Update on the Treatment of Hepatitis C Infection

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Learning Objectives:

Upon successful completion of this article, the pharmacist should be able to:

1. Review the pathophysiology of hepatitis C infection and understand the patient populations who should be screened for infection.
2. Explain why patient adherence to medications is paramount to successful treatment of hepatitis C infection.
3. Review the traditional treatment options for hepatitis C and describe why these treatments are problematic for patients.
4. Discuss new pharmacotherapy options for the treatment of hepatitis C infection.
5. Describe which treatment options are appropriate for the individual genotypes of hepatitis C.

Upon successful completion of this article, the pharmacy technician should be able to:

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INTRODUCTION

Hepatitis C virus (HCV) is the most common blood-borne infection in the United States, affecting around 4 million Americans and a further 180 million individuals worldwide. It is the leading cause of liver disease and liver-related deaths and the most common reason for liver transplantation. Approximately 17,000 deaths occur each year in the United States directly related to HCV infection. Unlike many other viral infections, HCV can be curable, but treatment has historically been difficult, with the few treatment options available that are often difficult to tolerate and with low rates of clinical cure. However, the past few years have seen a number of new agents brought to the market that have revolutionized the treatment of HCV. Pharmacists play a pivotal role in the management of these new pharmacotherapy agents, particularly with respect to patient education on medication adherence, which is critical to treatment success with these agents. This article will review the pathophysiology of HCV, the traditional treatment options, and focus on the new treatment options.

BACKGROUND

HCV is a single-stranded RNA virus belonging to the family Flaviviridae of the genus *Hepacivirus*. There are six different genotypes numbered from 1-6 with subtypes a, b, and c. In the United States, genotypes 1a and 1b are the most common types of HCV infection, accounting for approximately 75 percent of cases. Interestingly, genotypes 2 and 3 generally show a better treatment response to therapy compared to genotype 1. In most cases, initial infection with HCV causes an acute infection which then gradually progresses to chronic infection. In the acute phase, the virus begins to proliferate and activates the natural killer T-cells CD4 and CD8, as well as interferons, leading to the inhibition of viral replication. Further, infected hepatocytes lead to apoptosis of HCV. However, high levels of hepatocyte apoptosis is associated with increased damage to the liver, whereas low levels can lead to persistence of the infection. The virus elicits a potent immune response, resulting in inflammation which, over time, leads to hepatic damage. As many as 25 percent of patients are able to spontaneously eradicate the infection during the acute phase. The remaining patients, however, progress to chronic infection.

Symptoms of acute HCV infection are highly nonspecific and may include nausea, vomiting, diarrhea, anorexia, jaundice, and fatigue. Alanine aminotransferase (ALT) levels also rise during the acute phase. Many patients, however, do not exhibit any symptoms, resulting in a delayed diagnosis. If symptoms occur, the onset is generally 6-7 weeks after exposure to the virus. Symptoms of chronic HCV infection include fatigue, right upper quadrant pain, nausea, and loss of appetite. Hepatomegaly and necroinflammatory disease can also occur, leading to fibrosis. Physically, patients may have jaundice and spider angioma. Approximately 20 percent of patients with chronic infection will ultimately develop cirrhosis. Patients are further at risk for the development of hepatocellular carcinoma.

SCREENING AND DIAGNOSIS

HCV is primarily a blood-borne pathogen, with the most common mode of transmission in the United States being injection drug use. However, any type of exposure to infected blood can potentially lead to infection. Less common modes of transmission include sexual contact and perinatal transmission. Table 1 offers suggestions for which patients are appropriate to be screened for HCV infection.

Table 1. HCV Population Screening Recommendations

Injection drug users
HIV infection or Hepatitis B infection
Blood transfusions or solid organ transplantation prior to 1992
Receipt of clotting factors prior to 1987
Hemodialysis
Unknown cause of ALT elevation or other liver diseases
Children of HCV-infected mothers
Sexual partners of HCV-infected patients
Tattooing, acupuncture, or body piercing with unsterilized needles
All adults born between 1945 and 1965 should receive a one-time test, regardless of known risk factors

Diagnostic testing used in the screening for HCV includes serologic and molecular assays. Serologic assays are used in the initial screening for HCV infection and detect the presence of HCV antibodies. All patients who have been exposed to HCV will test positive for antibodies, regardless of whether or not they progress to chronic infection. Thus, patients who test positive for antibodies should undergo testing with molecular assays, specifically to detect HCV viral load. Patients with chronic HCV infection will have a detectable viral load. However, patients who have been exposed but cleared the infection on their own, or those who have undergone successful treatment, will test positive for antibodies but have undetectable viral loads. In patients with chronic infection, liver biopsies should be performed to evaluate the level of inflammation and fibrosis that has occurred.

PHARMACOTHERAPY TREATMENT

Treatment of HCV is recommended for all patients with chronic infection, with immediate treatment highly recommended to those patients with advanced fibrosis, compen-

sated cirrhosis, liver transplantation, or severe extrahepatic HCV. The goal of HCV treatment is to eradicate the infection from the body. This is called achieving a sustained virologic response (SVR) or "virologic cure" to reduce all-cause mortality, liver-related complications such as end stage liver disease or hepatocellular carcinoma, and risk of transmission. Strategies for achieving SVR differ between HCV genotype and previous treatment history and should be tailored based on patient specific factors such as presence of cirrhosis, renal impairment, and drug interactions.

The traditional standard of care approach was combination therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV). This therapy combination is associated with significant adverse effects, particularly from the PEG-IFN, to the extent that many patients are unable to successfully complete treatment. Because of the difficulty tolerating this treatment, significant effort was made to find new treatment options that could produce SVR while simultaneously be more tolerable for patients. The last few years have seen a number of agents, generally termed direct acting antivirals (DAAs), to be discussed in the following sections, brought to the market for HCV treatment. These agents are highly effective and produce significantly more tolerable adverse effects compared to PEG-INF/RBV and have thus caused a paradigm shift in the treatment of HCV infection. Up-to-date treatment guidelines can be found on a website maintained by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA) at www.hcvguidelines.org.

With these new treatment options, of paramount importance is strict patient adherence to the prescribed regimen. Clinical trials have consistently demonstrated that nonadherence, even missing only a few doses, can lead to an incomplete virologic response and increase the risk of the development of viral resistance. Because pharmacists are in the unique position to provide thorough patient counseling regarding these medications, their involvement in the treatment of HCV is of the utmost importance. Patients must be counseled on strict medication adherence not only at the beginning of treatment, but at follow-up physician visits and when refilling their medications. The risks of nonadherence must be thoroughly discussed with all patients and pharmacists should assess patient understanding. Suggestions should be provided to patients regarding ways to increase adherence, such as setting an alert message on their cellular phones. Further, follow-up assessments, such as telephone calls or face-to-face interactions, should be performed routinely with any patient undergoing treatment. The pharmacist should provide other counseling measures as well, such as discussing the deleterious effects of alcohol on the liver and what to do if a dose is missed.

Hepatitis C treatment guidelines may change when new agents are approved or additional studies are published. Up-to-date guidelines are available at www.hcvguidelines.org.

INTERFERON ALFA-2

Interferon alfa exerts its antiviral effect by stimulating the release of interferon-induced enzymes which in turn inhibit viral replication and translation of viral proteins. Beginning with its first described use for the treatment of HCV in 1986, recombinant interferon alfa-2 (IFN) became part of the cornerstone for treatment of chronic HCV infection up until the recent development of the DAAs. IFN therapy has improved over time with regard to efficacy and tolerability in combination with RBV, with the most impactful change occurring when IFN was pegylated with bis-monomethoxy polyethylene (PEG) to create a larger molecule, PEG-IFN, with prolonged absorption and half-life and decreased clearance. This allowed for once weekly dosing and improved the virologic response and tolerability compared to conventional interferon.

PEG-IFN alfa-2 is available in two different subtypes, 2a and 2b. Though differences exist with regard to structural, pharmacokinetic, and antiviral characteristics, historical perspectives have deemed the two subtypes equally efficacious. Indeed, guidelines have not differentiated between the two subtypes as part of their recommended treatment regimens. Two relatively large retrospective studies suggest that patients are less likely to discontinue PEG-IFN alfa-2a than PEG-IFN alfa-2b which may be attributable to the pharmacokinetic and tolerability differences between the subtypes, but did not determine if this had any clinically relevant impact on outcomes. Furthermore, a large prospective study determined that despite a lower discontinuation rate with PEG-IFN alfa-2a, there was no difference in SVR between PEG-IFN alfa-2a and PEG-IFN alfa-2b. PEG-IFN alfa-2a dosing varies depending on the subtype. PEG-IFN alfa-2a is weight based at 1.5 mcg/kg once weekly, whereas PEG-IFN alfa-2b has standard dosing at 180 mcg once weekly.

Despite the improvements of IFN products, adverse effects (such as fever, muscle pain, weight loss, depression, neutropenia, etc.), tolerability, and subcutaneous route of administration continue to be a major limiting factor to IFN therapy. Due to the adverse effect profile, some patients, such as those with cardiac disease, autoimmune disorders, or anemias are not candidates for treatment with PEG-IFN. Use of PEG-IFN is now generally reserved for add-on therapy to regimens based on newer agents for treatment-naïve patients or those who have failed previous therapy. PEG-IFN should never be used as monotherapy in treating HCV of any genotype and rarely as a part of dual therapy with RBV.

RIBAVIRIN

Ribavirin (RBV) is an orally available synthetic guanosine analog that exhibits antiviral activity as a nucleoside inhibi-

tor by way of inhibiting RNA synthesis and mRNA capping. Despite documented normalization in transaminase levels, monotherapy with RBV has not proven efficacious in the treatment of chronic HCV infection. In combination with PEG-IFN, however, it was established as an essential component of the standard of care for chronic HCV treatment.

A major factor for RBV efficacy (in combination with PEG-IFN) was found to be a patient's body weight. In a large randomized study, SVR decreased as body weight increased for patients receiving a fixed dose of RBV. Weight-based RBV had similar efficacy across all weight groups and less chance of relapse compared to fixed dosing. RBV should be dosed 1,000 mg/day in two divided doses for patients less than 75 kg and 1,200 mg/day in two divided doses for patients greater than or equal to 75 kg.

Although RBV is associated with fewer adverse effects compared to PEG-IFN, it may still produce adverse effects that lead to discontinuation, particularly in patients who have cirrhosis at the beginning of treatment. Common adverse events include a chronic dry cough and pruritus. RBV is also associated with the development of hemolytic anemia, particularly within the first 1-2 weeks of treatment, which may require intervention through a dose reduction or addition of an erythropoiesis-stimulating agent (ESA). RBV is also well known to be teratogenic and must be avoided in pregnancy. If undergoing treatment with RBV, regardless of patient gender, effective contraception methods must be practiced at all times, and must also be continued for six months after the last RBV dose.

Since the introduction of the new agents for the treatment of chronic HCV infection, dual therapy with PEG-IFN and RBV has been eliminated as therapeutic options with the exception of treatment of genotype 5. However, RBV has continued to be studied in combination with these new agents and maintains an important role in many treatment regimens for chronic HCV infection of all genotypes.

NS3/4A PROTEASE INHIBITORS

The first direct-acting antivirals to be approved for the treatment of HCV were selective nonstructural protein (NS) 3/4A serine protease inhibitors. Protease inhibitors develop resistance quickly if used alone and must therefore always be used in combination with other agents. Further, medication adherence is critical in order for these therapies to maintain efficacy, so patient counseling is particularly important with these agents.

Boceprevir and Telaprevir

Boceprevir (Victrelis®) and telaprevir (Incivek®) were approved in 2011 for the treatment of HCV genotype 1, to be used as part of a triple therapy regimen along with PEG-IFN and RBV. They were approved for use in both treatment naïve and treatment experienced patients, with duration of therapy varying from 24-48 weeks depending on patient type and patient response to treatment. Both agents require a heavy pill burden, dosing every 7-9 hours, and must be administered with food for optimal absorption. Due to high rates of resistance if doses are missed and strict futility rules, which require early discontinuation if specific efficacy parameters are not met at designated time points, throughout treatment, it is imperative that patients are able to adhere to these difficult regimens in order for treatment to be successful.

The most commonly reported adverse reactions with boceprevir are fatigue, anemia, nausea, headache, and taste disturbance (dysgeusia). Telaprevir is most commonly associated with skin rash, anemia, fatigue, pruritis, nausea/vomiting, diarrhea, and anorectal discomfort. One unique and potentially life-threatening adverse event associated with telaprevir is the risk of serious skin reactions. Telaprevir carries a black box warning for this risk, as some reactions have been fatal when treatment is continued despite development of progressive rash and systemic symptoms. For any serious skin reaction, triple therapy with telaprevir must be immediately discontinued and patients should urgently seek medical care.

Boceprevir and telaprevir have a similar drug interaction profile; they are both potent inhibitors of CYP3A and are both metabolized by CYP3A. Therefore, drugs that are metabolized primarily by CYP3A may have increased exposure when used concomitantly, and drugs that induce or inhibit CYP3A could decrease or increase exposure to boceprevir and telaprevir. Both agents are also substrates of p-glycoprotein (P-gp), so there is a risk of altered drug concentrations when P-gp inducers or inhibiters are used.

The drug-drug interactions and high occurrence of adverse effects, in addition to the complexity of the dosing regimens, have caused these agents to fall out of favor compared to newer therapies that have become available within the last two years. Current guidelines no longer recommend the use of boceprevir and telaprevir. Additionally, the manufacture of telaprevir was discontinued in August 2014. Nevertheless, it is still important to be aware of these drugs as some patients may have been previously treated with them when first brought to the market, which will in turn affect their current treatment should they not have achieved a SVR.

Simeprevir

Simeprevir (Olysio®) was the third NS3/4A protease inhibitor on the market, gaining approval for treatment for HCV genotype 1 in November 2013. Simeprevir has many advantages over boceprevir and telaprevir, including once daily dosing. Simeprevir can be used along with PEG-IFN plus ribavirin as part of a triple therapy regimen, or can be used in combination with sofosbuvir for those who are ineligible for interferon therapy. Treatment with simeprevir

is response-guided, and duration can last anywhere from 12 weeks (when taken in combination with sofosbuvir for those without cirrhosis) to 48 weeks total (when taken as part of a triple therapy regimen for prior non-responders). When simeprevir is used as part of triple therapy with PEG-IFN and RBV, patients with HCV genotype 1a should be screened for the NS3 Q80K polymorphism prior to beginning treatment, and alternative therapy is recommended when this is detected. This recommendation may be considered but is not strongly recommended when simeprevir is used in combination with sofosbuvir.

Adverse effects of simeprevir are primarily dermatologic in nature and most frequently occur during the first four weeks of treatment, although they can occur at any time. Photosensitivity reactions typically present as severe sunburns and are most commonly found on areas of exposed skin. Patients should be counseled on the risk of severe photosensitivity reactions and encouraged to use sun protection and limit exposure to sunlight while taking simeprevir. Any rash that develops should be monitored, and medications discontinued for severe rashes with mucosal or systemic symptoms. Other commonly reported adverse effects include pruritis, myalgia, dyspnea, nausea, and hyperbilirubinemia. Bilirubin elevations seen in clinical trials were primarily mild to moderate and quickly reversed at the completion of treatment. Simeprevir is primarily metabolized by CYP3A and therefore associated with significant drug interactions. Coadministration with substances that are moderate or potent inhibitors or inducers of CYP3A is not recommended due to the risk of increased or decreased simeprevir exposure, respectively.

Clinical trials evaluating simeprevir as part of triple therapy with PEG/RBV in treatment naïve patients showed clear improvements in SVR compared to PEG/RBV alone (75-92 percent with simeprevir vs. 46-65 percent without). Patients receiving simeprevir were more likely to achieve rapid virologic response (68-90 percent vs. 5-8 percent without) and thus were more likely to be eligible for the shorter duration of 24 weeks compared to 48 weeks. Relapse rates were lower with simeprevir therapy as well (8-17 percent vs. 18-36 percent without). Adverse effects were generally similar between groups. Simeprevir has also shown improved SVR rates in treatment-experienced patients when used as part of triple therapy (61-80 percent SVR with simeprevir vs. 23-36 percent placebo). In these studies, simeprevir also significantly improved the rate of rapid virologic response, which allowed for a greater number of patients to end treatment after 24 weeks rather than 48 weeks. In the most recently published PROMISE phase 3 study for this patient population, 77.2 percent of simeprevir patients obtained undetectable HCV-RNA levels at week 4 compared to only 3.1 percent of those receiving pegylated interferon and ribavirin alone, and 92.7 percent of patients in the simeprevir group were eligible to end treatment at 24 weeks. The SVR rate among these patients was 83 percent, validating this shortened duration. The ability for treatment-experienced patients to undergo 24-week treatment and still achieve such high rates of SVR is very promising and highly desirable, as this will reduce overall costs, drug exposure, and adverse effects associated with these treatments as compared to the standard 48 week therapies.

Another study evaluated simeprevir in combination with sofosbuvir, with or without ribavirin, in both treatment naïve and treatment experienced patients with HCV genotype 1. This regimen offers an interferon-free option for patients who have previously failed or are ineligible for interferon therapy. Rapid virologic response was seen in 81 percent of patients, and the overall SVR rate was 92 percent. Of note, patients in this study with the NS3 Q80K polymorphism at baseline achieved similar SVR rates to those without, indicating that the addition of sofosbuvir significantly reduces the ability of this genetic polymorphism to display resistance against simeprevir therapy. Relapse rates were low and adverse effects were significantly less than those seen in regimens containing interferon.

SOFOSBUVIR

On Dec. 6, 2013, the Food and Drug Administration approved sofosbuvir (Sovaldi®) for treatment of HCV infection. Sofosbuvir is a nucleotide analog NS5B polymerase inhibitor approved for use in combination with other agents to treat HCV infection. It is approved for use with RBV, RBV + PEG-IFN, and simeprevir with or without RBV. Sofosbuvir can be used to treat HCV genotypes 1, 2, 3, or 4. In treatment naïve patients with genotypes 1, 4, 5, and 6, overall SVR rates were 90 percent when sofosbuvir was used with RBV and PEG-INF. In treatment naïve patients with genotypes 2 and 3, overall SVR rates were 67 percent when sofosbuvir was used with RBV for 12 weeks (Genotype 2: 95 percent and Genotype 3: 56 percent). Overall SVR rates improved when genotype 3 patients were treated with sofosbuvir and RBV for 24 weeks instead of 12 weeks.

The most common adverse events seen with sofosbuvir in combination with RBV were fatigue and headache. The most common adverse events observed with sofosbuvir in combination with PEG-IFN and RBV were headache, nausea, fatigue, insomnia, and anemia. Potential drug interactions should be considered prior to treatment with sofobuvir as it is a substrate of P-glycoprotein. When sofosbuvir is used in combinations with drugs that are potent inducers of intestinal p-glycoprotein (P-gp), the sofosbuvir concentrations may be decreased leading to decreased efficacy. Potent intestinal P-gp inducers include medications such as rifampin and St. John's wort. The major metabolite of sofosbuvir (GS-33107) may accumulate up to 20-fold in patients with renal impairment and potentially lead to toxic-

ity. Therefore, the optimal dose for patients with estimated glomerular filtration rate less than 30 mL/min/1.73m2 or with end stage renal disease is not known.

Sofosbuvir has a relatively high barrier for resistance, but efficacy when used alone has not been proven. If patients stop any portion of their HCV treatment, they should also stop sofosbuvir. Sofosbuvir will likely continue to be used along with RBV in an all-oral regimen for treatment of genotype 2 and 3, but will still require PEG-IFN to treat genotypes 1 and 4 unless it is used in combination with simeprevir. However, the cost of the sofosbuvir+simeprevir combination may limit its use for treatment of genotype 1 chronic hepatitis C in the future.

LEDIPASVIR-SOFOSBUVIR

Ledipasvir-sofosbuvir (Harvoni™) is an all-oral regimen approved in 2014 for treatment-naïve and treatment-experienced patients with genotype 1 chronic HCV infection. Ledipasvir-sofosbuvir is a fixed-dose combination of two direct acting antiviral drugs (90 mg ledipasvir/400 mg sofosbuvir) that have distinctive mechanisms of action. Ledipasvir is an inhibitor of the HCV NS5A protein and sofosbuvir is an inhibitor of the HCV NS5B RNA dependent RNA polymerase, both of which are required for viral replication.

Studies have consistently shown SVR rates greater than 90 percent with a 12-week course of ledipasvir-sofosbuvir in patients with genotype 1 chronic HCV. For treatment-naive, non-cirrhotic patients who have a pretreatment HCV RNA level less than 6 million IU/mL, use of the shorter 8-week regimen may also be an option and should provide a considerable cost savings over the 12-week regimen. The addition of RBV may allow for 12 weeks instead of 24 weeks of treatment for some harder to treat patients who have failed previous treatment or have cirrhosis. Ledipasvir-sofosbuvir has also shown some effectiveness for treatment for genotypes 3, 4, 5, and 6, although it has not been FDA-approved for these genotypes. The most common adverse effects observed in clinical trials were fatigue and headache. One of the advantages of ledipasvir-sofosbuvir is that it can also be used in treatment-experienced patients with previous virologic failure to NS3/4A protease inhibitor (boceprevir, telaprevir, simeprevir) or for patients who have failed a sofosbuvir-based regimen. While ledipasvir-sofosbuvir is not specifically FDA-approved for the treatment of patients co-infected with HCV and HIV, it will likely be an option for these patients as well once potential drug interactions with antiretroviral medications have been addressed.

Like sofosbuvir, the two-drug combination of ledipasvir-sofosbuvir has significant drug-drug interactions with P-gp inducers such as St. John's wort and rifampin. The use of these P-gp inducers is not recommended while taking ledipasvir-sofosbuvir. Other potentially significant drug-drug interactions include acid reducing agents (decreased effect of ledipasvir), anticonvulsants (decreased effect of ledipasvir-sofosbuvir), rosuvastatin (increased risk of rhabdomyolysis), and some HIV antiretrovirals (increased risk for antiretroviral toxicity).

The fixed dose combination of ledipasvir-sofosbuvir provides an appealing alternative for HCV treatment due to its high SVR rates, one pill once daily dosing, and relatively limited adverse effect profile. The combination does have several potentially significant drug-drug interactions, and pharmacists and providers should screen for these interactions prior to treatment. Pre-treatment medication history review and recommendations for management of drug-drug interactions could help improve cure rates and prevent unnecessary adverse drug events.

OMBITASVIR/PARITAPREVIR/RITONAVIR/ DASABUVIR (VIEKIRA PAK™)

Viekira Pak™ contains three new, oral DAA agents: ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A protease inhibitor), and dasabuvir (non-nucleotide NS5B polymerase inhibitor). Ritonavir (Norvir®), a protease inhibitor commonly used in the treatment of HIV infection, is used as a pharmacokinetic booster to increase concentrations of paritaprevir, though it has no direct antiviral activity against HCV. Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) are combined in one tablet and are packaged together with two dasabuvir (250 mg) tablets. Viekira Pak™ was approved for use with or without RBV for patients with chronic HCV with or without cirrhosis on Dec. 19, 2014. Ombitasvir/paritaprevir/ritonavir plus dasabuvir is currently only FDA approved for use in patients with HCV genotype 1, though it has also shown to be effective for patients with genotype 4.

Approval of ombitasvir/paritaprevir/ritonavir plus dasabuvir was based on randomized, multi-center trials which included 2,308 patients with genotype 1 HCV infection. Overall SVR rates in these trials ranged from 89-100 percent. Ombitasvir/paritaprevir/ritonavir plus dasabuvir can be used with or without RBV and is recommended to be used for 12 weeks in the majority of patients. However, patients with cirrhosis and/or HCV subtype 1a are considered more difficult to treat and should take Viekira Pak for 24 weeks. Ombitasvir/paritaprevir/ritonavir plus dasabuvir has also been effective in liver transplant recipients and patients who are co-infected with HIV. Drug interactions will also be a significant consideration when starting treatment with ombitasvir/paritaprevir/ritonavir. Paritaprevir and ritonavir are primarily metabolized by CYP3A4 (with some metabolism via CYPA5 and CYP2D6, respectively). Dasabuvir is mostly metabolized by CYP2C8, with some CYP3A4 effects as well. The list of interacting drugs is extensive, so a thorough review of medication history is extremely important prior to starting treatment with ombitasvir/paritaprevir/ritonavir plus dasabuvir. Fatigue, nausea, pruritus, skin

reactions, insomnia, and asthenia were the most common side effects occurring in patients receiving ombitasvir/paritaprevir/ritonavir plus dasabuvir along with RBV.

Limitations to the use of ombitasvir/paritaprevir/ritonavir plus dasabuvir will likely be due to drug interactions. Compared to ledipasvir-sofosbuvir, ombitasvir/paritaprevir/ritonavir plus dasabuvir requires more doses per day, which could impact patient adherence, especially if it is also used in combination with twice-daily ribavirin. Ombitasvir/paritaprevir/ritonavir plus dasabuvir will also not be an option for patients who have failed previous treatment with regimens containing HCV protease inhibitors or sofosbuvir. One of the advantages of ombitasvir/paritaprevir/ritonavir plus dasabuvir is that there are no recommended dose

Table 2. All-oral (interferon-free) regimens for treatment of genotype 1 chronic HCV infection

	ledipasvir 90mg /sofosbuvir 400 mg (Harvoni®)	**paritaprevir 150 mg /ritonavir 100 mg/ ombitasvir 25 mg + dasabuvir 250 mg BID (Viekira Pak™) +/- ribavirin**	**Sofosbuvir (Sovaldi®) + simeprevir (Olysio®)**
Dosage	One tablet orally once daily	• Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) with food • Ribavirin: 1,000 mg/day for patients less than or equal to 75 kg or 1,200 mg/day for patients >75 kg; divided and administered twice-daily with food	One simeprevir (150 mg) tablet orally once daily + one sofosbuvir (400 mg) tablet orally once daily
Dosage Adjustments for specific populations:	• Safety and efficacy has not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or ESRD requiring hemodialysis • No dosage adjustment for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) • Safety and efficacy not established in patients with decompensated cirrhosis	• No dosage adjustment needed in patients with mild, moderate or severe renal impairment • Has not been studied in patients on dialysis. • Ribavirin dose adjustments: *see ribavirin prescribing information*	**Simeprevir** • not recommended for patients with severe hepatic dysfunction (Child-Pugh Class C) **Sofosbuvir** • Safety and efficacy has not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or ESRD requiring hemodialysis • No dosage adjustment for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) • Safety and efficacy not established in patients with decompensated cirrhosis
Administration	May be taken with or without food	Take with a meal without regard to fat or calorie content	• Take simeprevir with food • Sofosbuvir may be taken with or without food
Treatment duration	**Genotype 1a and Genotype 1b:** Treatment-naïve with or without • cirrhosis: 12 weeks* Treatment-experienced • without cirrhosis: 12 weeks • with cirrhosis: 24 weeks *8 weeks may be considered if HCV RNA less than 6 million IU/mL	**Genotype 1a treatment naïve or treatment experienced:** • without cirrhosis: Viekira Pak™ + ribavirin for 12 weeks • with cirrhosis: Viekira Pak™ + ribavirin for 24 weeks** **Genotype 1b and treatment naïve or treatment experienced:** • without cirrhosis: Viekira Pak for 12 weeks • with cirrhosis: Viekira Pak + ribavirin for 12 weeks **12 weeks may be considered in some patients see full prescribing information	**Genotype 1a and Genotype 1b** Treatment naïve or treatment experienced: • without cirrhosis: 12 weeks • with cirrhosis: 24 weeks

(Continued) Table 2. All-oral (interferon-free) regimens for treatment of genotype 1 chronic HCV infection			
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Contraindications	None	• Co-administration with drugs that are: highly dependent on CYP3A for clearance; strong inducers of CYP3A and CYP2C8; and strong inhibitors of CYP2C8 • Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome). •Severe hepatic impairment (Child-Pugh C). • If administered with ribavirin: *see ribavirin prescribing information*	None
Warnings/ Precautions	The use of P-gp inducers (e.g., rifampin, St. John's wort) may significantly decrease ledipasvir and sofosbuvir plasma concentrations and may lead to a decreased therapeutic effect the use of ledipasvir/sofosbuvir with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended	• Due to risk of ALT elevations, discontinue ethinyl estradiol-containing medications prior to starting treatment (use alternative contraceptive methods). • If administered with ribavirin: *see ribavirin prescribing information*	• Use of sofosbuvir and simeprevir along with amiodarone is not recommended due to possibility of symptomatic bradycardia • Serious photosensitivity reactions may occur during treatment with simeprevir. • Discontinue simeprevir if severe rash occurs.
ADRs (most common)	fatigue, headache, nausea, diarrhea, insomnia	fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia (with ribavirin) nausea, pruritus and insomnia (without ribavirin).	fatigue, headache, nausea, insomnia, pruritus, rash, photosensitivity, dizziness, and diarrhea
Drug interactions	• inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) (ledipasvir) • substrates of drug transporters P-gp and BCRP (ledipasvir and sofosbuvir) Ledipasvir solubility decreases as pH increases	• ombitasvir, paritaprevir, and dasabuvir-inhibitors of UGT1A1 • ritonavir-inhibitor of CYP3A4 • paritaprevir-inhibitor of OATP1B1 and OATP1B3 • paritaprevir ritonavir and dasabuvir-inhibitors of BCRP • paritaprevir and ritonavir-primarily metabolized by CYP3A • dasabuvir-primarily metabolized by CYP2C8 enzymes • ombitasvir, paritaprevir, dasabuvir and ritonavir -substrates of P-gp • ombitasvir, paritaprevir and dasabuvir-substrates of BCRP • paritaprevir-substrate of OATP1B1 and OATP1B3 • If administered with ribavirin: *see ribavirin prescribing information*	Simeprevir • mildly inhibits CYP1A2 activity • inhibits intestinal CYP3A4 activity • inhibits OATP1B1/3 and P-glycoprotein (P-gp) transporters • substrate of CYP3A Sofosbuvir • substrate of drug transporter P-gp and breast cancer resistance protein (BCRP)
Monitoring recommendations	Renal function as clinically indicated	•Live enzymes should be checked in the first 4 weeks of treatment, then as clinically indicated • If ALT is found to be elevated above baseline levels, it should monitored closely during treatment • If administered with ribavirin: *see ribavirin prescribing information*	Checking patients for NS3 Q80K polymorphism is not strongly recommended but may be considered prior to starting treatment. Renal function as clinically indicated

adjustments for patients with severe renal dysfunction and it can be used as an option for patients with estimated creatinine clearance less than 30 mL/min.

With the recent approvals of sofosbuvir (Sovaldi®), simeprevir (Olysio®), ledipasvir-sofosbuvir (Harvoni™), ombitasvir/paritaprevir/ritonavir plus dasabuvir (Viekira Pak™) there are now multiple interferon-free (all-oral) regimens available with similar efficacy for patients with chronic HCV infection. The choice of regimen will mostly depend on patient's HCV genotype, treatment history, and potential for drug-drug interactions. This is a key area for pharmacists to make an impact prior to patients starting treatment. Due to the ubiquitous nature of medications such as antacids, proton-pump inhibitors, and statins, a thorough chart review and patient counseling will be imperative prior to starting these new agents. The new all-oral regimens are much better tolerated than the interferon-containing regimens of previous years. However, patients may be required to take RBV, which will still require close monitoring due to its potential for serious adverse effects.

Although these new all oral regimens are now on the market, patients may still have difficulty with access to these new therapies due to the high cost. A course of treatment with the newer all-oral treatments ledipasvir-sofosbuvir (Harvoni™), or ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak™) has an approximate wholesale cost of $90,000 to $100,000 for 12 weeks of treatment. Insurance providers may require strict criteria for prior authorizations for these costly medications. Payers may restrict approval for these medications to those patients with the most advanced disease. Although they are very costly, recent studies have shown that they are likely cost effective for most patients due to decreased rates of HCV-complications and related costs over time. Gilead, the manufacturer of Sovaldi™ and Harvoni™, has established a patient assistance program called Support Path™ to help patients receive hepatitis treatment who do not have insurance or who are underinsured. Abbvie also has a program to assist patients with the cost of Viekira Pak™. If patients meet eligibility for Abbvie's ProCeed™ program, they may receive Viekira Pak™ at no cost or for a minimal co-pay.

FUTURE THERAPIES

The treatment of HCV is an ever-evolving field of study, with continued efforts to identify safe, effective treatment options. Several new agents are currently undergoing or have just completed clinical trials. A combination of three new agents, asunaprevir, daclatasvir, and beclabuvir, as a single-tablet regimen is currently being studied in two clinical trials, with the results expected soon. Daclatasvir is also currently being studied in combination with sofosbuvir. Two new agents, grazoprevir and elbasvir, are undergoing studies in HIV/HCV coinfected patients. Some of these agents are being studied for treatment durations shorter than the currently available DAAs. Other DAAs are currently in various stages of development. Pharmacists must be cognizant as other treatment options are brought to the market.

TREATMENT GUIDELINES ACCORDING TO GENOTYPE

Genotype 1

Treatment Naive

Treatment of genotype 1 HCV has evolved significantly over the past 10 years. Dual therapy with pegylated interferon (PEG-IFN) plus ribavirin (RBV) was the standard of care until the introduction of the protease inhibitors boceprevir and telaprevir. Now, three highly effective DAA-based regimens have replaced PEG-IFN based regimens as preferred regimens for treatment-naïve patient with genotype 1, though these may differ slightly based on the subtype. In the case that a subtype cannot be determined or is unknown, the patient should be treated as genotype 1a. The three DAA-based regimens include ledipasvir/sofosbuvir, paritaprevir/ritonavir/ombitasvir plus dasabuvir with or without RBV, and sofosbuvir plus simeprevir with or without RBV. Treatment selection depends on several factors, including preference for once daily dosing, contraindications to RBV, and respective drug interactions with the various new DAAs.

RBV use should now be reserved as an optional addition to sofosbuvir plus simeprevir for both subtypes regardless of cirrhosis status, but should be added to the treatment of cirrhotic patients with genotype 1a or 1b receiving paritaprevir/ritonavir/ombitasvir plus dasabuvir. PEG-IFN no longer has a role in the treatment of genotype 1 treatment-naïve patients, including dual therapy with RBV.

The treatment duration is generally 12 weeks, but should be extended to 24 weeks for most patients with cirrhosis. For patients with genotype 1b being treated with paritaprevir/ritonavir/ombitasvir plus dasabuvir, 12 weeks is sufficient therapy regardless of cirrhosis status.

Failed Previous Treatment with PEG-IFN Plus RBV

Preferred treatments of genotype 1 for those patients who have failed previous therapy with PEG-IFN plus RBV are similar to regimens used for treatment-naïve patients. Ledipasvir/sofosbuvir, paritaprevir/ritonavir/ombitasvir plus dasabuvir, and sofosbuvir plus simeprevir make up the three preferred regimens for treatment. RBV is an optional addition to sofosbuvir plus simeprevir for both subtypes, and should be added to paritaprevir/ritonavir/ombitasvir plus dasabuvir in genotype 1a patients regardless of cirrhosis status or genotype 1b patients with cirrhosis.

As with treatment-naïve patients, those who have failed previous treatment with PEG-IFN plus RBV should generally be treated for 12 weeks. Treatment should be extended to 24 weeks in patients who are cirrhotic, with the exception of genotype 1b patients being treated with paritaprevir/ritonavir/ombitasvir plus dasabuvir, who can complete treatment at 12 weeks.

Failed Previous Treatment with DAA-Based Regimen

Patients with genotype 1 who have failed previous therapy with a protease inhibitor-based regimen, should be treated with ledipasvir/sofosbuvir for 12 weeks, or 24 weeks if cirrhosis is present. For cirrhotic patients, ledipasvir/sofosbuvir duration can be reduced back to 12 weeks if weight-based RBV is added. Patients who have failed previous therapy with a sofosbuvir-containing regimen and have cirrhosis with advanced fibrosis can be retreated with ledipasvir/sofosbuvir with or without weight-based RBV for 24 weeks. In those who do not have fibrosis, it is recommended to defer retreatment until more evidence is available establishing successful treatment of this population so as to not influence resistance patterns.

Genotype 2

Historically, the standard of care for treatment naïve patients with HCV genotype 2 has been the PEG-IFN plus RBV combination, as no effective alternatives had been developed. With the introduction of new DAAs in 2014, the PEG-IFN plus RBV combination was replaced with a new regimen including sofosbuvir 400 mg daily plus weight-based RBV for 12 weeks, or extended to 16 weeks for those patients with cirrhosis (Class IIb, Level C). No alternative therapies are recommended for treatment-naïve patients (AASLD Guidelines). The same sofosbuvir based regimen is preferred for patients who have previously failed PEG-IFN plus RBV regimen alone. Alternatively, PEG-IFN can be added to sofosbuvir plus RBV for patients who have failed previous treatment and present with cirrhosis at the time of retreatment. Dual therapy with PEG-IFN or monotherapy with any agent is not recommended for either treatment-naïve or those who have failed previous treatment. Protease inhibitor-based regimens have not been approved or indicated for any patient with genotype 2.

Genotype 3

Currently, the preferred regimen for patients with genotype 3 is the same regardless of treatment history. Sofosbuvir 400 mg daily plus weight-based RBV for 24 weeks is preferred for treatment-naive patients (Class I, Level B) and those who have failed dual therapy with PEG-IFN and RBV (Class I, Level B). PEG-IFN can be added to this regimen to shorten the treatment duration to 12 weeks as an alternative treatment plan (Class IIa, Level A). Dual therapy with PEG-IFN, monotherapy with any agent, or regimens containing boceprevir, telaprevir, or simeprevir are not recommended for any patient diagnosed with genotype 3.

Genotypes 4-6

As with the other genotypes of HCV, PEG-IFN plus RBV has been the mainstay of treatment for genotype 4, 5, and 6, with a duration therapy lasting up to 48 weeks. Newer recommendations now prefer DAA based regimens that may include the addition of RBV and/or PEG-IFN for both treatment-naïve patients and those who failed previous treatment with PEG-IFN dual therapy. Dual therapy with PEG-IFN and RBV is not generally recommended for treatment of these genotypes, but does remain an alternative regimen for patient with genotype 5 who are treatment naïve or have failed previous therapy.

CONCLUSIONS

The treatment of HCV infection is a rapidly evolving field of study, with multiple new agents recently marketed that are associated with remarkably high cure rates and a tolerable adverse effect profile. With so many new drugs on the market, providers and patients may need assistance from pharmacists to provide education and recommendations regarding HCV management. Further, pharmacists play a critical role in maximizing medication adherence, essential for the cure of this potentially deadly disease. By staying up-to-date on HCV treatment options, providers and pharmacists can ensure the judicious use of these new agents, which will lead to greater quality of life for infected patients. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA), in collaboration with the International Antiviral Society–USA (IAS–USA), have released web-based guidelines that are updated regularly as new information or drugs become available. This resource may be helpful for pharmacists who encounter medications used for treatment of HCV. ■

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Continuing Education Quiz

Select the correct answer.

1. Which HCV genotype is the most prevalent in the United States?
a. Genotype 1
b. Genotype 2
c. Genotype 3
d. Genotype 4

2. The treatment goal for HCV chronic infection is to achieve a sustained virologic response (SVR).
a. True
b. False

3. Which of the following are possible outcomes caused by chronic HCV infection?
a. End stage liver disease
b. Hepatocellular carcinoma
c. Transmission of HCV
d. All of these

4. Which of the following patients should be screened for hepatitis C infection?
a. A 60-year-old man who underwent a kidney transplant in 1990
b. An otherwise healthy 23-year-old female with a history of asthma
c. A 45-year-old male with a PMH of diabetes, hypertension, and dyslipidemia
d. The newborn baby of a mother with preeclampsia

Use the following case to answer questions 5-7
C.D. is a 51-year-old white male who was diagnosed with chronic HCV genotype 1a infection following a routine screening at his recent primary care visit. He presents to your pharmacy with a prescription for ledipasvir/sofosbuvir (Harvoni®). He states that he has never taken medications for HCV before and would like to ask you some questions.

5. The prescribed regimen is appropriate for C.D.
a. True
b. False

6. Which of the following are possible common side effects to ledipasvir/sofosbuvir?
a. Pruritis
b. Insomnia
c. Myalgia
d. All of these

7. Which of the following are counseling points for ledipasvir/sofosbuvir?
a. Ledipasvir/sofosbuvir should be taken once a day for 12 weeks.
b. You should avoid antacids and acid suppression medications while on ledipasvir/sofosbuvir.
c. Ledipasvir/sofosbuvir can be taken with or without food.
d. All of these

Use the following case to answer questions 8 and 9
G.M. is a 46-year-old white male who is being seen by a local HCV clinic. He was diagnosed with HCV genotype 1a in 2002. G.M. was treated unsuccessfully with peginterferon and ribavirin due to discontinuation after intolerable side effects. Based on recent evaluation and tests, it was determined that G.M. has now developed cirrhosis.

8. Which of the following are common intolerable side effects to peginterferon use that may have led to discontinuation?
a. Myalgia
b. Dry cough
c. Neutropenia
d. Two of these
e. All the above

9. Which of the following regimens is a preferred treatment and duration for G.M.?
a. Ledipasvir/sofosbuvir (Harvoni®) for 24 weeks
b. Ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) plus ribavirin for 24 weeks
c. Sofosbuvir (Sovaldi®) and Simeprevir (Olysio®) for 24 weeks
d. All of the above

10. The fetal toxicity associated with ribavirin would affect a female patient who becomes pregnant but not the female partner of a male patient taking ribavirin.
a. True
b. False

11. What is the shortest possible FDA-approved duration of therapy for patients without cirrhosis receiving simeprevir (OLYSIO) and sofosbuvir (SOVALDI) dual therapy?
a. 8 weeks
b. 12 weeks
c. 24 weeks
d. 48 weeks

12. Which of the following patients should not receive treatment with simeprevir (OLYSIO)?
a. HCV genotype 2 and treatment naïve
b. HCV genotype 1 and ineligible for interferon therapy
c. HCV genotype 1a with the NS3 Q80K polymorphism
d. A and C
e. All of the above

13. What percentage of treatment-experienced patients receiving simeprevir (OLYSIO) + pegylated interferon + ribavirin in the PROMISE study were eligible to end treatment after 24 weeks?
a. 65.3 percent
b. 74.1 percent
c. 81.9 percent
d. 92.7 percent

14. Patients receiving which of these medications should be counseled on the risk of photosensitivity?
a. Boceprevir (VICTRELIS)
b. Telaprevir (INCIVEK)
c. Simeprevir (OLYSIO)
d. Sofosbuvir (SOVALDI)

15. Mr. Jones is receiving treatment for hepatitis C. His current medications include rosuvastatin 20 mg daily and omeprazole 20 mg daily. Mr. Jones is concerned about possible drug interactions with his ledipasvir/sofosbuvir (Harvoni®) regimen. What do you advise Mr. Jones regarding his medication regimen.
a. There are no drug interactions.
b. Rosuvastatin levels may increase while taking ledipasvir/sofosbuvir. He and his doctor should monitor for signs of rhabdomyolysis associated with rosuvastatin such as muscle pain or weakness.
c. Omeprazole may decrease the effectiveness of ledipasvir.
d. Both B and C

16. Which interferon-free regimen would be appropriate for a patient who has failed previous treatment with peginterferon and ribavirin? The patient is genotype 1a, without cirrhosis.
a. Ombitasvir/paritaprevir/ritonavir with dasabuvir + ribavirin for 12 weeks
b. Simeprevir + sofosbuvir for 24 weeks
c. Ledipasvir/sofosbuvir for 12 weeks
d. Both A and C

17. Which of the following statements about ombitasvir/paritaprevir/ritonavir with dasabuvir is true?
a. There are no dose adjustments required for renal dysfunction.
b. Ombitasvir/paritaprevir/ritonavir with dasabuvir should be taken with food.
c. Ombitasvir/paritaprevir/ritonavir with dasabuvir is contraindicated in patients with severe (Child-Pugh C) hepatic impairment.
d. All of the above are true.

18. A common adverse effect that patients could expect with ombitasvir/paritaprevir/ritonavir with dasabuvir is:
a. Weight gain
b. Dry mouth
c. Pruritus
d. Sedation

19. Which of the following interferon-free regimens would be appropriate for a patient with genotype 1a chronic hepatitis c infection who is treatment naïve but has cirrhosis?
a. Simeprevir + sofosbuvir for 12 weeks
b. Ledipasvir/sofosbuvir for 24 weeks
c. Ombitasvir/paritaprevir/ritonavir with dasabuvir + ribavirin for 24 weeks
d. Ombitasvir/paritaprevir/ritonavir with dasabuvir + ribavirin for 12 weeks

20. Female patients taking ombitasvir/paritaprevir/ritonavir with dasabuvir should not take ethinyl-estradiol-containing birth control due to risk of contraceptive failure.
a. True
b. False