New Direction of Hepatitis C Treatment

Corresponding Author:
Jennifer M. Johnson, PharmD
Pharmacist
Walgreens
Jennifer.macke@walgreens.com

Additional Author:
Raven Jackson, PharmD
Clinical Assistant Professor
Xavier University
Ravenjackson14@gmail.com

ACPE no. 0120-0000-16-028-H01-P
1.5 Contact Hour (.15 CEU's)
This is a knowledge based activity.
See the end of the article for CE details.
Target Audience: Pharmacists
Faculty Disclosure: Faculty have no conflicts of interest to disclose

Goal:
The goal of this review is to briefly discuss hepatitis C, evaluate new treatment options and assess their place in therapy.

Needs Statement
Hepatitis C virus (HCV) is the most common chronic blood-borne infection in the United States (U.S.). As of 2012, the Centers for Disease Control and Prevention (CDC) states that approximately 2.7 million persons are chronically infected. Unfortunately, no vaccine is currently available for prevention of this infection. Therefore, it is critical that persons at risk take preventative precautions, while infected patients properly adhere to their medication regimen. With the emergence of updated guidelines and a host of new drugs available, it is more important than ever for pharmacists to be well-educated and prepared to provide optimal care for patients diagnosed with chronic hepatitis C (CHC).

Learning Objectives

1. Identify risk factors of acquiring hepatitis C.
2. Describe the various genotypes of the hepatitis C virus and identify their associated prevalence.
3. Discuss appropriate treatment regimens using patient-specific factors.
4. Explain how to counsel a patient on the relevant side effects and drug interactions of hepatitis C treatment.

Definitions

- Child-Turcotte-Pugh (CTP) score: A prognostic marker for patients with cirrhosis and portal hypertension using five parameters: serum albumin, serum bilirubin, ascites, prothrombin time, and grade of encephalopathy. Patients are then classified into three groups (A, B, or C) based on those parameters. Class A predicts a life expectancy of 15-20 years and an abdominal surgery peri-operative mortality of 10%. Class B qualifies an individual for liver transplantation evaluation and predicts an abdominal surgery peri-operative mortality of 30%. Class C predicts a life expectancy of 1-3 years and an abdominal surgery peri-operative mortality of 82%.[1]
- Cirrhosis: An advanced stage of liver fibrosis accompanied by distortion of the hepatic vasculature. Major consequences of cirrhosis are impaired liver function, portal hypertension and hepatocellular carcinoma.[2]
- Compensated cirrhosis: Asymptomatic cirrhosis.[3]
- Decompensated cirrhosis: Symptomatic cirrhosis, including jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy.[3]
- Fibrosis: The encapsulation or replacement of injured hepatic tissue by collagenous scarring commonly caused

by damage from hepatitis and chronic alcohol abuse.[2]

- Metavir scoring system – System for grading activity and staging fibrosis using a five point scale. Chronic hepatitis without fibrosis (F0); portal fibrosis without septae (F1); portal fibrosis with a few septae (F2); septal fibrosis without cirrhosis (F3) and complete cirrhosis (F4).[4]
- Relapse: Undetectable HCV ribonucleic acid (RNA) at end of therapy, but detectable HCV RNA during follow-up.[5]
- Retreatment: Patient has received virologic treatment, but has not achieved a sustained virologic response (SVR). Retreatment will be initiated with a different medication regimen, or a different duration to help sustain a SVR.[5]
- Sustained virologic response (SVR): Undetectable HCV RNA level at twelve or more weeks after completion of antiviral therapy for chronic HCV infection; also known as "virologic cure".[6]
- Treatment Experienced: Previous treatment has not been effective for achieving SVR.
- Treatment Naïve: Patient has not been treated for HCV infection.

Introduction

HCV is an infection caused by a virus which attacks the liver, leading to inflammation and potentially liver failure.[7] Despite being the most common chronic blood-borne infection in the United States, many people infected by the virus are unaware as they may remain asymptomatic for years.[7] Hepatitis C can be an acute illness that is eliminated from the system without any treatment. However, 75 - 85% of hepatitis C infections become chronic, and many patients seek medical care only once they develop liver complications. With estimates of 2.7 million or more people in the U.S. infected with CHC, there is a substantial need for additional information and assistance in caring for this growing patient population.[8]

Hepatitis C Disease Overview

Prevalence/Incidence

Of the three types of viral hepatitis, A, B, and C, hepatitis C accounted for the most deaths in the U.S. from 2007 - 2011. In 2012, the U.S. reported an estimated 21,870 cases of acute HCV infections. The CDC predicts that deaths due to hepatitis C will double or triple in the next 15 to 20 years. This estimate is based upon data revealing the significant increase in HCV-attributable deaths between 1999 and 2007. Of the 75 - 85% of HCV infections which become chronic, 60 - 70% will develop chronic liver disease, 10 – 20% will develop cirrhosis, and 1 - 5% will develop hepatocellular carcinoma (HCC) (see **Figure 1**). Liver failure from CHC is one of the most common reasons for liver transplantation.[7] The number of liver transplants performed per year has been steadily increasing for more than 15 years. Currently, about 17,000 people are waiting for a liver transplant and about 6,000 liver transplants are performed per year. In years 2010 through 2019, direct medical costs of HCV-related liver disease are projected to reach $10.7 billion including related costs of transplants, treatments, and hospitalizations.[9]

Figure 1: Hepatitis C Statistics[10]

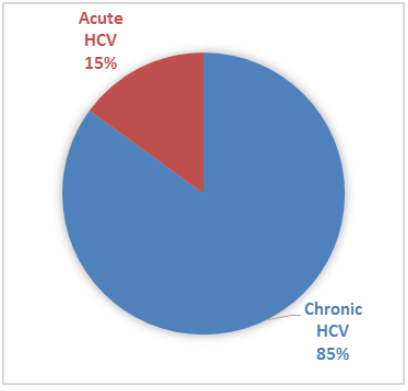
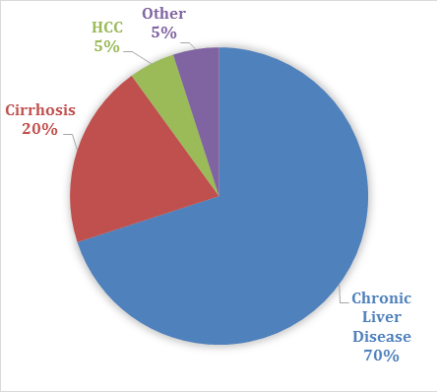


Figure 2: Chronic Hepatitis C Complications[10]



Principles of Transmission

Hepatitis C is a bloodborne pathogen, meaning the virus is spread when blood from a person infected with the HCV enters the body of someone who is not infected. Of those infected with hepatitis C, 60% acquire HCV via sharing needles, syringes or any other equipment to inject drugs.[11] Prior to implementation of widespread blood supply screening in 1992, hepatitis C was also spread through blood transfusions and organ transplants.[7] One-time testing for HCV infection is recommended for the following groups at increased risk: individuals who were born between 1945-1965 regardless of risk; injection or intranasal drug users (one-time or more); children born to HCV-infected women; persons ever incarcerated; healthcare, medical and public safety workers after needle-sticks, sharps or mucosal exposures to HCV-infected blood; individuals on long-term hemodialysis; anyone who received a solid organ transplant or transfusion of blood or blood components before July 1992; anyone who received clotting factors produced before 1987; persons infected with HIV; sexually active persons beginning pre-exposure prophylaxis (PreP); individuals with unexplained chronic liver disease or chronic hepatitis; and deceased and living solid organ donors[12].

Testing and Diagnosis

Hepatitis C screening is strongly recommended for the following groups (see **Table 1**) who are at an increased risk of contracting an HCV infection.[8,13] Testing for HCV is recommended at least once for people born between 1945 and 1965. All others should be screened for behavioral risk factors and exposures, and tested at least once if at increased HCV risk.[12]

- <u>HCV antibody testing</u>
  - A blood test called the Hepatitis C antibody test detects HCV antibody in the blood to indicate if someone has been infected with HCV.
  - Usually not detectable until 8 to 12 weeks after exposure.
  - A positive result occurs if the person was *ever* infected.
  - Does not test for active infection.
- <u>HCV viral load testing (qualitative and quantitative)</u>
  - A qualitative test determines the presence of HCV ribonucleic acid (RNA), confirming active infection.
  - A quantitative test determines the amount of virus in a measurement of blood, referred to as a patient's viral load.
  - HCV RNA is usually detectable within 1 to 2 weeks after exposure, before any signs of alanine aminotransferase (ALT) elevation.

Test results that are paired with clinical factors (ALT elevation, jaundice) help determine if the infection is acute or chronic. Available genotypic testing further directs therapy choice and length of treatment.[4,12] Genetic differences in the virus are grouped into 6 different genotypes with more than 90 subtypes among them. Genotype 1 is the most common in the U.S., making up 75% of all infections.
The condition of the liver is also assessed to determine treatment need, type, and duration. A liver biopsy and other noninvasive liver fibrosis tests, such as elastography (i.e. FibroScan®, FibroSure™) and evaluating serum markers, are used for determining the amount of inflammation and scarring of the liver. If the

elastography and serum markers indicate a cirrhotic liver, then an invasive liver biopsy may not be required for the patient. The Metavir scoring system is commonly used to interpret the results of a biopsy and noninvasive liver fibrosis tests. The results are interpreted using a grade indicating the amount if inflammation, and a stage indicating the degree of damage to the liver .[5, 4, 12]

Guideline Update[12]

The treatment protocol for HCV infection was greatly transformed by the introduction of highly effective HCV protease inhibitor therapies in 2011. Protease inhibitors, telapravir (Incivek™) and boceprevir (Victrelis™), have since been removed from the HCV treatment guidelines and are no longer available treatment options. This change reflects how quickly the treatment options for HCV are changing as new medications are approved by the FDA. The new treatment options, direct acting antivirals (DAA), are providing targeted and easy-to-manage therapeutic regimens.

To provide healthcare professionals with timely guidance as new therapies are available, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD), in collaboration with the International Antiviral Society–USA (IAS–USA), continue to provide updated information to support HCV treatment. The most recent revisions at this time occurred in July 2016. There is agreement to initiate treatment for any patient with CHC. Patients with advanced fibrosis, compensated cirrhosis, liver transplant recipients and severe extra-hepatic HCV should be treated with the highest priority.

Therapeutic Agents

Sofosbuvir (400mg) and valpatasvir (100mg)-Epclusa®[14]

Sofosbuvir/valpatasvir is a fixed-dose combination of sofosbuvir, a NS5B polymerase inhibitor, and valpatasvir, an NS5A inhibitor, both preventing viral replication.

Sofosbuvir/valpatasvir was FDA approved in 2016 and is indicated for the treatment of chronic HCV infections in adult patients without cirrhosis or with compensated cirrhosis for genotypes 1, 2, 3, 4, 5, or 6. It is also indicated for decompensated cirrhosis (CTP score B and C) when used in combination with ribavirin.

Dose Adjustments

Sofosbuvir/valpatasvir is contraindicated in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] less than 30 mL/min/1.73m^2) and end stage renal disease due to the expected significantly increased sofosbuvir metabolite plasma concentrations. However, no dosage adjustments are required for mild, moderate or severe hepatic impairment or mild to moderate renal impairment.

Drug Interactions

Sofosbuvir/valpatasvir administered with amiodarone is not recommended due to the risk of symptomatic bradycardia. If there are no alternatives to amiodarone, patients should be counseled on the risk of symptomatic bradycardia. Since amiodarone has a long half-life, patients discontinuing amiodarone therapy prior to therapy should still monitor for signs and symptoms of bradycardia.

The solubility of sofosbuvir/valpatasvir decreases as pH increases, therefore, administration of proton-pump inhibitors is not recommended. H_2 blockers should be administered simultaneously or twelve hours from the sofosbuvir/valpatasvir dose and should not exceed the equivalent of famotidine 40mg daily. Antacids should be separated by 4 hours when administered in combination.

efavirenz-containing regimens are not recommended in combination with sofosbuvir/valpatasvir due to decreased concentrations of velpatasvir.

Tipranavir/ritonavir is also not recommended in combination because co-administration decreases the concentration of both sofosbuvir and velpatasvir. Tenofovir-containing regimens should be monitored for increased risk of adverse reactions due to the increased concentrations of tenofovir.

HMG-CoA reductase inhibitors, rosuvastatin and atorvastatin, concentrations may increase when co-administered with sofosbuvir/velpatasvir. Therefore, patients

should be monitored for myopathy and rhabdomyolysis. Rosuvastatin can be co-administered as a dose not exceeding 10mg. Inducers of P-gp and CYP2B6, CYP2C8 or CYP3A4 may decrease plasma concentrations, potentially leading to a reduced therapeutic effect of sofosbuvir/valpatasvir.

Elbasvir (50mg) and grazoprevir (100mg) – Zepatier™[15]

Elbasvir/grazoprevir is a fixed-dose combination product containing elbasvir, a NS5A inhibitor, and grazoprevir, a NS3/4A protease inhibitor, a direct acting anti-viral agent used to inhibit viral replication. Elbasvir /grazoprevir was FDA approved in January 2016 and is indicated with or without ribavirin for treatment of chronic HCV infection in adult patients with genotypes 1 or 4. Liver function tests (e.g. ALT) should be performed prior to starting therapy and during treatment due to a warning of significant elevations of liver enzymes in approximately 1% of clinical trial participants.

Dose adjustments

Elbasvir/grazoprevir is contraindicated in patients with moderate or severe hepatic impairment (CTP score B and C) due to the expected significantly increased grazoprevir plasma concentration and the increased risk of ALT elevations. However, no dosage adjustment of elbasvir/grazoprevir is recommended for patients with mild hepatic impairment or any renal impairment, including hemodialysis.

Drug interactions

Elbasvir/grazoprevir is contraindicated with co-administration of CYP3A inducers, which cause loss of virologic response due to significant decreases in elbasvir and grazoprevir plasma concentrations (e.g. phenytoin and carbamazepine, rifampin, St. John's Wort and efavirenz). Also, OATP1B1/3 inhibitors are contraindicated because they can cause an increase in the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations:

HIV medications: atazanavir, darunavir, lopinavir, saquinavir, tipranavir

Immunosuppressants: cyclosporine

While not listed as contraindications, co-administration is not recommended with certain other medications with similar contraindicated mechanisms. These include nafcillin, ketoconazole, bosentan, etravirine, and modafinil. With use of tacrolimus, frequent monitoring of tacrolimus whole blood concentrations, changes in renal function, and tacrolimus-associated adverse events is recommended. Additionally, a dosage reduction in statins is likely recommended since elbasvir/grazoprevir may increase these statin concentrations (atorvastatin and rosuvastatin have been studied in healthy adults and include a dose limit recommendation, though others have not yet been studied).

Ombitasvir, paritaprevir and ritonavir – Technivie™[16]

Ombitasvir/paritaprevir/ritonavir contains a combination tablet of ombitasvir, a HCV S5A inhibitor, paritaprevir, a HCV NS3/4A protease inhibitor, and ritonavir, a CYP3A inhibitor used as a booster. The ombitasvir and paritaprevir are direct acting anti-virals, whereas the ritonavir helps increase the plasma concentrations of the two direct acting agents by inhibiting CYP3A4. It is used in combination with weight-based ribavirin and indicated for treatment of patients diagnosed with CHC genotype 4 without cirrhosis. Ritonavir is used to increase the plasma drug concentrations of paritaprevir and increase drug exposure overall. The combination tablet is recommended to be given as two tablets in the morning with food without regard to fat or calorie content.

Dose adjustments

Ombitasvir/paritaprevir/ritonavir is contraindicated in patients with moderate to severe hepatic impairment (CTP B and C). Treatment should be discontinued in patients who develop decompensated cirrhosis. Liver failure, liver transplantation and fatal outcomes have been reported in patients treated with ombitasvir/paritaprevir/ritonavir and paritaprevir/ritonavir/ombitasvir plus dasabuvir (Viekira Pak™) with or without ribavirin, primarily in patients with advanced cirrhosis. There is no dose adjustment needed in patients

with mild hepatic impairment (CTP A). There is no dose adjustment needed in patients with mild, moderate or severe renal impairment, but it has not been studied in patients on dialysis.

Drug Interactions

Ombitasvir/paritaprevir/ritonavir should not be used in combination with medications that are moderate or strong inducers of CYP3A or medications dependent upon CYP3A for clearance because paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes. When administered simultaneously, ombitasvir/paritaprevir/ritonavir can increase the concentration of antiarrhythmics (ex: digoxin, amiodarone). Digoxin doses should be reduced by 30-50%, and digoxin levels should be monitored routinely. Other antiarrhythmics should be used with caution and therapeutic concentrations monitored, if available.

Co-administration of anti-viral agents, atazanavir/ritonavir, lopinavir/ritonavir, and once daily rilpivirine with ombitasvir/paritaprevir/ritonavir are not recommended due to altered concentrations.

Use of simvastatin and lovastatin is contraindicated due to increased risk of myopathy. Certain anticonvulsants are also contraindicated due to decreased effects of ombitasvir/paritaprevir/ritonavir. Medications containing efavirenz are also contraindicated with ombitasvir/paritaprevir/ritonavir due to the potential for ALT elevations. Ethinyl estradiol-containing products should be discontinued prior to the initiation of ombitasvir/paritaprevir/ritonavir due to ALT elevations. Ethinyl estradiol-containing products can be re-initiated two weeks after the completion of treatment.

Daclatasvir – Daklinza®[17]

Daclatasvir is an inhibitor of the NS5A protein, preventing viral replication and virion assembly. It is approved for treatment of CHC genotype 1 or 3 infections. Daclatasvir must be administered with sofosbuvir (Sovaldi®).

Dose adjustments

There is no dose adjustment required for patients with mild (CTP A), moderate (CTP B), or severe (CTP C) hepatic impairment. Safety and efficacy has not been established in patients with decompensated cirrhosis. There is no dose adjustment required for any degree of renal impairment.

Drug interactions

Moderate to strong CYP3A inhibitors can increase the concentration of daclatasvir. When co-administered with a strong CYP3A inhibitor (ex: atazanavir/ritonavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin, voriconazole) the dose of daclatasvir should be decreased to 30mg once daily. When giving a moderate CYP3A inhibitor along with daclatasvir, monitor daclatasvir for adverse effects.

Moderate CYP3A inducers can decrease the concentration of daclatasvir. Increase the dose of daclatasvir to 90mg once daily when co-administered with moderate inducers of CYP3A (ex: bosentan, dexamethasone, efavirenz, etravirine, modafinil, nafcillin, rifapentine).

Coadministration of amiodarone with daclatasvir in combination with sofosbuvir (Solvaldi®) is not recommended because it may result in serious symptomatic bradycardia.

Daclatasvir can increase concentrations of digoxin. If a patient is already receiving digoxin prior to initiation of daclatasvir, obtain a baseline serum digoxin concentration and decrease the digoxin dose by 30-50% or modify the dosing frequency. If a patient is already receiving daclatasvir prior to initiation of digoxin, initiate digoxin treatment at lowest appropriate dose.

Daclatasvir may increase the concentration of statins. Monitor for statin associated adverse events such as myopathy and rhabdomyolysis.

Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus dasabuvir (250 mg) – Viekira Pak™[18,19]

This medication is a combination tablet of paritaprevir, ritonavir and ombitasvir as well as a separate dasabuvir tablet. It is approved for use with or without ribavirin for the treatment of CHC genotype 1 in patients with compensated cirrhosis; however, is not indicated in decompensated cirrhosis. Paritaprevir,

ombitasvir and dasabuvir have different mechanisms of action, all inhibiting the HCV life cycle at different steps. Ritonavir is used to increase the plasma drug concentrations of paritaprevir and increase drug exposure overall by inhibiting CYP3A4.

Dose adjustments

There is no dose adjustment required for patients with mild hepatic impairment (CTP A). It is not recommended in patients with moderate impairment (CTP B) and contraindicated in severe impairment (CTP C) because of liver failure, liver transplantation and fatal outcomes reported primarily in patients with advanced cirrhosis. There is no dose adjustment required for patients with mild, moderate or severe renal impairment.

Drug interactions

Use of strong CYP3A and CYP2C8 inducers and strong CYP2C8 inhibitors is contraindicated. The same drug interactions listed above for ombitasvir/paritaprevir/ritonavir (Technivie™) apply to paritaprevir/ritonavir/ombitasvir plus dasabuvir (Viekira Pak™). Ethinyl estradiol-containing products should be discontinued prior to the initiation of paritaprevir/ritonavir/ombitasvir plus dasabuvir due to ALT elevations. Ethinyl estradiol-containing products can be re-initiated two weeks after the completion of treatment.

Ledipasvir (90 mg)/sofosbuvir (400 mg) - Harvoni®[20,21]

Ledipasvir/sofosbuvir is a combination tablet of ledipasvir and sofosbuvir. Ledipasvir inhibits the NS5A protein, preventing viral replication. Sofosbuvir also prevents viral replication of the hepatitis C virus by inhibiting the NS5B RNA polymerase. Ledipasvir/sofosbuvir is a fixed-combination oral tablet approved for the treatment of CHC genotype 1, 4, 5 or 6 infection in adults. It was the first combination oral product that does not require administration with interferon or ribavirin.

Dose adjustments

For mild to moderate renal impairment, there is no dose adjustment necessary. There is not a dose recommendation given for patients with an eGFR < 30ml/min/1.73m^2 or end-stage renal disease due to lack of study and evidence in these patients. There is also no dose adjustment needed in mild, moderate or severe hepatic impairment (CTP score A, B or C), but the safety and efficacy of ledipasvir/sofosbuvir has not been determined in patients with decompensated cirrhosis.

Drug Interactions

Co-administration of ledipasvir/sofosbuvir and amiodarone is not recommended due to post-marketing studies resulting in bradycardia and cardiac arrest. Co-administration with p-glycoprotein (P-gp) inducers such as St. John's Wort and rifampin is also not recommended due to the decreased plasma concentrations of ledipasvir/sofosbuvir which leads to a decreased therapeutic effect. Other medications not recommended in combination due to decreased plasma concentrations of ledipasvir/sofosbuvir include anticonvulsants and antimycobacterials. Acid-reducing agents can also decrease the concentration of ledipasvir/sofosbuvir because the solubility of ledipasvir decreases as the pH increases. Acid-reducing agents can still be used during treatment with ledipasvir/sofosbuvir with appropriate counseling. Antacids and ledipasvir/sofosbuvir should be separated by four hours. H_2-receptor antagonists should be administered simultaneously or separated by 12 hours and should not exceed a dose equal to famotidine 40mg twice daily. Proton pump inhibitors (PPIs) should be administered simultaneously on an empty stomach at a dose equal to 20mg of omeprazole. Ledipasvir/sofosbuvir is administered once daily, therefore, a PPI should only be administered once daily simultaneously. Co-administration with rosuvastatin is not recommended due to increased concentrations of rosuvastatin. Ledipasvir/sofosbuvir can also increase the concentrations of digoxin; therefore, therapeutic concentrations of digoxin should be monitored.

Sofosbuvir - Sovaldi®[22,23]

Sofosbuvir is a nucleotide analog NS5B polymerase inhibitor approved for treatment of HCV genotypes 1, 2, 3, or 4. Sofosbuvir is a prodrug that undergoes metabolism to form a uridine analog that can be incorporated into the HCV RNA, causing chain termination. It is also approved for patients with hepatocellular carcinoma awaiting liver transplant as well as patients co-infected with HIV. Sofosbuvir must be administered with ribavirin for genotypes 2 and 3 or PEG-interferon alfa +/- ribavirin for genotypes 1 and 4.

Dose adjustments

There are no dose adjustments needed in renal or hepatic impairment. However, safety and efficacy has not been established in patients with an eGFR < 30 ml/min/1.73m^2

Drug interactions

Plasma concentrations of sofosbuvir can be decreased by potent P-gp inducers such as rifampin and St. John's wort. Co-administration of sofosbuvir and anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital and phenytoin) is not recommended due to the potential of decreased sofosbuvir concentrations, leading to a decreased therapeutic effect. Tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir and is not recommended to be co-administered.

Simeprevir – Olysio®[24]

Simeprevir is a HCV NS3/4A protease inhibitor, inhibiting viral replication, approved by the FDA for use in CHC genotype 1 in combination with sofosbuvir (Solvaldi®) or in combination with ribavirin and PEG-interferon alfa. It is recommended that patients with HCV genotype 1a undergo NS3 Q80K polymorphism screening prior to treatment. Simeprevir should not be used to treat patients who are infected with HCV genotype 1a with the presence of the NS3 Q80K. Simeprevir does contain a sulfonamide moiety; therefore, patients with a sulfonamide allergy should be counseled on the potential for an allergic reaction.

Dose adjustments

The efficacy of simeprevir has been established in patients with compensated liver disease. For patients with decompensated liver disease (moderate to severe hepatic impairment – CTP score B or C), simeprevir is not recommended because of the potential for adverse events due to increased drug exposure. For patients with East Asian ancestry, there is no dose recommendation due to increased drug exposure as shown in a Phase 3 clinical trial conducted in China and South Korea.

Drug interactions

Simeprevir is a mild inhibitor of CYP1A2 and intestinal CYP3A4, but it does not affect hepatic CYP3A4. Moderate to severe CYP3A inducers or inhibitors can significantly alter the concentration of simeprevir and are not recommended in combination. Amiodarone administered in combination with simeprevir and sofosbuvir is not recommended because the combination could result in serious symptomatic bradycardia. Caution should be used when amiodarone is administered in combination with simeprevir and an agent other than sofosbuvir; therapeutic drug monitoring is recommended. It is not recommended for anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital and phenytoin), which are strong CYP3A4 inducers, to be administered with simeprevir, because the combination may result in decreased concentrations of simeprevir.

Ribavirin – Copegus®, Ribasphere®, RibaPak®[25]

Ribavirin is a synthetic guanosine analog which is not effective as monotherapy. Ribavirin has direct antiviral activity against many RNA viruses, but its exact antiviral mechanism is not understood. It is currently recommended for use in combination with simeprevir, sofosbuvir, paritaprevir/ritonavir/ombitasvir plus dasabuvir, and ombitasvir/paritaprevir/ritonavir in certain genotypes. Ribavirin is dosed based on the patient's weight. When administered, ribavirin should be taken with food due to maximize bioavailability. Ribavirin is contraindicated in pregnancy and in male partners of women who are pregnant or trying to become pregnant, because significant teratogenic effects have been demonstrated. Ribavirin can also cause many other adverse effects such as: hemolytic anemia, severe hypersensitivity disorders, pulmonary

disorders, bone marrow suppression, severe depression and suicidal ideation among others.
Dose adjustments
Ribavirin dose should be reduced in patients with an eGFR < 30 ml/min/1.73m^2.
Drug interactions
Patients should be closely monitored for toxicities when ribavirin is co-administered with nucleoside reverse transcriptase inhibitors (NRTIs). Patients should also be closely monitored if taking both ribavirin and azathioprine due to the potential for accumulation of the azathioprine metabolite.

Table 2: Therapeutic Agent Summary[14-25]

Trade Name	Generic Name	Approval Date	Dosing	Common Side Effects
Epclusa®	sofosbuvir/ velpatasvir	2016	Once daily	Headaches and fatigue (>10% of patients)
Zepatier™	elbasvir/ grazoprevir	2016	Once daily	Moderate/severe fatigue (5% of patients), moderate/severe abdominal pain and diarrhea (2% of patients)
Daklinza™	daclatasvir	2015	Once daily (in combination with Sovaldi®)	Headache, fatigue (>10% of patients on combination therapy with Sovaldi®)
Technivie™	ombitasvir/ paritaprevir/ ritonavir	2015	Once daily	Asthenia, insomnia, fatigue and nausea (>10% of patients)

Viekira Pak™	ombitasvir/ paritaprevir/ ritonavir + dasabuvir	2014	Once daily (ombitasvir/paritaprevir/ ritonavir) + Twice daily - dasabuvir	Fatigue, nausea, asthenia, insomnia, pruritis and other skin reactions (>10% of patients on combination therapy with ribavirin) Nausea, pruritus, insomnia (>5% of patients not taking ribavirin)
Harvoni®	ledipasvir/ sofosbuvir	2014	Once daily	Fatigue, headache (>10% of patients)
Sovaldi®	sofosbuvir	2013	Once daily (in combination) +/- Ribavirin	Fatigue, headache (>20% of patients on combination therapy with ribavirin) Nausea, fatigue, insomnia, headache, anemia (>20% of patients on combination therapy with peginterferon alfa and ribavirin)
Olysio®	simepravir	2013	Once daily (in combination)	Nausea, pruritis, rash, photosensitivity (>20% of patients receiving combination therapy with peginterferon alfa and ribavirin)
Copegus®	ribavirin	2002	Twice daily (in combination)	Pyrexia, headache, myalgia, fatigue, asthenia (>40% of

Ribasphere® Ribapak®				patients on combination therapy)

Table 3: Treatment Guidelines[12]

Genotype 1a

Therapy of Choice	Patient History	Duration of Therapy
Epclusa®	Treatment-Naïve Without Cirrhosis	12 weeks
	Treatment-Naïve With Compensated Cirrhosis	12 weeks
	PEG interferon/Ribavirin Failure	
	Without Cirrhosis	12 weeks
	With Compensated cirrhosis	12 weeks
	With Decompensated Cirrhosis	12 weeks + ribavirin
Zepatier™ (elbasvir/grazoprevir)	No baseline high fold-change NS5A RAVs	
	Treatment-Naïve Without Cirrhosis	12 weeks
	Treatment-Naïve With Compensated Cirrhosis	12 weeks
	PEG interferon/Ribavirin failure	
	Without Cirrhosis	
	With Compensated Cirrhosis	12 weeks
	With baseline high fold-change NS5A RAVs	12 weeks
	Treatment naïve Without Cirrhosis	
	PEG interferon + ribavirin failure	16 weeks
	± cirrhosis	
*Harvoni® (ledipasvir/sofosbuvir)	Treatment–Naïve Without Cirrhosis	12 weeks

	Treatment-Naïve With Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks + ribavirin 12 weeks + ribavirin (low initial dose, 600mg, increase as tolerated)
Viekira Pak™ (ombitasvir/paritaprevir/ ritonavir + dasabuvir) + ribavirin	Treatment-Naïve Without Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis	12 weeks 12 weeks
Sovaldi® (sofosbuvir) + Olysio® (simeprevir)	Treatment–Naïve Without Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis	12 weeks 12 weeks
*Daklinza™ (daclatasvir)) + Sovaldi® (sofosbuvir)	Treatment-Naïve Without Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks + ribavirin (low initial dose, 600mg, increase as tolerated)

Genotype 1b

Epclusa® (sofosbuvir/velpatasvir)	Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis	12 weeks 12 weeks

	PEG interferon/Ribavirin failure	
	Without Cirrhosis	12 weeks
	With Compensated Cirrhosis	12 weeks
	With Decompensated Cirrhosis	12 weeks + ribavirin
Zepatier™ (elbasvir/grazoprevir)	Treatment-Naïve Without Cirrhosis	12 weeks
	Treatment-Naïve With Compensated Cirrhosis	12 weeks
	PEG-interferon/Ribavirin failure	
	Without cirrhosis	12 weeks
	With Compensated Cirrhosis	12 weeks
*Harvoni® (ledipasvir/sofosbuvir)	Treatment–Naïve Without Cirrhosis	12 weeks
	Treatment-Naïve With Compensated Cirrhosis	12 weeks
	PEG-interferon/Ribavirin failure	
	Without Cirrhosis	12 weeks
	With Compensated Cirrhosis	12 weeks
	With Decompensated Cirrhosis	12 weeks + ribavirin (low initial dose, 600mg, increase as tolerated)
Viekira Pak™ (ombitasvir/paritaprevir/ ritonavir + dasabuvir) + ribavirin	Treatment–Naïve Without Cirrhosis	12 weeks
	Treatment-Naïve With Compensated Cirrhosis	12 weeks
	PEG-interferon/Ribavirin failure	
	Without Cirrhosis	12 weeks
	With Compensated Cirrhosis	12 weeks

Sovaldi® (sofosbuvir) + Olysio® (simeprivir)	Treatment–Naïve Without Cirrhosis PEG-interferon/Ribavirin failure Without Cirrhosis	12 weeks 12 weeks
Daklinza™ (daclatasvir) + Sovaldi® (sofosbuvir)	Treatment-Naïve Without Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks + ribavirin (low initial dose, 600mg, increase as tolerated)

Genotype 2

Epclusa® (sofosbuvir/velpatasvir)	Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG interferon/Ribavirin failure Without Cirrhosis With Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks 12 weeks + ribavirin
Daklinza™ (daclatasvir) + Sovaldi® (sofosbuvir)	With Decompensated Cirrhosis	12 weeks + ribavirin (initial low dose, 600mg, increase as tolerated)

Genotype 3

Epclusa® (sofosbuvir/velpatasvir)	Treatment-Naïve Without Cirrhosis	12 weeks
	Treatment-Naïve With Compensated Cirrhosis	12 weeks
	PEG interferon/Ribavirin failure	
	Without Cirrhosis	12 weeks
	With Compensated Cirrhosis	12 weeks
	With Decompensated Cirrhosis	12 weeks + ribavirin
Daklinza™ (daclatasvir) + Sovaldi® (sofosbuvir)	Treatment–Naïve Without Cirrhosis	12 weeks
	Treatment-Naïve With Compensated Cirrhosis	24 weeks ± ribavirin
	PEG interferon/Ribavirin failure	
	Without Cirrhosis	12 weeks
	With Compensated Cirrhosis	24 weeks
	With Decompensated Cirrhosis	12 weeks + ribavirin (initial low dose, 600mg, increase as tolerated)

Genotype 4

Epclusa® (sofosbuvir/velpatasvir)	Treatment-Naïve Without Cirrhosis	12 weeks
	Treatment-Naïve With Compensated Cirrhosis	12 weeks
	PEG interferon/Ribavirin failure	
	Without Cirrhosis	12 weeks
	With Compensated Cirrhosis	12 weeks
	With Decompensated Cirrhosis	12 weeks + ribavirin
Technivie™ (ombistasvir/ paritaprevir/ritonavir) + ribavirin	Treatment–Naïve Without Cirrhosis	12 weeks
	Treatment-Naïve With Compensated Cirrhosis	12 weeks

	PEG-interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis	 12 weeks 12 weeks
Zepatier™ (elbasvir/grazoprevir)	Treatment-Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG-interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis	12 weeks 12 weeks 12 weeks
Harvoni® (ledipasvir/sofosbuvir)	Treatment–Naïve Without Cirrhosis Treatment-Naïve With Compensated Cirrhosis PEG-interferon/Ribavirin failure Without Cirrhosis With Compensated Cirrhosis With Decompensated Cirrhosis	12 weeks 12 weeks 12 weeks 12 weeks 12 weeks + ribavirin (low initial dose, 600mg, increase as tolerated)
Daklinza™ (daclatasvir) + Sovaldi® (sofosbuvir)	With Decompensated Cirrhosis	12 weeks + ribavirin (low initial dose, 600mg, increase as tolerated)

Genotype 5 or 6

Epclusa® (sofosbuvir/velpatasvir)	Treatment-Naïve With and Without Cirrhosis PEG-interferon/ribavirin failure With or without Cirrhosis	12 weeks 12 weeks

Harvoni® (ledipasvir/sofosbuvir)	Treatment–naïve With and Without Cirrhosis	12 weeks
	PEG-interferon/ribavirin failure	
	With or without Cirrhosis	12 weeks

*Although not recommended in the ISDA/AASLD treatment guidelines, ledipasvir/sofosbuvir (Harvoni®) treatment for 8 weeks can be considered in patients who are treatment naïve, not cirrhotic, and have a pre-treatment viral load less than 6 million IU/mL.[26]

Goals of Treatment[12, 27]

The goal of antiviral treatment for HCV is a SVR defined as an undetectable HCV RNA level (25 - 50 IU/ml) 12 or more weeks after stopping antivirals. Long term follow up of patients who achieve SVR at 24 weeks has shown that 90 - 100% remain HCV negative with clinical trials showing 0 - 1% of patients relapsed. SVR also has a substantial impact on other disease states. HCV can cause several hepatic and extrahepatic complications including glomerulonephritis, splenic lymphomas, and hepatocellular carcinoma. Chronic HCV has also been associated with insulin resistance and the development of diabetes mellitus. Successful treatment of HCV along with achieving a SVR can potentially reverse those complications and decrease the risk of developing diabetes, independent of other risk factors.

Conclusion

Our patients' ability to achieve a SVR is significantly improved with new treatment regimens as reflected in the HCV guidelines. The pill burden, side effects, duration of treatment and efficacy of available agents are aspects of therapy which have made drastic advancements. These improvements make it a desirable time for patients to seek treatment. As pharmacists entrusted with the role to assist patients with drug interactions, side effect management, and adherence, which is vitally important to the success of the treatment, we must stay up to date on the improving, quickly changing treatments for chronic HCV.

The Pharmacists Education Foundation (PEF) is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. To receive continuing pharmacy education (CPE) pharmacists MUST COMPLETE THE ONLINE QUIZ AND EVALUATION FORM. A score of 70% or above is required to receive CPE credit. The link to the quiz can be accessed from the home study section in the CE Portal of the IPA website, www.indianapharmacists.org. This is a free service for IPA members in 2016. Initial release date: 08/24/16. Expiration Date: 08/24/19. Questions: Call IPA office at 317-634-4968.

References

1. Durand F, Valla, D. Assessment of Prognosis of Cirrhosis. Semin Liver Dis. 2008;28(1):110-122.
2. Lancet. 2014 May 17;383(9930):1749-61. doi: 10.1016/S0140-6736(14)60121-5. Epub 2014 Jan 286.
3. Cox-North, P. Evaluation and Staging of Liver Fibrosis. http://www.hepatitis.uw.edu/go/evaluation-staging-monitoring/evaluation-prognosis-cirrhosis/core-concept/all. Updated January 16, 2014. Accessed June 18, 2014.
4. Rossi, E, Adams, L, et al. Assessing Liver Fibrosis with Serum Marker Models. Clin Biochem Rev. 2007;28.
5. Fox, R. Retreatment of Hepatitis C in Nonresponders and Relapsers. Virologic Hepatitis. 2007. US Department of Veteran Affairs. http://www.hepatitis.va.gov/provider/reviews/retreatment.asp. Accessed April 30, 2015.
6. Hepatitis C: The Basics. Can Medicines Cure Hepatitis C? Hep: Your Guide to Hepatitis. Last Updated January 12, 2015. http://www.hepmag.com/articles/2512_18755.shtml. Accessed April 30, 2015.
7. Viral Hepatitis: Statistics & Surveillance. Surveillance for Viral Hepatitis - United States 2012. CDC. Updated January 2015. http://www.cdc.gov/hepatitis/statistics/2012surveillance/commentary.htm. Accessed June 14, 2015.
8. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med. 2014;160(5):293-300.
9. Hepatitis Program: Data and Statistics. Health and Wellness for all Arizonians. Arizona Department of Health Services. 2009 - 2015. http://www.azdhs.gov/preparedness/epidemiology-disease-control/hepatitis/index.php. Accessed June 14, 2015
10. Poordad, F. Virologic Relapse in Chronic Hepatitis C. 2009. International Medical Press. 1359-6535. http://www.intmedpress.com/serveFile.cfm?sUID=690afbf7-b39b-4046-9eb8-0b456b16253d. Accessed April 30, 2015.
11. Rasada, P. Hepatitis C: Public Policy Implications of a Silent Disease. California State Library. July 2008. https://www.library.ca.gov/crb/08/08-009.pdf. Retrieved on June 14, 2015.
12. AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed July 7, 2016.
13. Global Alert and Response. Hepatitis C. WHO. 2002. http://www.who.int/csr/disease/hepatitis/Hepc.pdf?ua=1. Accessed June 14, 2015.
14. Epclusa® [package insert]. Foster City, CA; Gilead Sciences, Inc. 2016.
15. Zepatier™ [package insert]. Whitehouse Station, NJ; Merck & Co., Inc. 2016.
16. Technivie™ [package insert]. North Chicago, IL. AbbVie Inc.; 2015.

17. Daklinza™ [package insert]. Princeton, NJ. Bristol-Myers Squibb Company; 2015.
18. Viekira Pak™. Clinical Pharmacology. AbbVie Inc. North Chicago, IL. Accessed May 14, 2015.
19. Viekira Pak™ [package insert]. North Chicago, IL; AbbVie Inc.; 2014.
20. Harvoni®. Clinical Pharmacology. Gilead Sciences, Inc. Foster City, CA. Accessed May 7, 2015.
21. Harvoni® [package insert]. Foster City, CA; Gilead Sciences, Inc.; 2015.
22. Sovaldi® [package insert]. Foster City, CA; Gilead Sciences, Inc.; 2013.
23. Sovaldi. Clinical Pharmacology. Gilead Sciences, Inc. Foster City, CA. Accessed May 7, 2015.
24. Olysio® [package insert]. Titusville, NJ; Janssen Therapeutics; 2013.
25. Ribasphere® [package insert]. Warrendale, PA; Kadmon Pharmaceuticals Inc. 2002.
26. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis. *N Engl J Med*; 370:1879-88. DOI:10.1056/NEJMoal402355.
27. Goals for Treatment and Predicting Response. Hepatitis C Online. http://www.hepatitisc.uw.edu/pdf/evaluation-treatment/treatment-goals-predicting-response/core-concept/all. Accessed June 14, 2015.