Hepatitis C Virus Infection

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Table of Contents

Introduction ........................................... 3
Virology ............................................... 3
Natural History ...................................... 3
Transmission ......................................... 4
Laboratory Testing ................................. 5
Clinical Manifestations ......................... 7
Treatment ............................................ 8
References .......................................... 11

Cover Illustration by Kathryn K. Johnson
Hepatitis C Virus (HCV) is a major cause of liver disease, cirrhosis, and hepatocellular carcinoma (HCC) in many countries around the globe. HCV was discovered in 1989 and was found to be the cause of most cases of non-A, non-B hepatitis. The half-life of HCV is believed to be about 3 hours, and it is estimated that up to $10^{12}$ virions are produced daily in an infected individual. This is roughly 100-fold greater than the rate reported for HIV. It has been estimated that 50% to 85% of patients infected with HCV go on to develop chronic infection. The Centers for Disease Control and Prevention (CDC) estimates that 4.1 million (1.6%) Americans have been infected with HCV, of whom 3.2 million are chronically infected. The high rate of error in the RNA-dependant RNA replication has resulted in tremendous genetic diversity, complicating vaccine development. Over the last decade, significant advances have been made in the treatment of chronic HCV. Patients with HCV now have a greater than 40% probability of viral eradication with therapy. Currently, there are several new agents in development that will likely improve treatment outcomes. In this article, we will review HCV virology, natural history, transmission, clinical manifestations, diagnostic testing, and management.

**INTRODUCTION**

Hepatitis C virus (HCV) is a highly mutating single-stranded RNA virus belonging to the family Flaviviridae. The HCV genome is comprised of approximately 9600 nucleotides. Upon infection, the viral RNA enters the cell. The viral gene expression occurs outside the nucleus and encodes a polyprotein. This polyprotein is cleaved into separate protein components by cellular and viral proteases. The viral RNA genome is replicated by an RNA-dependant RNA polymerase, which is highly error prone. This replication process along with the high rate of virion turnover results in a rapid accumulation of mutations in the viral genome. Hence, multiple HCV variants or “quasispecies” exist in each infected host. The host is unable to produce an adequate response to each mutant, and this results in the development of chronic disease in up to 85% of infected individuals. In addition to this heterogeneity in individuals, variations in the HCV genome fall into a series of specific patterns that have been classified into genotypes. Studies indicate that there are up to 6 major genotypes, several of which are further differentiated into subtypes. Depending on the genomic region involved, HCV sequences in different genotypes may have a less than 60% nucleotide sequence identity. Within each genotype, stains are further subclassified into subtypes that have 75% to 85% nucleotide sequence identity. Genotypes tend to favor a geographical distribution, with genotype 1 accounting for 70% to 75% of all HCV infections in the United States. In contrast, genotype 4 infections are prevalent in Africa and the Middle East (Table 1). HCV genotype has been clearly linked to interferon treatment response, with genotype 1 associated with the poorest response to therapy and genotypes 2 and 3 associated with the best response to treatment.

With currently available therapeutic options, many viral infections such as chronic hepatitis B and HIV are impossible to eradicate: the hepatitis B virus integrates its DNA into host genome and the HIV virus establishes latency in memory CD4 cells. HCV lacks the ability to integrate its genetic material into chromosomal DNA and with its inherently unstable RNA genome, lacks the mechanism of virologic latency. Unlike these other chronic viral infections, HCV can be eradicated from patients if prolonged suppression of viral replication can be achieved.

**VIROLOGY**

HCV is the most common chronic RNA virus affecting humans. It is a highly mutating single-stranded RNA virus belonging to the family Flaviviridae. The HCV genome is comprised of approximately 9600 nucleotides. Upon infection, the viral RNA enters the cell. The viral gene expression occurs outside the nucleus and encodes a polyprotein. This polyprotein is cleaved into separate protein components by cellular and viral proteases. The viral RNA genome is replicated by an RNA-dependant RNA polymerase, which is highly error prone. This replication process along with the high rate of virion turnover results in a rapid accumulation of mutations in the viral genome. Hence, multiple HCV variants or “quasispecies” exist in each infected host. The host is unable to produce an adequate response to each mutant, and this results in the development of chronic disease in up to 85% of infected individuals. In addition to this heterogeneity in individuals, variations in the HCV genome fall into a series of specific patterns that have been classified into genotypes. Studies indicate that there are up to 6 major genotypes, several of which are further differentiated into subtypes. Depending on the genomic region involved, HCV sequences in different genotypes may have a less than 60% nucleotide sequence identity. Within each genotype, stains are further subclassified into subtypes that have 75% to 85% nucleotide sequence identity. Genotypes tend to favor a geographical distribution, with genotype 1 accounting for 70% to 75% of all HCV infections in the United States. In contrast, genotype 4 infections are prevalent in Africa and the Middle East (Table 1). HCV genotype has been clearly linked to interferon treatment response, with genotype 1 associated with the poorest response to therapy and genotypes 2 and 3 associated with the best response to treatment.

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**NATURAL HISTORY**

Human and animal models of HCV infection have demonstrated that HCV RNA can be detected in plasma within days of exposure. Viremia usually peaks at 8 to 12 weeks and then drops to lower levels. In approximately 15% of patients, plasma HCV RNA becomes undetectable within a few months and remains undetectable indefinitely. Viremia becomes persistent in up to 85% of patients. The chance of early resolution appears
to be age- and gender-dependant, with younger females most likely to eradicate infection. HCV-specific antibodies are detectable in blood as early as 8 weeks following exposure. These antibodies do not play a major role in recovery from HCV infection and remain positive even in patients who spontaneously clear virus.

HCV infection causes inflammation of hepatocytes. The major pathologic consequence of HCV infection is the development of hepatic fibrosis. Approximately 10% to 20% of patients with HCV infection will progress to cirrhosis, usually over a period of 20 years. Patients with HCV-related cirrhosis are at increased risk of developing end-stage liver disease (30% over 10 years). Patients with decompensated cirrhosis (ascites, jaundice, variceal bleeding, and encephalopathy) have a high rate of mortality without a liver transplantation. In the United States, HCV-induced liver failure is the leading cause for liver transplantation.

In comparison with the normal population, cirrhotic patients are at increased risk of developing HCC. It has been estimated that up to 3% of individuals with cirrhosis develop HCC each year. Twenty-five percent of patients with cirrhosis can be expected to develop HCC or liver failure in the course of their disease.

**TRANSMISSION**

HCV is the most common blood-borne pathogen in the United States. At the time of its discovery in 1989, HCV was suspected to be primarily a disease transmitted through unscreened blood transfusions. As further research has unearthed the natural history of HCV, novel modes of transmission have been reported as well. In some HCV-positive patients, no risk factor can be identified, and an estimated 30% are asymptomatic and unaware of their positive status.3

**TRADITIONAL RISK FACTORS**

Intravenous drug use is the foremost risk factor for transmission of HCV, accounting for almost 70% of all HCV-positive individuals.5 Needles, syringes, and paraphernalia can be contaminated by improper sterilization techniques as well as through sharing infected tools. There is a direct correlation between duration of intravenous drug use and positive HCV status.6 It has been estimated that a large percentage of individuals test positive within 6 to 12 months of initiation of drug use.

Prior to 1992, the risk of contracting a blood-borne disease through a blood transfusion was 10%. Since the advent of improved screening techniques, the CDC reports that the risk of contracting HCV from 1 unit of blood is approximately 1 in 2,000,000.7 Hemophiliacs were significantly affected by this mode of transmission. This group remained at high risk for acquisition of HCV until discovery of novel techniques to inactivate the viruses found in pooled blood products such as plasma and clotting factors. Transmission through high-risk sexual behavior may account for 10% to 15% of HCV infections. However, heterosexual monogamous sexual practices are associated with a low risk of transmission (0.4%–0.6% per year).8 Transmission of HCV through a single occupational needle stick (large-bore) injury is very low (1.8%), even in areas of high worldwide prevalence.9 Occupational mucous membranes exposure to contaminated blood has rarely been associated with contracting HCV. No cases have been reported to date of transmission due to exposure of intact skin to blood.10

**NOVEL RISK FACTORS**

Patients with end-stage renal disease on dialysis are at high risk for HCV infection. It is suspected that specific factors such as duration of dialysis, mode (hemodialysis versus peritoneal dialysis) and the prevalence within the particular dialysis unit are associated with HCV transmission.10 Due to the inability to determine when the patient was infected and the duration of positivity, the natural course of HCV in dialysis patients is uncertain. In addition, diagnosis is far from simplistic, with laboratory evaluations being unreliable due to the impaired immune response in end-stage renal dialysis patients resulting in false-negative tests.

Body art and tattoos are not considered to be traditional risk factors for HCV transmission. Over the last 20 years, less than 1% of all new cases have been associated with tattoos.5 This prevalence does not hold true in incarcerated individuals who use contaminated syringes or needles for tattooing.

In 1996, Esteban et al6 reported on transmission of HCV by a cardiac surgeon to 5 patients during surgery. The Society for Healthcare Epidemiology of America (SHEA) recommends that HCV-infected providers

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**Table 1. Geographic Genotype Distribution of Hepatitis C Virus**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Geographic Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70%–75% of U.S. infections</td>
</tr>
<tr>
<td>2</td>
<td>Worldwide</td>
</tr>
<tr>
<td>3</td>
<td>Worldwide</td>
</tr>
<tr>
<td>4</td>
<td>Africa and Middle East</td>
</tr>
<tr>
<td>5</td>
<td>South Africa</td>
</tr>
<tr>
<td>6</td>
<td>Asia and Australia</td>
</tr>
</tbody>
</table>
double glove for procedures. SHEA does not, however, recommend that these providers be excluded from any aspect of patient care unless clear epidemiologic proof of transmission of HCV to patients has been documented. Recently, incidental HCV transmission via previously unreported routes has been identified in literature: sclerotherapy, sharing of glucose meters, stress testing, acupuncture, and swapping of pierced body jewelry. Further research would be required to confirm the validity of these associations.

**VERTICAL TRANSMISSION/MOTHER-TO-CHILD TRANSMISSION**

Mother-to-child transmission is one of the main routes of HCV infection in children, with an estimated prevalence of 5%. Transmission is suspected to occur in utero and is not thought to be linked to breastfeeding, genotype, or method of delivery (vaginal versus cesarean section). Higher rates of mother-to-child transmission are seen in children born to mothers with HIV and HCV coinfection. Pregnant women with HCV should receive extensive counseling. It has been hypothesized that a high viral load during pregnancy, prolonged ruptured membranes intrapartum, or cracked bleeding nipples during breastfeeding can lead to higher rates of transmission. Serologic testing of infants should not be done prior to age 12 months to minimize the possibility of a false-positive test due to circulating maternal antibodies.

**LABORATORY TESTING**

All individuals with risk factors for HCV infection should be screened. The National Institutes of Health consensus panel and CDC both recommend screening in high-risk populations such as intravenous drug users, hemodialysis patients, and blood or organ transplant recipients. Various groups differ in their recommendations for screening (Table 2).

**LIVER FUNCTION TESTS**

Although liver enzyme testing is not diagnostic, in the acute setting, the alanine aminotransferase (ALT) level can be up to 15 times higher than the normal value. However, 8% to 33% of HCV-infected patients will have persistently normal ALT values, while some HCV-infected patients have fluctuating ALT levels at different points of testing. In 14% to 22% of cases with persistently normal ALT, the biopsy reveals moderate to severe fibrosis. Thus, liver enzyme test results are not reliable serologic markers of liver disease and cannot predict histologic severity.

**ANTIBODIES TO HCV**

HCV antibody testing is the initial screening test in patients with HCV risk factors. HCV antibodies (also known as anti-HCV antibodies) appear 8 to 12 weeks following exposure and are detected through enzyme immunoassay or enzyme-linked immunosorbent assay. Most patients remain HCV antibody–positive indefinitely. All patients with a positive HCV antibody test should undergo serum HCV RNA testing to determine if they have chronic HCV infection. Patients with HIV and dialysis-dependent end-stage renal disease can have false-negative antibody testing in 5% to 10% of cases. If clinical suspicion for HCV is high in these patients, further testing with HCV RNA is indicated.

**HCV RNA ASSAYS**

All patients who test positive for HCV antibodies should undergo HCV RNA testing. HCV RNA can be detected in blood by reverse-transcription polymerase chain reaction (RT-PCR), transcription-mediated amplification (TMA), and branched DNA techniques.
HCV RNA tests are commercially available as qualitative and quantitative assays. Results of qualitative assays are reported as positive or negative for the presence of virus and are not reported as a numerical value. Qualitative assays by and large detect lower copy numbers. The TMA-based qualitative assay Versant (Bayer Diagnostics, Tarrytown, NY) has a lower limit of detection of 10 IU/mL. However, TMA-based tests are fairly expensive and not available in all commercial labs.

Quantitative assays, which report actual virus load, are used pre-treatment to predict likelihood of response to therapy and during treatment to assess response. The FDA recently approved a newer HCV quantitative assay that uses real-time RT-PCR and has an extremely low level of detection of viremia.

A single negative HCV RNA test does not rule out chronic infection, as HCV viral loads may fluctuate. Patients with a positive HCV antibody test and a negative HCV RNA test should have repeat HCV RNA test in 3 to 6 months to rule in or rule out the presence of chronic HCV infection.

**HCV RIBA**

The recombinant immunoblot assay (RIBA) is generally used as a supplemental test. With the availability of HCV RNA testing, RIBA is no longer used as the sole confirmatory test. However, in patients with a positive HCV antibody test, a negative HCV RNA test, and low pretest probability for HCV infection, RIBA may be used to distinguish between previous infection and a false-positive HCV antibody test.

**GENOTYPING**

There are 6 major HCV genotypes. Pretreatment genotyping is an essential step to determine the type and duration of therapy (see Treatment on page 8).

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### Table 3. Metavir Staging System

<table>
<thead>
<tr>
<th>Fibrosis (Stage)</th>
<th>Necroinflammation (Grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Periportal fibrosis without septae</td>
</tr>
<tr>
<td>2</td>
<td>Portal fibrosis with portal-portal septae</td>
</tr>
<tr>
<td>3</td>
<td>Portal-central septae without cirrhosis</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>


### Table 4. Ishak Grading System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Fibrous expansion of some portal areas, with or without short fibrous septae</td>
</tr>
<tr>
<td>2</td>
<td>Fibrous expansion of most portal areas with or without short fibrous septae</td>
</tr>
<tr>
<td>3</td>
<td>Fibrous expansion of most portal areas with occasional portal-portal bridging</td>
</tr>
<tr>
<td>4</td>
<td>Fibrous expansion of portal areas with marked bridging (portal-portal or portal-central)</td>
</tr>
<tr>
<td>5</td>
<td>Marked bridging (portal-portal or portal-central) with occasional nodules (incomplete cirrhosis)</td>
</tr>
<tr>
<td>6</td>
<td>Cirrhosis</td>
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</table>


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**EVALUATION OF FIBROSIS**

**Liver Biopsy**

Liver biopsy is the gold standard for definitive staging of fibrosis and grading of inflammation. If no contraindications exist, a liver biopsy may be performed to evaluate the degree of fibrosis. Unfortunately, results can be misleading due to sampling error or inadequate sample size. Complications with this procedure are very uncommon, especially in the era of ultrasound-guided biopsy, but include pain at the biopsy site, bleeding, infection, pneumothorax, and rarely, death. Mortality rates for liver biopsy are approximately 1 in 10,000. Several scoring systems for defining the degree of inflammation (grading) and fibrosis (staging) have been described in the literature. Two of the more popular systems are the Metavir staging system (Table 3) and the Ishak grading system (Table 4). Some physicians who treat patients with HCV will opt not to perform liver biopsies on patients with genotype 2 and 3 and instead choose to proceed with treatment, as these patients have an excellent response to therapy.

**Noninvasive Markers of Fibrosis**

Given the risks and discomfort associated with liver biopsy, there has been considerable interest in the development of noninvasive modalities to evaluate fibrosis. A variety of surrogate serum markers have been evaluated for their ability to predict the degree of liver fibrosis. Markers that have been evaluated include α2-macroglobulin, haptoglobin, γ-glutamyltransferase (GGT), total bilirubin, apolipoprotein A1, matrix metalloproteases, type IV collagen, and serum hyaluronate, among others. The inability of single markers to
accurately predict fibrosis has lead to development of algorithms involving several different markers to increase prediction accuracy. Several different algorithms have been proposed and many of them have been patented. A major limitation of these algorithms is their inability to distinguish between various stages of liver fibrosis, although they are fairly accurate in identifying patients with advanced fibrosis.

Ultrasound Elastography

Ultrasound elastography is a novel, rapid, and non-invasive technique that measures liver rigidity. A shear wave is propagated through the liver tissue and its velocity is measured to predict the extent of fibrosis. In the future, fibrosis may be evaluated through a combination of noninvasive testing such as with biomarkers and ultrasound elastography. Early studies have shown that if results of these 2 modalities are congruent, accuracy is similar to liver biopsy.20

### CLINICAL MANIFESTATIONS

#### ACUTE HCV INFECTION

The number of new cases of acute HCV infection diagnosed annually has declined from 240,000 in the late 1980s to 26,000 in 2004. The World Health Organization estimates that following exposure, the incubation period for HCV is between 15 and 150 days. Approximately 60% to 70% of patients with acute HCV remain asymptomatic, but 10% to 30% have nonspecific symptoms. Early symptoms include fatigue, malaise, joint pain, right-sided abdominal pain, low-grade fever, anorexia, and diarrhea. Rarely, patients with acute HCV infection progress to fulminant hepatic failure. As the acute phase progresses, patients can experience jaundice (10%–20%), pale or clay-colored stools, and pruritus. A small proportion of infected patients (15%–20%) spontaneously clear the virus, and up to 85% of individuals become chronically infected. The presence of jaundice during acute infection has been associated with a favorable outcome. Additional factors that favor spontaneous resolution include female gender, age younger than 40 years, and an absence of underlying chronic immunosuppressive illness.21

#### CHRONIC HCV INFECTION

Chronic HCV infection is by and large “silent” or asymptomatic. Most patients are identified incidentally during routine screening or prior to blood donation. Chronic HCV evolves over a period of 15 to 20 years before progression to cirrhosis in 10% to 15% of patients. Some patients with HCV have symptoms such as fatigue, nausea, myalgia, arthralgia, and right upper quadrant discomfort, but a majority of patients lack any clinical features and do not come to clinical attention until they develop cirrhosis or hepatic decompensation.

#### CHRONIC ADVANCED HCV INFECTION

Once cirrhosis has developed, approximately 6% of patients per year develop decompensated liver disease. Complications of advanced liver disease include ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatoportal syndrome, variceal bleeding, and HCC. For further details regarding clinical manifestations of advanced liver disease, see Table 5.

#### EXTRAHEPATIC MANIFESTATIONS OF HCV

HCV infection is a systemic illness and can present with various extrahepatic manifestations. In some series, up to 38% of patients with HCV have been found to have at least 1 extrahepatic manifestation. Extrahepatic hematologic manifestations include mixed cryoglobulinemia, porphyria cutanea tarda (PCT), monoclonal gammopathies, and lymphoma. Lymphomas, predominantly B-cell, have been linked

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**Table 5. Selected Clinical Manifestations of Cirrhosis/Advanced Hepatitis C Virus**

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<td>Portal hypertension Portal hypertension</td>
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<td>Hematologic</td>
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<td>Asterixis Mental status changes</td>
<td>Cerebral edema enchephalopathy</td>
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with HCV. In a study by Hermine et al., in all 9 cases studied there was complete regression of splenic lymphoma after successful treatment of HCV.

Virtually all patients with type 2 mixed cryoglobulinemia have HCV as the underlying cause. Cryoglobulinemia can cause vasculitis, myalgias, and renal insufficiency.

Lichen planus is another dermatologic disorder commonly seen in individuals with HCV. Lichen planus is seen in less than 1% of the general population. In total, HCV infection will be seen in 10% to 30% of patients with lichen planus.

Another commonly recognized extrahepatic manifestation of HCV is PCT, a disease of bilirubin metabolism. PCT is a skin disease characterized by photosensitivity, skin fragility, bruising, and bullae that can occasionally become hemorrhagic. Individuals who develop the skin manifestations of PCT usually have an underlying liver disease. Given the strong association between sporadic PCT and HCV, all individuals with PCT should be screened for HCV. Membranoproliferative glomerulonephritis is the renal disorder most commonly associated with HCV. Although less frequent, membranous nephropathy has also been seen in HCV patients.

Urticarial vasculitis is another dermatologic disorder that may be seen with HCV infection. Ophthalmologic manifestations include Mooren’s corneal ulcer. Several studies have also found a link between HCV infection and endocrine disorders such as diabetes. Insulin resistance, even in the absence of diabetes, has been associated with HCV. Insulin resistance is thought to promote the progression of liver fibrosis in these patients.

### Treatment

The primary goal of HCV therapy is viral eradication. The secondary goal of treatment is to slow disease progression and improve liver histology.

#### General Measures

Following diagnosis of HCV infection, many health measures can be implemented to improve overall patient well-being and slow disease progression:

1. Patients should be counseled regarding prevention of spread of virus to others.
2. Alcohol avoidance counseling is a key step in the treatment of patients with HCV. No safe level of alcohol consumption has been delineated in patients with HCV. Drug and alcohol rehabilitation programs should be offered to patients with active substance abuse issues.
3. Physicians should actively screen for and treat depression at the time of diagnosis and during subsequent follow-up, especially if therapy is considered. Approximately 20% to 40% of patients develop depression on interferon-based regimens. Many patients benefit from participation in support groups.
4. Several over-the-counter medications and herbal supplements can be hepatotoxic, and patients should be encouraged to avoid their use unless discussed with their health care providers. In general, acetaminophen in the dose of 2 g over 24 hours is thought to be safe for these patients. In patients with advanced liver damage, acetaminophen may even be preferred to nonsteroidal anti-inflammatory drugs to avoid renal toxicities and platelet dysfunction.
5. All patients with HCV should be vaccinated against hepatitis A and B unless already immune as demonstrated by serologic testing. Pneumococcal vaccine and annual influenza vaccine should be offered to all patients with chronic liver disease, irrespective of age, especially those with cirrhosis.
6. A healthy diet and exercise program should be encouraged. Obese patients should be advised to lose weight to prevent disease progression and improve response to therapy.
7. Patients with cirrhosis should be screened for the presence of esophageal varices by endoscopy. It is also recommended that these patients be screened for HCC every 6 months with alpha-fetoprotein and liver ultrasound.

#### Chronic HCV Treatment

All patients with chronic HCV (those with detectable serum HCV RNA) should be considered as potential candidates for treatment (Figure). Treatment is more urgent in those with advanced liver fibrosis; however, patients with decompensated liver disease should be treated only in large liver transplant centers, as these patients are at high risk of decompensation during therapy.

The first reports of successful treatment of HCV with interferon emerged in 1989. However, early trials were plagued with limited success and high rates of relapse.
Most of the early trials used biochemical response (normalization of ALT) as a marker of treatment response. The introduction of new assays for the detection of HCV viral RNA has changed our approach to assessing successful response to therapy. The clinical endpoint of treatment is the achievement of a sustained virologic response, which is defined as the absence of detectable viremia for 6 months after the completion of therapy.

Over the years, incremental improvements have been made in therapy for HCV by increasing the duration of treatment and using interferon-alfa in combination with ribavirin. More recently, pegylated formulations of interferon-alfa in combination with ribavirin have now been accepted as the current standard of care.

Interferon-alfa is a cytokine that has an important function in the innate antiviral immune response. It acts by attaching to cell-surface receptors. Through different signaling pathways, it effects the expression of many genes with antiviral and antiproliferative effects.

Ribavirin is an oral nucleoside analogue with broad activity against viral pathogens. Its mechanism of action against HCV remains speculative, especially since it appears to have minimal direct activity against HCV replication. Numerous mechanisms of action have been proposed. It is believed that ribavirin has RNA mutagenic activity, which leads to the reduction of viral fitness. Ribavirin is also thought to have immune modulating properties.

Peginterferon alfa is produced by the addition of a polyethylene glycol molecule to standard interferon alfa and results in substantial changes in the metabolism of the drug. Its half-life is prolonged such that only 1 dose per week is required to maintain effective serum levels.

Several host and viral factors have been associated with response to HCV therapy. The most important predictors of sustained virologic response following combination therapy with pegylated interferon and ribavirin include:

- HCV genotype (higher response in patients with genotype 2 and 3 as compared with genotype 1)
- Viral load (higher response in patients with a viral load < 800,000 IU/mL)
- Histologic stage of disease (higher response with absence of bridging fibrosis and cirrhosis)
- Race (lower response in African Americans)
- Age (higher response with younger age)
- Body weight (higher response with a lower body mass index)

In patients with chronic HCV who are candidates for therapy, the American Association for the Study of Liver Diseases (AASLD) guidelines recommend combination therapy with pegylated interferon alfa and ribavirin. Two formulations of pegylated interferon (alfa-2a and alfa-2b) are available. Both are administered subcutaneously once weekly.

In patients with genotype 1 or 4, combination therapy with weekly pegylated interferon and daily weight-based oral ribavirin (ie, 1000 mg for those ≤ 75 kg and 1200 mg for those > 75 kg) should be administered for 48 weeks. In contrast, the recommendations for patients infected with hepatitis C genotype 2 or 3 include a lower daily dose of ribavirin (800 mg daily irrespective of weight) along with pegylated interferon administered once weekly for a total of 24 weeks.

Hepatitis C viral load should be checked pretreatment and again at weeks 4 and 12. Treatment can be
discontinued in those who do not achieve an early virologic response. This is at least a 2-log decline from baseline of the HCV RNA level at week 12, irrespective of genotype. Patients who do not achieve an early virologic response have been consistently shown to have a very low likelihood of achieving a treatment response. Recent data have emerged on the importance of early viral kinetics in determining response to therapy. Rapid virologic response, defined as undetectable HCV RNA at week 4, has recently been shown to be strongly predictive of achieving a sustained virologic response. This may have important implications in shortening treatment duration in some patients. Studies are ongoing, and no clear recommendations along these lines can be made at this point.

The importance of patient compliance with treatment cannot be overemphasized. It has been demonstrated that patients require to be compliant with 80% of their ribavirin and pegylated interferon dosing for at least 80% of the treatment duration in order to increase their chance of achieving a sustained virologic response.30

The registration trials for pegylated interferon alfa-2a and 2b, demonstrated a sustained virologic response of 42% to 56% in patients with genotype 1 HCV, and a sustained virologic response of 74% to 82% in genotype 2 and 3 HCV depending on the pretreatment viral load.31–33

**CONTRAINDICATIONS TO THERAPY**

Treatment is contraindicated in patients with uncontrolled major depression; untreated hyperthyroidism; renal, heart or lung transplant recipients; pregnant patients or those unwilling to comply with adequate contraception; and patients with active autoimmune disease. Other contraindications include conditions known to be exacerbated by interferon and severe underlying comorbid conditions such as severe hypertension, severe coronary artery disease, severe chronic obstructive pulmonary disease, congestive heart failure, and uncontrolled diabetes.3

**ADVERSE EVENTS OF THERAPY**

Unfortunately, up to 75% of patients treated with pegylated interferon and ribavirin will experience 1 or more treatment-related side effects. The main side effects associated with pegylated interferon alfa include neutropenia, thrombocytopenia, depression, hypo- or hyperthyroidism, concentration and memory impairments, visual disturbances, “flu-like” symptoms (low-grade fevers, muscle aches, headaches, nausea, vomiting), alopecia, tinnitus, and hearing loss.

Ribavirin-associated side effects include hemolytic anemia, fatigue, birth defects, itching, rash, and gout. Because of significant concern for teratogenicity associated with ribavirin, it is crucial to use strict contraceptive methods during treatment. Owing to the long half-life of accumulated drug, the risk of teratogenicity continues for 6 months after completion of treatment.2

**ACUTE HCV THERAPY**

Although the incidence of new HCV infections has declined, new cases of HCV continue to occur among intravenous drug users. Progression from acute to chronic HCV infection occurs in 50% to 85% of cases. As discussed previously, treatment of chronic HCV is not effective in a significant number of patients and is frequently associated with side effects. Due to the high risk of progression to chronic diseases, several studies have evaluated the rationale for early treatment of patients with acute HCV to attempt eradication of the infection. The study by Jaeckel et al34 showed very promising results with sustained virologic response achieved in 98% of treated patients with acute HCV.

Several studies have attempted to evaluate response to therapy in acute HCV. However, due to varying study designs, many questions regarding optimal time for initiation of treatment, use of regular versus pegylated interferons, and addition of ribavirin remain unanswered. It is currently recommended that patients with acute HCV should be treated in the context of clinical trials to help definitively answer these questions. The AASLD recommends delaying treatment for the first 12 weeks to permit spontaneous resolution and avoid unnecessary treatment.3 It is also believed that the use of pegylated interferon is appropriate in these patients given the improved ease of administration. Currently 6 months of therapy is recommended. The use of ribavirin is to be considered on a case-by-case basis.

**HCV NEW DRUG PIPELINE**

Although combination therapy with pegylated interferon and ribavirin remains the current standard of care, a substantial proportion of patients either fail to achieve a sustained virologic response following treatment or have significant side effects, thereby limiting their use.

Efforts at drug development were slowed initially by the inability to culture the virus in vitro. In 1999, Lohman et al34 finally described a stable cellular system, which allowed detailed molecular studies of HCV and assisted in drug development. A better understanding of HCV replication has allowed the design of small molecule agents targeting specific steps in the viral life cycle: cell entry, translation and cleavage of viral proteins, replication of viral RNA, and assembly and release of
new viruses. Each of these stages in the replication cycle is, in theory, susceptible to inhibition by new drugs. Development of new drugs could ostensibly lead to shorter course therapies with lesser drug toxicities and higher rates of sustained virologic response. This has led to the era of the Specifically Targeted Antiviral Therapy for HCV (the STAT-C drugs).

Several new classes of drugs are currently in clinical development. Inhibitors of the HCV NS3-4A serine protease are probably the closest to clinical application. Two protease inhibitors now being studied are VX-950 (Telaprevir; Vertex Pharmaceuticals, Cambridge, MA) now in phase 3 trials and SCH-503034 (Boceprevir; Schering-Plough, Kenilworth, NJ), now in phase 2 trials. Nucleoside and nonnucleoside inhibitors of the nonstructural protein 5B (NS5B) polymerase, an essential enzyme required for viral replication, are currently in phase 1 and 2 clinical trials. Other areas of drug development include alternate forms of interferon and ribavirin, with reduced toxicities and greater ease of administration, caspase inhibitors that inhibit cell apoptosis, and other novel agents that inhibit viral assembly and release. Efforts at HCV vaccine development are also underway.

Anti-HCV therapy is entering a new age. Early results from clinical trials of new drugs are promising. The ultimate goal is to develop therapies that will guarantee a durable response with minimal side effects in all patients.

REFERENCES


