



Late-Breaking Clinical Developments
MANAGED CARE CONSULTANT[®]

Practical Strategies to Minimize the Clinical and Economic Burden of Hepatitis C

A review of the epidemiologic characteristics, prevalence patterns, and natural history of hepatitis C with a focus on the role of viral kinetics in guiding treatment strategies



Jointly sponsored by Medical Education Collaborative (MEC) and Princeton CME

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This activity is designed to educate managed markets physicians and pharmacists on the prevalence and burden of hepatitis C virus (HCV) and evidence-based approaches for HCV management.

PURPOSE STATEMENT

TARGET AUDIENCE

Managed markets physicians and pharmacists, including medical directors, pharmacy directors, formulary directors, and consultant pharmacists.

LEARNING OBJECTIVES

After completing this activity, participants should be able to:

- Describe the prevalence and clinical and economic burden of HCV in the United States
- Explain the frequency and implications of HCV progression to hepatocellular carcinoma (HCC) and end-stage liver disease (ESLD)
- Summarize current data regarding HCV medication dosing, monitoring, and duration
- Apply current data and guidelines to assist clinicians and patients to maximize outcomes in HCV diagnosis and management

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Estimated time to complete: 1 hour

There is no fee associated with this activity.

Dr. Sulkowski: Consultant—Human Genome Sciences, Idenix Pharmaceuticals, Merck, Novartis, Roche, Schering-Plough Corporation, Vertex Pharmaceuticals Incorporated, Wyeth; Research—Human Genome Sciences, Idenix Pharmaceuticals, Merck, Roche, Schering-Plough Corporation, Valeant Pharmaceuticals, Vertex Pharmaceuticals Incorporated, Wyeth

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Practical Strategies to Minimize the Clinical and Economic Burden of Hepatitis C

As an infectious disease caused by the hepatitis C virus (HCV), hepatitis C represents a global health problem associated with a significant clinical and economic burden. The World Health Organization (WHO) estimates that as many as 200 million people are infected worldwide.¹ HCV affects an estimated 4.1 million individuals in the United States and is a major cause of morbidity and mortality.² Overall, the mortality rate in patients with cirrhosis, a common effect of HCV, is approximately 4% annually.³

Viral hepatitis encompasses 5 major types of infection—A through E—each targeting the liver and causing a range of inflammation or damage to this vital organ. Severe injury to the liver is concerning due to its debilitating impact on essential metabolic functions, including digestion and filtering of toxins or waste products from the blood. The natural history of hepatitis C is highly variable; the virus can cause progressive liver damage—or fibrosis—which can lead to cirrhosis, end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), and death. Despite the potential severity, acute hepatitis C infection is asymptomatic in up to 80% of HCV-infected patients, concealing the presence of disease for decades.² Lack of clinical manifestations of HCV often delays diagnosis and treatment, promoting the development of chronic infection, in which the virus evades the immune system and renders it unable to clear the disease. Chronic infection is present in 75% to 85% of acutely-infected individuals and warrants close monitoring of patient health and lifestyle to minimize disease complications.⁴ Furthermore, chronically infected patients are at increased risk for disease progression and devastating consequences of HCV, including ESLD and HCC, which are associated with high mortality rates.^{3,4} Ultimately, approximately 1% to 5% of infected individuals will die of chronic liver disease.²

Clinicians alert to risk factors based on lifestyle, medical conditions, and clinical signs of HCV can diagnose, manage, and potentially cure the condition with appropriate medical therapy. By understanding and following evidence-based clinical guidelines that outline proper med-

ication dosing, duration, and monitoring of viral response, clinicians can maximize patient outcomes via timely and aggressive HCV diagnosis and management.

HCV CLASSIFICATION AND GENOTYPE DISTRIBUTION

HCV is a member of the *Flaviviridae* family of viruses; this family includes other viruses causing common tick- and mosquito-borne diseases, such as West Nile virus and Yellow Fever, which infect both humans and animals. These viruses are able to replicate in cell culture and offer insight into the life cycle of HCV. One of the most important characteristics of HCV is its rapid rate of viral production; a patient infected with HCV produces approximately 10 trillion new viral particles daily.⁵ The high viral turnover rates may account for an increased likelihood that HCV will escape interception by the immune system or antiviral therapy.⁵ Furthermore, ribonucleic acid (RNA)-dependent RNA polymerase, the critical enzyme in HCV replication, is error-prone and leads to frequent mutations; in fact, multiple HCV variants exist within a single infected individual—known collectively as a quasi-species.⁵

The discovery of HCV was first reported in 1989, and the virus is now recognized to exist as 6 major genotypes, which are spread throughout various geographic areas. HCV genotype 4 (found in Egypt), HCV genotype 5 (found in South Africa), and HCV genotype 6 (found in western Pacific countries) are studied less widely than genotypes 1, 2, and 3.^{1,6} According to the National Health and Nutrition Examination Survey (NHANES III), genotype 1 accounts for approximately 75% of HCV infection in the United States, while genotypes 2 and 3 account for the majority of the remaining infections.^{6,7} Each hepatitis C genotype is comprised of different genomic sequences, which appear to modify response to interferon-based treatment. Genotypes 2 and 3 achieve a better response to HCV therapies, while genotype 1 infections are generally more challenging to treat.⁸ Although genotype correlates with viral response rates, it does not predict the extent of liver damage caused by hepatitis infection.⁷

HCV DISEASE PROGRESSION

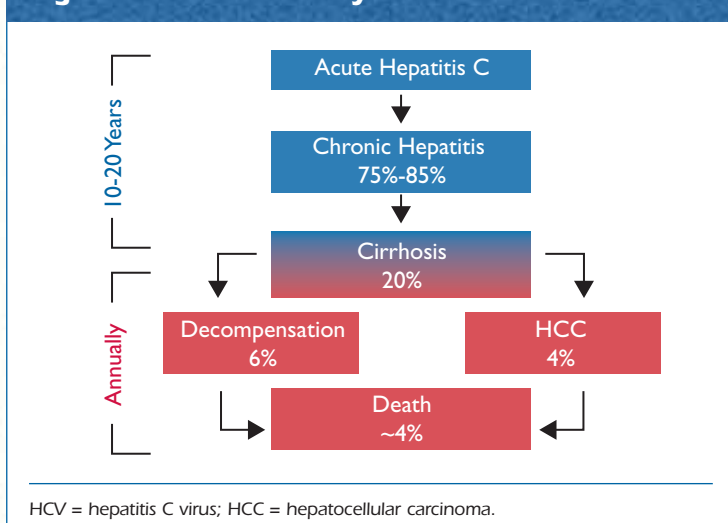
Despite advancing insight into HCV, the natural history of HCV-related liver disease remains poorly understood. Acute infection, the first stage of the disease, typically develops within 6 to 12 months after the virus is acquired.⁹ Although less than 25% of patients are able to achieve spontaneous clearance and control HCV infection, the remaining 75% to 85% of patients with acute infection will become chronically infected.⁴ In the presence of continuing infection, progressive fibrosis—the replacement of liver tissue by fibrotic scar tissue—can lead to cirrhosis in some patients. Over the course of 20 years, 20% of chronically-infected HCV patients will develop cirrhosis despite a lack of clinical signs or symptoms.³ HCV-related cirrhosis fosters further decline in liver function; approximately 6% of patients can be expected to develop hepatic decompensation per year, 4% will develop HCC per year, and 3% to 4% of patients per year can be expected to require liver transplantation or die (Figure 1).^{3,4}

Rates of disease progression vary substantially for individual patients. Poynard et al measured the median fibrosis progression rate in more than 2000 HCV-infected individuals and found that the median expected time to cirrhosis development in untreated patients was approximately 30 years¹⁰; however, one third of patients had a median expected time to cirrhosis of less than 20 years, while another third progressed to cirrhosis in 50 years or more.¹⁰

The most serious progression of HCV-related disease to hepatic decompensation and/or liver cancer can only be treated with liver transplantation.^{6,11} The 3-year survival rate for transplantation patients has been estimated to be as high as 87%; however, transplantation is challenging due to a shortage of available organs and the fact that nearly 100% of the new livers become infected with HCV following transplantation. Patients have been found to have a 10% to 30% incidence of recurrent HCV-related graft cirrhosis at a median of 5 years after surgery and a dramatically increasing viremia level with postimplant immunosuppression.^{6,11}

Average mortality rates associated with HCV disease progression

Figure 1. Natural History of HCV^{3,4}



have been examined in several studies. An analysis of 384 European patients with cirrhosis treated at 7 tertiary referral hospitals revealed that the 5-year risk of decompensation and HCC was 18% and 7%, respectively.¹² Over a 10-year period, about 30% of patients with cirrhosis decompensated and approximately 10% developed cancer.¹² The research further indicates that about 50% of patients with cirrhosis who had ascites or a variceal bleed will die within 5 years of the decompensating event.¹² HCV natural history progression is insidious, and its serious implications underscore the importance of intercepting the disease in its earlier stages.

CLINICAL AND ECONOMIC BURDEN

The estimated incidence of acute hepatitis C in the United States has declined over the past 30 years.¹³ Transfusion of blood or blood products that occurred prior to July 1992 has been identified as a major source of infections, involving approximately 300,000 individuals in the United States.¹⁴ Surrogate testing of blood donors initiated in the 1980s resulted in recognition of high-risk individuals and drove a decline in HCV incidence among blood transfusion recipients, while new methods of blood screening via antibody and nucleic acid testing developed in the early 1990s increased the safety of blood supplies and eliminated the risk of contracting HCV from transfusions.^{13,14} The leading risk factor of HCV infection in the United States is injection drug use; however, a decrease in HCV infection among injection drug users also occurred during the early 1990s, possibly due to saturation of the population or to safer drug injection practices, prompted by the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) epidemic.¹³ Currently, the number of new acute HCV cases in the United States is estimated to be between 30,000 and 60,000 per year.¹³

Although HCV incidence is declining, the burden of prevalent HCV infection is a major concern. An analysis of NHANES survey results estimates that 1.6% of Americans are infected with HCV.¹⁵ Peak prevalence occurs among individuals 40 to 49 years of age at a rate of approximately 4.3%.¹⁵ This analysis may underestimate the infection prevalence, as the survey did not include certain patient populations among whom there is less opportunity to conduct clinical studies, such as incarcerated patients, homeless individuals, veterans, and civilians living below the poverty level.¹⁵⁻²¹ Because most HCV-infected individuals are 30 to 49 years of age, the number of deaths attributable to HCV-related chronic liver disease will likely increase substantially during the next 10 to 20 years as this cohort reaches ages at which complications from chronic liver disease typically occur. HCV prevalence also varies by ethnicity: a NHANES analysis of 21,000 individuals found that hepatitis C was most prevalent among African Americans, with high rates also observed among Hispanic Americans.²²

The clinical and economic burden of HCV-related liver disease in the United States has been traced back to the 1970s and is predicted to continue to grow over the next decade.² A historical analysis of HCV disease progression showed that HCC incidence rates increased from 1.4/100,000 from 1976 to 1980 to 2.4/100,000 from 1991 to 1995, driving a 41% increase in the liver cancer mortality rate and a 46% increase in hospitalization.²³ The incidence of HCV-related liver disease among African-American men was highest at 6.1/100,000, compared with 2.8/100,000 among Caucasians.²³

Estimates for the future clinical and economic burden of this disease are considerable; a computer cohort simulation of the natural history progression of HCV in the US population projected 165,900 deaths from chronic liver disease and 27,200 deaths from HCC between 2010 and 2019.²⁴ An estimated \$10.7 billion in direct medical expenditures will be attributed to HCV care, largely due to costs associated with liver failure and liver transplant. Furthermore, during this period, HCV is predicted to cause 720,700 years of decompensated cirrhosis and HCC as well as the loss of 1.83 million years of life in individuals younger than 65 years of age, at a societal cost of \$21.3 billion and \$54.2 billion, respectively.²⁴ Other studies conducted in France and Australia extrapolate a dramatic increase in HCC-related mortality, and cirrhosis or HCC, respectively, by 2020.^{25,26} Similarly, a model based on prevalence data from NHANES III and incidence data from the Centers for Disease Control and Prevention (CDC) anticipates a 61% increase in the prevalence of cirrhosis, 68% for HCC, and 233% for liver-related death in the United States by 2008.²⁷

HCV RISK FACTORS

Prevention of hepatitis is dependent on the type of virus: type E can be avoided by ensuring safe quality of drinking water, while pre- and postexposure immunizations can prevent hepatitis A and B, as well as hepatitis D by its dependence on hepatitis B for pathogenesis.²⁸ In contrast, there is no vaccine to protect the body from being infected with hepatitis C. To minimize the increasing burden of HCV and HCV-related liver disease, it is important to identify the risk factors associated with disease transmission. The bloodborne infection is most effectively transmitted through exposure to contaminated needles or blood supplies. Since blood transfusions have been eliminated as a source for spreading the disease, the CDC has recently studied the major social practices, lifestyle choices, or circumstances that facilitate HCV transmission.²⁹ Although 44% of acute hepatitis C cases in the United States are of unknown origin, the CDC has found the primary known source of infection—with a 26% incidence—to be injection drug use with contaminated needles and/or drug use paraphernalia that provide direct exposure to blood.²⁹ In a study of HCV incidence in a cohort of 142 injection drug users, researchers reported that the cumulative incidence of hepatitis C infection over 96 months was nearly 30%, substantially higher than that of HIV infection.³⁰ Although sexual contact with an HCV-infected individual confers only a 6% risk of disease transmission, the CDC found that contact with multiple sexual partners is associated with a greater likelihood of HCV seropositivity.²⁹ Other sources of infection included percutaneous injury (eg, needlestick) and surgery.²⁹ Household contact with an infected person, hemodialysis, and employment in the medical and dental fields represent less common risk factors.²⁹

DIAGNOSIS

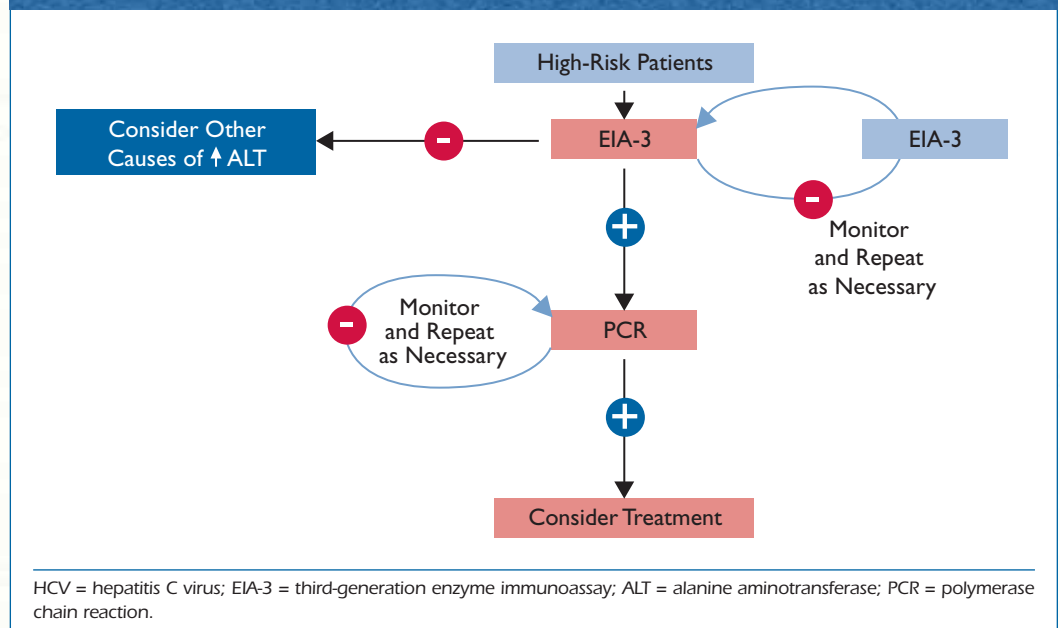
To establish an HCV diagnosis, the third-generation enzyme immunoassay (EIA-3)—a highly sensitive and specific test for hepatitis C—should be performed on individuals at risk and individuals with nonspecific signs of infection (eg, abnormal liver enzyme levels).^{6,31} Individuals who are HCV-EIA positive should undergo additional testing with assays to detect HCV RNA and establish active HCV infection. In high-risk individuals with elevated alanine aminotransferase (ALT) levels or liver disease, positive EIA and RNA test results are sufficient to confirm hepatitis C diagnosis.^{6,31} Because samples may not be positive until approximately 8 weeks postinfection, high-risk patients should be monitored and then retested if test results are initially negative (Figure 2).^{6,31}

In low-risk individuals with normal ALT levels and no other clinical signs of liver disease, a negative EIA rules out HCV infection. However, in individuals with elevated ALT levels, other causes of elevation should be considered, such as drug toxicity, congestive heart failure, or inherited liver disease. If EIA is positive, supplemental recombinant immunoblot assays and/or polymerase chain reaction (PCR) testing should be performed due to the possibility of false-positive results.^{6,31}

EVIDENCE-BASED TREATMENT GUIDELINES

A confirmed hepatitis C diagnosis does not always necessitate pharmacotherapy; clinical judgment must be exercised to determine patients who are at risk for disease progression. Although some HCV-infected individuals have mild disease, other individuals will develop life-threatening HCV infection characterized by cirrhosis, ESLD and/or HCC. Host and viral factors associated with disease progression include older age, longer duration of infection, male gender, iron overload, alcohol intake, and the existence of other conditions or viral infections, such as fatty liver disease, HIV, and hepatitis B.¹⁰ The primary goal of treatment for patients who are appropriate candidates for

Figure 2. Diagnostic Algorithm for HCV^{6,31}



The primary goal of treatment for patients who are appropriate candidates for HCV therapy is to eradicate hepatitis C infection, thereby preventing progression of fibrosis to liver failure and HCC.

HCV therapy is to eradicate hepatitis C infection, thereby preventing progression of fibrosis to liver failure and HCC.

Interferon and ribavirin have historically been used to treat HCV, and enhancements to interferon therapy have yielded cumulatively higher viral response rates.³²⁻³⁴ Interferons are proteins naturally produced by the immune system in response to viral infections to inhibit the spread of foreign agents—such as cancer or infectious diseases—in the body. HCV treatment protocols are based on 2 approved preparations of interferon—interferon α -2a and interferon α -2b—which specifically bind to the interferon- α receptor. In 1990, interferon- α was prescribed as monotherapy 3 times weekly for 24 weeks and led to viral eradication in only about 6% of patients.³² Extending treatment to 48 weeks increased response rates to 16%.³² However, the addition of ribavirin, an antiviral agent, to interferon treatment for 48 weeks more than doubled response rates to 41%.^{33,34} In the early 2000s, the pharmacologic composition of HCV therapeutic agents changed. Interferon- α was modified by the addition of polyethylene glycol (PEG) interferon; the new chemical composition of peginterferon prolonged the half-life of the drug and thereby reduced the dosing frequency to once weekly. By 2002, peginterferon given once weekly, in combination with oral ribavirin, led to a 54% to 61% sustained viral response (SVR).^{8,35,36}

Although monotherapy with peginterferon α -2a, peginterferon α -2b, and interferon alphacon-1—also known as consensus interferon—is available, peginterferon α /ribavirin is currently the standard of care for the treatment of HCV in the United States.⁶ Clinical studies indicate that therapy with peginterferon α -2a and peginterferon α -2b, in combination with ribavirin, yields similar therapeutic results.⁶ According to the 2002 National Institutes of Health (NIH) Consensus Conference Statement on the management of HCV, peginterferon/ribavirin combination therapy is more effective than both standard interferon/ribavirin combination therapy and peginterferon monotherapy.⁶ These guidelines recommend that genotype 1 infection be treated with peginterferon- α once weekly and ribavirin at a weight-based dose of 1000 to 1200 mg/day for 48 weeks.⁶ Genotype 2 and 3 infections should be treated with peginterferon- α once weekly plus ribavirin at a fixed dose of 800 mg for 24 weeks.⁶ Nevertheless, select patient populations respond differently to treatment. Using peginterferon via weekly subcutaneous injection and ribavirin twice-daily by mouth yields varying response rates. Viral eradication rates are 75% to 80% for

genotype 2 or 3, 45% to 52% for genotype 1, 19% to 25% for African Americans with genotype 1 infection, and 18% to 29% for genotype 1 patients with HIV coinfection.^{8,35}

Patterns of Viral Response. The pattern of viral response correlates with efficacy of treatment; HCV RNA levels should be monitored at 4, 12, and 24 weeks of therapy to determine patient response and to establish the likelihood of therapy success or failure.⁶ Several patterns of response to therapy have been identified. A rapid viral response (RVR) is defined as the absence of virus in the blood (HCV RNA <50 IU/mL) after 4 weeks of treatment.⁶ An early viral response (EVR) is defined as achieving a minimum 2 log₁₀ decrease or undetectable viral load during the first 12 weeks of treatment, while nonresponse is defined as failure to achieve undetectable HCV RNA by week 12.⁶ SVR is defined as undetectable HCV RNA persisting through 24 weeks following the end of treatment.⁶

Achieving SVR. SVR can be considered synonymous with hepatitis C viral eradication, signifying a cure. A recent study followed 997 treatment-naïve HCV patients who achieved 24-week posttreatment SVR with peginterferon plus placebo, or interferon/peginterferon plus ribavirin. HCV RNA testing revealed that 99.2% of these patients had no evidence of the virus at 5-year follow-up.³⁷ SVR is also associated with improved clinical outcomes.³⁸ A retrospective database analysis of 920 patients with cirrhosis treated with standard interferon- α between 1992 and 1997 found that the 13.5% of patients who achieved SVR had a significantly lower risk of liver cancer and liver-related death.³⁸

A number of studies have evaluated the ability of HCV treatment to achieve SVR. A randomized controlled trial involving 1121 chronic hepatitis C patients reported that greater numbers of patients were able to achieve SVR using peginterferon α -2a/ribavirin combination therapy compared with patients using either standard interferon α -2b/ribavirin or peginterferon α -2a plus placebo (46% vs 37% and 21% of genotype 1 patients, respectively, and 76% vs 61% and 45% of genotype 2 and 3 patients, respectively).¹¹

In another randomized trial, peginterferon α -2b/ribavirin was compared with standard interferon α -2b/ribavirin in 1530 patients with chronic hepatitis C.³⁵ Patients were assigned to 1 of 3 groups: interferon α -2b plus ribavirin (1000-1200 mg/day); peginterferon α -2b 0.5 mcg/kg weekly plus ribavirin (800 mg/day); or peginterferon α -2b 1.5 mcg/kg per week for 4 weeks and then 0.5 mcg/kg per week plus ribavirin (1000-1200 mg/day).³⁵ Researchers found that after 48 weeks, the SVR rate was significantly higher (54%) in the higher-dose peginterferon group than in the lower-dose peginterferon (47%) or interferon (47%) groups.³⁵ Similarly, 42% of patients with HCV genotype 1 infection achieved SVR with higher-dose peginterferon, compared with 34% in the lower-dose peginterferon group and 33% in the interferon group.³⁵ Genotype 2 and 3 rates were similar (about 80%) across all treatment options.³⁵

Additional research indicates improved efficacy with higher doses of ribavirin in individuals infected with HCV genotype 1.^{39,40} A randomized controlled trial by Hadziyannis et al compared SVR rates in patients receiving peginterferon α -2a (180 mcg/week for 24 or 48 weeks) plus a low-dose (800 mg/day) or a standard weight-based

dose (1000 or 1200 mg/day) of ribavirin.³⁹ The researchers found that SVR rates were significantly higher with the higher dose of ribavirin at 24 weeks (42% vs 29%) and 48 weeks (52% vs 41%).³⁹ Other data have shown that weight-based dosing of ribavirin at 10.6 mg/kg/day provides optimal response rates and supports a ribavirin dose of 800 to 1400 mg based on body weight.⁴⁰ Further research has confirmed the importance of ribavirin concentrations in predicting response to HCV therapy.⁴¹ Researchers assessed the population pharmacokinetics of ribavirin in patients with chronic hepatitis C treated with interferon α -2b and ribavirin in 4 clinical efficacy studies and found that higher serum concentration of ribavirin at week 4 was associated with a higher response to treatment at week 24.⁴¹

RVR and EVR—Determining Treatment Duration Based on Individual Response Patterns. Patients who respond to HCV treatment more quickly have a greater likelihood of achieving SVR.¹⁰ According to the NIH Consensus Conference Statement, EVR is an important predictor of SVR and should be evaluated by clinicians to determine if treatment is effective.¹⁰ A retrospective analysis of data from a randomized multinational study involving 1121 chronic hepatitis C patients undergoing treatment indicated that 91% of patients who achieved RVR (a negative viral load by week 4) had a high probability of virologic response, compared with 60% to 70% of patients who achieved EVR (a negative viral load by week 12), and 43% to 48% of patients who achieved SVR (a negative viral load by week 24).⁴²

In recent years, experts have questioned whether duration of therapy should be individualized based on rapidity of viral response to therapy. Researchers have considered whether patients achieving RVR may be effectively treated with a shorter duration of therapy compared with slow responders⁴³; conversely, slow responders may require therapy for longer than 48 weeks.^{44,45} Evidence of shorter therapy for genotype 1 patients is based on small studies; therefore, more research is needed to confirm the effect of shorter therapy in this population. Additional studies have focused on genotype 2 and 3 patients. One study examined a short course of peginterferon α -2b/ribavirin in 233 genotype 2 and 3 infected patients, treating some rapid responders for 12 weeks and others for 24 weeks; SVR rates were comparable—85% in the 12-week course and 91% in the standard 24-week course—which suggested the potential for reducing the duration of therapy in rapid responders.⁴⁴ However, the ACCELERATE study, a large randomized, multinational, noninferiority trial, compared treatment with peginterferon α -2a (180 mcg weekly) and ribavirin (800 mg daily) for 16 versus 24 weeks in 1469 genotype 2 and 3 patients.⁴⁵ Researchers found that response rates were better at 90% with 24-week therapy, compared with 82% with 16-week therapy.⁴⁵ Given these findings, the recommended duration of therapy has not been shortened, but remains at 48 weeks for genotype 1 and 24 weeks for genotypes 2 and 3.⁴⁵

Patients without RVR have a high relapse rate with standard-duration therapy and therefore may require extended treatment. The tera virus C (TeraViC-4) study, a phase 3 multicenter study of 517 patients in Spain, randomized patients with detectable HCV RNA levels at week 4 to complete 48 or 72 weeks of treatment. Extension of treatment to 72 weeks resulted in higher SVR rates in all patients (45% vs 32%) and was also specifically shown to be beneficial in genotype 1 patients (44% vs 28%).⁴⁶ For genotype 1 patients who do

not achieve a negative viral load by week 12, clinicians can consider extending therapy to 72 weeks.⁴⁶ For genotype 2 and 3 patients who do not achieve a negative viral load by week 4, clinicians should consider extending the duration of therapy to 48 weeks.⁴⁶ However, because the primary role of extended duration of therapy is to prevent virologic relapse, this strategy should only be considered in individuals in whom HCV RNA becomes undetectable during the first 24 weeks of therapy.⁴⁶ In general, individuals with detectable HCV RNA after 24 weeks of therapy will not achieve an SVR and should discontinue therapy.⁴⁶

ADVERSE EFFECTS OF HCV THERAPY

Although treatment guidelines are available to direct therapeutic decisions, the adverse effects that commonly occur with peginterferon/ribavirin therapy may limit the effective delivery of HCV treatment. In some cases, these effects may prevent the initiation of therapy for HCV patients, including individuals who actively abuse drugs or alcohol and those with untreated mental illness. The most common serious adverse effects of HCV therapy include neuropsychiatric symptoms and cytopenias—particularly anemia and neutropenia.⁴⁷⁻⁴⁹

Neuropsychiatric Symptoms. Patients receiving interferon commonly experience neuropsychiatric adverse effects such as depression, irritability, insomnia, fatigue, and decreased libido.⁴⁷ Capuron et al assessed the expression and treatment responsiveness of neuropsychiatric symptoms during the first 3 months of interferon- α therapy. Researchers found that patients receiving interferon- α experienced a wide array of behavioral adverse effects.⁴⁷ Depressive symptoms included depressed mood (60%), anhedonia (30%), suicidal thoughts (10%), and feelings of guilt (5%).⁴⁷ Anxious symptoms included tension/irritability (50%), anxious mood (45%), and fear (15%).⁴⁷ Cognition was also affected, as demonstrated by a loss of concentration (30%), memory disturbances (15%), word-finding problems (15%), episodes of confusion (10%), and indecisiveness (10%).⁴⁷ Neurovegetative functions were impaired through fatigue/loss of energy (80%), abnormal sleep (45%), psychomotor retardation (40%), and abnormal appetite (35%).⁴⁷ Somatic symptoms included pain (55%) and gastrointestinal symptoms (50%).⁴⁷ A number of these adverse effects can be effectively treated using antidepressant therapies such as selective serotonin reuptake inhibitors.

Anemia. Ribavirin has been associated with hemolytic anemia, a condition involving the destruction of red blood cells. Anemia often results in fatigue, shortness of breath, and decreased quality of life.⁴⁸

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In addition, interferon has also been shown to inhibit bone marrow.⁴⁸ The net result of combination therapy is the loss of approximately 3 or more grams of hemoglobin in the first 4 weeks of therapy. A retrospective pooled analysis evaluated treatment-related changes in hemoglobin in 677 chronic hepatitis C patients who participated in 1 of 2 studies involving treatment with interferon α -2b/ribavirin.⁴⁸ Researchers found that 54% of all patients experienced a decrease in hemoglobin of 3 g/dL; women were 4.4 times as likely as men to experience a hemoglobin level of less than 10 g/dL, although men had a 40% greater risk of experiencing a hemoglobin decline of greater than 3 g/dL from baseline.⁴⁸ Thirty percent of men lost at least 4 g/dL of hemoglobin, and 10% lost at least 5 g/dL.⁴⁸

In some patients, anemia is sufficiently severe to necessitate a reduction in the ribavirin dose or discontinuation of treatment with this agent. However, a number of studies have examined the use of epoetin- α to manage peginterferon/ribavirin-induced anemia. A multicenter trial randomized 185 patients to epoetin- α (40,000 U subcutaneously weekly) or placebo; researchers found that 84% of patients treated with epoetin- α experienced an increase in hemoglobin of 1 g/dL, while 57% experienced an increase of 2 g/dL.⁴⁹ Hemoglobin increases were associated with corresponding increases in level of activity, energy, and overall quality of life as measured by the Linear Analog Scale Assessment score.⁴⁹ Ribavirin doses were maintained in 88% of patients receiving epoetin- α compared with 60% of patients on placebo.⁴⁹

Neutropenia. HCV therapy can also cause neutropenia, a decline in white blood cell count. Data gathered for the FDA submission for peginterferon α -2a indicated that absolute neutrophil count declined by 1500 to 1999 cells/mm³ in 23.8% of patients on interferon/ribavirin therapy and in 8.2% of patients on peginterferon/ribavirin therapy; by 1000 to 1499 cells/mm³ in 38.2% of patients on interferon/ribavirin therapy and in 36.7% of patients on peginterferon/ribavirin therapy; and by 500 to 999

cells/mm³ in 21.3% of patients on interferon/ribavirin therapy and in 45.6% of patients on peginterferon/ribavirin therapy.⁵⁰ Judicious peginterferon dose reductions are sufficient to manage the majority of patients who develop neutropenia during therapy. Clinicians must work with each individual patient to determine whether the benefits of treating HCV outweigh the risks for adverse effects.

COST-UTILITY ANALYSIS

Studies have suggested that current recommended HCV treatment is cost-effective.^{51,52} Wright et al examined the financial benefit of interferon- α and ribavirin in mild chronic hepatitis C, compared with no treatment, and found a \$12,259 gain in costs per quality-of-life years for patients with genotype non-1 and \$44,528 for patients with genotype 1 infection.⁵¹ Similarly, Yeh et al performed a cost-utility analysis and examined the cost effectiveness of peginterferon α -2a/ribavirin, peginterferon α -2b/ribavirin, and no treatment.⁵² Compared with no treatment, therapy with either regimen resulted in an incremental net monetary benefit of approximately \$128,000, a cost decrease of \$26,000 to \$30,000, and a gain of 2.35 quality-of-life years.⁵² Thus, treatment of HCV infection for most patient groups, even those with HCV genotype 1 infection, is considered highly cost-effective compared with a strategy of observation.

EMERGING THERAPEUTIC OPTIONS

Novel therapies are needed to treat individuals who fail to respond to peginterferon/ribavirin and for those in whom treatment with these agents is contraindicated. A number of therapeutic strategies are currently under investigation, with the most promising being specifically targeted antiviral therapies for hepatitis C, also known as STAT-Cs. These agents include viral enzyme inhibitors that target hepatitis C polymerase and hepatitis C protease (Figure 3).

A protease inhibitor, telaprevir, has now reached phase 2 clinical trials. Data from an investigational study, Investigation of HCV Protease Inhibition for Viral Eradication Trial (PROVE 1), demonstrated the rapid potent suppression of HCV with treatment including telaprevir in combination with standard therapy.⁵³ Oral telaprevir, given 3 times daily, combined with peginterferon α /ribavirin was compared with standard treatment with peginterferon/ribavirin.⁵³ Researchers noted a markedly higher RVR rate in the telaprevir containing arms compared with the standard of care arm.⁵³ According to an intent to treat analysis, 79% of patients who received triple therapy were HCV RNA negative at week 4, compared with only 11% who received standard of care.⁵³ Furthermore, 67% of patients who achieved RVR at week 4 and discontinued treatment after 12 weeks were HCV RNA negative at 20 weeks posttreatment.⁵³ By 12 weeks, 70% of patients who received triple therapy were HCV RNA negative, compared with 39% who received standard of care.⁵³ However, although telaprevir is potentially promising, issues related to viral resistance and adverse effects require further study.

Albumin interferon is a novel recombinant protein, genetically fused to human albumin, that is

Figure 3. Emerging HCV Therapies

Viral Enzyme Inhibitors	Genome Sequence-Based	Other
Polymerase	RNA Interference	<ul style="list-style-type: none"> • Other IFNs -cIFN, gamma, alb-IFN • RBV Refinements -Viramidine
Protease	Ribozymes	<ul style="list-style-type: none"> • Immune Approaches -CpG oligonucleotides -Isatoribine -Therapeutic vaccines -HClg -Monoclonal antibodies
Helicase	Antisense Oligonucleotides	Antifibrotic Therapy

HCV = hepatitis C virus; RNA = ribonucleic acid; IFNs = interferons; cIFN = consensus interferon; alb-IFN = albinterferon; RBV = ribavirin; CpG = cytosine and guanine separated by a phosphate molecule; HClg = hepatitis C immunoglobulin.

currently in phase 3 clinical trials. Compared with peginterferon, the molecule has a very long half-life; albinterferon-based therapy can be administered every 2 to 4 weeks. A phase 2 trial involving more than 400 patients reported SVR rates at week 4, week 12, and 12 weeks posttherapy to be similar to those observed with peginterferon α -2a/ribavirin. For example, at 12 weeks posttreatment, SVR occurred in 54% of patients on peginterferon α -2a/ribavirin therapy, compared with 53% to 59% for patients on albumin interferon/ribavirin therapy.⁵⁴

CONCLUSION

Affecting more than 4 million individuals in the United States, hepatitis C is a common infectious disease that can lead to cirrhosis, ESLD, HCC, and sometimes death. Although the incidence of HCV has declined, the symptomatic disease burden is increasing and is predicted to peak within the next decade based on the long duration

of infection. Proper administration of cost-effective combination therapy can help patients achieve SVR and may help to reduce the clinical and economic burden of hepatitis C.

For patients who are appropriate candidates for HCV therapy, standard of care involves peginterferon α /ribavirin combination therapy, with data strongly supporting the use of weight-based ribavirin dosing for genotype 1 infection. Treatment duration should be individualized based on pattern of viral response; for slow responders, a longer duration of therapy may be indicated to increase the probability of SVR. Adverse effects, including depressive symptoms and cytopenias, need to be managed aggressively to prevent the interruption or discontinuation of therapy. Early identification of risk factors, timely diagnosis, appropriate administration of available pharmacotherapy, and close monitoring of viral response will enable clinicians to maximize outcomes for patients with HCV. ■

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Clinical Commentary

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There is a delicate interplay between each of the participants responsible for managing the treatment of hepatitis C—health-care provider, patient, and pharmacist. Providers are challenged to educate themselves and apply their knowledge of the disease state and its treatment to individualize hepatitis C virus (HCV) therapeutic regimens and eradicate infection. Physicians need to translate the essential role of viral kinetics during therapy to effectively treat individuals with HCV infection both by limiting adverse effects in those with insufficient viral response and maximizing efficacy in those who are responsive. Patient understanding of individual risk of HCV disease progression and adherence to peginterferon and ribavirin therapy are essential to attain a successful clinical outcome; however, the task can be daunting given the litany of adverse effects associated with these agents, which are linked to more than 40% of dose reductions during therapy.¹

Pharmacists are uniquely situated amidst the provider and patient to complement physician services and champion the individual to promote favorable clinical outcomes and improve patient satisfaction. Encouraging compliance is a function well-served by the pharmacist, who understands the need for adherence to HCV therapy: If individuals take more than 80% of the prescribed peginterferon dose and 80% of the prescribed ribavirin dose for more than 80% of the prescribed treatment dura-

tion, the probability of sustained viral response increases significantly—up to 63%.²

If effective pharmacotherapy fails to cure a patient as a result of intolerance or lack of virological response, waiting until novel antiviral regimens are available in the next 5 to 10 years may be appropriate. Several classes of novel HCV-specific antivirals are in the development pipeline, including protease inhibitors and polymerase inhibitors, which offer promising therapeutic avenues either in combination with—or as a replacement for—existing standard treatments. With nearly half of patients failing to achieve a sustained response, the need for a more effective medication is evident.³ The dynamic between the provider, pharmacist, and patient should be capitalized on in the current clinical environment to maintain communication, consider all treatment possibilities, and eradicate the infection when possible. ■

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Managed Care Commentary

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The future healthcare burden of hepatitis C represents a major concern for both caregivers and managed care organizations, despite the sharp decline in hepatitis C virus (HCV) incidence in the United States since 1989.¹ Many HCV-infected patients are currently in their 40s and 50s, and the clinical manifestations of their chronic infection will require management as their disease evolves over the next 10 years.² Although most of the aging HCV patient population is fully employed and covered under employer health plans, managed care organizations must understand the financial impact of collective future therapy for these patients. Upcoming expenditures can be estimated from existing data; however, true costs of treating the impending influx of HCV-infected patients with liver failure and cancer will depend on the ability to successfully treat hepatitis C which, to date, has been challenging to manage. Existing standard-of-care treatments appear to be cost-effective; however, they are not successful in treating the entire infected population. Emerging therapies, which look promising for difficult-to-treat patients, are still several years away—around 2010.

Managed care organizations must become actively involved in managing the increasing HCV disease burden. The process should include promoting awareness of risk factors for HCV and

encouraging patients with a history of risk factors to come forward for screening. Support of patients who have been identified as appropriate treatment candidates is also essential through the development of programs aimed at increasing adherence and the administration of therapeutic regimens to treat HCV, with accompanying aggressive management of the adverse effects of HCV therapy. Clinicians must utilize cost-effective therapies and promote treatment algorithms that encourage the identification of early responders to optimize outcomes.

It is crucial for managed care organizations to acquire a complete understanding of the natural history of HCV, educate both patients and clinicians on disease management, and encourage collaborative treatment approaches to control this very complex illness. ■

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