continuing education for pharmacists

Volume XXXIV, No. 10

Hepatitis C: Disease Review and New Era of Treatment

Mona T. Thompson, R.Ph., PharmD

Dr. Mona T. Thompson has no relevant financial relationships to disclose.

Goal. The goal of this lesson to provide an overview of hepatitis C virus (HCV) disease and its treatment, including background disease state information, current treatment guidelines for genotype 1, along with a review of agents, and the cost-effectiveness of the new oral direct-acting antiviral (DAA) agents.

Objectives. At the completion of this activity, the participant will be able to:

1. recognize epidemiology, etiology, and prevalence of HCV disease;
2. list oral direct-acting pharmacologic treatment options;
3. identify appropriate patient counseling points for each treatment regimen; and
4. demonstrate an understanding of the cost effectiveness and limitations of access to all-oral DAA agents for HCV treatment.

Background

Hepatitis C is an infectious disease of the liver caused by the blood-borne pathogen, Hepatitis C virus (HCV). The worldwide prevalence is estimated to be 2 to 3 percent, with the highest rates in the Middle East and Africa (2 to 15 percent), and the lowest rates in Europe, Australia, North America, and Japan (<2 percent). HCV is a single-stranded RNA virus in the Flaviviridae family that is transmitted primarily through contact with infected blood. The natural targets of HCV are hepatocytes and possibly, B lymphocytes. Individuals most at risk for exposure are 1) injection drug users; 2) healthcare workers with needlestick injuries; 3) chronic hemodialysis patients; 4) children born to HCV-infected mothers; and 5) patients with Human Immunodeficiency Virus (HIV). Hepatitis C can cause both acute and chronic hepatitis.

The Centers for Disease Control and Prevention (CDC) estimates that 2.7 to 3.9 million people in the U.S. have chronic hepatitis C. In 2014, a total of 2,194 cases of acute hepatitis C were reported to CDC from 40 states. However, with adjustments for under-reporting and under-ascertainment, it is estimated that there were 30,000 acute hepatitis C cases in 2014. Approximately 20 percent of patients infected with HCV will spontaneously clear the virus within six months of exposure. Viral clearance is associated with the development and persistence of strong virus-specific responses by cytotoxic T lymphocytes and helper T cells. The remaining 80 percent often progress to chronic infection characterized by persistent viremia leading to degrees of hepatic inflammation and fibrosis. Chronic and progressive HCV infection over many years can ultimately result in cirrhosis, hepatocellular carcinoma, and the need for liver transplantation.

Acute hepatitis C infection is generally asymptomatic. When symptoms do occur, they are often nonspecific (fever, fatigue, discolored urine and stool, abdominal pain, and loss of appetite). The majority of patients are unaware of infection until they are screened for blood donation, have elevated alanine aminotransferase (ALT) levels on routine lab work, or experience symptoms of advanced liver disease several years post-exposure. Because many chronic infections go unnoticed for years, persons known to be at an increased risk for HCV infection should be screened periodically. Table 1 summarizes these patient populations.

All new hepatitis C diagnoses are required to be reported to the local health department. As infection is often asymptomatic, diagnosis is based on serological tests for anti-HCV antibodies. Once patients are identified as having current (active) HCV, they should be referred to a practitioner who can provide comprehensive management, including counseling and education on interventions to reduce the progression of liver disease and prevention of transmission. Testing for HCV genotype is also required to aid in appropriate antiviral treatment selection.

At the time of writing this lesson, six distinct HCV genotypes (1-6) and over 50 subtypes have been identified. The American Association for the Study of Liver Diseases

Table 1
Screening recommendations for HCV infection

1. Birth Cohort	• One time HCV-testing is recommended for all patients born between 1945 – 1965 from all countries of origin without prior ascertainment of risk
2. Risk Behaviors*	• Injection drug users (current or past, including those who injected once)** • Intranasal illicit drug use
3. Risk Exposures*	• Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood • Long-term hemodialysis (current or past) • Getting a tattoo in an unregulated setting • Children born to HCV-infected women • Prior recipients of transfusions or organ transplants, including persons who: a. Were notified that they received blood from a donor who later tested positive for HCV infection b. Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992 c. Received clotting factor concentrates before 1987 • Persons who were ever incarcerated
4. Other*	• HIV infection** • Unexplained chronic liver disease and/or chronic hepatitis including elevated ALT levels • Solid organ donors (deceased and living)

Adapted from AASLD/IDSA and CDC
*One-time testing should be performed for all persons with behaviors, exposures, and conditions with an increased risk of HCV infection. Periodic testing should be offered for persons with ongoing risk factors for exposure to HCV.
**Annual HCV testing is recommended for persons who inject drugs and for HIV seropositive men who have unprotected sex with men.

(AASLD) and Infectious Diseases Society of America (IDSA) have jointly published recommendations for the testing, management, and treatment of hepatitis C. Similar to HIV/AIDS guidelines, these recommendations are continually changing based on the most current data available. Healthcare professionals are encouraged to visit hcvguidelines.org to obtain the most up-to-date information.

AASLD/ISDA Treatment Goal and Overview

The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR). Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies who cannot be remediated by treating HCV, by transplantation, or by other directed therapy. SVR is defined as the continued absence of detectable HCV RNA at least 12 weeks after completion of therapy. SVR is a marker for cure of HCV infection and has shown to be durable in large prospective studies in more than 99 percent of patients followed for five years or more. Patients who are cured of HCV infection gain multiple health benefits, including reduction of liver inflammation, reduction in rate of progression of liver fibrosis, up to a 70 percent reduction in the risk of liver cancer, and a 90 percent reduction in the risk of liver-related mortality and liver transplantation. Additionally, patients who achieve SVR have substantially improved qualities of life, which include physical, emotional, and social health. Therefore, current recommendations encourage initiating treatment early in the course of chronic HCV infection and before fibrosis progression. This treatment goal replaces previous recommendations that singled out specific populations of patients regarded as high priority for treatment based on presence of HCV-related manifestations or other risk factors. However, due to the high cost of oral direct-acting antiviral (DAA) HCV treatment and insurance coverage limitations, access to medications may not be available for all patients.

Until 2011, the pharmacologic standard of care for hepatitis C had been pegylated (PEG) interferon alfa (IFN) and ribavirin (RBV) for 24 to 72 weeks. While only a minority of patients were treated, individuals treated with IFN + RBV treatment achieved a real-world SVR of 40 to 50 percent along with clinically significant adverse events. The most common side effects encountered with this regimen included flu-like symptoms, fatigue, neuropsychiatric symptoms, and hematologic effects secondary to IFN. Common side effects of RBV included hemolytic anemia, fatigue, pruritis and rash. RBV is also a known teratogen. Between 2011 and 2013, two first-generation protease HCV protease inhibitors, boceprevir and telaprevir, were introduced and used in combination with IFN + ribavirin. This expanded combination resulted in a modest increase in SVR by 20 percent, but not without major toxicities. Favorable responses to interferon-based treatments were less common in patients with cirrhosis compared with those without cirrhosis.

Combination Regimens for HCV Genotype 1

Today, numerous second-generation, direct-acting antiviral agents enabling the use of IFN-free, all-oral regimens have been approved

by the Food and Drug Administration (FDA), and have been shown to be highly effective, even in patients with cirrhosis. Currently, there are six DAA oral combination regimens that are recommended by the AASLD/IDSA for patients with HCV genotype 1. The elimination of IFN (and possibly ribavirin) is expected to reduce the incidence and severity of adverse events, simplify treatment, and provide an option for patients who were previously ineligible to receive IFN.

Table 2 lists the preferred treatment options according to AASLD/IDSA by genotype and patient population, as well as the recommended duration. Regimens are generally selected based on the genotype; efficacy, duration, and adverse effect profile of the regimen; potential drug interactions; the patient's history of prior treatment, and the stage of fibrosis. Importantly, for genotype 1, the AASLD/IDSA guidelines do not recommend the use of PEG-IFN/RBV with or without sofosbuvir, simeprevir, telaprevir, or boceprevir for 12 to 48 weeks. Neither is monotherapy with PEG-IFN, RBV, or a direct-acting antiviral advised. Despite FDA approval of these agents, they are considered inferior to the newer regimens. However, AASLD/IDSA does not take into consideration the availability and cost of the DAA agents in their recommendation statements. Therefore, it is important to note that in some regions or socioeconomic groups, access to IFN-free treatment may not be available.

The full product insert should be consulted for complete prescribing information for each of the agents. The product inserts outline the approved treatment durations and regimens specific to the patient's treatment experience, presence of cirrhosis or other hepatic complications, and combination with ribavirin. While ribavirin dosing and product information is not discussed in this lesson, it should be noted that contraindications for ribavirin treatment apply to all combination regimens and that ribavirin is associated with several undesirable side effects.

Table 2
AASLD/IDSA preferred treatment options

Genotype/Patient Population	**Preferred Therapy** *(listed in groups by level of evidence)*
1a/Treatment-naïve without cirrhosis	•Elbasvir/Grazoprevir (*Zepatier*) 50 mg/100 mg PO daily x 12 weeks (no baseline evidence of NS5A resistance) •Ledipasvir/Sofosbuvir (*Harvoni*) 90 mg/400 mg PO once daily x 12 weeks •Paritaprevir/Ritonavir/Ombitasvir 150/100/25 mg PO once daily + Dasabuvir (*Viekira Pak*) 250 mg PO BID + weight based RBV x 12 weeks •Sofosbuvir (*Sovaldi*) 400 mg + Simeprevir (*Olysio*) 150 mg PO once daily x 12 weeks •Sofosbuvir 400mg + Velpatasvir 100mg (*Epclusa*) PO once daily x 12 weeks
1a/Treatment-naïve with compensated cirrhosis	•Elbasvir/Grazoprevir (*Zepatier*) 50 mg/100 mg PO daily x 12 weeks •Ledipasvir/Sofosbuvir (*Harvoni*) 90 mg/400 mg PO once daily x 12 weeks •Sofosbuvir 400mg + Velpatasvir 100mg (*Epclusa*) PO once daily x 12 weeks
1b/Treatment-naïve without cirrhosis	•Elbasvir/Grazoprevir (*Zepatier*) 50 mg/100 mg PO daily x 12 weeks •Ledipasvir/Sofosbuvir (*Harvoni*) 90 mg/400 mg PO once daily x 12 weeks •Paritaprevir/Ritonavir/Ombitasvir 150/100/25 mg PO once daily + Dasabuvir (*Viekira Pak*) 250 mg PO BID x 12 weeks •Sofosbuvir (*Sovaldi*) 400 mg + Simeprevir (*Olysio*) 150 mg PO once daily x 12 weeks •Sofosbuvir 400mg + Velpatasvir 100mg (*Epclusa*) PO once daily x 12 weeks
1b/Treatment-naïve with compensated cirrhosis	•Elbasvir/Grazoprevir (*Zepatier*) 50 mg/100 mg PO daily x 12 weeks •Ledipasvir/Sofosbuvir (*Harvoni*) 90 mg/400 mg PO once daily x 12 weeks •Paritaprevir/Ritonavir/Ombitasvir 150/100/25 mg PO once daily + Dasabuvir (*Viekira Pak*) 250 mg PO BID x 12 weeks •Sofosbuvir 400mg + Velpatasvir 100mg (*Epclusa*) PO once daily x 12 weeks

Unfortunately, drug interactions with hepatitis C antiviral agents are common. While these drug interactions may be challenging to manage, attention is required to ensure adequate plasma drug concentrations of antivirals to achieve SVR without unintended toxicities or consequences. HEP Drug Interactions is a website sponsored by the University of Liverpool in the United Kingdom and several drug manufacturers that allows healthcare professionals to query for possible drug interactions with HCV medications. The website can be accessed at: http://hep-druginteractions.org. This valuable tool is also available as a downloadable app for smartphones. Additionally, the product inserts of these agents contain detailed drug interaction charts which are not included in this lesson. Commonly encountered medication classes that may interact with HCV treatment include antacids, lipid-lowering drugs, anti-epileptics, and antiretrovirals.

Elbasvir-Grazoprevir (Zepatier)

Zepatier, approved in 2016, is a fixed-dose combination product containing 50mg of the HCV NS5A inhibitor elbasvir, and 100mg of HCV NS3/4A protease inhibitor grazoprevir. It is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection. It can be used in treatment-naïve and treatment-experienced patients including those with prior failures to IFN-RBV or protease inhibitors. Prior to initiation of treatment, testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended to determine the dosage regimen and duration. The SVR at 12 weeks was 92 percent in treatment-naïve patients with HCV genotype 1a infection and 99 percent in genotype 1b. The presence or absence of compensated cirrhosis does not appear to alter the efficacy of this regimen. The recommended dose is one tablet taken orally once daily with or without food.

In clinical trials, the presence of one of more baseline NS5A resistance-associated polymorphisms resulted in lower SVR rates among genotype 1a-infected patients. Patients with evidence of this resistance treated with Zepatier should also receive weight-based ribavirin for a total of 16 weeks.

No dosage adjustments are recommended in the presence of renal impairment including dialysis dependent. Zepatier is contraindicated in patients with moderate or severe hepatic impairment; organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors (such as atazanavir, lopinavir, and saquinavir), strong CYP3A4 inducers, and efavirenz. Hepatic laboratory testing intended to detect ALT elevations is indicated prior to therapy, at treatment week 8, and at 12 weeks, if 16 weeks of treatment is required. One percent of patients experienced ALT elevations from normal levels to greater than five times the upper limit of normal, occurring generally at or after treatment week 8. These ALT elevations were typically asymptomatic with most resolving with ongoing or completion of therapy. Patients should be instructed to consult their doctor if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or discolored feces. Discontinuation of Zepatier may be considered if ALT levels remain persistently greater than 10 times the upper limit of normal.

In subjects receiving Zepatier for 12 weeks, the most commonly reported adverse reactions (greater than or equal to 5 percent in placebo-controlled trials) were fatigue, headache, and nausea. In subjects receiving Zepatier + ribavirin for 16 weeks, anemia and headache were most commonly reported. Co-administration of moderate CYP3A4 inducers and certain strong CYP3A4 inhibitors is not recommended as these can alter Zepatier plasma concentrations.

Ledipasvir-Sofosbuvir (Harvoni)

Harvoni, approved in 2014, is a fixed-dose combination of ledipasvir and sofosbuvir and is indicated with or without ribavirin for the treatment of HCV genotype 1 (as well as genotypes 4, 5, and 6) infection. Ledipasvir is an inhibitor of the HCV NS5A protein which is required for viral replication. Sofosbuvir also inhibits viral replication by exerting its action on the HCV NS5B RNA-dependent RNA polymerase. This dual antiviral inhibitor has been studied for the treatment of HCV in multiple genotype 1 populations, including: treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A); treatment-experienced without cirrhosis; treatment-experienced with compensated cirrhosis (Child-Pugh A); treatment-naïve and treatment-experienced with decompensated cirrhosis (Child-Pugh B or C); and treatment-naïve and treatment-experienced with decompensated cirrhosis. Prior to the recent approval of Epclusa (July 2016), Harvoni was the only DAA agent that could be used in patients with decompensated cirrhosis (ascites, hepatic encephalopathy, or gastroesophageal variceal hemorrhage), but should only be done in consultation with a hepatology expert. In treatment-naïve patients, a SVR of 97 percent to 99 percent was reported with no clinical difference between patients with or without cirrhosis.

The recommended dosage is one tablet, formulated with 90 mg of ledipasvir and 400 mg of sofosbuvir, taken once daily with or without food. The regimen and duration of treatment is determined by the patient population that is being treated as described above. No dosage adjustments are required for patients with mild-moderate renal impairment. No dosage recommendations are provided by the manufacturer for patients with severe renal impairment (GFR < 30mL/min) as the safety and efficacy has not been established in this patient population. No dosage adjustments are required for patients with mild, moderate, or severe hepatic impairment.

In 2015, FDA released a drug safety communication warning clinicians about the serious symptomatic bradycardia that can occur when agents containing sofosbuvir are taken together with amiodarone and another direct-acting antiviral drug. This is a particular concern in patients who also receive beta-blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Therefore, coadministration is not recommended. In the absence of viable treatment options, cardiac monitoring is recommended. Additionally, co-administration with P-gp inducers such as rifampin and St. John's Wort is not recommended as they may alter concentrations of Harvoni. Drugs that increase gastric pH can decrease ledipasvir concentrations; therefore, the lowest possible dose of these agents should be used if necessary.

The most common adverse reactions (incidence greater than or equal to 10 percent, all grades) observed with treatment with

Harvoni were fatigue, headache, and asthenia. Other less common adverse events occurring in clinical trials include bilirubin, lipase, and creatinine kinase elevations, as well as depression. Skin and subcutaneous tissue disorders such as rash, blisters, or angioedema-like swelling has been reported post-marketing with unknown rate of incidence or certain causal relationship.

For treatment-naïve patients, where cost or insurance provider limitations are not prohibitive, some experts previously favored this regimen due to its favorable adverse effect profile, minimal drug interactions, and ease of administration (single dosage unit once a day). For these same reasons, it is also a desirable choice in treatment-experienced patients who have failed IFN + ribavirin or protease inhibitors. Newly approved Epclusa, which will be discussed further in this lesson, also has many of these same treatment advantages.

Ombitasvir-Paritaprevir-Ritonavir plus Dasabuvir (Viekira Pak)

Viekira Pak, approved in 2014, is ombitasvir, paritaprevir, ritonavir 12.5mg/75mg/50mg fixed-dose combination tablets co-packaged with dasabuvir 250 mg tablets. The regimen contains three direct-acting HCV antiviral agents with three distinct mechanisms of actions. Ombitasvir is an inhibitor of HCV NS5A which is essential for viral RNA replication and virion assembly. Paritaprevir is an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein and also essential for viral replication. Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene which is essential for replication of the viral genome. Finally, ritonavir is not active against HCV; instead, it acts as a potent CYP3A inhibitor to increase peak and trough plasma concentrations of paritaprevir and overall drug exposure. Viekira Pak is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) involving genotype 1b without cirrhosis or with compensated cirrhosis, and for genotype 1a without cirrhosis or with compensated cirrhosis for use in combination with ribavirin. This includes treatment experienced patients with prior failure to IFN+ RBV. The recommended dose is two ombitasvir, paritaprevir, ritonavir tablets once daily in the morning, and one dasabuvir tablet twice daily (morning and evening) with a meal without regard to fat or calorie content for genotype 1b. For all HCV genotype 1a patients, ribavirin must be added. The role of ribavirin in the treatment of genotype 1a was confirmed as SVR was lower in the RBV-free arm than in the RBV-containing arm (90 percent vs 97 percent).

No dosage adjustments are required in patients with mild, moderate or severe renal dysfunction including those on dialysis. Viekira Pak is contraindicated in patients with moderate to severe hepatic impairment. Prior to initiation of this agent, patients should be assessed for laboratory and clinical evidence of hepatic decompensation. Reported cases typically occurred within one to four weeks of initiating therapy, and were characterized by the acute onset of rising direct serum bilirubin levels without ALT elevations associated with clinical signs and symptoms of hepatic decompensation. In 2015, FDA issued a drug safety communication to advise prescribers and patients regarding the risk of hepatic injury. The AASLD/ISDA guidelines advise prescribers to discuss the unlikely possibility of drug-induced liver injury that can occur in patients with Child-Pugh Class A cirrhosis. Viekira Pak should be discontinued in patients who develop evidence of hepatic decompensation immediately. Experts also advise against using this regimen in patients where heightened monitoring during the first four weeks of treatment cannot occur.

This combination should also not be coadministered with drugs that are highly dependent on CYP3A4 for clearance; moderate or strong inducers of CYP3A4 and strong inducers of CYP2C8; and strong inhibitors of CYP2C8. It should also not be used in patients with known hypersensitivity to ritonavir. ALT elevations were significantly more frequent in females who were using ethinyl estradiol-containing medications such as combined oral contraceptives, contraceptive patches, or contraceptive vaginal rings. These agents must be discontinued prior to starting therapy with Viekira Pak.

In subjects receiving Viekira Pak with ribavirin, the most commonly reported adverse reactions (greater than 10 percent of subjects) were fatigue, nausea, pruritis, other skin reactions, insomnia, and asthenia. In subjects receiving Viekira Pak without ribavirin, the most commonly reported adverse reactions (greater than or equal to 5 percent of subjects) were nausea, pruritis, and insomnia.

Because Viekira Pak contains ritonavir, which is also an HIV-1 protease inhibitor, it can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients treated with Viekira Pak should also be on suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

Simeprevir (Olysio) plus Sofosbuvir (Sovaldi)

Simeprevir (Olysio) is an HCV NS3/4A protease inhibitor that is indicated for the treatment of adults with chronic HCV infection in combination with sofosbuvir in patients with genotype 1 without cirrhosis or with compensated cirrhosis (also approved in combination with INF + ribavirin). Olysio is not recommended in patients who have previously failed therapy with a treatment regimen that included simeprevir or other HCV protease inhibitors. Screening for the pres-

ence of virus with the NS3 Q80K polymorphism may be considered prior to initiation of this combination.

As with other HCV treatments, simeprevir is not recommended in patients with moderate or severe hepatic impairment. Hepatic decompensation and hepatic failure, including fatal cases, have been reported. Most cases were reported in patients with advanced and/or decompensated cirrhosis who are at risk for these complications. Serious symptomatic bradycardia may occur when co-administered with sofosbuvir and amiodarone, particularly in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease. Co-administration of Olysio with drugs that are moderate or strong inducers or inhibitors of CYP3A4 may significantly affect the plasma concentration of simeprevir. Serious photosensitivity reactions have been observed during Olysio combination therapy; therefore, the use of sun protection measures is recommended. Reactions may present as an exaggerated sunburn reaction. Manifestations may include burning, erythema, exudation, blistering, and edema. Rash has also been reported, most frequently in the first four weeks of treatment. The most common adverse events reported with this regimen during 12 or 24 weeks of treatment include fatigue, headache, and nausea.

No dosage adjustment of Olysio is required in patients with mild, moderate, or severe renal impairment. Simeprevir is highly protein-bound; therefore, dialysis is unlikely to result in significant removal of simeprevir.

Sofosbuvir (Sovaldi), approved in 2013, is a HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of genotype 1, 2, 3 or 4 as a component of combination antiviral treatment. Product insert warnings, precautions, drug interactions, and adverse reactions are similar to those outlined with Harvoni, in which sofosbuvir is an active component.

In clinical trials, simeprevir plus sofosbuvir achieved SVR rates of 97 percent and 95 percent among treatment-naïve and treatment-experienced patients. However, in patients with HCV genotype 1a and the Q80K mutation, lower rates of SVR were achieved. Therefore, when used in this population, treatment should be extended to 24 weeks with the possible addition of RBV. However, some experts may choose an alternative regimen in the presence of Q80K mutations. Twenty-four weeks of treatment is also required in patients with cirrhosis or treatment-experienced with prior failures to IFN-RBV. Data for this regimen are limited compared to previously discussed agents. Simeprevir plus sofosbuvir is not an option for those with a history of treatment failures to protease inhibitors and for those with an essential drug that cannot be administered due to drug interaction (i.e., amiodarone). Even though each of these agents is FDA-approved for genotype 1, the regimen has not been approved by FDA and, therefore, some insurers may not be willing to cover this therapy option.

The recommended dose is simeprevir 150 mg taken once daily with food plus sofosbuvir 400 mg once daily. Sofosbuvir may be taken with or without food.

Sofosbuvir-Velpatasvir (Epclusa)

Sofosbuvir-Velpatasvir (Epclusa) is the newest fixed-dose combination therapy approved for the treatment of chronic HCV infection both in patients with or without cirrhosis. Epclusa combination tablet contains 400 mg of sofosbuvir, which has been previously reviewed in this lesson as a component of other HCV treatments, along with 100 mg of velpatasvir, a new HCV NS5A inhibitor. This is the first single tablet approved to treat all six major genotypes of HCV infection (1,2,3,4,5 and 6).

In patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A), the recommended dose is one tablet once daily with or without food for 12 weeks. In patients with decompensated cirrhosis (Child-Pugh B and C), Eplusa is given along with weight-based ribavirin for 12 weeks. No dosage adjustments are required for patients with mild to moderate renal impairment or any grade of hepatic impairment. No dosage recommendation can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate less than 30 mL/min/1.73 m^2) or with end stage renal disease due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.

The most common adverse reactions (incidence greater than or equal to 10 percent, all grades) observed during treatment with Epclusa include headache and fatigue. The most common adverse reactions (incidence greater than or equal to 10 percent, all grades) observed with treatment of Epclusa + ribavirin in patients with decompensated cirrhosis are fatigue, anemia, nausea, headache, insomnia, and diarrhea.

The product insert for ribavirin should be reviewed for contraindications to Epclusa + RBV treatment. Because Epclusa contains sofosbuvir, the same warnings and precautions for sofosbuvir exist with this therapy (including symptomatic bradycardia when co-administered with amiodarone). Coadministration of amiodarone with Eplusa should be avoided unless alternative viable treatment options do not exist. Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 may significantly decrease concentrations of Epclusa leading to reduced therapeutic effect.

Safety and efficacy of Epclusa were evaluated in three clinical trials in subjects without cirrhosis or with compensated cirrhosis. The results of the trials demonstrated 95 to 99 percent of the patients achieved a SVR at 12 weeks. In patients with decompensated cirrhosis, 94 percent achieved SVR

when taking Epclusa plus ribavirin for 12 weeks.

The sixth option, daclastasvir plus sofosbuvir, is also effective in treatment genotype 1 HCV infections. However, this regimen will not be detailed as daclastasvir is not FDA-approved for use in the United States for genotype 1 and, therefore, the regimen is also not FDA-approved. It is unclear what benefit this regimen has over the previously discussed combinations.

Cost-Effectiveness Considerations for HCV Treatment

All-oral antiviral treatment is becoming a possibility for a vast majority of patients. However, while it is curative and more tolerable than previous HCV treatment, cost is a major issue. Since there are more than three million patients worldwide who may be eligible for these medications, the high cost has sparked ethical debate, and manufacturers have come under fire for refusing to lower prices, citing the cost of research and development and the lifetime value.

AASLD/IDSA HCV guidance currently recommends offering treatment to everyone, but many patients are unwilling or unable to fill their prescriptions. A number of studies have been conducted to examine the cost-effectiveness of these regimens by creating statistical models that make assumptions on efficacy of DAA HCV treatment, disease progression rates, and the impact on quality of life upon achieving SVR versus the negative effect of PEG-IFN.

The cost-effectiveness analysis (CEA) compares the relative costs and outcomes of two or more interventions. CEA is used when budget limitations are recognized for healthcare spending and seeking to maximize public health benefits within those budget constraints. CEA is expressed as an incremental cost-effectiveness ratio (ICER). It is understood as the ratio of change in costs between two or more interventions to the change in effects. These comparisons must consider the following questions. 1) How much more will be spent on the new intervention? This takes into account direct medical costs including cost of treatment drugs over a lifetime and the cost savings from the prevention and attenuation of disease complications. 2) How much more benefit accrues from a new intervention? This benefit is measured in terms of quality-adjusted life years (QALYs). 3) How much is society willing to pay to gain one additional QALY? These values vary by country, and finite budgets must consider that the amount spent on healthcare also effects the amount available for other areas like education, defense, or the environment.

Additionally, interventions that are considered cost-effective may still not be affordable. It can be difficult to gain perspective on the cost, and to consider lifetime costs and benefits of a therapy. For instance, from a business budget planning perspective, decisions are based on one to five years' expenditures and revenue, while CEA considers lifetime costs and benefits.

Recently published studies compare all-oral DAA regimens to previous IFN-based regimens to calculate ICERs. In general, treating patients with more advanced fibrosis and cirrhosis provides a better value (lower ICERs) than treating those with milder disease. Hence, the cost-effectiveness of these regimens is more evident in patients with evidence of more advanced HCV infection. Published ICERs of all-oral regimens for treatment-naïve patients with HCV genotype 1 infection in the U.S. range from cost-savings of zero to $31,452 per QALY gained, depending on the presence or absence of cirrhosis. However, ICERs as high as $84,744 to $178,295 per QALY gained have been reported among the more recalcitrant IFN-experienced patients with fibrosis who are being retreated using an IFN-free regimen.

Due to the lack of transparency among pharmaceutical companies, pharmacy benefit managers, and insurance companies, the actual cost of these treatments is difficult to estimate. Many manufacturers offer coupons and financial assistance to improve the affordability of the drugs. The American Liver Foundation supports a website that can be used to connect patients with various forms of assistance and programs. It is located at http://hepc.liverfoundation.org. The HCV Advocate also has created a HCSP fact sheet (hcvadvocate.org) as part of the Hepatitis C Support Project to assist patients and their families.

Summary

Hepatitis C is a serious and progressive infectious disease that attacks the liver leading to hepatic failure, need for liver transplant, and death. The new era of all-oral direct-acting antiviral agents offers an exciting breakthrough for treatment that will essentially cure over 90 percent of the patients afflicted. While the new treatment regimens are well tolerated, they come with a high price tag, causing delays and prioritization in care. In addition to counseling patients on side effects and diligent monitoring of symptoms of hepatic dysfunction, pharmacists can exercise their public health role in connecting patients with financial assistance programs.

• • • • • • • • • • • • • • • • • •

This lesson is a knowledge-based CPE activity and is targeted to pharmacists in all practice settings. Disclosure. The OPF trustees and other individuals responsible for planning OPF continuing pharmacy education activities have no relevant financial relationships to disclose.

Program 0129-0000-16-010-H01-P

Release date: 10-15-16

Expiration date: 10-15-19

CPE Hours: 1.5 (0.15 CEU)

The Ohio Pharmacists Foundation Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

continuing education quiz

Hepatitis C: Review and New Era of Treatment

1. The highest rates of hepatitis C are found in:
   a. Europe.
   b. Australia.
   c. North America.
   d. Africa.

2. Individuals most at risk for exposure to HCV include all of the following EXCEPT:
   a. injection drug users.
   b. patients with HIV.
   c. healthcare workers experiencing needlestick injuries.
   d. patients receiving blood transfusions after 1992.

3. Which of the following symptoms are experienced in patients with acute hepatitis C?
   a. Loss of appetite, discolored urine and stool, fatigue
   b. Fever, fatigue, elevated serum creatinine
   c. Abdominal pain, fatigue, elevated serum creatinine

4. Advantages of DAA HCV treatment include all of the following EXCEPT:
   a. all-oral regimens.
   b. less expensive.
   c. more tolerable.

5. AASLD/ISDA recommends which of the following regimens for genotype 1a in treatment-naïve patients without cirrhosis?
   a. PEG-IFN + RBV
   b. PEG-IFN + RBV + boceprevir
   c. Sofosbuvir monotherapy
   d. Ledipasvir-Sofosbuvir

6. Which of the following DAA regimens may be used in patients with decompensated cirrhosis?
   a. Elbasvir-Grazoprevir
   b. Ledipasvir-Sofosbuvir
   c. Ombitasvir-paritaprevir-ritonavir + dasabuvir

7. The potential serious drug interaction that can occur in patients taking amiodarone with sofosbuvir + another DAA is:
   a. increased clearance of amiodarone.
   b. increased risk of pulmonary fibrosis.
   c. symptomatic bradycardia.

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c] [d]	6. [a] [b] [c]	11. [a] [b] [c]
2. [a] [b] [c] [d]	7. [a] [b] [c]	12. [a] [b] [c]
3. [a] [b] [c]	8. [a] [b] [c] [d]	13. [a] [b] [c] [d]
4. [a] [b] [c]	9. [a] [b] [c]	14. [a] [b]
5. [a] [b] [c] [d]	10. [a] [b] [c]	15. [a] [b] [c]

❑ **I am enclosing $5 for this month's quiz made payable to: Ohio Pharmacists Association.**

1. Rate this lesson: (Excellent) 5 4 3 2 1 (Poor)
2. Did it meet each of its objectives? ❑ yes ❑ no
   If no, list any unmet_____
3. Was the content balanced and without commercial bias?
   ❑ yes ❑ no If no, why?_____
4. Did the program meet your educational/practice needs?
   ❑ yes ❑ no
5. How long did it take you to read this lesson and complete the quiz? _____
6. Comments/future topics welcome.

Please print.

Program 0129-0000-16-010-H01-P
0.15 CEU

Name_____

Address_____

City, State, Zip_____

Email_____

NABP e-Profile ID_____Birthdate_____ (MMDD)

Return quiz and payment (check or money order) to Correspondence Course, OPA, 2674 Federated Blvd, Columbus, OH 43235-4990

8. Which of the following drugs in the Viekira Pak is not a direct-acting HCV antiviral agent?
   a. Ritonavir
   b. Ombitasvir
   c. Paritaprevir
   d. Dasabuvir

9. Patients taking elbasvir-grazoprevir should be counseled to report all of the following EXCEPT:
   a. photosensitivity reaction.
   b. fatigue, weakness, or nausea/vomiting.
   c. jaundice or discolored feces.

10. Patients initiating Viekira Pak should be instructed to discontinue which of the following medications?
   a. Amiodarone
   b. Warfarin
   c. Oral contraceptives containing ethinyl estradiol

11. Patients taking regimens containing simeprevir should be counseled on all the of the following EXCEPT:
   a. photosensitivity reactions.
   b. the importance of lab testing for ALT elevations.
   c. symptomatic bradycardia when used with amiodarone + sofosbuvir.

12. Ribavirin must be added to Epclusa therapy for:
   a. patients without cirrhosis.
   b. patients with decompensated cirrhosis.
   c. patients with compensated cirrhosis.

13. What genotype(s) is/are Epclusa approved to treat?
   a. 1
   b. 2
   c. 3 and 4
   d. All 6 genotypes

14. Cost-effectiveness is more evident in studies in which of the following HCV patient populations?
   a. Mild disease, no cirrhosis
   b. Advanced disease with cirrhosis and previous treatment failure

15. A financial assistance resource that pharmacists can share with patients is:
   a. hcvadvocate.org.
   b. hcvguidelines.org.
   c. hep-druginteractions.org.

To receive CPE credit, your quiz must be received no later than October 15, 2019. A passing grade of 80% must be attained. CPE credit for successfully completed quizzes will be uploaded to the CPE Monitor. CPE statements of credit can be printed from the CPE Monitor website. Send inquiries to opa@ohiopharmacists.org.