

PHOENIX™ MISSION STATEMENT

To provide health care professionals with a comprehensive continuing medical education program focused on evolving concepts in the management of hepatitis C treatment failures that results in improved patient care

TIPS FOR HCV PATIENT CARE AND SIDE EFFECT MANAGEMENT

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INTRODUCTION

Hepatitis C, affecting 3–5 million individuals in the United States, is the most common cause of cirrhosis and the most common indication for liver transplantation in the US. The main complications of chronic infection include cirrhosis, end-stage liver disease, and hepatocellular carcinoma. In general, the degree of viremia seems to be the most significant factor in transmission of infection.^{1,2,3}

The time course of infection due to hepatitis C virus (HCV) is extremely variable among patients. Most cases of disease progression occur over decades, but rapid disease progression has also been documented. Approximately 20% of adults with chronic hepatitis C have evidence of cirrhosis within 20 years. Progression of disease, namely cirrhosis, is enhanced by alcohol intake, obesity and/or hepatic steatosis, coinfection with human immunodeficiency virus (HIV) and/or other hepatitis viruses, male gender, and older age at infection⁴. When cirrhosis is present, the risk of hepatocellular carcinoma (HCC) is 1%–4% per year.^{1,3,5}

OPTIMAL TREATMENT

Several large clinical trials have demonstrated that the highest overall response rates are in treatment-naïve HCV-infected patients treated with pegylated interferon in combination with ribavirin (sustained viral response [SVR] of 54%–56%) as opposed to combination therapy with standard interferon and ribavirin (SVR of 44%–47%) or monotherapy with pegylated interferon (SVR of 29%).⁶

According to current practice guidelines of the American Association for the Study of Liver Disease (AASLD) published in April 2004, the primary objective of treatment is eradication of virus to prevent the complications of HCV infection.⁴ Infection is considered eradicated when an SVR is achieved, meaning that there is no

detectable HCV RNA in the serum 6 months after discontinuation of therapy. Optimal treatment for chronic hepatitis C is combination therapy with pegylated interferon and ribavirin. These guidelines also indicate that all patients with hepatitis C are possible candidates for antiviral therapy. Patient selection for therapy should be based upon assessment of potential risks and benefits on an individual basis. However, treatment for hepatitis C is specifically recommended for those patients who are at risk for developing cirrhosis. Such patients are those with detectable serum levels of HCV RNA in the setting of portal or bridging fibrosis with moderate inflammation and/or necrosis on liver biopsy. Although the clinical efficacy of treatment for other patients with hepatitis C has not been definitively established, antiviral therapy should be considered in the following patients: those with normal alanine aminotransferase (ALT) levels; elevated ALT levels but minimal histologic abnormalities; compensated cirrhosis; recurrence after liver transplantation; acute hepatitis C; concomitant HIV infection; and those who are younger than 18 years old. In addition, based on limited data, treatment for HCV infection should not be withheld because of alcohol use and/or intravenous drug use (IVDU). Nevertheless, abstinence and substance abuse treatment are recommended prior to treatment.^{1,4}

Recommendations on duration of HCV treatment varies with the genotype. In patients with genotype 1, peginterferon and weight-based ribavirin (1000–1200 mg daily) for a total of 48 weeks is recommended. However, in patients with genotypes 2 or 3, peginterferon with a lower dose of ribavirin (800 mg daily) over a 24-week period appears to be adequate.^{4,6}

BASELINE EVALUATION

In the management of chronic hepatitis C, the goals of combination therapy with interferon and ribavirin are to maximize antiviral effects and minimize adverse side effects. The benefits of antiviral therapy outweigh the potential risks of treatment in most patients with chronic hepatitis C, especially those with a high likelihood of SVR. Factors associated with a likelihood of achieving SVR include low viral load, HCV genotype other than type 1, absence of moderate fibrosis or cirrhosis on liver biopsy, lower body weight, and early viral response (EVR).^{1,6,7,8}

In hepatitis C, liver biopsy serves diagnostic and prognostic purposes. In this setting, liver biopsy is the only study that can provide definitive information about the degree of inflammation and fibrosis/cirrhosis. As such, it establishes a baseline for evaluation of progression of disease in the future. However, no set guidelines have

Table 1. Contraindications to Combination Therapy with Peginterferon and Ribavirin⁴

Absolute contraindications

- Severe or uncontrolled psychiatric disease
- Poorly controlled epilepsy
- Active serious infection
- Pregnancy or inadequate contraception
- Severe heart disease
- Advanced renal failure
- Documented poor compliance
- Hemoglobinopathy
- Uncontrolled serious medical condition

Relative contraindications

- Hepatic decompensation
- Solid organ transplantation (except liver)
- Autoimmune diseases
- Neutropenia with ANC < 750/mm³
- Thrombocytopenia with platelet count < 50,000/mm³
- Severe anemia
- Ongoing alcohol or substance abuse

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been established regarding subsequent liver biopsy during the course of disease or treatment in hepatitis C.^{1,9,10}

Similarly, there are no established guidelines for noninvasive monitoring with routine labs, such as hepatic enzymes, during the course of disease. Such assessment depends on patient age, stage of liver disease, and comorbid conditions. Of note, levels of ALT do not correlate with extent of disease in hepatitis C. Although assessment of ALT over time may provide some evidence of disease activity, the accuracy of serial measurements is not yet proven. Most studies have demonstrated only a weak association between ALT elevation and severity of histopathology on liver biopsy. Nevertheless, generalized recommendations for noninvasive monitoring with routine blood tests in chronic HCV-infected patients not on therapy consist of the following:

- Testing of liver function every 6–12 months in all HCV patients
- Testing with AFP and ultrasound of the liver every 6 months in patients with cirrhosis
- Liver biopsy every 3–5 years in patients without cirrhosis

Prior to initiating HCV therapy, assessment for contraindications to therapy and other safety factors is needed. Routine blood and urine screening would include complete blood count (CBC) with differential, basic metabolic panel, hepatic function panel, thyroid stimulating hormone (TSH), glycated hemoglobin (A1c), and urinalysis to provide baseline levels and identify any previously undiagnosed medical problems. If the urinalysis is positive for protein, further screening can be done for cryoglobulinemia or other conditions involving the kidneys. Assess patients for the presence of other liver diseases such as Wilson's disease, alpha-1 antitrypsin deficiency, hemochromatosis, nonalcoholic steatohepatitis, and autoimmune hepatitis. Patients with cirrhosis need to be evaluated for contraindications to therapy, such as the presence of decompensation with symptoms such as varices, ascites, jaundice, and encephalopathy. Because of similar risk factors for HCV, HBV, and HIV infections, screening for HBV and HIV coinfection should be considered in HCV-infected patients.

MONITORING OF TREATMENT

In the clinical studies of HCV-infected patients on peginterferon plus ribavirin combination therapy, serum blood tests for safety monitoring have been done at 1, 2, and 4 weeks of therapy and then every 4–6 weeks thereafter (or sooner if needed). Blood tests for this routine monitoring include a CBC with differential, liver function tests, renal function tests, and electrolyte tests.^{1,5,11–16} Since autoimmune diseases may present during interferon therapy, laboratory monitoring every 12 weeks with a TSH, and glycated hemoglobin

can provide for early detection. Monitoring for efficacy of therapy is done through a HCV RNA quantitative measurement at baseline at 12 and 24 weeks of treatment, and 24 weeks after discontinuation of treatment to assess for SVR. Early viral response (EVR) is defined as at least a 2 log decrease in HCV RNA from baseline at 12 weeks of treatment. Patients who have not achieved an EVR or undetectable HCV RNA at week 24 have less than a 3% chance of achieving an SVR. Accordingly, discontinuation of antiviral therapy may be considered in an effort to prevent side effects for those patients who do not demonstrate an EVR. Nevertheless, the potential benefit of continued therapy should be determined on a case-by-case basis.^{17,18} Preliminary evidence is also available indicating that patients who have undetectable HCV RNA at week 4 of treatment (rapid viral response [RVR]) have a higher rate of response to treatment and may be able to be treated for a shorter duration.^{19,20}

In addition, there are no established guidelines for noninvasive monitoring with quantitative tests of liver function, such as prothrombin time, or for radiologic imaging of the liver during the course of disease or treatment in hepatitis C. Although there are limited data on screening for HCC in the setting of HCV infection, measurement of alpha-fetoprotein (AFP) and hepatic ultrasound are routinely obtained every 6 months in those patients with hepatitis C complicated by cirrhosis.^{1,8}

MANAGEMENT OF SIDE EFFECTS

Most adverse effects are dose-related and can be addressed by dose reduction. Dose modification is sometimes required during combination therapy; however, current data indicate that dose reduction of interferon and/or ribavirin may adversely affect response rates.^{21,22} Such interventions must be tailored to each individual and evaluated frequently during the course of therapy. The most common side effects of combination therapy for chronic hepatitis C with interferon and ribavirin are fatigue, influenza-like symptoms, gastrointestinal symptoms, hematologic abnormalities, and neuropsychiatric symptoms. Acute side effects include fever, chills, headache, myalgias, arthralgias, nausea, vomiting, and diarrhea. These influenza-like side effects are common and usually due to interferon; they typically improve over the course of prolonged therapy.^{7,8,23}

The principal hematologic abnormalities caused by such antiviral therapies for hepatitis C consist of neutropenia and thrombocytopenia associated with interferon, and hemolytic anemia associated with ribavirin. As a complication of interferon therapy, neutropenia occurs more frequently than does thrombocytopenia. In contrast to neutropenia, thrombocytopenia does not commonly drop to a level requiring dose

reduction or discontinuation. Furthermore, pegylated interferons result in neutropenia more frequently than does standard interferon. The usual pattern of interferon-induced neutropenia involves a rapid decrease in neutrophil count during the first 2 weeks of therapy, with stabilization of the neutrophil count over the subsequent 4 weeks; neutrophil counts return to baseline rapidly after discontinuation of therapy. The most serious complication of ribavirin is dose-dependent hemolytic anemia. It occurs in most patients, but resolves with discontinuation of ribavirin. While hemolytic anemia develops in approximately 70% of patients, the severity of anemia varies. In patients with hepatitis C treated with interferon and ribavirin, hemoglobin levels typically decrease within the first 2–4 weeks of therapy by an average maximal decrease of 3 g/dL. Given the incidence rate of hemolytic anemia with ribavirin, patients at risk of ischemia require frequent monitoring and dose reduction may be necessary.^{7,8,23}

According to the package inserts, guidelines for dose reduction and discontinuation of pegylated interferon and ribavirin related to hematologic parameters are given in Table 2. Assess patients with decreases in hemoglobin for symptoms of anemia such as fatigue, dizziness, increased thirst, sweating, tachycardia, tachypnea, shortness of breath, leg cramps with exercise, and chest pain. In order to minimize the risk of infectious complications associated with interferon-induced neutropenia in patients with hepatitis C, dose reduction is recommended for an ANC < 750 cells/mm³ based on data involving patients undergoing cancer chemotherapy where the risk of infection is increased at an ANC < 500 cells/mm³. Of note, measurement of neutrophil counts just before dosing probably reflects the effect of interferon most accurately in patients with hepatitis C. Furthermore, the low rate of infection associated with neutropenia may reflect a lower risk of infection for patients with hepatitis C compared with patients undergoing cancer chemotherapy. Thus, in the setting of hepatitis C, dose reduction for interferon-induced neutropenia may allow more liberal parameters for ANC safety.^{1,6,7,8}

Use of hematopoietic growth factors may be warranted as adjunctive therapy with antiviral therapy for hepatitis C, but guidelines for such treatment and cost effectiveness have not been determined. Multiple studies of patients undergoing cancer chemotherapy have demonstrated the clinical benefit of hematopoietic growth factors such as erythropoietin for management of anemia and granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) for management of neutropenia. In one small study of patients with hepatitis C, hemoglobin levels and ribavirin doses were better maintained

in patients treated with erythropoietin than in those who received standard care for anemia. Data regarding the use of GCSF in patients with hepatitis C are limited. Several small studies have shown that higher neutrophil counts can be maintained during antiviral therapy when GCSF is used as an adjunctive measure. However, the parameters for such therapy and its benefits and risks in the setting of hepatitis C have not been established. Issues that remain to be determined include values for hemoglobin level and ANC that should be used as indicators for treatment, whether treatment should be limited to symptomatic patients, and whether treatment will affect achievement of SVR.^{7,24}

The neuropsychiatric side effects associated with antiviral therapy for hepatitis C are defined as new neurologic or psychiatric manifestations that develop during treatment, or as worsening of preexisting signs and symptoms. The main cause of neuropsychiatric adverse effects in the setting of hepatitis C treatment is interferon. The neuropsychiatric side effects of interferon are dose-dependent and reversible. Ribavirin does not accentuate the neuropsychiatric side effects of interferon. The estimated incidence of neuropsychiatric side effects associated with interferon monotherapy is similar to that associated with combination therapy of interferon and ribavirin, approximately 30–40%. However,

depression may occur less frequently with pegylated interferon compared with standard interferon.^{7,17,25,26}

The neuropsychiatric side effects of hepatitis C therapy represent a broad spectrum of clinical manifestations, including fatigue, myalgia, arthralgia, depression, irritability, insomnia, and anxiety. Subclinical neurologic toxicity occurs in 30–50% of patients but is clinically significant in fewer than 5% of patients; complications include neuropathy/paresthesias, seizure, extrapyramidal ataxia, retinopathy, and ototoxicity. Psychiatric symptoms occur in 30–40% of patients and include depression, suicidal ideation, anxiety, panic reactions, insomnia, irritability, emotional lability, personality change, memory loss, confusion, delirium, psychosis, coma, and substance abuse relapse. The most common neuropsychiatric complications are mood disorders, primarily depression and anxiety. Interferon-induced depression may be difficult to distinguish from the influenza-like symptoms of interferon therapy. However, unlike influenza-like symptoms that typically occur early in the course of therapy, interferon-induced depression usually develops after months of therapy. Frequent follow-up examinations by a hepatologist during the course of antiviral therapy permit early identification of this complication. In addition, standardized self-administered mood inventories

and depression scales have been introduced in an effort to detect this adverse effect early on. Furthermore, psychiatry consultation is warranted for assessment of such signs and symptoms. Prior history of depression as well as dose and duration of interferon therapy are the most important predictors of neuropsychiatric side effects in patients with hepatitis C. Factors that may prevent and/or minimize side effects include appropriate patient selection, timing initiation of therapy when depression is controlled, adequate patient and family education, and frequent follow-up assessments.^{1,6,7,17,23,25,26}

Management of neuropsychiatric side effects of antiviral therapy for chronic hepatitis C must be tailored to each individual. Such treatment is guided by input from both a hepatologist and a psychiatrist. For worsening depression unresponsive to antidepressant therapy and dose reduction, severe depression, or suicidal ideation/attempt, immediate discontinuation of antiviral therapy and urgent psychiatric evaluation are necessary. Of note, the use of prophylactic antidepressant therapy warrants study in selected patients and must be used with caution in patients with other psychiatric disorders such as bipolar disorder.^{6,7,25,26}

TREATMENT FAILURES

In chronic hepatitis C, the mechanisms of relapse involve viral factors, host factors, and treatment-related factors. Different HCV genotypes respond to antiviral therapy differently. Higher rates of relapse are found in patients with genotype 1. Host factors that affect outcome include age, ethnicity, and pathologic findings on liver biopsy. Higher rates of relapse are found in older patients, non-Caucasian patients, and patients with advanced fibrosis. Although clearance of viremia due to HCV infection can be measured, it is impossible to accurately assess clearance of HCV infection within hepatocytes.²⁷

Relapse of HCV infection is not uncommon after initial interferon monotherapy or combination therapy with interferon and ribavirin. Retreatment of hepatitis C depends on the initial response to therapy, the efficacy of the initial therapy, and host-viral factors. Individuals who fail to respond to previous treatment are classified into two groups, nonresponders and relapsers. According to current AASLD guidelines, retreatment with peginterferon and ribavirin should be considered for nonresponders or relapsers with significant fibrosis or cirrhosis and who have been treated previously with nonpegylated interferon. However, retreatment with peginterferon and ribavirin for the purpose of HCV clearance is not warranted in patients who have failed to respond to an adequate previous therapy with peginterferon and ribavirin.⁴

Table 2. Guidelines for Dose Modification of Peginterferon and Ribavirin for Hematologic Toxicities (Source: Physicians' Desk Reference, 2005)

		Peginterferon alfa-2a	Peginterferon alfa-2b	Ribavirin
Hemoglobin (patients without cardiac history)	< 10.0 g/dL			Dose reduce
	< 8.5 g/dL	Discontinue	Discontinue	Discontinue
Hemoglobin (patients with stable cardiac disease)	≥ 2 g/dL decrease during any 4-week interval		Dose reduce by 50%	Dose reduce by 200 mg/day
	< 12 g/dL after 4 weeks of dose reduction	Discontinue	Discontinue	Discontinue
White blood cell (WBC)	< 1.5 x 1000 /mm ³		Dose reduce by 50%	
	< 1.0 x 1000 /mm ³		Discontinue	Discontinue
Absolute neutrophil count (ANC)	< 750 /mm ³	Reduce to 135 mcg/week	Dose reduce by 50%	
	< 500 /mm ³	Discontinue	Discontinue	Discontinue
Platelets	< 70,000 /mm ³		Dose reduce by 50%	
	< 50,000 /mm ³	Reduce dose to 90 mcg/week	Discontinue	Discontinue (with alfa-2b)
	< 25,000 /mm ³	Discontinue		

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Table 3. Management of Side Effects to Combination Therapy with Peginterferon and Ribavirin⁴**Flu-like symptoms**

Premedicate with acetaminophen or ibuprofen
Increase fluid intake
Give peginterferon at bedtime

Headaches

Increase hydration, especially day of
peginterferon shot
Relaxation techniques (yoga or meditation)
Consider migraine medications

Rash

Increase fluid intake
Suggest warm (not hot) baths/showers
Avoid scratching and rubbing, as they increase
itching
Encourage use of skin lotions
Use of gentle soaps to cleanse skin
Use of sunscreens as increased photosensitivity
Consider antihistamines
Evaluate for bacterial skin infection

Fatigue

Increase hydration
Conserve energy and prioritize activities
Distraction with enjoyable activities
Regular, moderate exercise program

Insomnia

Move evening ribavirin dose earlier in evening
Good sleep hygiene with consistent bedtime
routine
No stimulants within 3-4 hours of bedtime
Discourage daytime naps or keep to
< 60 minutes
Consider prescribing a hypnotic for sleep

Nausea

Encourage intake of fluids
Suggest taking ribavirin with food
Encourage small meals every 2-3 hours
Avoid spicy, fatty, or heavy meals
Recommend foods/drinks with ginger
Monitor weight and electrolytes
Consider prescribing antiemetics

Anorexia

Encourage small, frequent meals
Suggest hard candy or yogurt prior to meal
Avoid metal utensils or food from cans
Monitor for weight loss
Encourage meal supplements (Boost[®], Ensure[®])
Consider appetite stimulant

Diarrhea

Restrict diet to bananas, rice, applesauce,
and toast (BRAT)
Monitor fluid and electrolyte balance
Consider antidiarrheal agents

Mouth sores

Keep the oral membranes moist (baking soda
and saline rinse)
Suggest oral products for dry mouth
(toothpaste, etc)
Avoid oral products with alcohol base
Consider oral anesthetic or triamcinolone

Alopecia

Avoid harsh chemicals on the hair
Decrease manipulation of hair (brushing,
ponytails, etc)
Consider satin pillowcase to reduce friction

Depression

Assess frequently and consider a standardized
instrument
Discuss management with a close family
member
Dose reduction of peginterferon
Consider prescribing an SSRI
Consider referral for psychiatric evaluation

Anemia

Monitor for symptoms, especially in cardiac
patients
Dose reduction of ribavirin
Consider erythropoietin
Monitor hemoglobin frequently

Neutropenia

Monitor for signs of infection
Encourage handwashing
Dose reduction of peginterferon
Consider GMCSF
Monitor neutrophils frequently

Thrombocytopenia

Monitor for signs of bleeding
Counsel patients on bleeding precautions
Dose reduction of peginterferon
Monitor platelets frequently

In patients who relapse after treatment with peginterferon and ribavirin, possible options include a repeat course of treatment for a longer duration of therapy, such as 72 to 96 weeks, consensus interferon, maintenance therapy with interferon, or watch and wait. There are no data regarding the efficacy of higher doses of therapy, which likely would be complicated by increased rates of adverse side effects.²⁷

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