Acute Care Nursing Considerations in the Era of Direct-Acting Hepatitis C Antivirals

Jennifer L Cole* and Jennifer E Stark

Veterans Health care System of the Ozarks, Fayetteville, USA

*Corresponding author: Jennifer L Cole, Pharm D, BCPS, BCCCP, Veterans Health Care System of the Ozarks, 1100 North College Avenue, Fayetteville, AR 72703, USA, Tel: 479-444-4020, E-mail: Jennifer.cole@va.gov

Abstract

Chronic hepatitis C virus (HCV) has a major impact on healthcare globally. Comorbidities are common in HCV-infected patients and as this population ages, acute care admissions are on the rise. With the introduction of the direct-acting antiviral (DAA) regimens, treatment for HCV has become better tolerated and more effective with shorter durations. Treatment rates for HCV are on the rise with the DAA agents, making it more likely to encounter patients on these medications during hospital admissions. There are limited data in the published literature regarding DAs in the acute care setting and this remains an unmet need. This review focuses on important clinical considerations for the hospitalized patient prescribed DAA therapy.

Keywords

Hepatitis C Infection, Direct-Acting antivirals, Inpatient care, Acute care

Introduction

Hepatitis C viral (HCV) infections are a major healthcare issue across the globe with an estimated 2.7-3.9 million cases of chronic hepatitis C infection in the United States alone [1]. Research indicates there are 3-4 million new infections each year globally [2] and the Centers for Disease Control (CDC) reported an increased, but stabilizing, prevalence in the United States from 2010 to 2014 [3]. In addition to the complications imposed by the development of cirrhosis, chronic HCV infection is the leading cause of hepatocellular cancer, the leading indication for liver transplantation, and recently surpassed HIV as a cause of death in the United States [4,5].

Although acute complications of viral hepatitis C can be severe, the major burden of the disease lies in the chronic condition. Because of the slow progression of HCV, diagnosis can be delayed for years. Research indicates that HCV detection in elderly patients is likely to increase and that these patients are more likely to have hepatic complications like cirrhosis and progressive liver disease [6]. Early detection is paramount to improved outcomes and limiting transmission. Subsequently, the CDC now recommends a one-time HCV screening for all individuals born between the years 1945 and 1965 in addition to testing those with known HCV risk factors [7]. Patients born during this time period are disproportionately affected, such as Harvoni® and Viekira Pak™, have an average wholesale price (AWP) of $1,350 and $1,190 per day of therapy, respectively.

Historically, HCV has been difficult to treat with interferon-based therapy that was fraught with adverse events and high treatment failures as evidenced by low sustained virologic response (SVR) [8]. Since 2011, a new era of direct-acting antivirals (DAA) has revolutionized HCV treatment. These newer treatment combinations have demonstrated shorter treatment durations, improved tolerability and efficacy with SVR estimated at 90-100% [9]. Current DAs fall within three classes: Protease Inhibitors (simeprevir, paritaprevir, and grazoprevir), NSSA inhibitors (daclatasvir, ledipasvir, ombitasvir, velpatavir and elbasvir), and NS5B polymerase inhibitors (sofosbuvir and dasabuvir). Many of the DAs agents are combined into fixed dose combinations (ledipasvir/sofosbuvir, elbasvir/grazoprevir, sofosbuvir/velpatavir or co-packaged product packs (e.g. paritaprevir/ritonavir/ombitasvir with or without dasabuvir). Ribavirin is an older antiviral agent, but it continues to be a component of some DAA treatment regimens (Table 1). The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) offer expert guidance for the treatment of adults with HCV [7].

Since these newer agents have reached the market, treatment rates for HCV have grown [10]. Additionally, research shows that hospital admissions rates for HCV patients is expected to rise in the coming years [11]. Given the aging HCV population coupled with newer, well tolerated treatment strategies, patients on DAA therapy with other comorbidities are more commonplace. Nurses in the hospital setting can expect to encounter these newer agents as part of their patients’ existing drug therapy upon admission. There is a need for more publication on clinical experience in the acute care arena with DAA regimens. This review is a focus on some of the common clinical considerations when dealing with these patients.

Cost

One of the more noteworthy issues of the DAA regimens is the staggering cost of therapy. Treatment combinations have been reported to cost on average between $75,000-$94,500 for a 12-week treatment period [12]. Higher cure rates and ease of therapy have been coupled with higher treatment cost. Co-packaged preparations, such as Harvoni® and Viekira Pak™, have an average wholesale price (AWP) of $1,350 and $1,190 per day of therapy, respectively.

Historically, pharmaceutical companies have defended these prices by citing the high costs of research and development,
production, marketing, distribution, and, ultimately, the value of SVR. These unusually high drug costs contributed to a noticeable increase in overall spending on prescription drugs in the US in recent years and, understandably, raise concerns for healthcare facilities as well as third-party payers [13]. Simulated prediction models have shown DAA regimens to be cost effective from a societal perspective [14], however application to “real world” treatment scenarios are lacking [15,16].

In recent practice, some payers have prioritized patients for treatment by severity of liver disease. In these cases only patients with advanced cirrhosis or fibrosis are covered and patients with milder liver disease are not [17]. This practice of resource allocation is under debate, however, and some argue that treatment deferral is unethical and could ultimately raise overall costs [18].

Minimizing Therapy Interruptions

Chronic medications that are unrelated to the acute process are often times not continued at hospital admission, particularly in ICU admissions [19]. Non-adherence with antiviral treatment is associated with treatment failures [20]. Other variables that impact DAA treatment response include age, gender, HCV genotype and subtype, degree of liver fibrosis, previous treatment, certain comorbidities, such as HIV co-infection or renal failure, and the presence of resistance-associated variants (RAV) [21]. The presence of RAVs indicates a variance in the binding site of DAAAs to the HCV target protein, leading to an altered antiviral response and increased risk of treatment failure.

The hepatitis C virus has a high rate of replication. Multiple antivirals are often employed in HCV treatment regimens in order to target different mechanisms [22]. It is therefore important to resume all agents of a given regimen to minimize selection pressure.

Unfortunately, little is known about the effects of altered physiology seen in critically ill patients on the DAA agents. The systemic inflammatory response often seen in critically ill patients can alter the absorption and distribution of medications. Additionally, metabolism and elimination of medications can be either increased or decreased in some scenarios [23]. Careful consideration regarding risks and benefits should be taken. DAA therapy should be resumed as soon as it is considered to be safe for the patient, ensuring that no component of the patient’s HCV treatment regimen is causing the problems for which the patient is being admitted. Prolonged therapy interruptions should be discussed with the patient’s infectious diseases or hepatology specialist.

Crushing Tablets

Many patients in the acute care setting may lose their ability to swallow whole medications due to either dysphagia or decreased levels of consciousness. In such cases, a feeding tube is often placed necessitating the consideration of crushing oral dosage forms of medications. Crushing tablets or opening capsules can alter drug delivery and in doing so create adverse events [24]. This is especially notable in sustained release formulations. Specific to antiviral therapy, there may be clinical concerns for subtherapeutic drug levels leading to resistance or increased drug exposure leading to toxicity [25,26].

None of the DAA agents are currently available in a parenteral or oral suspension formulation. Although there are no published data on the safety or efficacy of crushing tablets for administration, most of the currently available DAA agents are not enteric coated nor intended to be sustained release. Until further pharmacokinetic studies are available, the benefit of continuing DAA therapy in a crushed form appear to outweigh the risks.

One notable exception regarding tablet crushing is the recently approved extended-release formulation of Viekira XR™ [27]. This is a reformulated product of conventional Viekira™ that combines ingredients into three film-coated bilayer tablets that are to be taken once daily. The tablets include an extended-release layer of dasabuvir and an immediate-release layer of ombitasvir, paritaprevir, and ritonavir. The extended release tablets should not be crushed, chewed or split. The package labeling indicates Viekira XR™ tablets must be taken once daily with a meal and alcohol must be avoided within 4 hours of the daily dose. Although alcohol ingestion should not be an issue in the inpatient setting, it is not clear whether the alcohol found in many medication syrups and elixirs may also interact with Viekira XR™. This is important as alcohol impairs release of dasabuvir and could result in decreased dasabuvir serum levels [27].

The American Journal of Health-System Pharmacy has published a review of medication administration through feeding tubes [28]. Considerations for holding tube feeds around DAA administration may be necessary depending on absorption during fasting or fed states. Nurses and providers should consult with the pharmacy department in these situations.

Table 1: Currently available DAA agents, common adverse events, renal and hepatic function considerations.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>HCV genotype</th>
<th>Adverse Event Reported &gt; 10%</th>
<th>Renal function limits</th>
<th>Hepatic function limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir</td>
<td>Olysio®</td>
<td>1 when combined with sofosbuvir</td>
<td>Photosensitivity, fatigue, headache, dizziness, insomnia, nausea, increased bilirubin, diarrhea, myalgia, dyspnea</td>
<td>None</td>
<td>Avoid in decompensated cirrhosis or Child-Pugh B or C</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Sovaldi®</td>
<td>1 when combined with ledipasvir, 3 when combined with daclatasvir</td>
<td>Fatigue, nausea, headache, insomnia, weakness</td>
<td>Not recommended for CrCl &lt; 30 ml/min</td>
<td>None</td>
</tr>
<tr>
<td>Ledipasvir/Sofosbuvir</td>
<td>Harvoni®</td>
<td>1 and 4</td>
<td>Headache, fatigue, insomnia</td>
<td>Not recommended for CrCl &lt; 30 ml/min</td>
<td>None</td>
</tr>
<tr>
<td>Ombitasvir/Paritaprevir</td>
<td>Viekira Pak™</td>
<td>1</td>
<td>Fatigue, headache, insomnia, rash, pruritis, diarrhea, nausea, anemia, increased bilirubin, increased ALT, weakness, muscle spasm, cough</td>
<td>None</td>
<td>Avoid in decompensated cirrhosis or Child-Pugh B or C</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Daklinza™</td>
<td>3 when combined with sofosbuvir</td>
<td>Fatigue, nausea, headache, anemia</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ombitasvir/Paritaprevir</td>
<td>Techevie™</td>
<td>4</td>
<td>Fatigue, insomnia, rash, pruritis, nausea, increased ALT, anemia</td>
<td>None</td>
<td>Avoid in decompensated cirrhosis or Child-Pugh B or C</td>
</tr>
<tr>
<td>Elbasvir/Grazoprevir</td>
<td>Zepatier™</td>
<td>1 &amp; 4</td>
<td>Fatigue, headache, nausea</td>
<td>None</td>
<td>Avoid in decompensated cirrhosis or Child-Pugh B or C</td>
</tr>
<tr>
<td>Sofosbuvir/Velpatasvir</td>
<td>Epclusa®</td>
<td>1,2,3,4,5 &amp; 6</td>
<td>Headache, fatigue</td>
<td>Not recommended for CrCl &lt; 30 ml/min</td>
<td>None</td>
</tr>
</tbody>
</table>

Data obtained from product package insert [27,33,34,46-51].
Drug Interactions

Given the frequent comorbidities of HCV patients, polypharmacy is common. Drug-drug interactions are a significant risk in the DAA treatment population [29]. This can be especially problematic in hospitalized patients given new medications for acute illness. Many of the clinically significant drug interactions with the DAA agents are related to decreased drug levels resulting in increased risk of treatment failure. This can be due to increased metabolism of the DAA by the interacting agent or due to decreased absorption of the DAA. However, some drug interactions are concerning for severe toxicity due to either the DAA or the interacting drug. One recent example is the unexpected interaction between sofosbuvir and amiodarone that resulted in several cases of severe bradyarrhythmias requiring pacemaker placement and even death [30].

Three co-packaged product packs (Viekira ™, Viekira XR ™ and Technivie ™) contain an additional agent, ritonavir. Ritonavir is not active against HCV, but is a potent inhibitor of CYP3A [31]. This interaction is intentionally used to augment serum drug concentrations of the co-packaged component paritaprevir. However, an unintended consequence is severe interactions with several non-HCV medications. A recent observational study noted a somewhat paradoxical finding of decreased dose response trends in patients previously stable on warfarin when DAA agents were added [32]. For this and other safety reasons, INR should be monitored closely in patients on both warfarin and DAA therapy.

A common practice in hospitalized patients is the use of proton pump inhibitors (PPI) and other acid-blocking agents. Ledipasvir and velpatasvir require an acidic environment for adequate absorption and each have different timing and fasting requirements with PPI therapy. The daily dose of PPIs should not exceed that equivalent to omeprazole 20 mg when co-prescribed with these agents [33,34]. Other less potent acid-blocking agents (histamine receptor blockers or antacids) can still decrease absorption of ledipasvir or velpatasvir resulting in increased risk of treatment failure. Each class of acid-blocking agent has different timing recommendations with ledipasvir or velpatasvir that must be adhered to. Ledipasvir must be taken at the same time as the PPI under fasting conditions to avoid significant decreased drug serum levels. According to package labeling, concomitant velpatasvir and PPI use should be avoided. If a PPI must be co-administered, the velpatasvir should be taken with food, and then the PPI should be administered exactly 4 hours later. When ledipasvir or velpatasvir are administered with histamine receptor blockers (e.g. famotidine, ranitidine), they can be given either at the same time or separated by 12 hours. When these agents are given with antacids, they should be separated by at least 4 hours before or after the antacid dose [33,34].

Mental health disorders are common among chronic hepatitis C patients [35]. Antipsychotics and antidepressants that may be co-prescribed with DAAAs increase the risk of drug interactions. Drugs that are extensively metabolized through cytochrome P450 enzymes or affect P-glycoprotein transport may accumulate or cause significant changes in DAA plasma concentration [36]. Due to the potential for QTc prolongation, close ECG monitoring may be required in these situations.

Strong inducers of P-glycoprotein, such as rifampin and St. John’s Wort should be avoided with many DAAAs. Other medications commonly seen continued or initiated in the acute care setting that are particularly problematic in the cytochrome P450 pathways are lipid-lowering agents (e.g. simvastatin, atorvastatin, gemfibrozil) antiarrhythmics (e.g. amiodarone, diltiazem), and anticonvulsants (e.g. carbamazepine, phenytoin, valproic acid) [37]. Clinicians should seek out expert consultation prior to co-administration of these medications with DAA regimens. It is also imperative that clinicians recognize that many hospitals’ electronic medical records may not identify drug interactions between currently prescribed medications due to errors or gaps in electronic interface.

Adverse Events

Although the newer DAA regimens are generally reported as being well tolerated, they are not without adverse events. Anemia, headache, fatigue, and GI disturbances were frequently seen during clinical trials and varied by agent. Insomnia, irritability, and pruritus were also commonly reported (Table 1).

Patients on regimens containing ribavirin are especially at risk for developing anemia, a common finding in acute care patients. Careful work up may be indicated to determine other causes of anemia, such as blood loss, iron deficiency, non-HCV drugs, or chronic disease. If ribavirin is determined to be the culprit, treatment strategies include reducing the dose, the addition of erythropoietin therapy, or red blood cell transfusions [38].

Hepatotoxicity is a less common but potentially severe adverse effect of DAA therapy, although this could be attributable to the underlying disease. Alterations in hepatic metabolism seen in advanced liver disease may lead to drug induced toxicity [39]. The protease inhibitors (simeprevir, paritaprevir, and grazoprevir) have the potential to be hepatotoxic. These medications are contraindicated in patients with decompensated cirrhosis or Child-Pugh class B or C. Hepatotoxicity risk is increased with the protease inhibitors when they are administered with other hepatotoxic agents. Liver function should be carefully evaluated during the acute care process. Physical exam findings such as new ascites and the development of dark amber urine should be immediately reported to the medical team.

Another common acute care consideration is the presence or development of acute kidney injury [40]. There are limited treatment options in patients with severe renal failure (CrCl < 30 ml/min). Options include Zepatier ™, Viekira ™, Viekira XR ™ and Technivie ™. Ribavirin has dosing recommendations for patients with renal impairment, but is typically not well tolerated in this population due to severe anemia and prolonged drug clearance. Sofosbuvir is a backbone in many different treatment regimens but it is not recommended for use in patients with CrCl < 30 ml/min (Table 1). Careful attention should be paid to the patient’s renal function as DAA therapy may require interruption until renal failure resolves.

Perhaps more pertinent to nurses in the acute care setting is the development of unexpected adverse events. Clinicians should note the relatively limited clinical experience of the DAA agents globally. Adverse event rates are largely determined by those observed in clinical trials. Rarely seen side effects may take a much larger patient population to be recognized. Once a drug gains FDA approval, post marketing surveillance is needed to evaluate the effect of newer agents in a larger, non-study population. Vigilant reporting can lead to important changes in prescribing and safety labeling [41]. Clinicians are encouraged to report any suspected drug related adverse events to the FDA’s safety reporting program MedWatch (www.fda.gov/safety/medwatch).

Hospital Policy

Acute care facilities should have a plan in place for handling these high cost, high priority medications. Some hospitals may need to make exceptions to existing “no home medications” policies. If the patient did not bring in their outpatient supply, every effort should be employed to retrieve and identify these prescriptions. Given the substantial cost of any “missing doses”, facilities may consider handling these agents similar to narcotics for increased accountability. Hospitals with mobile dose tracking technology may benefit from a decrease in missing doses [42].

At the authors’ facility the pharmacy processes both inpatient and outpatient prescriptions. Many patients are treated through the on-site Hepatitis C clinic. If these patients are admitted during their treatment course, the pharmacy department will generate an outpatient prescription fill and dispense these as inpatient unit dose medications until the patient is discharged. Any remaining meds can then be dispensed home when the patient leaves. For other
patients, attempts are made to contact family members to bring in any current DAA prescriptions. These are delivered to the pharmacy where they are identified, stored, packaged, and barcoded as a unit dose prescription for the designated patient. Unit doses are then hand delivered directly to the patient’s nurse at the time of administration to avoid storage in medication rooms or automated dispensing machines.

Hospitals vary in their implementation of The Joint Commission on Accreditation of Healthcare Organizations patient safety goal of medication reconciliation [43]. Nurses play a vital role in medication reconciliation as they are often the first clinicians to assess the patient and the last to communicate with them before discharge [44]. Asking the patient open-ended questions about what medications they take and how could reveal important information that may have been missed upon admission.

Conclusion

Chronic hepatitis C infection affects a large population and treatment rates with the new DAA medications are on the rise. With the recent rapid progression in understanding of hepatitis C replication and blocking key pathways, research in treatment strategies shows no signs of stopping. Future developments include pan-genotypic therapy with shorter treatment durations. There is further need for the development of ribavirin-free strategies, hard-to-treat cases, and treatment failures [45]. There is limited information in the medical literature on these agents in the acute care setting, however clinical experience is growing rapidly. There is a need for further research on the pharmacologic and pharmacokinetic effects on DAA agents seen in the critically ill population. Nurses and other clinicians are encouraged to check for updated information on medication reconciliation [44]. Asking the patient open-ended questions about what medications they take and how could reveal important information that may have been missed upon admission.

References

33. (2016) Harvoni (ledipasvir/sofosbuvir) prescribing information, Gilead Sciences, Inc, Foster City, CA.
34. (2016) Epclusa (sofosbuvir/velpatasvir) prescribing information, Gilead Sciences, Inc, Foster City, CA.

ISSN: 2469-5823

Cole et al. Int Arch Nurs Health Care 2016, 2:057

Page 4 of 5


46. (2016) Olysio (simeprevir) [package insert], Janssen Therapeutics, Titusville, NJ.

47. Sovaldi (sofosbuvir) [prescribing information], Gilead Sciences, Foster City, CA.

48. (2016) Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir) [prescribing information], AbbVie Inc, North Chicago, IL.

49. (2016) Daklinza (daclatasvir) [prescribing information], Bristol-Myers Squibb Co, Princeton, NJ.

50. (2016) Technivie (ombitasvir, paritaprevir, and ritonavir) [prescribing information], AbbVie, North Chicago, IL.

51. (2016) Zepatier (elbasvir and grazoprevir) [prescribing information], Merck Sharp & Dohme Corp, Whitehouse Station, NJ.