Hepatitis C

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Objectives

1. Describe the etiology and epidemiology of hepatitis C virus (HCV) infection.
2. Discuss the basic pathophysiology of HCV infection.
3. List the screening recommendations and diagnostic tests for HCV infection.
4. Evaluate pharmacologic and non-pharmacologic HCV treatments.

Introduction

Chronic hepatitis C virus (HCV) is the most common blood-borne pathogen and has a prevalence of 3.2 million people in the United States.\(^1\) Nearly 150,000 new cases occur annually in the United States and in Western Europe.\(^2\) Ultimately, about 5%-7% of HCV infected individuals may die from disease-related complications. If untreated, and in some treated cases, HCV can develop into cirrhosis and hepatocellular carcinoma. Close to 75% of those who are infected with the virus may not be identified.\(^1\)

The primary route of transmission for HCV is through percutaneous exposure to blood.\(^1,2\) Other possible routes of transmission include mother-to-infant, contaminated devices shared for non-injection and injectable drug use and transmission among HIV-infected men who have unprotected sex with men. There are two stages of hepatitis C, acute and chronic. Acute HCV is considered a short-term illness which occurs within the first 6 months from initial infection.\(^3\) After 6 months from initial infection HCV is classified as chronic. Chronic HCV can last a lifetime and lead to serious liver complications. Since most patients do not know they have hepatitis until symptoms present weeks to months later, most patients have typically progressed to chronic hepatitis at diagnosis. A majority of acutely diagnosed HCV patients (85%) will go on to develop chronic hepatitis C.

Pathophysiology

The body’s response to an acute HCV infection is typically insufficient and unable to eradicate the virus.\(^1\) Once a person is infected with hepatitis C, there is rapid and continual HCV-RNA replication and viral particles are continuously released into circulation. RNA-dependent RNA polymerase, used in HCV replication, lacks proofreading and will generate a large number of mutants. The minor molecular variations will show 1-2% nucleotide heterogeneity.\(^4\) This heterogeneity causes a challenge to immune mediated control of HCV and may explain the variable clinical course as well as difficulties in vaccine development. Upon entrance into the host immune system, HCV uses several means to nullify the immunological pressure. The targets of HCV are hepatocytes and, possibly, B lymphocytes causing apoptosis. The action of apoptosis is thought to correlate with the extent of the disease.\(^1\) A higher level of apoptosis is associated with liver damage, whereas lower levels are correlated with viral persistence and could promote an environment conducive for other immune responses. The immune response associated with lower levels of apoptosis will damage the liver resulting in hepatic inflammation and fibrosis. HCV typically only infects 10% of the hepatocytes, but nearly 20% of hepatocytes are activated for apoptosis.\(^1,3\) Genomic mutations of HCV are normally detected within one year of infection. Those who have a resolved case of HCV have a vigorous T-cell response that is accompanied with highly active CD8 and persistent CD4 cell response. CD8 is thought to actively mediate a protective immunity but requires the help of CD4 cells to maintain the response during viral mutations. The proximate goal of HCV therapy is sustained virologic response (SVR), defined as the continued absence of detectable HCV RNA at least 3 months after completion of therapy. Reinfection is possible if the patient continues to engage in high-risk situations.

Risk Factors

Those who are at risk for HCV infection include current and past injection drug users, recipients of donated organs and blood products before 1992 or clotting factors before 1987, patients who have spent many years on hemodialysis for kidney failure, patients with body piercing or tattoos done with non-sterile instruments, HIV-
infected persons, and children born to mothers infected with the hepatitis C virus. There are also some less common risk factors associated with HCV including men having sexual contact with HCV-infected men and sharing personal care items, such as razors or toothbrushes, that may have come in contact with the blood of an infected person.

**Symptoms**

Hepatitis C can have an incubation period of 2 weeks to 6 months following initial infection. The majority of patients (80%) will not exhibit any symptoms. Acute symptoms that can occur include fever, fatigue, decreased appetite, nausea, vomiting, abdominal pain, dark urine, grey-colored face, joint pain and jaundice of the skin and whites of the eyes. Symptoms will typically begin to present around 7 weeks after infection, with a range of 3 to 12 weeks.

**Screening**

The CDC recommends anyone born between 1945 and 1965 have a one-time test for hepatitis C. Others who should be screened for HCV include the following:

- Current or past injection-drug use (yearly)
- Co-infection with HIV (yearly)
- Received blood transfusions or organ transplantations before 1992
- Received clotting factors before 1987
- Patients who have ever been on hemodialysis
- Patients with unexpected elevated ALT levels or evidence of liver disease
- Healthcare and public safety workers after a needle-stick or mucosal exposure to HCV-positive blood
- Children born to HCV-positive mothers
- Sexual partners of HCV-positive patients


**Diagnosis**

The American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidelines recommend HCV antibody and HCV RNA testing whenever an acute infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels. Diagnosis of acute HCV infection is best supported by either 1) a positive HCV-RNA test along with a negative HCV antibody test or 2) a positive HCV antibody test after prior negative HCV antibody test.

Lab documentation of acute HCV infection is easiest to achieve in individuals who have had a discrete exposure (e.g. new onset drug injection practice or sexual assault). In cases of discrete exposure, baseline HCV antibody and HCV-RNA testing is recommended within 48 hours of exposure. If baseline tests are negative, repeat testing is recommended. If baseline HCV antibody testing is positive while RNA testing is negative, guidelines recommend repeat HCV-RNA and ALT testing to identify an acute reinfection. When both baseline HCV antibody and RNA testing are positive, the person most likely has chronic HCV. In cases of discrete exposure, repeat testing should be conducted, at a minimum, 4 to 6 months later and is dependent on individual management goals. When earlier identification of infection or reinfection due to discrete exposure is desired, HCV-RNA and ALT testing should be done every 4 to 6 weeks and is recommended for 6 months.

If no discrete exposure or baseline testing is present, an acute infection could be suspected if a rise in ALT level is present without another cause or when there are low or fluctuating HCV-RNA values or spontaneous clearance, which do not commonly occur outside of the first 6 months after acute infection. When a patient is suspected of having an acute HCV infection, they should have testing to exclude other or coexisting causes of acute hepatitis and for HIV. The different diagnostic tests are shown in Table 1.
### Table 1: Interpretation of HCV Diagnostic Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation for Diagnosis of Acute HCV Infection</th>
<th>Frequency</th>
</tr>
</thead>
</table>
| **HCV antibody**      | • May be negative in the first 6 weeks after exposure  
• May be delayed or absent when the individual is immunosuppressed  
• Presence alone does not distinguish between acute and chronic infection  
• Low signal-to-cutoff ratio may be present during acute infection or represent a false-positive result | • Recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels |
| **HCV RNA**           | • Viral fluctuations greater than 1 log_{10} IV/mL may indicate acute infection  
• May be transiently negative during acute HCV infection  
• Alone does not distinguish between acute and chronic infection | • Recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels  
• Once diagnosed, every 4 weeks to 8 weeks for 6 months to 12 months to determine spontaneous clearance of HCV infection versus persistence of infection |
| **Alanine aminotransferase (ALT)** | • Fluctuating peaks suggest acute infection  
• May be normal during acute infection  
• May be elevated due to other liver insults such as alcohol consumption | • Every 2 weeks to 4 weeks and continue until ALT level normalizes |

HCV genotyping is recommended for treatment guidance. The patient’s genotype will determine the duration of therapy. There are currently 6 different genotypes present (genotypes 1 to 6). The genotype is a classification based on the RNA strands of the virus. Genotypes may be further classified into subtypes (a, b, etc.). Type 1 is the most common genotype accounting for about 75% of Americans with HCV and also the most complicated to treat. Nearly 20–25% have genotype 2 or 3, and only a small number of patients will present with genotypes 4, 5, or 6. Typically patients will only present with one genotype. The specific genotype has not been shown to play a large role in the progression of liver disease.

**Non-pharmacological treatment**

Patients infected with HCV should be counseled on appropriate behaviors to eliminate the possible transmission to others. Counseling points to include are sharing of injection equipment or high-risk sexual practices. When appropriate, patients with a history of recent intravenous drug use should be referred to an addiction specialist. Patients who consume alcohol and smoke marijuana should be advised that continued use of these substances are known risk factors for disease progression and severity. Anti-viral therapy may be withheld if patient is actively drinking alcohol excessively or using injectable drugs.

**Immunizations**

There is currently no vaccine for the hepatitis C virus. The vaccines recommended by the CDC for patients who have chronic liver disease are located in Table 2.
Table 2: Vaccine Recommendation for HCV Patients

<table>
<thead>
<tr>
<th>Immunization</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu (Influenza)</td>
<td>Yearly</td>
</tr>
<tr>
<td>Td/Tdap (tetanus, diphtheria, pertussis)</td>
<td>1 dose of Tdap, followed by Td booster every 10 years</td>
</tr>
<tr>
<td>Shingles (Herpes Zoster)</td>
<td>1 dose if 60 years or older</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>PCV13: 1 dose may be recommended PPSV23: 1-2 doses</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>1 or more doses may be recommended</td>
</tr>
<tr>
<td>MMR (measles, mumps, rubella)</td>
<td>1 or 2 doses</td>
</tr>
<tr>
<td>HPV (Human papillomavirus)</td>
<td>Women: 3 doses through age 26 years Men: 3 doses through age 21 years</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>2 doses</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>2 doses</td>
</tr>
<tr>
<td>HIB (Haemophilus influenza type b)</td>
<td>1 or 3 doses may be recommended</td>
</tr>
<tr>
<td>Chickenpox (Varicella)</td>
<td>2 doses</td>
</tr>
</tbody>
</table>

**Goals of Therapy**

The primary goal of treatment is to eradicate HCV infection by achieving virologic cure which is evidenced by a sustained virologic response (SVR). SVR rates are measured 12 weeks after completing therapy and is warranted to reduce all-cause mortality and liver-related health adverse consequences including end-stage liver disease and hepatocellular carcinoma.

**Pharmacotherapy**

HCV treatment is necessary because chronic HCV is associated with the risk of developing cirrhosis, end-stage liver disease, and hepatocellular carcinoma. HCV infection is the most common indication for liver transplant. Even patients who are unable to achieve a virologic cure may see an improvement of liver histology findings resulting in improved liver biopsies after antiviral therapy.

Therapy is indicated for several patient populations including previously treated or untreated chronic HCV patients, those with circulating HCV RNA, and increased ALT levels. Therapy is not recommended in patients with persistently normal ALT levels, decompensated liver disease (Child-Pugh score >6), and advanced cirrhosis who could be at risk for decompensation. Patients who are currently drinking alcohol excessively or actively injecting illegal drugs should delay antiviral therapy until alcohol consumption and injection drug use has been discontinued for at least six months, but this time frame varies in clinical practice. Cessation of alcohol consumption and injection drug use should be advised in all patients, and routine drug tests are conducted in clinical practice to ensure cessation is continued throughout treatment.

**Pegylated interferon (peg-IFN)** is a synthetic glycoprotein that resembles natural interferons that have antiviral, anti-proliferative, and immune-regulating activity. Peg-IFN was historically used as monotherapy with an SVR rate of less than 20%. There are two types of pegylated interferon including Pegasys® (interferon alfa-2a) and Peg-Intron® (interferon alfa-2b). These two pegylated interferons are similar in efficacy, metabolism and excre...
tion, but the dosing differs between the two.\textsuperscript{13,14,15} Pegasys\textsuperscript{®} has a fixed dosing schedule of 180mcg per week subcutaneous injection, and Peg-Intron\textsuperscript{®} has a weight dependent dosing schedule of 1.5mcg per kilogram per week subcutaneous injection. The peg-interferons are found to be more effective in improving SVR rates when given in combination regimens with ribavirin and protease inhibitors such as boceprevir, telaprevir, and simeprevir.\textsuperscript{1} The side effect profile of the interferon containing regimens can be limiting and may even be considered intolerable by patients.\textsuperscript{15} Patients who are on these regimens complain of severe flu-like symptoms (37-54%), fatigue (56%), insomnia (30%), depression (20%), and dry skin and mouth (10%).\textsuperscript{14} Peg-interferons can also cause several laboratory abnormalities such as neutropenia, thrombocytopenia, anemia, and transaminitis. The side effect profile and hematologic irregularities cause some patients to be ineligible to receive interferon therapy. Interferon ineligible is defined as one or more of the following\textsuperscript{6}:

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune diseases such as thyroiditis and systemic lupus erythematosus
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease (Child-Pugh score >6)
- Major uncontrolled depressive illness
- A baseline neutrophil count below 1500/mm\textsuperscript{3}, a baseline platelet count below 90,000/mcL or baseline hemoglobin below 10 g/dL
- A history of preexisting significant and unstable cardiac disease (undefined)

Ribavirin is a synthetic guanosine analog with an unknown mechanism of action.\textsuperscript{1} It is ineffective as monotherapy for HCV and should not be used alone. It is used in combination with peg-interferon and protease inhibitors to significantly improve SVR rates, especially in genotypes 2 and 3. Ribavirin is dosed based on weight resulting in 1,000mg per day if the patient weighs less than 75 kilograms or 1,200mg per day if the patient weighs greater than or equal to 75 kilograms.\textsuperscript{13,14} It causes fatigue in 60% to 70% of patients, dermatologic side effects in approximately 30% of patients, and gastrointestinal complications in 25% to 47% of patients.\textsuperscript{14} Ribavirin also causes hematologic irregularities such as leukopenia and neutropenia in up to 45% of the treatment population. Ribavirin’s use with peg-interferon results in many adverse effects, but ribavirin has individual contraindications to consider which include.\textsuperscript{14,15}

- Patients with hemoglobinopathies (i.e. sickle cell anemia)
- Patients with autoimmune hepatitis, a chronic disease in which the body’s immune system causes inflammation and liver damage.
- Hepatic decompensation in cirrhotic chronic hepatitis C mono-infected or HIV coinfected patients
- Women who are pregnant or may become pregnant and males whose female partners are pregnant or could become pregnant. (Category X)
  - Two forms of birth control are recommended during therapy and continued for 6 months after completion of therapy due to the risk of birth defects.

Interferon Containing Regimens

For many years, the standard therapy for chronic HCV genotype 1 infection was 48 weeks of subcutaneously-injected pegylated interferon alpha and oral ribavirin.\textsuperscript{17} This combination resulted in a SVR in 40-50% of patients with HCV genotype 1 infection. The addition of protease inhibitors to the treatment regimen of ribavirin and peg-interferon increased SVR rates to 60% to 75%, which then made this the new standard of care in 2011.\textsuperscript{18} Higher response rates were seen in genotypes 2 and 3 and only require 24 weeks treatment.

Victrelis\textsuperscript{®} (boceprevir) and Incivek\textsuperscript{®} (telaprevir) are both inhibitors of NS3/4A serine protease used in genotypes 1-4. They demonstrate profound HCV inhibition when combined with ribavirin and peg-interferon for genotype 1 infections.\textsuperscript{1} They are not recommended for other genotypes or monotherapy, and should be given every eight hours to decrease the risk of developing resistance.\textsuperscript{17} Multiple drug interactions, such as lurasidone, fentanyl, and quetiapine, are seen with both of these agents due to their strong inhibition of CYP3A4 and P-glycoprotein transporters.\textsuperscript{13,15} Boceprevir and telaprevir have different dosing schedules described in Table 3.

Table 3: Protease Inhibitors in HCV Therapy
Comparison of Protease Inhibitors in HCV Therapy

<table>
<thead>
<tr>
<th></th>
<th>Boceprevir</th>
<th>Telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>800mg Q8h with snack</td>
<td>750mg Q8h with 20g of fat</td>
</tr>
<tr>
<td><strong>Initiation in treatment</strong></td>
<td>Requires a 4 week lead in with PEG and ribavirin. Start Boceprevir on week 5 of treatment</td>
<td>Started with PEG and ribavirin on day 1 of treatment</td>
</tr>
<tr>
<td><strong>Duration of use</strong></td>
<td>(Variable) 20-48 weeks depending on previous treatment history and virologic response at week 8.</td>
<td>Usually 12 weeks total, but duration can vary from 24-48 weeks depending on virologic response and liver status</td>
</tr>
</tbody>
</table>

Boceprevir SVR rates are 66% in treatment naïve patients and ranged from 52% to 75% in treatment experienced patients. Telaprevir SVR rates were higher in treatment naïve patients with a SVR rate of 75%-79%. The range was much broader for treatment experienced patients fluctuating from 33% to 88%. Boceprevir and telaprevir's side effect profile of rash (17-56%), fatigue (55-58%), irritability (22%), anemia (36-50%), and nausea (39-46%) increased intolerability of the peg-interferon and ribavirin therapy. Boceprevir and telaprevir's tolerability and effectiveness were evaluated in a large integrated care setting in 2014. This study found that side effect-related discontinuation was common (31%) and SVR rates were lower compared to earlier clinical trials displaying SVR rates of 53% for boceprevir and 56% for telaprevir. Overall, the SVR rates increased with the addition of these protease inhibitors, but the additive drug interactions and adverse effects proved to be an obstacle to successful patient completion of therapy.

Olysio® (simeprevir) is the third oral protease inhibitor to be approved for use in combination with peg-interferon and ribavirin in HCV- genotype 1 patients. Pruritus, photosensitivity, nausea, myalgia, rash, and dyspnea are common adverse effects of simeprevir. Simeprevir has numerous drug interactions due to its involvement with cytochrome P450 system and P-glycoprotein and OAT1B1/3 transporters. Patients with the NS3 QQ80K polymorphism with genotype 1a has substantially reduced efficacy of simeprevir, and it should not be used in this patient population. Testing for this mutation should be completed at baseline prior to initiating treatment in all patients with genotype 1a who plan to initiate simeprevir. The recommended dosage of simeprevir is 150mg taken orally once daily with food in combination with peg-interferon alpha and ribavirin. Simeprevir’s efficacy was evaluated in three phase 3 trials (QUEST 1, QUEST 2, and PROMISE trials), and patients had significantly higher SVR rates in all the trials. All three clinical trials resulted in 80% SVR rates among treatment naïve and experienced patients. Mild to moderate transient elevations in indirect bilirubin occurred in 49% of patients, but were not associated with hepatotoxicity. Twelve weeks of simeprevir alone costs approximately $66,000, and it's dosing regimen is outlined in Table 4.

Table 4: Simeprevir Dosing Regimen

<table>
<thead>
<tr>
<th>Patients with or without cirrhosis</th>
<th>FDA Approved Regimens</th>
<th>Total Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naïve OR Prior relapse to PEG/rib</td>
<td>Simeprevir plus PEG/rib for 12 weeks, then PEG/rib for an additional 12 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Prior Partial Responder Or Prior Null Responder to PEG/rib</td>
<td>Simeprevir plus PEG/rib for 12 weeks, then PEG/rib for an additional 36 weeks</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Treatment Futility</td>
<td>HCV RNA should be monitored at weeks 4, 12, and 24. If HCV RNA ≥ 25IU/mL at any of these time points, discontinue all treatment</td>
<td></td>
</tr>
</tbody>
</table>

PEG=pegylated interferon; rib=ribavirin
Solvaldi® (sofosbuvir) is a uridine nucleotide analog prodrug that inhibits the HCV NS5B RNA-dependent RNA polymerase in HCV genotypes 1 through 6. Some of the common adverse effects that have occurred with sofosbuvir containing regimens include fatigue, headache, and anemia. These side effects are generally associated with the use of peg-interferon and ribavirin within the regimen. Sofosbuvir is a P-glycoprotein (P-gp) substrate, and should not be administered with P-gp inducers such as rifampin. For patients with HCV genotype 1 or 4 infection, sofosbuvir 400mg daily with or without food should be given with peg-interferon and ribavirin for 12 weeks. If interferon cannot be used then sofosbuvir should be given with ribavirin for 12 weeks in HCV genotype 2 patients and 24 weeks in those with HCV genotype 3 infection. A 12 week supply of sofosbuvir costs approximately $84,000, which is more expensive than previous antiviral therapies. Sofosbuvir’s SVR rates are 90% in HCV genotype 1 patients, 93% to 97% in genotype 2 treatment naïve patients, and 86% to 94% in genotype 2 treatment experienced patients. The SVR rates were lower in HCV genotype 3 patients at 84% in treatment naïve and experienced patients. Sofosbuvir is associated with higher SVR rates, shorter treatment durations, and less adverse events than previous HCV treatment; however, the cost of using this agent can be an obstacle.

Interferon-Free Regimens

Treatment for HCV is rapidly evolving. Use of older, interferon-based regimens (interferon, boceprevir and telaprevir) is declining due to lower SVR rates and increased adverse effects in comparison to newer options. Interferon-free regimens consisting of oral combination products are now becoming the mainstream approach to HCV. The newest FDA-approved oral products are Harvoni® (ledipasvir/sofosbuvir) and Viekira Pak® (ombitasvir/paritaprevir/ritonavir and dasabuvir). These products are both fixed-dose combinations approved for the treatment of chronic HCV genotype 1 infection.

Harvoni® and Viekira Pak® have similar efficacies, with SVR rates greater than 90% in pivotal clinical trials; however, some key differences may need to be considered when determining the best individualized therapy. Harvoni® is more expensive than Viekira Pak® costing around $94,500 versus $84,000, respectively, for 12 weeks of therapy. Although less expensive, Viekira Pak® therapy requires a heavier pill burden and is associated with more drug interactions and adverse effects than Harvoni®. In addition, Viekira Pak® patients may require the addition of ribavirin which is contraindicated in pregnancy.

Current guidelines recommend Harvoni®, Viekira Pak® with or without ribavirin, and sofosbuvir plus simepravir with or without ribavirin as first-line options for HCV genotype 1 infection. These options have similar efficacies and the level of evidence is higher for the Harvoni® and Viekira Pak® regimens versus sofosbuvir plus simepravir regimens. In addition, sofosbuvir plus simepravir combination therapy is more expensive than the newer options costing around $150,000 for 12 weeks.

Harvoni® (ledipasvir/sofosbuvir) was FDA-approved in October 2014 as a fixed-dose combination for the treatment of chronic HCV genotype 1 infection. Ledipasvir is a new drug while sofosbuvir was previously approved as single-agent Sovaldi®. Both agents directly target components essential for viral replication. After hepatic metabolism, sofosbuvir’s active metabolite inhibits HCV NS5B RNA-dependent RNA polymeras. Ledipasvir inhibits the HCV NS5A protein. Harvoni® has been shown to produce SVR rates greater than 90% in clinical trials. The most common adverse effects reported with Harvoni® are headache, fatigue, nausea, diarrhea and insomnia. It is classified as pregnancy Category B.

Ledipasvir’s absorption is pH-dependent and may require separation of pH-altering drugs. It is recommended to separate antacid and Harvoni® administration by 4 hours. H2-receptor antagonists and Harvoni® may be taken simultaneously or 12 hours apart at doses comparable to famotidine 40 mg twice daily or lower. Under fasting conditions, proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with Harvoni®.

Both ledipasvir and sofosbuvir are P-glyco-protein (P-gp) substrates and ledipasvir is also a P-gp inhibitor resulting in various P-gp drug interactions. Coadministration of Harvoni® and P-gp inducers (including St. John’s wort or rifampin) may decrease Harvoni® serum concentrations and is not recommended. Harvoni® may also
increase the serum concentrations of rosuvastatin (which may increase rhabdomyolysis and myopathy risk), tenofovir, and digoxin.

One Harvoni® tablet (ledipasvir 90mg and sofosbuvir 400mg) should be taken orally once daily with or without food for 8, 12, or 24 weeks. Recommended treatment durations are found below in Table 5 (adapted from Harvoni® package insert).

Table 5: Harvoni® Treatment Duration

<table>
<thead>
<tr>
<th>Treatment-naïve Patients</th>
<th>Treatment-experienced Patients (failed treatment with either PEG/rib or HCV protease inhibitor + PEG/rib)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With or Without Cirrhosis</td>
<td>Without Cirrhosis</td>
</tr>
<tr>
<td>12 weeks*</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

PEG=pegylated interferon; rib= ribavirin; HCV= hepatitis C virus

*Harvoni® therapy for 8 weeks may be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL

Viekira Pak® (ombitasvir/paritaprevir/ritonavir combination tablets co-packaged with dasabuvir tablets) was FDA-approved in December 2014 for the treatment of chronic HCV genotype 1 infection. As previously mentioned, Viekira Pak® can be administered with or without ribavirin. Ombitasvir, paritaprevir and dasabuvir each directly inhibit different HCV proteins essential for viral replication. Ombitasvir inhibits HCV NS5A protein and paritaprevir is a HCV NS3/4A protease inhibitor, while dasabuvir (like sofosbuvir) is an HCV non-nucleoside NS5B palm polymerase inhibitor. Ritonavir, a CYP3A4 inhibitor, has been included to increase paritaprevir exposure.

The most common adverse effects (greater than or equal to 5%) with Viekira Pak® therapy are pruritus, nausea and insomnia. For patients also taking ribavirin, these adverse effects may be increased (greater than 10%) and skin reactions, fatigue and generalized weakness may also occur. ALTs should be monitored for the first 4 weeks of treatment due to increases in serum alanine aminotransferase (ALT) levels greater than 5 times the upper limit of normal in approximately 1% of patients during clinical trials. Use is contraindicated in patients with severe hepatic impairment.

Viekira Pak® is classified as pregnancy Category B but ribavirin is contraindicated (Category X) in women who are or may become pregnant and in males whose female partners are pregnant or may become pregnant due to the risk of birth defects. Paritaprevir and ritonavir are CYP3A4 substrates and dasabuvir is a CYP2C8 substrate; therefore, use of Viekira Pak® is contraindicated with strong CYP2C8 inhibitors and CYP3A inducers or with strong CYP2C8 inhibitors. Some of these medications include lovastatin, simvastatin, midazolam, ergot alkaloids and ethinyl estradiol-containing products. In addition, use of inhaled fluticasone or salmeterol (both CYP3A4 substrates) and rosuvastatin (doses greater than 10mg daily) is not recommended.

Coadministration of Viekira Pak® is also not recommended with voriconazole, rilpivirine, or ritonavir-boosted darunavir or lopinavir. Atazanavir may be used if taken in the morning. Ethinyl-estradiol containing drugs (e.g. contraceptives) should not be used with Viekira Pak® and for 2 weeks after finishing therapy due to risk of liver damage and coadministration is contraindicated. Coadministration of Viekira Pak® with efavirenz is also contraindicated due to high risk of liver enzyme elevation.

The recommended dosage is 2 combination tablets (ombitasvir 12.5mg/ paritaprevir 75mg/ ritonavir 50mg) each morning and 1 dasabuvir 250mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content. Recommended treatment and duration are dependent on HSV genotype 1 subtype and presence or absence of cirrhosis. The labeled treatment options are found in Table 6 below (adapted from Viekira Pak® package insert).
Table 6: Viekira Pak® Treatment Options

<table>
<thead>
<tr>
<th></th>
<th>HCV Genotype 1a Patients</th>
<th>HCV Genotype 1b Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without Cirrhosis</td>
<td>With Cirrhosis</td>
</tr>
<tr>
<td>Viekira Pak® +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Viekira Pak® administered with ribavirin for 12 weeks may be considered in this population except for patients who were prior null responders to PEG/rib as clinical trial data has shown that 12 weeks of therapy was highly effective.

Patients with cirrhosis or genotype 1a infection should receive ribavirin 1000mg/day or 1200mg/day (if weighing greater than 75kg).\(^28\) Patients with HCV/HIV-1 co-infection should receive dosage recommendations in the table above. The recommended duration of therapy is 24 weeks for liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score of 2 or lower). Therapy with Viekira Pak® is not recommended for patients with a history of treatment failure with telaprevir, boceprevir, or simeprevir (HCV protease inhibitors).

**Potential Future Therapies**

Merck is conducting clinical trials of another combination (MK-5172 and MK-8742) to evaluate its effectiveness in HCV infection.\(^29\) A three drug combination of daclatasvir with asunaprevir and BMS-791325 is also being studied, as well as a two-drug combination of daclatasvir plus sofosbuvir.

**Conclusion**

Chronic HCV is the most common blood-borne pathogen in the US with nearly 150,000 new cases annually in the US and Western Europe. HCV infection is the most common indication for liver transplant. The goal of treatment in HCV-infected persons is to reduce all-cause mortality and liver-related adverse consequences by achieving virologic cure which is determined by SVR rates measured 12 weeks after end of therapy. Interferon-containing regimens were once the main standard of care. Today, HCV infection treatment is rapidly evolving as interferon-free regimens consisting of oral combination products are becoming the mainstream approach. Despite improved SVR rates with interferon-free regimens, cost of therapy may still be a barrier as prices range from $84,000 to $94,500 for 12 weeks of therapy. Fast-paced improvements in HCV therapy are likely to continue as future therapies show promising results in clinical trials.

**References:**


