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Treatment of Hepatitis C Virus
An Update on Medications and Patient Education

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The treatment of hepatitis C virus (HCV) has evolved significantly, marked by the approval of combination, direct-acting antiviral medications, which have improved the tolerability and efficacy of therapy. As the number of patients engaged in HCV treatment increases, it is important that all members of the healthcare team remain current on treatment options and equipped with the knowledge to educate patients. Nursing staff play a critical role in understanding the role of new medications in treatment, significant drug interactions, and patient counseling points on administration, potential adverse reactions, and the importance of adherence.

Introduction

Hepatitis C virus (HCV) is a major cause of liver disease, leading to the progression to cirrhosis and hepatocellular carcinoma and the need for liver transplantation (American Association for the Study of Liver Diseases, 2018). In 2015, the World Health Organization (WHO, 2017) estimated that 71 million individuals were living with chronic HCV worldwide. The Centers for Disease Control and Prevention (2018) estimates that there are 3.5 million individuals living with chronic HCV in the United States and, as of 2016, the estimated incident rate of new infections was rising. Of those who become infected with HCV, approximately 75% will go on to develop chronic infection, which requires treatment with direct-acting antiviral (DAA) medications to prevent complications (CDC, 2018).

Despite public health initiatives to increase screening and linkage to care, it is estimated that 50% of individuals with HCV are unaware of their infection (Thomas & Seeff, 2005). In 2016, the WHO endorsed a goal to eliminate HCV as a public health threat by the year 2030. To achieve this, 90% of infected individuals require diagnosis and the majority of those diagnosed will require treatment.

Hepatitis C virus is a single-stranded RNA, bloodborne, virus, with six different genotypes worldwide (Liang, Rehermann, Seeff, & Hoofnagle, 2000). The most common genotype in the United States is genotype 1, including both 1a and 1b, followed by genotypes 2 and 3. Treatment of HCV has undergone significant development over the last 20 years. In 2000, the first HCV medications included injectable interferon and oral ribavirin, which had lengthy treatment durations, intolerable adverse effects, and limited efficacy (Fried et al., 2002; Manns et al., 2001). In 2011, oral agents, boceprevir and telaprevir, were added to interferon and ribavirin for the treatment of genotype 1, shortening treatment durations and improving efficacy, but have since been removed from the market for poor tolerability and outcomes in patients with cirrhosis (Jacobson et al., 2011; Poordad et al., 2011). In 2013, a second generation of DAA medications came to market. Agents such as sofosbuvir and simeprevir improved efficacy to nearly 90% when used with interferon and ribavirin in genotype 1 infections (Lawitz et al., 2013).

The newest era of HCV treatment regimens eliminated the need for interferon treatment and improved both efficacy and tolerability. As of May 2018, there are 13 Food and Drug Administration (FDA)-approved HCV medications currently available for the treatment of chronic infection. These medications are primarily formulated in single-tablet regimens and boast shorter treatment durations between 8 and 12 weeks, tolerable side effect profiles, and efficacy rates of more than 90%. Because of the improved tolerability of these regimens, the WHO has begun applying similar concepts of "task shifting" utilized in human immunodeficiency virus (HIV) care to those patients being treated for HCV. The concept of task shifting encompasses the distribution of patient management among all members of the healthcare team, including nursing staff (Yoo, Perumpail, Cholankeril, Jayasekera, & Ahmed, 2017). There are a variety of opportunities for nursing involvement in the management of HCV, including patient education and monitoring for adverse effects and drug interactions of DAA medications. As national and global initiatives highlight the importance of continued efforts to screen for HCV infection, link patients to the

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Table 1. Summary of First-Line Agents for HCV

Brand Name (Generic Name)	Genotypes Treated	Common Side Effects	Pill Burden	Clinical Pearls
Mavyret (glecaprevir/pibrentasvir)	1-6	Headache, fatigue	Three-tablet regimen once daily (blister packaging)	8-week regimen available in certain clinical scenarios
Epclusa (sofosbuvir/velpatasvir)	1-6	Headache, fatigue	Single-tablet regimen once daily	May require ribavirin
Zepatier (elbasvir/grazoprevir)	1, 4	Headache, fatigue, nausea	Single-tablet regimen once daily (blister packaging)	Baseline resistance testing required in genotype 1a May require RBV
Harvoni (ledipasvir/sofosbuvir)	1, 4, 5, 6	Headache, fatigue	Single-tablet regimen once daily	8-week regimen available in certain clinical scenarios May be used in children ≥12 years May require RBV
Ribavirin	Add-on medication for all genotypes	Black Box Warnings: hemolytic anemia, birth defects Rash	Dependent on dose (typically multiple tablets twice daily)	Dosing based on patient weight/HCV genotype Dose-dependent hemolytic anemia toxicity Administered with food Contraception must be used during treatment and 6 months following

Note. HCV = hepatitis C virus.

care continuum, and promote viral eradication, all members of the healthcare team play a role to ensure patient success.

Current HCV Treatment Regimens

Although there are 13 available HCV medications on the market, not every medication is appropriate for every patient. Medication selections are based on HCV genotype, previous treatment attempts, the presence or absence of cirrhosis or kidney disease, and other concomitant medications. The following section highlights commonly used first-line coformulated HCV treatment regimens, as recommended by the American Association for the Study of Liver Diseases (2018), and are summarized in Table 1. The majority of HCV treatment regimens are approved for 12 weeks of therapy, although in certain clinical scenarios, duration of therapy may be abbreviated or extended. The addition of ribavirin may also be required in some patient scenarios, increasing both pill burden and the risk of adverse effects.

Overall, these medications are well tolerated and easy to administer; however, risk of drug interactions should be considered prior to initiation. It is also important to note that all HCV medications hold an FDA Black Box Warning for the risk of reactivation of hepatitis B virus (HBV) in patients who are coinfected with both viruses. All patients should be screened for HBV before starting HCV treatment to determine whether additional medications or monitoring throughout treatment is necessary.

Mavyret (Glecaprevir/Pibrentasvir)

Mavyret is a pangenotypic agent with a high barrier to resistance that can be used to treat any HCV genotype in patients with or without cirrhosis (Child Pugh Class A only), regardless of previous treatment experience (U.S. National Library of Medicine, 2018). It is also safe to administer in patients with end-stage renal disease receiving hemodialysis. Mavyret showed slightly better efficacy rates when used in genotypes 1, 2, 5, and 6, compared with genotypes 3 and 4. It has an FDA indication for an 8-week regimen in patients who are treatment-naive without cirrhosis; however, for patients with cirrhosis, a 12-week course of treatment is required. Regardless of therapy duration, Mavyret remains the most cost-effective agent currently available.

Mavyret is a completely ribavirin-free regimen, making it very well tolerated. Common side effects include headache and fatigue. This agent is administered as three tablets once daily and is manufactured in daily blister packs to aid patient adherence. This regimen can be taken without regard to meals.

Epclusa (Sofosbuvir/Velpatasvir)

Epclusa was the first pangenotypic agent available for the treatment of all HCV genotypes in patients with or without cirrhosis (U.S. National Library of Medicine, 2018). Epclusa can also be used with the addition of ribavirin in patients with more severe cirrhosis (Child Pugh Class B & C). Epclusa also provided the first interferon- and ribavirin-free treatment regimen for Genotype 3 patients. Unlike Mavyret, Epclusa has not been approved for an abbreviated 8-week regimen for treatment of any genotype and is given for a minimum of 12 weeks in the majority of patients.

Epclusa is well tolerated when used as monotherapy, with common side effects including headache and fatigue. When paired with ribavirin, the regimen is not as well tolerated, given the significant side effects associated with ribavirin described in a later section. Without ribavirin, this regimen is administered once daily as a single tablet and can be taken without regard to meals.

Harvoni (Ledipasvir/Sofosbuvir)

Harvoni was the first interferon- and ribavirin-free, HCV therapy approved for the treatment of most patients with genotypes 1, 4, 5, and 6 (U.S. National Library of Medicine, 2018). In specific cases, Harvoni requires the addition of ribavirin to maintain efficacy, including patients with cirrhosis and those previously treated for HCV. Harvoni holds an FDA indication for an 8-week regimen in noncirrhotic patients who are treatment-naive, nonblack, and with lower HCV viral loads. Harvoni may be utilized in patients with more advanced cirrhosis (Child Pugh Class B & C); however, safety and efficacy have not been established in patients with severe renal impairment. Harvoni has also been proven effective in the pediatric population in children aged 12 years and older.

Harvoni, when used without ribavirin, is very well tolerated. The most common side effects associated with this regimen include headache and fatigue. Harvoni is a once-daily, single-tablet regimen that can be administered with or without a meal.

Zepatier (Elbasvir/Grazoprevir)

Zepatier is approved for use in treatment of HCV genotypes 1 and 4 in patients with or without renal disease and regardless of past treatment experience (U.S. National Library of Medicine, 2018). This regimen, however, requires baseline resistance testing in patients with genotype 1a virus due to a lower barrier to resistance that can lead to treatment resistance. If testing reveals baseline viral resistance, Zepatier requires the addition of ribavirin and an extension from 12 weeks to 16 weeks of therapy to be effective. In addition, ribavirin is required in certain patient populations who have been exposed to related HCV medications in the past. Despite this, Zepatier remains a favorable option in patients with significantly impaired renal function, including those receiving hemodialysis.

Zepatier is a once-daily, single-tablet regimen that is manufactured in a patient-friendly blister package to guide patients through each day of treatment. Zepatier may be taken without regard to meals. When used without ribavirin, Zepatier is a well-tolerated regimen with common side effects including headache, fatigue, and nausea.

Ribavirin

Ribavirin is an oral antiviral medication that has been used in the treatment of HCV therapy since the first regimens including interferon. Ribavirin, unlike other medications used for HCV treatment, was not specifically developed for the eradication of HCV; rather, it is a nonspecific agent with antiviral properties (U.S. National Library of Medicine, 2018). Although the newest, pangenotypic agents are potent enough to not require ribavirin, it still plays a role in certain clinical scenarios. It is used as an add-on medication in difficult-to-treat patient populations to improve efficacy of other HCV medications. Ribavirin can be added to HCV regimens for any viral genotype; however, the dosing varies on the basis of the genotype and patient weight. Ribavirin is manufactured as an oral tablet and is often given as multiple tablets twice daily with food.

Ribavirin is a poorly tolerated medication. This agent has two FDA Black Box Warnings that require additional monitoring and counseling to prevent and manage. The first is for the risk of hemolytic anemia, which may be severe and require dose reductions or discontinuation of the medication. The other is for birth defects and potential fetal death. Ribavirin therapy requires negative pregnancy tests prior to, during, and up to 6 months after use in both female and male partners, as well as two forms of birth control. Ribavirin is also associated with rashes of variable severity and insomnia.

Drug Interactions

Risk of drug interactions varies depending on the properties of the DAA. Thorough evaluation of potential drug interactions should be completed prior to selection and initiation of DAA therapy. The University of Liverpool (2018) provides a free hepatitis C drug interaction checker (www.hep-druginteractions.org) that is updated frequently and may be a useful resource to guide management of drug interactions.

Several of the DAAs undergo hepatic metabolism mediated through the cytochrome P450 system with p-glycoprotein (P-gp) utilized as a transporter. Medications such as rifampin, rifabutin, phenytoin, carbamazepine, phenobarbital, and St. John's wort are moderate or strong inducers of cytochrome P450 enzymes and P-gp, which can lead to decreased concentrations of the DAAs and HCV treatment failure. Therefore, all of these medications are either contraindicated or not recommended for concomitant use with the DAAs. Medications used to treat HIV may also impact the metabolism of the DAAs and the risk should be evaluated carefully in patients who are coinfected with both viruses.

Many DAAs also have the potential to inhibit the metabolism or transport of other medications. Statins, such as rosuvastatin, simvastatin, and atorvastatin, are variably affected by the different DAAs. The concentration of statin medications is likely to be increased by DAAs, placing patients at an increased potential risk of myopathy and rhabdomyolysis. Management will vary depending on the statin therapy and DAA regimen chosen. Rosuvastatin, for example, is not recommended for use with Harvoni, but may be used with other frequently used combination DAAs at a maximum dose of 10 mg/day. Evaluation for interaction potential should be assessed in patients on a statin medication before starting a DAA regimen. If a statin is held or undergoes dosage adjustment prior to initiation of a DAA regimen, it is important that the patient is restarted on the appropriate statin therapy following completion of that treatment.

Medications may also interfere with absorption of DAAs or concomitant use may lead to an increased risk of adverse effects. Both ledipasvir (found in Harvoni) and velpatasvir (found in Epclusa) require acidic environments to be absorbed. Medications that increase the pH of the stomach, such as proton-pump inhibitors (PPI), histamine-2 inhibitors, or antacids, have the potential to impact the absorption of these medications.

Coadministration of omeprazole 20 mg/day or an equivalent dose of another PPI may be used with Harvoni if given simultaneously on an empty stomach. Proton-pump inhibitors use is not recommended with Epclusa. If PPI use is medically necessary, Epclusa should be administered with food and omeprazole 20 mg daily may be given 4 hours later. Amiodarone coadministration with sofosbuvir-containing combinations (i.e., Epclusa and Harvoni) has been associated with severe, symptomatic bradycardia and should also be avoided.

In addition, as liver function may improve with successful treatment of HCV, the effects of other medications may be altered. Although warfarin does undergo metabolism by the liver, it is unlikely to be impacted directly by the DAAs. However the liver is responsible for the production of clotting factors that are inhibited by warfarin. As liver function improves, changes in International Normalized Ratio (INR) may result. The INR should be monitored closely during therapy and following discontinuation.

Patient Education

Appropriate patient education and counseling are essential aspects of HCV treatment. Nonadherence to an HCV treatment regimen has been identified as the most important risk factor for treatment failure. In one study of patients treated with Harvoni, nonadherence was associated with a 16-fold increased risk of treatment failure (Sarpel et al., 2016). Nonadherence includes missing doses, taking medications at inconsistent times each day, or not taking with regard to food, if indicated. Not taking medications as prescribed will lead to decreased drug exposure and may allow for HCV replication and potentially the development of viral resistance. Factors that can contribute to nonadherence include educational, motivational, circumstantial, or environmental barriers.

Assessment of a patient's adherence to any current medications could help elucidate any preexisting barriers to medication compliance. The importance of medication adherence must be discussed with the patient before initiating any HCV regimen and include discussion of the risks associated with nonadherence. This counseling should include discussion of medication administration and medication timing with regard to the patient's daily routine, food, or other medications, as appropriate. Patients should be advised to avoid stopping HCV medications if they develop an adverse effect. Instead, patients should call their healthcare provider for assessment of the adverse effect prior to abrupt discontinuation. Commonly encountered adverse effects are not serious or life-threatening and many times may be managed effectively. For example, headache may be managed with over-the-counter pain medications.

Other circumstantial or environmental barriers may include cost, lost medication, homelessness or unpredictable housing, or hospitalization. Although the DAA regimens have a high cure rate, they also currently have a high price tag. Because of the high cost of these medications, the patient's out-of-pocket cost can vary depending on the patient's medication insurance plan and the eligibility of manufacturer copay coupons. The out-of-pocket cost should be discussed prior to initiation to identify barriers in the ability to pay for the medication. Many times, specialty or mail-order pharmacies are required by the medication insurance provider to dispense these costly medications, which may be new to patients. The patient must be counseled on how to refill these medications and to order refills several days in advance. Given these are specialty medications, and especially if the dispensing pharmacy is mail-order only, these instructions are important because same-day pickup may not be an option. Because of medication cost, insurance companies may not approve replacement of lost medications. Patients must be made aware of this and informed of the importance of keeping the medications in a safe location, especially if they have an unpredictable living situation. Similarly, many hospitals will not keep these medications on their formularies. Patients who require hospitalization should be advised to bring their medication with them to prevent any missed or delayed doses.

Upon achievement of a clinical cure, or sustained virologic response, patients should be counseled that successful treatment will not protect them from reinfection with HCV. Patients must receive counseling to avoid activities or behaviors that could lead to reexposure to HCV.

Conclusion

The new DAA medications are highly effective in achieving clinical cure in patients who are infected with HCV. This has opened the door for a new goal to eradicate HCV infection in United States and worldwide. Providing patients with counseling on appropriate use of these medications is an essential aspect of care to move closer to the goal of HCV elimination and is a critical component in which all healthcare professionals on the team must be engaged.

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