

Diagnosing and Treating Hepatitis C Virus Infection

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Abstract

Hepatitis C virus (HCV) infection is the leading cause of cirrhosis and liver transplantation in the United States. It is difficult to assess the prevalence of HCV infection; the asymptomatic nature of acute infection and early chronic infection leaves many infected individuals undiagnosed. Exposure to infected blood is the primary means for HCV transmission, with intravenous drug use the most common source. Genotype 1 HCV infection accounts for approximately 75% of cases. Because of the asymptomatic and slow course of HCV infection, many physicians and healthcare advocates support routine testing at the primary care level, especially in patients 40 to 65 years of age. Approximately 80% of individuals infected with HCV fail to clear the virus, although this varies considerably based on sex, age at infection, immune status, route of infection, race, alcohol use, and presence of steatosis. Long-term outcomes of chronic HCV infection are cirrhosis, end-stage liver disease, and hepatocellular carcinoma. The current standard of care for patients with chronic HCV infection is combination therapy with subcutaneous injections of peginterferon plus oral ribavirin for 48 weeks. A sustained virologic response (SVR) is also considered a virologic "cure." There is a trend toward response-guided therapy, in which treatment duration is shortened or lengthened based on viral genotype, patient characteristics, and viral kinetics. The efficacy and tolerability of peginterferon therapy, however, is limited. Approximately 45% of patients infected with HCV genotype 1 achieve an SVR, whereas 65% of those infected with genotype 2 or 3 do so. Moreover, retreatment or switching to other interferons provides little benefit. Several new therapies for HCV infection are in development. Protease inhibitors are expected to become the new standard of care for nonresponders, with the potential to become a first-line treatment for chronic HCV infection.

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For author information and disclosures, see end of text.

Introduction

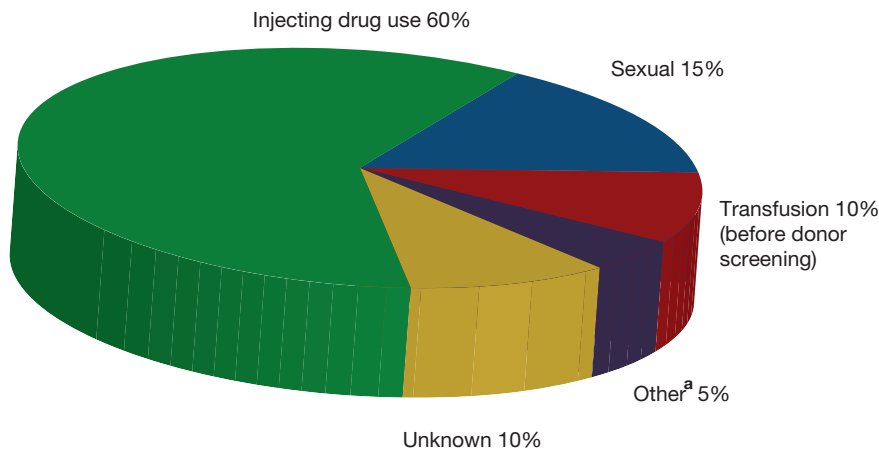
Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States, and it is the leading cause of cirrhosis and liver transplantation.¹⁻³ The Centers for Disease Control and Prevention (CDC) estimated that approximately 18,000 new HCV infections occurred in 2008, and that 2.7 to 3.9 million individuals in the United States are living with chronic infection.⁴ It is difficult to assess the prevalence of HCV infection; the asymptomatic nature of acute infection and early chronic infection leaves many infected individuals undiagnosed.¹ Therefore, it is estimated that up to 5 million people in the United States are infected with HCV. In a large screening program conducted in patients from a Veterans Affairs Medical Center (n = 36,422), 5.4% of patients tested positive for HCV antibodies and 4.2% tested positive for HCV ribonucleic acid (RNA).⁵ In a study designed to assess the prevalence of HCV infection in patients admitted to 2 urban hospitals' general internal medicine and trauma services (n = 786), 16% of patients tested positive for HCV antibodies.⁶ Of the 16%, half (8%) had no prior record of a positive test or diagnosis. An estimated 5.6% of all patients had undiagnosed chronic HCV infection.

Approximately 75% to 80% of individuals acutely infected with HCV will progress to chronic infection, and 60% to 70% will develop chronic liver disease.¹ An estimated 20% of patients develop cirrhosis 20 to 30 years after infection, making HCV the leading indication for liver transplant in the United States.¹ In the United States, chronic HCV is responsible for 8,000 to 12,000 deaths each year.⁴ Given the mutability and different strains of the virus, individuals can be reinfected or infected with more than 1 viral genotype.¹

Transmission and Risk Factors for HCV Infection

Exposure to infected blood is the primary means for HCV transmission.⁷ The leading source of infection is intravenous (IV) drug users who share needles and other infected items.¹ Other sources of transmission include blood or blood component transfusions prior to 1992; transplantation of solid organs from infected donors; birth to an infected mother; multiple sexual partners, particularly men having sex with men; and occasional exposure to blood, as with healthcare workers.⁸ The **Figure** depicts the primary sources of infection for individuals with HCV.⁹

■ **Figure.** Sources of Infection for Persons with Hepatitis C⁹



^aHemodialysis; healthcare work; perinatal.

Adapted from Centers for Disease Control and Prevention. *National Hepatitis C Prevention Strategy*. Summer 2001. <http://www.cdc.gov/hepatitis/HCV/Strategy/NatHepCPrevStrategy.htm>. Accessed February 14, 2001.

Risk factors for acquiring HCV include injection drug use, sexual or household contact with a person with hepatitis, blood transfusion prior to 1992, receiving clotting factor concentrates prior to 1987, hemodialysis, maternal-infant transmission, needle sticks, intranasal use of cocaine using shared equipment, surgery, and being a healthcare worker who was in contact with human blood.^{1,10} However, up to 30% of patients with chronic hepatitis have sporadic or community-acquired infection, meaning they do not have any known risk factors or exposure to infected blood.¹⁰

Pathogenesis of HCV Infection

Hepatitis C is a small, enveloped, single-stranded RNA virus that was first identified in 1989.^{10,11} Since then, 6 major genotypes have been identified and at least 50 subtypes. The most common genotypes in the United States are 1a and 1b, which account for approximately 75% of cases; a total of 10% to 20% of patients are infected with genotypes 2 and 3; these genotypes are most likely to respond to treatment.¹⁰

HCV infects the host, then uses some form of viral receptor to enter cells, primarily hepatocytes, where it releases its RNA for replication.¹² It is able to avoid immune-mediated destruction, even in immunocompetent individuals, despite an aggressive humoral and cellular immune response. Although the specific mechanisms that enable HCV to escape eradication are unknown, the virus's propensity to mutate is certainly involved.¹²

Clinical Symptoms and Signs of HCV Infection

HCV infection rarely causes any symptoms in the acute phase. Approximately 20% to 30% of patients develop

jaundice or other symptoms such as fever, fatigue, dark urine, clay-colored stool, abdominal pain, anorexia, nausea, vomiting, and arthralgia.^{1,13}

Acute HCV infection is rarely fulminant, and symptoms usually subside in 3 to 12 weeks.¹¹ Serum viral RNA is detectable within 1 to 2 weeks of exposure and RNA levels continue to rise for several weeks. Levels of serum alanine aminotransferase (ALT) also rise within 4 to 12 weeks, indicating liver injury, and then subside.¹³

Like acute infection, chronic HCV is often asymptomatic in its early stages, with fatigue being the

most common complaint.¹⁴ Other symptoms are similar to those described for acute HCV. Because of the nonspecific nature, such symptoms are not often attributed to HCV infection unless there is a reason to suspect it. Symptoms may not correlate to serum ALT concentrations or liver histology, although they do tend to become more common and severe as cirrhosis develops.^{14,15}

Screening and Diagnosis

All individuals seen in medical settings should be screened for risky behavior (past or present) that increases risk of HCV infection. Those who meet certain criteria, described in **Table 1**, should be tested for the virus and, if the results are positive, counseled on how to avoid transmission.^{7,15,16} Because of the asymptomatic and slow course of HCV infection (described in detail below), many physicians and healthcare advocates support routine testing at the primary care level, especially in patients 40 to 65 years of age.

Current guidelines recommend that patients with suspected acute or chronic HCV infection first be tested for antibodies to HCV (anti-HCV). HCV RNA testing is recommended in those who tested positive for anti-HCV, those in whom antiviral treatment is being considered, and immunocompromised or other patients with unexplained liver disease and a negative anti-HCV test.^{7,17}

The Food and Drug Administration (FDA) has approved 2 enzyme immunoassays (EIA) for HCV testing, both of which have 99% or better specificity for HCV antibodies.⁷ In June 2010, the FDA approved the first rapid test for HCV infection. The test uses whole venous blood, requires no laboratory processing, and returns results in about 20 minutes.

Table 1. Individuals for Whom HCV Screening is Recommended^{7,16}

Individuals who have ever injected drugs, even once
Individuals with medical conditions associated with HCV infection, including: <ul style="list-style-type: none"> • HIV infection • Hemophilia, in those who received clotting factor concentrates prior to 1987 • Hemodialysis • Unexplained abnormal aminotransferase levels
Individuals who received transfusions or organ transplants prior to July 1992, when screening programs for human tissue were implemented
Children born to HCV-positive mothers
Health care workers, including public safety workers, after a needle stick or mucosal exposure to HCV-positive blood
Current sexual partners of HCV-infected individuals
HCV indicates hepatitis C virus; HIV, human immunodeficiency virus. Adapted from Centers for Disease Control and Prevention. <i>MMWR Recomm Rep.</i> 1998;47(RR-19):1-39; and Ghany MG, Strader DB, Thomas DL, et al. <i>Hepatology.</i> 2009;49(4):1335-1374.

Positive results should be followed up with a confirmatory test using traditional HCV testing methods.¹⁸ In addition, an enhanced chemiluminescence immunoassay and recombinant immunoblot assay are available, although the latter is rarely used given the excellent specificity of EIAs.⁷

Several qualitative and quantitative assays for HCV RNA are also available. The high sensitivity of the real-time polymerase chain reaction (PCR)-based assay has caused qualitative assays to fall out of use. Genotyping can be accomplished once infection is confirmed; it is useful to guide treatment and is recommended in all patients with HCV infection prior to interferon treatment.⁷

Liver biopsy, considered the “gold standard” for assessing liver disease status, should be reserved for patients with chronic HCV (and only when information about the fibrotic status of the liver is required for treatment decisions). A biopsy is usually not required in patients with HCV genotype 2 or 3, as they are more likely to obtain a sustained virological response (SVR) to treatment.⁷

The risks associated with liver biopsy, including bleeding, pain, and organ perforation, have led to efforts to identify less invasive options to assess liver status. Biomarker panels, particularly the Original European Liver Fibrosis Panel, and transient elastography are 2 options under investigation.^{19,20}

Natural History of HCV Infection

Approximately 80% of individuals infected with HCV fail to clear the virus, although this varies considerably based on sex, age at infection, immune status, route of infection, race, alcohol use, and presence of steatosis (accumulation of fat in the liver).^{11,12,21,22}

Beyond that, defining the natural history of the disease is challenging. As noted earlier, most patients are asymptomatic during acute infection, thereby making time of infection difficult if not impossible to determine. Second, the slow

course of HCV infection means that many patients may be infected for decades before they are diagnosed. When such patients are finally diagnosed, the disease has often advanced to cirrhosis, decompensation, or hepatocellular carcinoma (HCC).²³ Moreover, it is unclear if progression of HCV infection is linear and to what degree the mode of transmission (eg, IV drug use) influences clinical sequelae.^{11,12,23,24}

Long-term outcomes of chronic HCV infection are cirrhosis, end-stage liver disease, and HCC. The risk of developing cirrhosis over 30 years ranges from 5% to 25%, although patients who were infected as children and women infected in their 20s are less likely to develop cirrhosis. In addition, patients with persistent ALT elevations but no fibrosis and minimal necroinflammatory changes are likely to have a very slow progression to cirrhosis.^{3,12} Individuals who are infected at an older age, are immunocompromised (ie, have human immunodeficiency virus infection [HIV]), are obese, or consume more than 50 g of alcohol a day are more likely to develop cirrhosis.

One review of 111 studies on the natural history of HCV infection estimated that approximately 16% of patients develop cirrhosis 20 years after infection (95% confidence interval: 14%-90%).²⁵ Another meta-analysis of data on the natural history of HCV and HIV coinfection determined that 21% of patients developed cirrhosis after 20 years and 49% after 30 years, with a longer duration of HCV infection associated with a slower progression of fibrosis. Compared with patients with HCV infection, those with HCV and HIV infection had a higher rate of cirrhosis regardless of highly active antiretroviral therapy.²⁶ One-third of patients who develop cirrhosis will progress to hepatic decomposition over 10 years, while 1% to 3% each year will develop HCC.²⁷

Mortality due to HCV infection varies. Patients followed for 25 years after a posttransfusion infection demonstrated

■ **Table 2.** Virologic Responses in HCV Therapy⁷

Virologic Response	Indication	Predictor of SVR
Sustained virologic response (SVR)	Absence of HCV RNA from serum by a sensitive PCR assay 24 weeks after therapy discontinuation	NA
End-of-treatment response (ETR)	Undetectable virus at end of either 24 or 48 weeks of therapy	Required for SVR but does not predict its occurrence
Rapid virologic response (RVR)	Undetectable HCV RNA at week 4 of treatment using a sensitive test with a lower limit of detection of 50 IU/mL	Highly predictive of SVR
Early virologic response (EVR)	≥2 log reduction or complete absence of serum HCV RNA at week 12 of therapy compared with baseline	Failure to achieve EVR is most accurate predictor that SVR will not be achieved
Complete EVR	Undetectable HCV RNA at week 12 of treatment	
Delayed virus clearance	HCV RNA test is negative between weeks 12 and 24	NA
Virologic breakthrough	Reappearance of HCV RNA while still on therapy	NA
Virologic relapse	Reappearance of HCV RNA in serum after documentation of ETR	NA
Null responder	Failure to suppress HCV RNA by 1 log after 4 weeks and <2 logs after 12 weeks of therapy	NA
Partial nonresponder	HCV RNA levels decrease by ≤2 logs but never become undetectable	NA
Nonresponder	Failure to clear HCV RNA from serum after 24 weeks of therapy	NA

HCV indicates hepatitis C virus; NA, not applicable; PCR, polymerase chain reaction; RNA, ribonucleic acid.
Adapted from Ghany MG, Strader DB, Thomas DL, et al. *Hepatology*. 2009;49(4):1335-1374.

no difference in all-cause mortality from a control group, although patients with HCV infection had an increased rate of liver mortality (4.1% vs 1.3%, respectively). In addition, 17% had or were suspected to have cirrhosis.²⁸

The most common extrahepatic manifestation of HCV infection is HCV-related cryoglobulinemia (presence of abnormal proteins in the blood). Although it occurs in less than 1% of patients, up to half of these patients have clinical manifestations, including low levels of serum cryoglobulins, rheumatoid factor, and immunologic markers of vasculitis. Untreated cryoglobulinemia can lead to progressive renal disease and severe vasculitic complications. Thus, its presence is an indication for HCV treatment.^{7,11,29,30}

Management of HCV Infection

The goal of treatment for chronic HCV is to prevent complications and HCV-related mortality. However, the slow course of the disease makes it difficult to determine if treatment prevents liver-related complications. In the short term, a reduction in serum ALT levels, the absence of HCV RNA, and improvement in necroinflammatory score with no worsening in fibrosis score may be used to evaluate therapy.⁷

Over the long term, however, viral kinetics are used to evaluate therapy. Virologic responses are explained in [Table 2](#). The most important is an SVR, also considered a virologic “cure.”⁷

Current Treatment Options

The current standard of care for patients with chronic HCV infection is combination therapy with subcutaneous injections of peginterferon plus oral ribavirin (RBV) for 48 weeks.^{3,31,32} Recommended dosages are peginterferon α -2a at 180 μ g per week, and RBV at a weight-based dosage of 1000 mg for those 75 kg or less in weight and 1200 mg for those weighing more than 75 kg. The dosage for peginterferon α -2b is 1.5 μ g/kg per week, with a weight-based dosage of RBV at 800 mg for those less than 65 kg, 1000 mg for those more than 65 kg but less than 85 kg, 1200 mg for those between 85 kg and 105 kg, and 1400 mg for those more than 105 kg.⁷

Although each agent carries the risk of serious side effects, risks are greater with combined therapy. Neutropenia and anemia are particularly concerning. In 2 phase 3 trials with peginterferon and RBV, approximately 20% of patients experienced neutropenia or anemia requiring dose reductions or discontinuation.^{31,33}

■ **Table 3.** Recommendations for When to Treat Chronic HCV³

Patient Category	Recommendation
Normal ALT levels or levels <2 times the upper limit of normal^a	Base treatment decision on individual considerations, including favorable genotype, presence of hepatic fibrosis, patient motivation, symptoms, severity of comorbid illness, and patient's age.
Mild liver disease (persistent ALT elevations but no fibrosis and minimal necroinflammatory changes)	Slow progression may not require treatment. Patients should be monitored and treatment decisions determined on individual basis.
Advanced liver disease	Liver transplant remains the therapy of choice, particularly for patients with decompensated cirrhosis, although HCV may reoccur following liver transplantation and, owing to immunosuppression, may progress more rapidly.
Patients with renal disease, depression, and/or active substance abuse; children.⁷	Little evidence available regarding efficacy.

^aMay still progress to advanced fibrosis and cirrhosis.
ALT indicates alanine aminotransferase; HCV, indicates hepatitis C virus.

Common side effects of influenza-like symptoms, depression, headache, and fever, coupled with neuropsychiatric conditions such as depression, irritability, and insomnia, can lead to dosage reduction and discontinuation.^{31,33} Such adverse events, as well as individual patient characteristics, lead to lower rates of adherence (and therefore treatment efficacy) over time.³⁴ One study found that patients were willing to accept a lower viral response in exchange for fewer adverse effects, particularly depression and flu-like symptoms. The study, which provided patients with a choice-format conjoint survey, identified an 80% adherence to therapy with no flu-like symptoms, and an adherence rate of just 66.4% when flu-like symptoms were expected for 4 days.³⁴

Because the adverse effects of combination therapy tend to increase over time, the shortest possible treatment time is recommended. Thus, guidelines call for discontinuing therapy in patients who do not achieve an early virologic response (EVR) at 12 weeks and retesting patients who do not achieve HCV RNA negativity at 24 weeks.³²

There is a trend toward response-guided therapy, in which treatment duration is shortened or lengthened based on viral genotype, patient characteristics, and viral kinetics. For instance, patients with HCV genotype 2 or 3 who demonstrate a rapid virologic response (RVR) at week 4 are significantly more likely to achieve an SVR following a 16-week course of treatment. This shorter regimen is most effective in patients up to 45 years of age with low baseline HCV RNA levels (<400,000 IU/ml) and minimal fibrosis.³⁵ Conversely, treatment duration may be extended to 72 weeks in patients with genotype 1 HCV infection, who may experience a delayed virus clearance.^{7,36} After patients achieve SVR, those with cirrhosis should be regularly monitored for the development of HCC.⁷

Decision to Treat

Although all patients with HCV infection are candidates for treatment, the indolent course of the disease, social history of some patients, and adverse effects and cost of therapy require that clinicians and patients determine when and if it is appropriate to begin therapy. The economic considerations of treatment initiation are discussed in the accompanying articles in this supplement; the focus of this article is the clinical implications of those decisions.

The 2002 National Institutes of Health Consensus Statement on the Management of Hepatitis C recommends treatment in patients with histological evidence of progressive disease. Such patients have detectable HCV RNA levels higher than 50 IU/mL, liver biopsy results demonstrating portal or bridging fibrosis, and “at least” moderate inflammation and necrosis. Most patients will also have persistently elevated ALT values.³ The panel also recommended that patients with less severe histological disease be managed on an individual basis, and that patient selection for treatment not be based on the presence or absence of symptoms, the mode of acquisition, the genotype of HCV RNA, or serum HCV RNA levels. Specific recommendations are highlighted in **Table 3**.³

Although liver transplantation is typically recommended in patients with cirrhosis, a recent analysis of 568 patients at 26 centers with clinically compensated HCV-related cirrhosis undergoing treatment with peginterferon- α /RBV reported an SVR in treatment-naïve patients of 30.7% after a median follow-up of 35 months.³⁷ Predictors of SVR were non-genotype 1, low baseline viral load, low serum gamma-glutamyl transpeptidase, no signs of portal hypertension (via ultrasonography), and an RVR at week 4. Patients who achieved an SVR had an event-free survival rate at 5 years of 98% versus 59% in nonresponders ($P < .001$).

Consensus interferon (CIFN) is also indicated for the treatment of chronic HCV in adults with compensated liver disease and, in combination with RBV, for patients with HCV infection who need retreatment.³⁸ It was approved for that indication prior to the approval of the current standard of treatment, however, and has not been evaluated in treatment-naïve patients. Today, CIFN is primarily used for patients who have failed peginterferon/RBV therapy and can tolerate interferon.³⁹

Nonresponders to Interferon Therapy

The efficacy and tolerability of peginterferon therapy is limited. Approximately 45% of patients infected with HCV genotype 1 achieve an SVR, whereas 65% of those infected with genotype 2 or 3 do so.³¹ Retreatment or switching to other interferons provides little benefit.^{40,41}

Unfortunately, long-term treatment is not associated with additional benefits. The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial was designed to evaluate long-term maintenance treatment on the progression to cirrhosis, but reported no benefits.⁴² Long-term treatment (median, 6.1 years) was not associated with a lower incidence of HCC.⁴³ It did, however, demonstrate a significant reduction in clinical outcomes (including Child-Turcotte-Pugh score, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal hemorrhage, hepatocellular carcinoma, and mortality) in patients who reached viral RNA suppression of at least 4 log₁₀. The number of patients who reached this threshold was low (178/763, or 23%), however, and only 30 patients had a sustained virologic reduction.⁴⁴

Another option in nonresponders is extending peginterferon therapy to 72 weeks. In the REPEAT (Retreatment with Pegasys in patients Not Responding to Peg-Intron Therapy) trial, which included 950 nonresponders, patients who received 72 weeks of combination therapy had an SVR rate of 16% compared with 8% of those who received the standard 48 weeks of treatment (relative risk, 2.00; confidence interval, 1.32 to 3.02; *P* <.001). The likelihood of SVR could be determined based on viral response at week 12.⁴⁵ Based on the trial results, current guidelines call for retreatment with peginterferon/RBV in nonresponders or those who relapse and were previously treated with nonpeginterferon with or without RBV, or with peginterferon monotherapy, particularly in those with bridging fibrosis or cirrhosis.⁷

Nonresponders may also be treated with CIFN, which received FDA approval in June 2010 for retreatment of nonresponders based on results from the DIRECT (Daily-Dose

Consensus Interferon and Ribavirin: Efficacy of Combined Therapy) trial. In this open-label trial, 487 nonresponders were randomized to CIFN 9 µg/day monotherapy; 15 µg/day + oral RBV based on body weight; or to a control, no treatment group. Approximately 60% of patients had documented advanced fibrosis at baseline liver biopsy.⁴⁶

Overall, SVR rates were 6.9% in the 9-µg group and 10.7% in the 1-µg group, with higher SVR rates in patients with less disease progression and greater viral load decline. Relapse rates were 52% in the 9-µg group and 42% in the 15-µg group.⁴⁶ Treatment was well tolerated, with 83.6% of patients in the 9-µg group and 71.7% of patients in the 15-µg group receiving at least 80% of the CIFN dose. Treatment failure was the most common reason for early termination.

Potential Impact of Future Therapies

The article in this supplement by Poordad et al⁴⁷ provides a comprehensive overview of the current environment for novel therapies, including the results of late-stage clinical trials. There is significant excitement in the field about these new options, particularly the protease inhibitors. A survey of 78 US physicians who treat at least 10 patients with chronic HCV infection each month found that one-third were “warehousing” their patients, or delaying therapy, in anticipation of new therapies.⁴⁸

The expectation is that the protease inhibitors will become the new standard of care for nonresponders, with the potential to become a first-line treatment for chronic HCV infection. Initially, it is expected that these direct-acting antivirals will be used as add-on therapy to current peginterferon/RBV regimens at the current treatment duration of 48 weeks or 24 weeks with significantly improved efficacy.⁴⁹

However, these options will not be applicable to all patients with HCV infection, particularly those who have HCV genotype 2 or 3, and those who are intolerant to or have contraindications to peginterferon or RBV, leaving a continuing unmet need for effective therapies for these patients with chronic HCV infection.⁴⁹

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