatic decompensation or Child-Pugh B or C</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Influenza-like symptoms, anemia, neutropenia, fatigue, decreased kidney function, psychiatric disorders</td>
<td>Dose-dependent hemolytic anemia, fatigue, depression</td>
<td>Dose-dependent hemolytic anemia, fatigue, decreased kidney function</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Interactions with hepatic metabolic isoenzymes</td>
<td>CYP1A2</td>
<td>CYP3A4/5</td>
<td>CYP1A2</td>
<td>CYP3A4/5</td>
<td>CYP3A4/5</td>
<td>CYP3A4/5</td>
</tr>
</tbody>
</table>

Abbreviations used: BOC, boceprevir; CrCl, creatinine clearance; CYP, cytochrome P450; EOD, every other day; IFN, interferon; LFT, liver function test; MA, mechanism of action; RBV, ribavirin; SCr, serum creatinine; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
Table 4. Categories of patients who qualify for newly developed therapies for hepatitis C virus infections

<table>
<thead>
<tr>
<th>Highest priority with highest risk for severe complications</th>
<th>High priority with high risk for complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)</td>
<td>Fibrosis (Metavir F2)</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>HIV-1 coinfection</td>
</tr>
<tr>
<td>Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations</td>
<td>Other coexistent liver disease</td>
</tr>
<tr>
<td>Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis</td>
<td>HBV coinfection</td>
</tr>
<tr>
<td></td>
<td>Debilitating fatigue</td>
</tr>
<tr>
<td></td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td></td>
<td>Porphyria cutanea tarda</td>
</tr>
</tbody>
</table>

Abbreviations used: HBV, hepatitis B virus; HIV-1, human immunodeficiency virus type 1.
Source: American Association for the Study of Liver Diseases guidelines, 2014

Boceprevir and telaprevir
First-generation DAAs include BOC and TVR. Both agents were approved in 2011 for treatment in combination with IFN and RBV for HCV genotype 1 infection. BOC and TVR inhibit the viral NS3/4A protease, which is responsible for cleaving HCV viral protein into mature proteins. Phase III clinical trials that formed the foundation for FDA approval demonstrated SVR rates of approximately 65% after 24 to 48 weeks of therapy. Factors that predicted SVR with BOC included low viral load, IL-28B genotype, absence of cirrhosis, and race other than black. In the latest guidelines, neither of these drugs is recommended for treatment of any HCV genotype.

Although treatment with BOC and TVR can improve SVR, not all patients achieve SVR, nor is treatment without complications. One single-center study reported an SVR rate of 57% and 59.7% with BOC and TVR, respectively. These results suggest that in almost one-half of patients treated in the real-world setting with BOC or TVR with RBV–IFN, BOC and TVR are not as effective at controlling the disease as anticipated. Furthermore, anemia is the most common treatment-limiting adverse effect of BOC. Dermatologic responses, particularly a persistently itchy rash, have developed in patients with HCV. Severe rash with death has occurred in some patients, prompting FDA to issue a new warning to discontinue TVR if a rash develops.

These adverse effects compound those associated with RBV and especially IFN. BOC and TVR can also cause decreased kidney function, as evidenced by a decrease in MELD score (a scoring system for assessing the severity of chronic liver disease). The greater concern with BOC and TVR therapy is the emergence of viral resistance to these medications. More specifically, mutations at amino acid 54 and/or 155 were seen with BOC treatment, and mutations at amino acid 54 and/or 155 were seen with TVR treatment.

Simeprevir
SMV was the third DAA to be approved for HCV and the first of the new-generation DAAs. SMV is a highly specific, potent NS3/4A protease inhibitor used with RBV and IFN in patients with HCV genotype 1. Biochemical assays have shown that SMV can inhibit the NS3/4A protease of genotypes 1a and 1b, which are traditionally considered difficult to treat. Unlike BOC and TVR, which have a high pill burden, SMV is dosed as a convenient, once-daily 150-mg tablet to be taken with food. Overall, adverse effects of SMV combined with RBV–IFN are similar to those of RBV–IFN except there is milder, reversible jaundice.

Approval of SMV was based on the results of a series of Phase III trials, including QUEST 1 and 2, PROMISE, and ASPIRE. The pooled analysis of QUEST 1 and 2 studies showed that among 521 treatment-naive patients with HCV genotype 1, 88% achieved an SVR at 12 weeks after being treated with SMV combined with RBV–IFN. The PROMISE trial was a randomized, double-blind, placebo-controlled study examining 260 patients with HCV genotype 1 who relapsed after prior IFN-based therapy. In the intention-to-treat analysis, 93% of patients were found to have an SVR at 12 weeks after receiving SMV+IFN+RBV.

The ASPIRE trial evaluated patients with HCV genotype 1 who were prior relapsers, partial responders, or null responders. Results indicated that genotype 1a and 1b patients who received SMV+RBV+IFN achieved SVR rates of 47% and 77% at 24 weeks compared with RBV–IFN SVR rates of 13% and 7% at 24 weeks, respectively. In addition, the SVR at 24 weeks was 72.9% for patients treated with SMV 150 mg daily and RBV–IFN, 65.5% for patients treated with SMV 100 mg daily and RBV–IFN, and 22.7% for patients treated with placebo and RBV–IFN.

SMV is currently approved for treatment of patients with HCV genotype 1, including those with cirrhosis. FDA noted that SMV is less effective in genotype 1a patients who have an NS3 Q80k polymorphism at baseline. Therefore, screening patients for this polymorphism is strongly recommended, and alternative therapy should be considered for affected patients. Table 5 summarizes the clinical studies that led to approval of SMV.

Sofosbuvir
SOF is a second-generation DAA that received FDA approval a few months after SMV was approved. As a class, second-generation DAAs have been shown to be superior to BOC and TVR for improved SVR, better tolerability, and substantially reduced pill burden. SOF is a nucleotide analogue that inhibits the NS5B polymerase inhibitor. More specifically, it is a prodrug with an active metabolite that acts as a chain terminator in HCV replication. It has been evaluated for HCV genotypes 1 through 6 among patients with HCV infections who were treatment-naive, had previously failed IFN because of lack of efficacy.
The SVR rates seen with RBV–IFN and SOF combination therapy have been remarkable, as evidenced by an SVR of more than 85% for the more difficult-to-treat genotype 1 and a higher SVR for genotypes 4, 5, and 6 at 12 weeks from the end of treatment (SVR12). In addition, IFN discontinuation is historically 10% to 14% with dual therapy because of adverse effects, whereas discontinuation was 2% with RBV–IFN and SOF combination therapy. Results from the FUSION trial combining SOF with only RBV produced remarkable SVR rates of 86% at 12 weeks and 94% at 16 weeks in patients who previously failed IFN therapy. Table 6 provides a summary of key studies that have evaluated SOF in HCV.

Overall, SOF has been shown to be effective for achieving SVR in many genotypes, different patient populations, various regimens, and different durations of treatment. It produces a viral load reduction in a few days and is associated with a high resistance barrier. Its pharmacokinetics is unaffected by food, age, gender, body mass index, race, or cirrhosis status. It has an approximate 60% binding to serum proteins. In addition, it has no clinically relevant interactions with antiretroviral agents, which is particularly important given the not-uncommon coinfection of HCV with HIV.

SOF is currently approved for HCV genotypes 1 and 4 in combination with RBV and IFN and for HCV genotypes 2 and 3 with RBV alone. It is the first anti-HCV combination therapy to exclude IFN and may lead the way for new regimens that achieve SVR without the intolerability of IFN. SOF is conveniently administered as a 400-mg daily oral tablet. Its most commonly cited adverse effects are fatigue, headache, nausea, insomnia, and pruritus.
Treatment guidelines

AASLD and the Infectious Diseases Society of America maintain a "living" Practice Guideline about testing, managing, and treating HCV. Given the rapid rate at which the understanding of HCV is unfolding, this guideline is updated as new information becomes available. Here we summarize the first-line recommendations for HCV treatment in newly diagnosed patients (Table 7) and refer the reader to the guidelines for alternative treatment options.

The Practice Guideline recommendations include grades based on level of scientific evidence, strength of evidence, and expert opinion. To summarize, Class I represents conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective; Class II represents conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment; Class IIa represents the weight of evidence and/or opinion in favor of usefulness and efficacy; Class IIb represents usefulness and efficacy that are less well established and/or opinion; and finally, Class III represents conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or in some cases may be harmful.

Strength of evidence is graded based on the following characteristics: Level A, data derived from multiple randomized clinical trials, meta-analyses, or equivalent; Level B, data derived from a single randomized trial, nonrandomized studies, or equivalent and Level C, consensus opinion or experts, case studies, or standard of care.

After a diagnosis of HCV and before the discussion about which type of treatment to pursue, a commitment to treatment should be confirmed with the patient. Cost is an important factor: a 12-week regimen of SOF currently costs $84,000, which is equivalent to $1,000 per tablet. Given that a course of combined IFN and RBV costs $65,000, the total for the recommended triple-drug regimen of SOF, IFN, and RBV for HCV exceeds $100,000. While cure rates are exceeding 90% in most genotypes, and cost-effectiveness analysis of SOF+RBV+IFN combination therapy appears favorable in the long term, the high price associated with treatment should be well understood by the health professional and patient.

The pharmacoeconomic assessment of SOF is currently undergoing considerable debate.

Once pursuit of treatment is elected, patients should have an established baseline quantification of their HCV RNA viral load to allow for a relative comparison with future measures of viremia. Viral genotyping is also very important, as this will be used to determine the HCV regimen. Different combinations of anti-HCV agents of various treatment durations are recommended for each genotype.

Throughout the guidelines, various combinations of anti-HCV therapies are recommended. In some cases, duration of therapy depends on whether the patient is eligible or ineligible for IFN treatment. Ineligibility for IFN treatment is defined as intolerance to IFN; having comorbid autoimmune disorder, decompensated hepatic disease, depression, or cardiac disease; and having baseline laboratory values of neutrophil count less than 1,500/µL, platelet count less than 90,000/µL, and hemoglobin less than 10 g/dL. For all genotypes, monotherapy with RBV, IFN, or a DAA is not recommended because these agents used alone are not effective.

Table 7 provides a summary of recommendations for HCV treatment-naive patients. Among patients who are treatment-naive, patients with genotypes 1 or 4 should receive SOF+RBV–IFN treatment with duration of therapy dependent on the patient’s IFN eligibility status. For patients with genotype 1 who are IFN ineligible, the duration is unchanged, but SMV replaces IFN. IFN-free therapy with SOF and RBV is recommended for genotypes 2 and 3.

Treatment-experienced patients

Treatment-experienced patients may be considered relapers or nonresponders. Relapers are defined as being HCV RNA negative at the end of treatment but thereafter have disease relapse. The NEUTRINO study evaluated SOF+RBV–IFN treatment in treatment-naive patients with genotypes 1, 4, 5, and 6. Using the findings from this study, FDA has extrapolated the results to relapers, concluding that relapers have a similar treatment response as treatment-naive persons and should be treated similarly.

Nonresponders are patients who have a reduced treatment response and can be further classified as being null responders or partial responders. Similar to the therapy recommendations for treatment-naive patients, those for patients in whom prior RBV–IFN treatment has not been effective are as follows: 12 weeks of SOF+SMV+RBV for those with genotype 1; 12 weeks of SOF–RBV for genotype 2 (extend to 16 weeks for patients with cirrhosis); 24 weeks of SOF–RBV for genotype 3; and 12 weeks of SOF+RBV+IFN for genotypes 4, 5, and 6.

Unique patient populations

Four groups of persons with HCV are considered unique given the challenges associated with effective treatment for...
them: patients with HIV/HCV coinfection, cirrhosis, recurrent HCV infection after liver transplantation, and renal impairment.

Treatment of HCV in HIV/HCV coinfected individuals is particularly challenging because of lower response rates, adverse events with IFN, limited treatment options, and complex drug interactions among the antiviral medications for both conditions. As demonstrated in a small cohort study, rapid onset of fibrosis from HCV infection in HIV-positive persons should be not considered a benign development. Decompensated cirrhosis and death within 2 to 8 years have ensued. Liver histopathophysiology at death revealed that liver destruction was secondary to HCV infection. In addition, the rate of liver failure may be related to the degree of the HIV-induced immunocompromise, which further complicates treatment and management in this population.

In a Phase III trial evaluating SOF+RBV in treatment-naive HIV/HCV coinfected persons with well-controlled HIV, the SVR at 12 weeks was 76% in patients with HCV genotype 1 (n = 114), 88% in genotype 2 (n = 26), and 67% in genotype 3 (n = 42), results that improve upon the 25% to 30% SVR seen with RBV–IFN therapy. The mean CD4 counts of the patients were 559–636 cells/µL. Patients were treated with the anti-retroviral agents efavirenz, atazanavir–ritonavir, darunavir–ritonavir, raltegravir (Isentress—Merck), and rilpivirine with tenofovir–emtricitabine (Complera—Gilead).

Table 8 provides a general summary of the regimens recommended for HIV/HCV coinfection. SOF can be used with antiretroviral agents except didanosine, zidovudine, or tipranavir. Concurrent antiretroviral agents with SMV are limited to raltegravir, rilpivirine, maraviroc (Selzentry—Viiv Healthcare), enfuvirtide (Fuzeon—Roche), tenofovir, emtricitabine, lamivudine, and abacavir.

HCV-positive patients who have cirrhosis are considered to have compensated or decompensated liver damage. Treatment is the same for patients with compensated cirrhosis as for treatment-naive patients without cirrhosis. For patients with decompensated cirrhosis, the guidelines recommend referral to a liver transplant center (strength of recommendation, IC) or treatment with SOF+RBV for 48 weeks (IIbB). Unfortunately, cirrhosis is a predictor for treatment failure, which underscores the importance of providing excellent patient education about preventing further liver damage.

Patients who develop posttransplantation HCV infections may be treated according to the following first-line recommendations: SOF–SMV with or without RBV for compensated allograft genotype 1 and SOF–RBV for compensated allograft genotypes 2 or 3 with close monitoring of creatinine clearance (CrCL) and hemoglobin. Neither BOC nor TVR should be used in this patient population because these first-generation DAAIs have toxicities and drug interactions with calcineurin inhibitors.

The fourth unique group of HCV-positive patients is those with renal impairment, defined as having a CrCL less than 30 mL/min or end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis. SOF has an inactive metabolite that is almost entirely renally eliminated via glomerular filtration and active tubular secretion. No dosage adjustment of SOF is necessary for those with higher CrCL rates. Because no dosing data exist for CrCL below 30 mL/min, SOF is not recommended in patients with ESRD.

Unlike with SOF, renal clearance represents less than 1% of elimination of SMV and its metabolites; therefore, concern for renal accumulation is not important and renal adjustment is not required. While SMV exposure was calculated to be higher in patients with ESRD, no clinically important difference was noted in SMV protein plasma binding. For RBV and IFN therapy, the guidelines recommend that practitioners follow FDA-approved product labeling recommendations for patients with renal impairment, ESRD, or hemodialysis.

Hemoglobin must be monitored closely when RBV is used in this patient population. This is particularly relevant to pharmacists involved in the care of hemodialysis patients. The incidence of acute HCV infection among hemodialysis patients is high because of the risk for nosocomial infections. If RBV is to be given, practitioners should prescribe low doses (200 mg daily), monitor hemoglobin levels weekly, administer epoetin alfa to manage anemia, and provide iron intravenously to promote erythropoietin activity.

Next steps

Traditionally, HCV has been treated with combination RBV and interferon. While this dual regimen was effective in approximately one-half of patients treated, many patients were left with limited treatment options. Among those who benefited from RBV and interferon, management of adverse effects was an ongoing challenge. In this setting, agents such as SOF and SMV offer people worldwide a chance for cure. Evidence from clinical trials suggests that these agents are highly effective. In addition, the combination of SOF and SMV has been evaluated in HCV genotype 1 nonresponders to RBV–IFN and found to be effective and well tolerated.

These positive findings add to the growing body of positive evidence regarding IFN-free regimens. In October 2014, the first combination once-daily tablet of ledipasvir and SOF (Harvoni—Gilead) without need for concomitant RBV–IFN
was approved by FDA for genotype 1 infection.47,48 Similarly, one-daily SMV has received expanded approval to be given in combination with once-daily SOF as an all-oral, IFN-free, and RBV-free treatment for genotype 1 chronic HCV infection.49 In addition, combination ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A protease inhibitor), ritonavir, and dasabuvir (NS5B polymerase inhibitor) was just approved for HCV genotype 1 infection, including compensated cirrhosis, as Viekira Pak (AbbVie).50 The various mechanisms of action inherent in this combination therapy appear to be effective for genotypes 1a and 1b in treatment-naive and treatment-experienced patients.51 (Of note, since the writing of this review article, Vertex has stopped sales of telaprevir in the United States.52) Current ongoing Phase III clinical studies include fixed-combination daclatasvir, asunaprevir, and BMS-791325 for chronic HCV genotype 1 infection and fixed-dose grazoprevir–elbasvir for genotypes 1, 4, or 6.53,54

Conclusion

HCV is a well-known blood-borne disease associated with substantial morbidity and mortality worldwide. The leading risk factor for HCV is injection drug use. Screening, testing, and patient education are important components to successful treatment and management of the disease. No vaccine for HCV is available, and effective treatment has eluded the medical community until recently. Though new anti-HCV agents such as SOF, which is the backbone of current treatment recommendations, are in their early days of real-world practice, they offer hope that cure is truly possible. The combination of anti-HCV agents and the duration of treatment are based on genotype, patient treatment status, and patient risk factors. Monotherapy with interferon, RBV, or any DAA is not recommended for any genotype. Given the estimated rise in chronic HCV infection over the next few decades, the emergence of potent targeted therapies is welcome. In addition, the rapid development of interferon-free regimens is broadening treatment options and is especially relevant for patients who cannot tolerate IFN.

The long-term effects of these novel therapies remains to be seen. In the meantime, we can hope they will perform in the real-world setting as remarkably as they did in clinical trials.

References


54. Grazoprevir (MK-5172) and elbasvir (MK-8742) combination for chronic hepatitis C therapy. www.pharmacytoday.org
55. Grazoprevir (MK-5172) and elbasvir (MK-8742) combination for chronic hepatitis C therapy. www.pharmacytoday.org
CPE assessment

Instructions: This exam must be taken online; please see “CPE information” for further instructions. The online system will present these questions in random order to reinforce the learning opportunity. There is only one correct answer to each question.

1. Which is a risk factor for HCV infection?
   a. Breastfeeding  
   b. Kissing  
   c. History of incarceration  
   d. Hugging

2. Which is a correct statement about HCV?
   a. HCV is a single-stranded deoxyribonucleic acid virus.  
   b. HCV is a single-stranded ribonucleic acid virus.  
   c. HCV is a double-stranded deoxyribonucleic acid virus.  
   d. HCV is a double-stranded ribonucleic acid virus.

3. When should the hepatitis C vaccine be given?
   a. When a person becomes sexually active  
   b. Before a patient receives blood transfusion or organ transplant  
   c. When a patient is considered high risk for infection  
   d. There is no vaccine for HCV.

4. On which enzyme does SOF act?
   a. NS5A  
   b. NS5B  
   c. NS3  
   d. NS4

5. Who should be tested for HCV?
   a. A 60-year-old man who tried intranasal illicit drug once during college  
   b. A child whose adopted mother is HCV-positive and adopted father is HCV-negative  
   c. A 49-year-old man with cirrhosis due to a long history of alcohol abuse  
   d. A motor vehicle crash patient who needs emergent hemodialysis

6. Which genotype is the most common in the United States and traditionally considered the most difficult to treat?
   a. Genotype 1  
   b. Genotype 3  
   c. Genotype 4  
   d. Genotype 6

7. Regarding which practice should patients who are HCV-positive receive intensive education?
   a. Sexual abstinence  
   b. Avoiding crowds  
   c. Alcohol cessation  
   d. Avoiding sharing utensils

8. What is the mechanism of action of BOC and TVR?
   a. NS3/4A polymerase inhibitor  
   b. NS5B polymerase inhibitor  
   c. NS3/4a protease inhibitor  
   d. NS5B protease inhibitor

9. Which currently approved direct-acting agent is less effective in those with the Q80k polymorphism?
   a. SOF  
   b. SMV  
   c. TVR  
   d. BOC

10. Which of the following is a true statement?
    a. IFN alpha-2a is given as a fixed dose.  
    b. IFN alpha-2b is given as a weight-adjusted dose.  
    c. Both IFN products are given as weekly subcutaneous injections.  
    d. Both IFN products are given as daily subcutaneous injections.

---

CPE information

To obtain 2.0 contact hours (0.2 CEUs) of CPE credit for this activity, you must complete the online assessment and evaluation. A Statement of Credit will be awarded for a passing grade of 70% or better on the assessment. You will have two opportunities to successfully complete the assessment. Pharmacists who successfully complete this activity before February 1, 2018, can receive CPE credit. Your Statement of Credit will be available upon successful completion of the assessment and evaluation and will be stored in your 'My Training Page' and on CPE Monitor for future viewing/printing.

CPE instructions:
1. Log in or create an account at pharmacist.com and select LEARN from the top of the page; select Continuing Education, then Home Study CPE to access the Library.
2. Enter the title of this article or the ACPE number to search for the article and click on the title of the article to start the home study.
3. To receive CPE credit, select Enroll Now or Add to Cart from the left navigation and successfully complete the assessment (with randomized questions) and evaluation.
4. To get your Statement of Credit, click “Claim” on the right side of the page. You will need to provide your NABP e-profile ID number to obtain and print your Statement of Credit.
   ■ Live step-by-step assistance is available Monday through Friday from 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing education@aphanet.com.
11. What is the major dose-dependent adverse effect of RBV?
a. Cardiac arrhythmias
b. Anemia
c. Diarrhea
d. Gastrointestinal problems

12. What is the recommended dosing schedule for SOF?
a. 400-mg oral tablet taken daily
b. 400-mg oral tablet taken twice daily
c. 150-mg oral tablet taken daily
d. 150-mg oral tablet taken twice daily

13. What is the approximate cost for a regimen of SOF, IFN, and RBV?
a. $25,000–$50,000
b. $50,000–$75,000
c. $75,000–$100,000
d. More than $100,000

14. Which two-drug combination was recently submitted to FDA for approval as the first INF-sparing regimen?
a. BOC+SOF
b. SOF+SMV
c. RBV+SOF
d. TVR+SOF

15. Which group is considered a unique population for HCV treatment?
a. Health professionals
b. Patients with renal dysfunction (CrCL < 60 mL/min)
c. Patients with HIV/HCV coinfection
d. Patients with significant alcohol use

16. SOF has drug interactions involving which cytochrome P450 (CYP) isoenzyme?
a. CYP3A4
b. CYP1A2
c. CYP3A4/5
d. SOF has no interactions involving the CYP isoenzymes.

17. Which anti-HCV agent acts as a nucleoside analogue?
a. BOC
c. RBV
b. SMV
d. IFN

18. How is sustained virologic response defined?
a. 50% reduction in viral load
b. 80% reduction in viral load
c. Nondetectable virologic response at a certain time after anti-HCV therapy begins
d. Nondetectable virologic response at a certain time after anti-HCV therapy ends

19. Below which CrCL was SMV not studied?
a. 60 mL/min
c. 40 mL/min
b. 50 mL/min
d. 30 mL/min

20. For treatment-naive patients with genotype 1 who are IFN eligible, what is the recommended first-line treatment?
a. SOF + RBV–IFN for 12 weeks
b. SOF + SMV–IFN for 12 weeks
c. SOF + RBV–IFN for 24 weeks
d. SOF + SMV–IFN for 24 weeks