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VA TREATMENT RECOMMENDATIONS (VERSION 5.0)

Patients with Chronic Hepatitis C

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This supplement to Federal Practitioner *contains the fifth version of the* VA Treatment Recommendations for Patients with Chronic Hepatitis C. *The VA has more experience with hepatitis C than any other U.S. health system. Some 180,000 veterans with hepatitis C virus (HCV) infection were cared for by the VA in fiscal year 2002.*

These recommendations were prepared by experts from the VA's National Hepatitis C Program, Hepatitis C Resource Centers, and Hepatitis C Technical Advisory Group. The first version was developed after the 1997 National Institutes of Health (NIH) Consensus Development Conference on hepatitis C. This latest version includes the newest FDA-approved HCV therapies and reflects the June 2002 NIH Consensus Statement. The recommendations are the result of an extensive review of published data; CDC recommendations for identifying, counseling, testing, and referring people at risk for HCV infection; and input from thought leaders involved in the care of veterans with HCV infection.

Within this supplement, the recommendations have been edited for length, clarity, and journal style (including the substitution of generic names for trade names) by the editors of Federal Practitioner. *This supplement to* Federal Practitioner *was prepared and produced with funding assistance from the VA, and the VA reviewed the final version. No funding was obtained from any pharmaceutical company or other private corporation.*

The opinions expressed in this supplement are those of the recommendations' authors and do not necessarily represent the views of Federal Practitioner *or Quadrant HealthCom Inc. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

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INTRODUCTION

Hepatitis C virus (HCV) is an infection that rarely resolves spontaneously. The prevalence of HCV is approximately 1.8% in the general U.S. population and is believed to be higher in veterans who use VA medical services. People aged 40 to 59 years, which includes the age group of veterans who served during the Vietnam era, have the highest prevalence of HCV infection—and among this age group, the prevalence is greatest in blacks (6.1%).

After initial exposure to hepatitis C, HCV RNA is detectable in blood within one to three weeks. By three months, antibodies to hepatitis C are present in 90% of patients (Table 1). Approximately 85% of patients with acute infection eventually progress to chronic infection, with the majority having evidence of liver disease, such as elevated serum alanine aminotransferase (ALT) or abnormal liver histology.

Approximately 15% to 20% of patients with chronic HCV infection go on to develop cirrhosis. The natural history of HCV is highly variable, however, with some patients advancing to cirrhosis within 15 years and others never progressing this far.[1] Nevertheless, HCV clearly is linked to advanced liver disease and has become the leading indication for liver transplantation in the VA. This, combined with the rising incidence of hepatocellular carcinoma (one of the most lethal complications of long-standing HCV infection), demonstrates the need for effective therapies for veterans with HCV.

Treatment of chronic HCV is aimed at slowing disease progression, preventing complications of cirrhosis, and treating any complications that occur. For many patients, interferon (IFN)-based antiviral regimens result in a sustained virologic response (SVR), which is defined as the eradication of viral replication.

Approximately 50% of treated patients, however, do not achieve an SVR with therapy, regardless of dose and duration of treatment. Patients also may be unwilling to undergo IFN-based HCV treatment, which must be administered parenterally and can have significant adverse effects. In view of these problems, it's important to determine which patients are most likely to benefit from antiviral therapy. These patients include those at risk for progressive liver disease and those whose chronic infection has diminished their quality of life.

A substantial number of patients with HCV have clinical conditions—particularly psychiatric or substance use disorders[2,3]—that are considered contraindications to IFN treatment. Many of these contraindications are based on limited data. Therefore, it's possible that treatment options in these patients are being limited arbitrarily. More research is needed to clarify appropriate therapeutic

TABLE 1.

General Management Guidelines for Hepatitis C Virus (HCV) Infection

For all patients who test positive for HCV antibodies by enzyme-linked immunosorbent assay, management should include:

- Diagnosis of chronic infection using appropriate laboratory tests for antibody status or detection of viremia (see the VA Under Secretary for Health's Information Letter on Diagnostic Testing for Hepatitis C Virus)
- Prompt notification of test results with appropriate counseling
- Education regarding factors that increase the risk of progressive liver injury (such as alcohol or medications)
- Counseling on modes of HCV transmission, including parenteral and sexual transmission
- Medical assessment regarding need for vaccination against hepatitis A and B
- Testing for HIV infection
- Evaluation for potential antiviral therapy

strategies in these and other patients not currently considered candidates for treatment.

These treatment recommendations have been updated since the FDA approval of peginterferon alfa-2a (40 kD) and peginterferon alfa-2b (12 kD), as monotherapy and in combination with ribavirin, and since the National Institutes of Health (NIH) Consensus Statement in June 2002. They are the result of an extensive review of published data; CDC recommendations for identifying, counseling, testing, and referring people at risk for HCV infection; and input from thought leaders involved in the care of veterans with HCV infection.[4,5]

SELECTING PATIENTS FOR TREATMENT

All patients with chronic HCV infection are potential candidates for therapy. Given limitations of current therapies, however, treatment is recommended more clearly in some patients than in others. Treatment decisions should be made on an individual basis with the patient, following discussions of the natural history of HCV as well as the potential risks and benefits of therapy.

A. Patients in Whom Treatment is Clearly Indicated

1. Histologically Moderate Disease or Compensated Cirrhosis

The 2002 NIH Consensus Development Conference determined that treatment is recommended for patients with chronic HCV who are at greatest risk for progression to cirrhosis.[4] These are patients with detectable serum HCV RNA and liver histology showing hepatic fibrosis. Most patients in this group have persistently or intermittently elevated ALT values. Good response is achievable in patients with significant fibrosis, including cirrhosis[6–12]—though patients with bridging fibrosis or cirrhosis appear to respond less well to therapy than those with minimal or no fibrosis.[10,11]

Data on treating patients with compensated cirrhosis are derived largely from subgroup analyses of clinical trials; few prospective studies have focused on this population alone. Such patients are considered candidates for therapy, however, and important goals for treating them are to delay histologic disease progression and prevent clinical complications, both of which are being evaluated in the NIH-sponsored Hepatitis Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial.

In the veteran population, certain relative contraindications to HCV treatment are more common than they are in the general U.S. population. These include substance use disorders (for example, injection drug use or alcohol abuse) and psychiatric disease. Given other clinical indications, patients with a history of substance abuse who have been stabilized with appropriate addiction treatment are candidates for HCV therapy.[4] For example, patients taking methadone for opioid dependence have been treated successfully with antivirals for HCV.

When therapy is provided to patients with a history of substance use disorders, proactive steps should be taken to minimize the risk of relapse. Optimal treatment is provided through collaboration between the treating physician, addiction specialists, and mental health professionals.

B. Patients in Whom Treatment Benefits are Not as Well Documented

Note: Given the inadequacy of data regarding the benefits of treatment in the patient groups discussed in this section, treatment should be conducted in the context of a clinical trial whenever possible.

1. Histologically Mild Disease

Patients in whom liver biopsy demonstrates grade 1 inflammation without evidence of fibrosis are at low risk for progression to cirrhosis,

with most never developing advanced liver disease. In such situations, after a thorough discussion of HCV natural history, prognosis, and treatment options, the physician may advise observation without treatment. During observation, serum ALT should be measured periodically and liver biopsy repeated in three to five years, particularly if serum ALT is persistently abnormal. If liver disease has progressed, treatment may be reconsidered.

Treatment may be provided to patients with mild liver disease who seek intervention or who have significant extrahepatic HCV symptoms. To avoid unnecessarily exposing patients to the adverse effects of therapy, however, the risks and benefits should be discussed thoroughly with each patient.

2. Persistently Normal Serum ALT

Approximately 30% of patients with chronic HCV have persistently normal serum ALT levels. This does not preclude histologic evidence of liver injury, but injury in these patients generally is milder than that observed in patients with elevated ALT levels.

Factors influencing the decision to treat include:

- patient motivation,
- age,
- likelihood of response to therapy,
- severity of symptoms,
- severity of comorbidities, and
- presence of hepatic fibrosis.

A liver biopsy may be necessary to stage liver disease. Patients with minimal or no fibrosis on liver biopsy may be reassured about their favorable prognosis and may choose to defer therapy.[4]

The limited data that exist regarding response to IFN plus ribavirin in this patient population suggest that SVR is similar in patients with normal or mildly elevated serum ALT compared to those with clearly elevated serum ALT.[4] Studies of pegylated IFN plus ribavirin have not been completed in this population. Since patients with significant hepatic fibrosis (stage 2 or higher) may be at risk for progressive liver disease, therapy should be considered.

3. Age > 60 or Significant Nonhepatic Disease

Treatment is not routinely indicated in patients who are over the age of 60 years or have significant nonhepatic disease (such as symptomatic coronary artery disease, uncontrolled diabetes, renal insufficiency, or symptomatic chronic obstructive pulmonary disease). In these individuals, the reduced life expectancy from comorbid conditions, as well as the potential for increased adverse effects from HCV treatment, should be taken into account when determining the potential benefits of treatment. In otherwise healthy patients, however, age over 60 years alone does not preclude treatment.

4. History of Solid Organ Transplantation

There are limited data regarding the risks and benefits of HCV treatment in patients who have undergone solid organ transplantation. Preliminary results on the efficacy of HCV treatment with IFN plus ribavirin or with pegylated IFN in liver allograft recipients suggest that SVR rates are lower in this population than in immunocompetent individuals.[13,14]

Due to a higher prevalence of renal insufficiency, transplant recipients exhibit less tolerability for ribavirin, which often leads to ribavirin-associated anemia. IFN is contraindicated in recipients of renal or cardiac allografts because of an increased risk of severe allograft rejection. Since this risk is lower in recipients of liver allografts, treatment can be administered in this population.

5. HCV-HIV Coinfection

All patients with HIV should be tested for and counseled about HCV. Conversely, those with HCV infection should be offered HIV testing and counseling. Patients infected with both HIV and HCV appear to be at higher risk for liver disease progression than those with HCV infection alone. Therefore, HCV treatment should be considered seriously in these individuals.[15]

To date, studies have enrolled only patients with stable HIV infection and well compensated liver disease.[4] Outcomes with standard or pegylated IFN plus ribavirin are not yet well defined—though preliminary data suggest better responses to pegylated IFN plus ribavirin than to standard IFN plus ribavirin.[4]

These patients may be less able to tolerate ribavirin because of antiretroviral-associated anemia. In addition, lactic acidosis has been reported in patients receiving antiretroviral therapy concurrent with ribavirin therapy.[16,17] This may be due to interactions between ribavirin and HIV antiretrovirals, such as didanosine and stavudine.

6. Acute Hepatitis C

Acute HCV infection rarely is recognized and diagnosed. Studies of treatment for acute HCV infection have been heterogeneous and limited by such factors as small sample size; lack of randomization; and differences in dose, schedule of administration, endpoints, and follow-up duration.[4,18] Although high SVRs have been reported in patients receiving IFN monotherapy, data guiding treatment recommendations are limited.

Some question the necessity of treating acute HCV infection, since cases can resolve spontaneously. Furthermore, the optimal treatment regimen and timing in these patients are unknown.[4,18] In the absence of such data, it seems appropriate to treat patients with acute HCV[4]—probably with at least three months of combination therapy.

7. Active Injection Drug Use with Histologically Moderate Disease or Compensated Cirrhosis

Patients with prior or ongoing injection drug use comprise the largest group of individuals with HCV in the United States. Successful treatment of such patients has the potential not only to benefit the individual but also to prevent transmission to others.

Results of a recent, small trial have demonstrated the feasibility and effectiveness of treating HCV in people who recently used illicit injection drugs and were enrolled in a monitored drug treatment program for illicit injection drug use.[19] These findings should be confirmed in other settings or with larger populations, however, before the risks and benefits of treatment in this population can be evaluated fully.

If treatment of such patients is undertaken, it should be administered with close collaboration between HCV providers and substance abuse specialists.

8. Ongoing Alcohol Use with Histologically Moderate Disease or Compensated Cirrhosis

Alcohol is an important cofactor in the progression of HCV disease to cirrhosis and hepatocellular carcinoma,[4] but a history of alcohol abuse is not a contraindication to therapy. Limited data suggest that heavy alcohol consumption of more than 80 g (approximately eight drinks) per day compromises response to HCV therapies, though the amount of alcohol intake that leads to this compromise is unclear. Even less is known about the effects of lower levels of alcohol consumption on treatment response.[4] Ideally, patients should be treated for active alcohol use or abuse successfully before beginning HCV therapy.

9. Complications of Cirrhosis

Once patients develop clinical complications of cirrhosis (such as gastroesophageal bleeding, ascites, encephalopathy, impaired hepatic synthetic function, or hepatocellular carcinoma), liver transplantation is the treatment of choice. While few prospective studies have been conducted in this population, there are limited data on the outcomes of antiviral therapy.

Typically, patients with cirrhosis have reduced responses to treatment and may be at risk for further hepatic decompensation. Additionally, patients with decompensated liver disease are at risk for life threatening infection—a risk that may be increased further with the administration of IFN-based therapies. Even with low doses of IFN-based preparations, cytopenias occur frequently, often precipitating dose reduction or therapy discontinuation.

Consultation with a transplant hepatologist is recommended prior to initiation of antiviral therapy. If treatment is undertaken, patients should have the option of liver transplantation available, whenever possible, in the event that their clinical condition worsens.

PRETREATMENT ASSESSMENTS

All patients with confirmed, chronic HCV infection should be evaluated for antiviral therapy. Because of limitations in efficacy and the potential for toxicity, each patient needs careful assessment of the relative risks and benefits of beginning therapy immediately, delaying therapy until a later time, or deferring it indefinitely. The assessments described in this section should be performed in all patients as part of the pretreatment evaluation (Table 2).

A. Evidence of Liver Disease

All patients treated for HCV must have evidence of associated liver disease (abnormal transaminase levels or histologic evidence of liver damage) with preserved hepatic synthetic function as indicated by a normal or near normal serum albumin, direct serum bilirubin, and normal prothrombin time, unless abnormalities in these test results can be explained by conditions other than liver disease.

B. Laboratory Testing

- A platelet count of more than 75×10^9/L and an absolute neutrophil count of over 1.5×10^9/L are necessary for patients to tolerate therapy. Patients with lower counts may begin therapy but typically require dose reductions.
- Patients receiving ribavirin must demonstrate adequate hemoglobin (Hb) (over 13 g/dL for men and over 12 g/dL for women) and normal renal function (creatinine less than 1.5 mg/dL).
- Baseline viral load must be established using a quantitative HCV RNA assay. Information regarding the viral load may aid in counseling patients as to their likelihood of response. Patients should be counseled that people with initially low viral loads (generally defined as less than 800,000 IU/L) are more likely to respond to treatment than are those with initially high viral loads (greater than 800,000 IU/L). There is no absolute predictor of response based on HCV RNA level, however. For consistency, the same quantitative assay should be used to evaluate change in viral load throughout the course of therapy. Conversion rates of common quantitative HCV RNA assays from copies/mL to IU/L are not linear and should be used only to approximate a calculated conversion (Table 3).
- Patients should be tested for infecting HCV genotype, which is an important predictor of SVR for all treatment regimens (see “Antiviral Treatment” on page 13) and a key factor in determining treatment duration.

C. Psychiatric Assessment

All patients should be evaluated for psychiatric disorders, particularly depression

TABLE 2.

Pretreatment Assessments

NECESSARY

- Medical history, including complications of liver disease, presence of significant extrahepatic disease, and symptoms of chronic HCV that may diminish quality of life
- Psychiatric history, including past or ongoing psychiatric and substance use disorders
- Previous antiviral therapies and response
- Biochemical markers of liver injury and assessment of hepatic synthetic function, including serum ALT, serum albumin, serum bilirubin (particularly direct bilirubin), and prothrombin time
- Hb, Hct, WBC with differential, and platelet count
- TSH
- Serum glucose or HbA_{1C} in diabetics
- Pregnancy test (necessary for women with childbearing potential)
- Serum HBsAg
- HIV serology
- Quantitative HCV RNA measurement by PCR or bDNA
- HCV genotype
- Anti-HBc (total), anti-HBs, anti-HAV (total)
- ECG in patients with preexisting cardiac disease
- Screening for depression and alcohol use*
- Eye exam for retinopathy in patients with diabetes or hypertension

HIGHLY RECOMMENDED

- Liver biopsy to stage the severity of liver disease (especially in patients with genotype 1 infection)
- Serum ferritin and serum ANA
- Urine toxicology screen for opiates, cocaine, and amphetamines

Abbreviations: ALT = alanine aminotransferase; ANA = antinuclear antibody; anti-HAV = antibody to the hepatitis A virus; anti-HBc = antibody to the hepatitis B core antigen; anti-HBs = antibody to the hepatitis B surface antigen; bDNA = branched DNA amplification; ECG = electrocardiogram; Hb = hemoglobin; HbA_{1C} = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; Hct = hematocrit; HCV = hepatitis C virus; PCR = polymerase chain reaction; TSH = thyroid-stimulating hormone; WBC = white blood cell count. *Validated screening instruments for depression and alcohol use are available online at: www.oqp.med.va.gov/cpg/MDD/MDD_cpg/content/appendices/mdd_app1_fr.htm and www.oqp.med.va.gov/cpg/SUD/SUD_CPG/ModuleA/frameset.htm, respectively.

and suicide risk. Uncontrolled depression is an absolute contraindication to IFN-based therapies (Table 4). Psychiatric disorders in remission or stabilized with treatment are not contraindications, but their presence usually necessitates involvement of a mental health professional during antiviral therapy.

D. Substance Use

All patients should be evaluated carefully for current substance use disorders using

TABLE 3.

Comparison of HCV RNA Quantitative Assays

ASSAY	APPROXIMATE COPIES/mL = 1 IU/L
Abbott LCX HCV-RNA*	3.8
Bayer bDNA 3.0†	5.2
NGI Superquant‡	3.4
Roche Amplicor Monitor 2.0§	2.4

Abbreviations: bDNA = branched DNA amplification; HCV = hepatitis C virus. *Abbott Laboratories, Abbott Park, IL. †Bayer Diagnostics, Tarrytown, NY. ‡National Genetics Institute, Los Angeles, CA. §Roche Molecular Systems Inc., Branchburg, NJ.

validated screening instruments.[20] The presence of current heavy alcohol use (more than 14 drinks per week for men or more than seven drinks per week for women), binge alcohol use (more than four drinks per occasion at least once a month),[21] or active illicit injection drug use requires referral to an addiction specialist prior to treatment initiation. Since the use of illicit noninjection drugs theoretically may pose an obstacle to treatment adherence, each case should be evaluated individually. Establishing abstinence prior to initiating treatment is recommended. Urine toxicology for injectable drugs (such as opiates, cocaine, or amphetamines) may be used to supplement patients' self-reports.

Patients with substance use disorders who have been stabilized with substance abuse treatment are candidates for antiviral HCV therapy. If there is concern about recidivation due to the adverse effects of therapy, HCV treatment may be deferred. Antiviral therapy should be initiated in patients with substance use disorders that are in full remission. These patients may require additional monitoring and care coordination by addiction specialists.

E. Adherence

Patients' ability to adhere to treatment should be assessed. Evidence of prior nonadherence to medical, psychiatric, or addiction therapies are markers of likely nonadherence to HCV therapies. The decision to treat also should be based on patients' willingness to make necessary lifestyle changes, their adherence to the pretreatment evaluation instructions, the availability of social support systems, and the presence of an adequate environment for storage and administration of IFN.

F. Autoimmune Disorders

Patients with stable or controlled autoimmune thyroid disease (with replacement therapy if necessary), diabetes (with normal or near normal serum glycosylated Hb [HbA_{1C}]), psoriasis, rheumatoid arthritis, or other autoimmune diseases can be treated for HCV infection. Because IFN can aggravate underlying autoimmune disorders, however, these patients should be monitored closely for signs of worsening disease.

Patients should be evaluated for coexisting autoimmune liver disease using a serum antinuclear antibody (ANA) test. If ANA is present in high titer, HCV treatment should be administered with caution. In the absence of other clinical evidence of autoimmune disease, even high titers of detectable serum antinuclear antibody do not preclude HCV therapy.

TABLE 4.

Contraindications to HCV Therapy

- Life determining extrahepatic disease (malignancy, unstable angina, severe COPD)
- Clinically decompensated liver disease*
- Uncontrolled autoimmune disorders
- Pregnancy or unwillingness to use adequate birth control
- Documented serious nonadherence to prior medical treatment or failure to complete HCV disease evaluation appointments and procedures
- Inability to self-administer or to arrange appropriate administration of parenteral medication
- Severe uncontrolled psychiatric disease, particularly depression with current suicidal risk
- Recent illicit injection drug use without substance use disorder treatment
- Ongoing alcohol abuse†

Abbreviations: COPD = chronic obstructive pulmonary disease; HCV = hepatitis C virus. *Select patients with clinically decompensated liver disease may be candidates for treatment. †Definitions of alcohol abuse in HCV are evolving and await further data. The National Institutes of Health Consensus Statement concluded, "Continued alcohol use during therapy adversely affects response to treatment, and alcohol abstinence is strongly recommended before and during antiviral therapy."[4]

G. Hepatitis A and B Immunizations

Patients should be tested for hepatitis B surface antigen, antibodies to the hepatitis B core antigen, antibodies to the hepatitis B surface antigen, and antibodies to the hepatitis A virus to evaluate the need for hepatitis immunization.

H. Other Causes of Liver Disease

Serum ferritin should be obtained to evaluate patients for hemochromatosis, a treatable liver disease.

I. Pregnancy

A pregnancy test should be obtained from women of childbearing age prior to the initiation of HCV treatment.

J. Ocular Function

A baseline ophthalmic exam should be performed in patients with retinal disease risk factors (such as hypertension or diabetes) to help identify any disease that might be worsened by ribavirin or IFN.

K. Liver Disease Staging

Liver biopsy is the best method for determining the severity of liver injury (that is, degree of fibrosis or stage of disease).[1] It also may be helpful in excluding other causes of liver disease.

SVR rates are high (70% to 80%) in patients with genotype 2 or 3 HCV infection who receive antiviral treatment. For this reason, the provider and patient may choose to initiate therapy regardless of the severity of liver disease. In such cases, the findings of liver biopsy may not influence the treatment decision.

ANTIVIRAL TREATMENT

A. Definition of Response

Treatment efficacy is measured biochemically (by normalization of serum ALT), virologically (by undetectable serum HCV RNA), and histologically (by reduction in liver inflammation or fibrosis on posttreatment liver biopsy). The two main endpoints for HCV treatment are end-of-treatment response (ETR) and SVR, which are measured by the levels of HCV RNA at the completion of therapy and six months later, respec-

TABLE 5.

Endpoints for Chronic Hepatitis C Virus (HCV) Treatment

ENDPOINT	DEFINITION	TIME POINT FOR MEASURING HCV RNA
EVR	Early virologic response	12 weeks after therapy initiation
ETR	End-of-treatment response	Completion of therapy
SVR	Sustained virologic response	Six months after completion of therapy

tively (Table 5). Biochemical and virologic improvements usually are associated with histologic improvement. Since histologic changes themselves typically have no effect on treatment decisions, posttreatment liver biopsies are not routinely recommended.

Recently, data have been reported regarding the utility of "on-treatment response" or "early virologic response" (EVR), which is measured at 12 weeks after treatment initiation. EVR is defined as undetectable HCV RNA or a 2 $\log_{10}$ reduction in HCV RNA from the pretreatment value, and failure to achieve this outcome is a strong predictor of ultimate nonresponse.[4,22] In one trial, only 3% of the patients who failed to achieve an EVR had an SVR with continued therapy.[11] Therefore, discontinuation of therapy may be appropriate in patients who have not achieved a decline in viral load.

EVR cannot be assessed adequately if different assays are used for baseline and 12-week HCV-RNA measurements or if the baseline value is outside the range of reliable quantification for the assay being used.

B. Therapy for Treatment-Naïve Patients

The current standard of care for treating most patients with chronic HCV infection is a regimen of pegylated IFN plus ribavirin. There are small subgroups of patients in whom the optimal therapy remains undefined and for whom standard IFN plus ribavirin combination therapy or pegylated IFN monotherapy may be acceptable alternatives (Table 6).[4]

1. Pegylated IFNs

Pegylation of IFN, which entails linking the IFN to a molecule of polyethylene glycol (PEG), reduces IFN clearance compared with the standard formulation. Peginterferon alfa-2a (40 kD) and peginterferon alfa-2b (12 kD) are both FDA approved for use as monotherapy and in combination with ribavirin.[8,9] While the IFN molecules alfa-2a and alfa-2b are similar, there are differences in the size of the PEG molecule (40 kD versus 12 kD) and in the way the two proteins are linked to PEG.

These differences alter the drugs' pharmacologic properties. By attaching a 12-kD PEG moiety to IFN alfa-2b, drug clearance is reduced 10-fold and the molecule is eliminated both renally and hepatically.[8,23] The clearance of peginterferon alfa-2a is reduced 100-fold compared with nonpegylated IFN, and the drug is eliminated primarily through the liver.[9,24] Both pegylated IFNs are administered once weekly—instead of three times weekly, as is necessary with standard IFN.

No direct comparison has been made between peginterferon alfa-2a and peginterferon alfa-2b, either as monotherapies or in combination with ribavirin. Therefore, no definitive conclusions can be drawn regarding dif-

TABLE 6.

Antiviral Treatments for Chronic HCV*

TREATMENT	RECOMMENDED DOSE	MAJOR ADVERSE EFFECTS
Peginterferon alfa-2a (40 kD) (Pegasys†) with ribavirin	• 180 µg SC once weekly regardless of weight • 135 µg SC once weekly if receiving hemodialysis • For ribavirin dose, see below	• Similar to IFN • Higher reported rates of neutropenia and thrombocytopenia compared to IFN alfa-2b[9] • Lower reported rates of flulike symptoms and depression compared to IFN alfa-2b[11] • See ribavirin adverse effects below
Peginterferon alfa-2b (12 kD) (PEG-Intron‡) with ribavirin	• 1.5 µg/kg SC once weekly in combination with ribavirin • 1.0 µg/kg SC once weekly as monotherapy • FDA-approved ribavirin dose: 800 mg PO daily (in two divided doses); higher doses may be beneficial, however, in genotype 1 infection (see below)	• Similar to IFN • Higher reported rates of neutropenia, thrombocytopenia, and injection site reactions compared to IFN alfa-2b[8] • See ribavirin adverse effects below
IFN alfa-2a (Roferon-A†), IFN alfa-2b (Intron A‡), IFN alfacon-1 (Infergen§)	• IFN alfa-2a: 3 million U SC three times weekly • IFN alfa-2b: 3 million U SC three times weekly • IFN alfacon-1: 9 µg SC three times weekly	• Flulike symptoms • Bone marrow suppression • Aggravation of autoimmune disorders • Neuropsychiatric symptoms • Seizures • Acute cardiac and renal failure • Retinopathy • Interstitial pulmonary fibrosis
IFN alfa-2b plus ribavirin (Rebetron‡)	• IFN alfa-2b: 3 million U SC three times weekly • Ribavirin: 1,000 mg PO daily if patient ≤ 75 kg OR 1,200 mg PO daily if patient > 75 kg (in two divided doses)	• Adverse effects of IFN • See ribavirin adverse effects below
Ribavirin (Rebetol,‡ Copegus†) used in combination with pegylated IFN	• Genotype 1 patients: 1,000 mg PO daily if ≤ 75 kg OR 1,200 mg PO daily if > 75 kg (in two divided doses) • Genotype 2 and 3 patients: 800 mg PO daily (in two divided doses)	• Hemolytic anemia • Significant teratogen for both men and women • Rashes • Headaches • Shortness of breath • Gastrointestinal effects

Abbreviations: HCV = hepatitis c virus; IFN = interferon. *For more information on the agents discussed here, see the following product web sites: www.rocheusa.com/products/pegasys/pi.pdf, www.schering-plough.com/documents/24564746%20Peg-ntron8.5x11.pdf, www.spfiles.com/pirebetron.pdf, www.spfiles.com/pirebetol.pdf, and www.rocheusa.com/products/copegus/pi.pdf. †Roche, Nutley, NJ. ‡Schering-Plough, Kenilworth, NJ. §InterMune, Brisbane, CA.

TABLE 7.

Comparison of Reported Response Rates for Peginterferon Alfa-2a Combination Therapy, Peginterferon Alfa-2a Monotherapy, and Standard IFN Combination Therapy Given Over 48 Weeks[11]

PATIENT GROUP	SVR RATE*		
	PEGINTERFERON ALFA-2A (40 kD) PLUS RIBAVIRIN†	PEGINTERFERON ALFA-2A (40 kD) PLUS PLACEBO‡	IFN PLUS RIBAVIRIN§
Overall	56%‖	29%	44%
HCV genotype 1	46%¶	21%	36%
High viral titer**,††	41%	13%	33%
Low viral titer††,‡‡	56%	39%	43%
HCV genotype 2 or 3	76%§§	45%	61%
High viral titer††	74%	40%	58%
Low viral titer††	81%	58%	65%

Abbreviations: HCV = hepatitis C virus; IFN = interferon; SVR = sustained virologic response. *Reported SVRs from package insert are lower than those published by Fried et al.[9] †Regimen: peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 or 1,200 mg/day for 48 weeks. ‡Regimen: peginterferon alfa-2a 180 µg/week plus placebo for 48 weeks. §Regimen: IFN 3 million U three times weekly plus ribavirin 1,000 or 1,200 mg/day for 48 weeks. ‖$P < .001$ compared to standard IFN plus ribavirin. ¶$P = .01$ compared to standard IFN plus ribavirin. **Defined as > 2 million copies/mL (COBAS AMPLICOR HCV Test, v. 2.0, sensitivity 100 copies/mL). ††Statistical analysis not performed. ‡‡Defined as ≤ 2 million copies/mL (COBAS AMPLICOR HCV Test, v. 2.0, sensitivity 100 copies/mL). §§$P = .005$ compared to standard IFN plus ribavirin.

ferences in efficacy between these two preparations.

Efficacy and adverse effects have been compared, however, between pegylated IFNs and standard IFN (in combination with ribavirin). As monotherapy, both peginterferon alfa-2a and alfa-2b produce superior treatment responses compared to standard IFN monotherapy but inferior responses compared to standard IFN plus ribavirin.[11,25,26] As with other IFN-based preparations, pegylated IFNs have produced lower SVR rates in patients with genotype 1 infection than in those with genotype 2 or 3 infection.

Peginterferon Alfa-2a Plus Ribavirin

A multinational, randomized trial compared peginterferon alfa-2a plus either placebo or ribavirin to standard IFN plus ribavirin in treatment-naïve patients with chronic HCV (Table 7).[11] SVR rates were higher in patients receiving peginterferon alfa-2a plus ribavirin (dosed at 1,000 mg/day for patients weighing 75 kg or less or 1,200 mg/day for those weighing over 75 kg) compared to those receiving standard IFN alfa-2b plus ribavirin. Both combination regimens were more effective than peginterferon alfa-2a monotherapy.

Improved efficacy of peginterferon alfa-2a plus ribavirin over standard IFN plus ribavirin was observed in patients with genotype 1, 2, or 3 HCV infection. The difference in treatment response between peginterferon alfa-2a plus

TABLE 8.

Comparison of Reported Response Rates for Peginterferon Alfa-2a Combination Therapy, Peginterferon Alfa-2a Monotherapy, and Standard IFN Combination Therapy, According to Level of Fibrosis[11,29]

PATIENT GROUP	SVR RATE (95% CONFIDENCE INTERVAL)		
	IFN ALFA-2B PLUS RIBAVIRIN*	PEGINTERFERON ALFA-2A (40 kD) PLUS PLACEBO†	PEGINTERFERON ALFA-2A (40 kD) PLUS RIBAVIRIN‡
Patients with bridging fibrosis and cirrhosis	33% (22%–47%)	21% (10%–37%)	43% (30%–56%)
Patients with no fibrosis or portal fibrosis only	47% (42%–52%)	31% (25%–38%)	58% (53%–63%)

Abbreviations: IFN = interferon; SVR = sustained virologic response. *Regimen: IFN alfa-2b 3 million U three times weekly plus ribavirin 1,000 or 1,200 mg/day. †Regimen: peginterferon alfa-2a 180 µg once weekly plus placebo. ‡Regimen: peginterferon alfa-2a 180 µg once weekly plus ribavirin 1,000 or 1,200 mg/day.

ribavirin and standard IFN alfa-2b plus ribavirin was 12% overall: 10% for HCV genotype 1 and 15% for HCV genotypes 2 and 3. Patients with bridging fibrosis and cirrhosis achieved SVR rates of 43% with peginterferon alfa-2a plus ribavirin and 33% with standard IFN alfa-2b plus ribavirin (Table 8).[11] Patients with early-stage disease receiving peginterferon alfa-2a with or without ribavirin generally achieved better results than those with either cirrhosis or transition to cirrhosis.[11,27]

Three independent factors were associated with a favorable response to peginterferon alfa-2a plus ribavirin: genotype non-1, younger age (40 years or younger), and lighter body weight (75 kg or less).[11] Neutropenia and thrombocytopenia appear to be greater in patients receiving peginterferon alfa-2a plus ribavirin compared to those receiving standard IFN plus ribavirin (Table 9).[9] Incidence of flulike symptoms and depression were lower in patients receiving peginterferon alfa-2a plus ribavirin compared to those receiving standard IFN plus ribavirin (P = .02 for myalgia, P < .001 for pyrexia and rigors, and P = .01 for depression).[11]

The optimal ribavirin dose and treatment duration with peginterferon alfa-2a plus ribavirin appear to differ depending on the infecting genotype (Table 10).[28] In patients with genotype 1 infection, SVR was highest (51%) in patients receiving 48 weeks of peginterferon alfa-2a plus ribavirin 1,000 or 1,200 mg/day. In patients with genotype 2 or 3 infection, SVRs were similar in all treatment groups regardless of treatment duration or ribavirin dose (SVR range, 73% to 78%). Therefore, patients with genotype 2 or 3 infection can be treated with peginterferon alfa-2a in combination with ribavirin 800 mg/day for 24 weeks.

Peginterferon Alfa-2b Plus Ribavirin

A randomized, multinational trial compared peginterferon alfa-2b

TABLE 9.

Comparison of Reported Adverse Event Rates for Peginterferon Alfa-2a and Standard IFN Combination Therapies[9]

ADVERSE EVENT	PEGINTERFERON ALFA-2A (40 kD) PLUS RIBAVIRIN* (N = 451)	IFN ALFA-2B PLUS RIBAVIRIN† (N = 443)
Injection site reaction	23%	16%
Pyrexia	41%	55%
Rigors	25%	37%
Myalgia	40%	49%
Neutropenia	27%	8%
Anemia	11%	11%
Thrombocytopenia	5%	< 1%
Depression	20%	28%
Irritability/anxiety	33%	38%
Nausea/vomiting	25%	29%
Diarrhea	11%	10%

Abbreviation: IFN = interferon. *Regimen: peginterferon alfa-2a 180 µg once weekly plus ribavirin 1,000 or 1,200 mg/day. †Regimen: IFN alfa-2b 3 million U three times weekly plus ribavirin 1,000 or 1,200 mg/day.

plus ribavirin to standard IFN alfa-2b plus ribavirin in treatment-naïve patients with chronic HCV (Table 11).[10] There was no difference in SVR rates between the lower dose of peginterferon alfa-2b (1.5 µg/kg once weekly, reduced to 0.5 µg/kg once weekly after four weeks) plus ribavirin and standard IFN alfa-2b plus ribavirin.[8,10] The difference in treatment response between peginterferon alfa-2b at the higher dose (1.5 µg/kg once weekly maintained throughout the course of therapy) plus ribavirin compared to standard IFN alfa-2b plus ribavirin was 7% overall and 9% for genotype 1.[10] These higher SVR rates were accounted for largely by patients with low viral loads. Among patients with both genotype 1 infection and a high viral load (over 2 million copies/mL, or over 800,000 IU/mL), the response rates were similar between those who received the higher dose of peginterferon alfa-2b plus ribavirin and those who received standard IFN alfa-2b plus ribavirin (30% and 29%, respectively).[8]

Results in patients with early-stage disease were better than those in patients with bridging fibrosis and cirrhosis (Table 12).[10] Independent variables associated with a favorable response to treatment with peginterferon alfa-2b plus ribavirin included HCV genotype non-1, low pretreatment HCV RNA level, lighter body weight, younger age, female gender, and absence of bridging fibrosis or cirrhosis.[10] Adverse effects—such as neutropenia, thrombocytopenia, and injection site reactions—appear to be greater in patients receiving peginterferon alfa-2b plus ribavirin than in those receiving standard IFN alfa plus ribavirin (Table 13).[8,10]

There has been much discussion about the appropriate dose of

TABLE 10.

Comparison of 24 and 48 Weeks of Peginterferon Alfa-2a Combination Therapy[28]

PATIENT GROUP	SVR RATE			
	24 WEEKS OF TREATMENT		48 WEEKS OF TREATMENT	
	RIBAVIRIN 800 mg/DAY	RIBAVIRIN 1,000 OR 1,200 mg/DAY	RIBAVIRIN 800 mg/DAY	RIBAVIRIN 1,000 OR 1,200 mg/DAY
HCV genotype 1	29%	41%	40%	51%
High viral titer*	16%	26%	35%	46%
Low viral titer†	41%	51%	53%	61%
HCV genotype 2 or 3	78%	78%	73%	77%
High viral titer	82%	79%	70%	77%
Low viral titer	72%	77%	78%	77%

Abbreviations: HCV = hepatitis C virus; SVR = sustained virologic response. *Defined as > 2 million copies/mL (COBAS AMPLICOR HCV Test, v. 2.0, sensitivity 100 copies/mL). †Defined as ≤ 2 million copies/mL (COBAS AMPLICOR HCV Test, v. 2.0, sensitivity 100 copies/mL).

ribavirin administered in combination with peginterferon alfa-2b. The FDA-approved dose of 800 mg/day is lower than that approved to be used in combination with standard IFN alfa-2b. Subsequent data from trials of peginterferon alfa-2a have suggested that the 800-mg daily dose is sufficient for the treatment of genotype 2 or 3 HCV infection, but that higher doses (1,000 or 1,200 mg/day, based on body weight) are necessary for effective treatment of genotype 1 HCV infection (see "Ribavirin in Combination with Pegylated or Standard IFN" on this page).[28]

Note: Several of the recommendations in this document are derived from data generated with pegylated IFN alfa-2a plus ribavirin. Comparable data currently do not exist in patients receiving pegylated IFN alfa-2b plus ribavirin. These include recommendations for:

- **treatment duration for patients with genotype 2 or 3 HCV infection;**
- **use of a 12-week rather than a 24-week time point for EVR; and**
- **ribavirin dosing of 1,000 mg/day for patients with genotype 1 HCV infection who weigh 75 kg or less, 1,200 mg/day for patients with genotype 1 HCV infection who weigh over 75 kg, and 800 mg/day for patients with genotype 2 or 3 HCV infection.**

2. Standard IFN

IFN alfa-2b plus ribavirin is more effective than monotherapy with either pegylated or standard IFN (Table 14).[6,7,11] For patients who cannot tolerate pegylated IFN, standard IFN alfa-2b plus ribavirin is an acceptable alternative (see "Pegylated Versus Standard IFN Combination Therapy" on next page).

3. Ribavirin in Combination with Pegylated or Standard IFN

Ribavirin is indicated for use in chronic HCV only when administered

TABLE 11.

Comparison of Peginterferon Alfa-2b and Standard IFN Combination Therapies[10]

PATIENT GROUP	SVR RATE*	
	PEGINTERFERON ALFA-2B (12 kD) PLUS RIBAVIRIN†	IFN PLUS RIBAVIRIN‡
Overall	54%§	47%
HCV genotype 1	42%‖	33%
High viral titer¶,**	30%	29%
Low viral titer††	Not reported	Not reported
HCV genotypes 2 and 3	82%	79%
HCV genotypes 4–6	50%	38%

Abbreviations: HCV = hepatitis C virus; IFN = interferon; SVR = sustained virologic response. *Reported SVRs from package insert are lower than those published by Manns et al.[8] †Regimen: peginterferon alfa-2b 1.5 µg/kg once weekly plus ribavirin 800 mg/day for 48 weeks. ‡Regimen: IFN 3 million U three times weekly plus ribavirin 1,000 or 1,200 mg/day for 48 weeks. §P = .01 compared to standard IFN plus ribavirin. ‖P < .05 compared to standard IFN plus ribavirin. ¶Defined as > 2 million copies/mL (NGI, sensitivity 100 copies/mL). **Statistical analysis not performed; data from Peg-Intron package insert.[8] ††Defined as ≤ 2 million copies/mL (NGI, sensitivity 100 copies/mL).

in combination with IFN-based preparations.

The optimal dose of ribavirin needed to achieve maximum efficacy with tolerable adverse effects in combination with pegylated IFN is under investigation. The ribavirin dose most extensively studied with IFN alfa-2b is 1,000 mg/day for patients weighing 75 kg or less or 1,200 mg/day for patients over 75 kg, administered in two divided doses.[6,7,11,28] Results of a recent study indicate that for patients infected with HCV genotype 2 or 3, ribavirin 800 mg/day in combination with peginterferon alfa-2a is sufficient.[28] In contrast, for genotype 1 patients, 48 weeks of ribavirin at 1,000 or 1,200 mg/day in combination with peginterferon alfa-2a yielded higher SVR rates compared with lower doses of ribavirin and with shorter treatment durations. The incidence of dose modifications due to anemia was greater in patients receiving 48 weeks of the higher ribavirin dose, compared to those receiving 48 weeks of the lower dose.[28]

The ribavirin dose studied in the peginterferon alfa-2b combination trials was 800 mg/day, independent of weight or genotype.[8,10] A retrospective analysis of patients receiving peginterferon alfa-2b 1.5 µg/kg once weekly suggests that improved SVR was associated with ribavirin doses greater than 10.6 mg/kg per day (or greater than 795 mg/day for an average 75-kg person).[10] Prospective studies of weight-based ribavirin dosing in combination with peginterferon alfa-2b are underway.

4. Pegylated Versus Standard IFN Combination Therapy

Compared to standard IFN, pegylated IFN offers the convenience of once weekly versus three times weekly

TABLE 12.

Comparison of Peginterferon Alfa-2b and Standard IFN Combination Therapies, According to Level of Fibrosis[10,29]

PATIENT GROUP	SVR RATE (95% CONFIDENCE INTERVAL)	
	IFN ALFA-2B PLUS RIBAVIRIN*	PEGINTERFERON ALFA-2B (12 kD) PLUS RIBAVIRIN†
Patients with bridging fibrosis and cirrhosis	41% (33%–50%)	44% (36%–53%)
Patients with no fibrosis or portal fibrosis only	49% (44%–54%)	57%‡ (51%–62%)

Abbreviations: IFN = interferon; SVR = sustained virologic response. *Regimen: IFN alfa-2b 3 million U three times weekly plus ribavirin 1,000 or 1,200 mg/day. †Regimen: peginterferon alfa-2b 1.5 µg/kg once weekly plus ribavirin 800 mg/day. ‡$P < .05$ compared to standard IFN plus ribavirin.

dosing and superior response when used in combination with ribavirin—especially in patients with genotype 1 infection. Pegylated IFNs are associated with a greater incidence of cytopenias and injection site reactions, however, when compared with standard IFN alfa-2b.[8–12]

Peginterferon alfa-2a plus ribavirin is associated with a lower incidence of flulike symptoms and depression compared to standard IFN plus ribavirin.[11] Without direct comparative studies, and with differences in the analyses of adverse effects between the peginterferon alfa-2a and peginterferon alfa-2b combination therapy trials, it's difficult to draw definitive conclusions about safety differences between peginterferon alfa-2a and peginterferon alfa-2b when used in combination with ribavirin.[10,11]

The risks and benefits of both pegylated and standard IFNs in combination with ribavirin should be explored fully prior to initiation of therapy. For example, in patients with compensated cirrhosis, particularly those who have leukopenia prior to therapy, IFN alfa-2b might be preferred because of its shorter half-life and reduced likelihood of cytopenias requiring dose reductions.[10,11,29]

5. Monotherapy with Pegylated or Standard IFN

For patients with contraindications to ribavirin, monotherapy with standard or pegylated IFN should be considered.[26,30] Pegylated IFN monotherapy has been shown to be superior to standard IFN monotherapy, and thus, there are few clinical circumstances in which standard IFN remains indicated as monotherapy.

Indications for Monotherapy with IFN-Based Preparations

Contraindications to Ribavirin

- Renal insufficiency or failure (serum creatinine greater than 1.5 mg/dL); pegylated IFN should be used with caution in patients with a creatinine clearance of less than 50 mL/min, and a dose reduction may be necessary[8,9]
- Anemia (baseline Hb less than 13 g/dL for men or less than 12 g/dL for women)
- History of thalassemia or other hemoglobinopathies,

TABLE 13.

Comparison of Reported Adverse Event Rates for Peginterferon Alfa-2b and Standard IFN Alfa-2b Combination Therapies[8]

ADVERSE EVENT	PEGINTERFERON ALFA-2B (12 kD) PLUS RIBAVIRIN* (N = 511)	IFN ALFA-2B PLUS RIBAVIRIN† (N = 505)
Injection site reaction	75%	49%
Pyrexia	46%	33%
Rigors	48%	41%
Myalgia	56%	50%
Neutropenia	26%	14%
Anemia	12%	17%
Thrombocytopenia	5%	2%
Depression	31%	34%
Irritability/anxiety	47%	47%
Nausea/vomiting	57%	45%
Diarrhea	22%	17%

Abbreviation: IFN = interferon. *Regimen: peginterferon alfa-2b 1.5 µg/kg once weekly plus ribavirin 800 mg/day. †Regimen: IFN alfa-2b 3 million U three times weekly plus ribavirin 1,000 or 1,200 mg/day.

even in the absence of anemia, because of theoretical risk of precipitating profound hemolysis
- Significant cardiac disease (arrhythmias, angina, coronary artery bypass surgery, myocardial infarction) in the past 12 months
- Men and women who fail to practice adequate contraception during the course of treatment and for six months following treatment

Ribavirin Intolerability

The primary adverse effect of ribavirin is hemolytic anemia. While most patients who develop this complication respond to ribavirin dose reductions, some are unable to maintain stable Hb levels with any exposure to the drug. Other significant adverse effects include nausea, vomiting, diarrhea, shortness of breath, and rashes. If these toxicities are intolerable, ribavirin must be discontinued.

SUMMARY

In patients previously untreated for HCV infection, the following regimens are recommended:

- **Genotype 1:** pegylated IFN plus ribavirin 1,000 mg/day (in patients weighing 75 kg or less) or 1,200 mg/day (in patients weighing over 75 kg) in two divided doses
- **Genotype 2 or 3:** pegylated IFN plus ribavirin 800 mg/day in two divided doses OR standard IFN plus ribavirin 1,000 mg/day (in patients weighing 75 kg or less) or 1,200 mg/day (in patients weighing over 75 kg) in two divided doses

Treatment decisions should be individualized based on patient specifics and adverse effect profiles of the IFN-based preparations in combination with ribavirin. Treatment duration should be tailored according to the infecting genotype

TABLE 14.

Comparison of 24 and 48 Weeks of IFN Monotherapy or Combination Therapy[7]

	IFN* PLUS PLACEBO		IFN* PLUS RIBAVIRIN†	
OUTCOME	24 WEEKS	48 WEEKS	24 WEEKS	48 WEEKS
Overall ETR	29%	24%	53%	50%
Overall SVR	6%	13%	31%	38%
Genotype 1 SVR	2%	7%	16%	28%
Genotype non-1 SVR	16%	29%	69%	66%

Abbreviations: ETR = end-of-treatment response; IFN = interferon; SVR = sustained virologic response.
*IFN dose: 3 million U three times weekly. †Ribavirin dose: 1,000 or 1,200 mg/day.

and response to therapy (see "Treatment Duration" on next page).

C. Therapy for Previously Treated Patients

Limited data are available regarding treatment of patients who had an initial response to previous HCV treatment followed by a loss of virologic response (relapsers) and those who were treated previously but never attained a virologic response (nonresponders).

1. Relapsers or Nonresponders to IFN Monotherapy

Both IFN alfa-2b plus ribavirin therapy and IFN monotherapy are FDA approved for treating relapsers to IFN monotherapy.[31,32] Preliminary data suggest that retreatment with pegylated IFN plus ribavirin results in a response of 20% to 25%, which may justify therapy.[33] Since combination therapy has been the standard of care over the past five years, however, few patients currently being evaluated for treatment have received standard IFN monotherapy.

2. Relapsers to Combination Therapy with Standard IFN and Ribavirin

There is insufficient data from clinical trials to recommend retreatment with pegylated IFN plus ribavirin. Clinicians have observed a favorable treatment response, however, in some of these patients.

3. Nonresponders to Combination Therapy with Standard IFN and Ribavirin

Further treatment with pegylated IFN plus ribavirin resulted in an SVR of only about 15% to 20%. Risks and benefits of retreatment should be evaluated on a case-by-case basis.[4] The severity of underlying liver disease, infecting genotype, and tolerability of prior treatment regimens should be included in the decision to retreat.[4] Maintenance therapy with pegylated IFN regimens aimed at inducing viral suppression and preventing complications of liver disease is under evaluation for this population.

D. Monitoring Treatment Safety and Efficacy

1. Monitoring Therapy

Periodic monitoring of such values as Hb, hematocrit, white blood cell count with differential, platelet count, and serum AST/ALT is necessary in all patients receiving HCV an-

tiviral therapy (Table 15). Increasing the frequency of these tests is advised in patients with significant reductions in hematocrit, white blood cell count, or platelet count or who have experienced significant adverse events, including psychiatric disease. Particular attention must be given to the development of anemia in patients receiving combination therapy with IFN-based preparations and ribavirin.

Additional recommendations for monitoring patients during HCV therapy include the following:

- Evaluate patients for treatment-related adverse effects at one- to two-month intervals. Provide guidance in managing these adverse effects.
- Check serum ALT at month 1 and then at two- to three-month intervals to monitor biochemical response.
- Measure HCV RNA by quantitative assay at 12 weeks to assess for EVR. Consider discontinuing treatment in patients who, at this point, have failed to achieve at least a 2 $\log_{10}$ reduction in HCV RNA.[4,28]
- Measure HCV RNA by sensitive assay (lower detection limit of no more than 50 IU/mL) at the end of therapy and six months later to determine the presence and durability of response.
- Evaluate patients for depression at each clinic visit using a standardized questionnaire, such as the Beck Depression Inventory (BDI) or the Brief Symptom Inventory (see Appendix 1 of the VA/DoD Clinical Practice Guideline on the Management of Major Depressive Disorder in Adults, available online at: www.oqp.med.va.gov/cpg/MDD/MDD_cpg/content/appendices/mdd_app1_fr.htm).[34,35] Patients with BDI scores greater than 10 should be evaluated further for depression by a mental health professional and may be considered for antidepressant treatment. Patients with pretreatment scores below clinical cutoffs also should receive a clinical evaluation by a mental health professional if their depression scores increase during treatment.
- Consider urine toxicology screening in patients with a history of a substance use disorder. Assess alcohol intake and illicit drug use monthly. Indications of relapse warrant consultation with treatment specialists.
- Assess adherence to therapy at every visit through patient interviews and prescription reviews.
- To prevent HCV transmission, instruct patients to refrain from donating blood, organs, tissue, or semen. Strongly encourage patients with multiple sexual partners to use safe sexual practices. Advise patients to avoid sharing razors or toothbrushes.
- Measure thyroid function using serum thyroid-stimulating hormone testing every six months.
- Instruct all patients to practice adequate contraception (barrier contraceptives plus at least one other reliable form of contraception) during therapy and for six months afterward. The only exception is patients who underwent surgical sterilization at least one year prior.
- Consider monthly pregnancy tests to aid in timely decision making in the event that a patient becomes pregnant during or six months after therapy.

2. Dose Modification

See Tables 16 and 17 on page 26.

E. Treatment Duration

Recent data with peginterferon alfa-2a in combination with ribavirin at a dose of 800 mg/day suggest that 24 weeks of

TABLE 15.

Monitoring Parameters for IFN-Based Preparations With or Without Ribavirin

PARAMETER	INTERVAL	COMMENTS
Hb, Hct, WBC with differential, platelet count	Week 1 or 2, week 4, then monthly or bimonthly during therapy; monthly intervals are recommended in patients with values below the lower limit of normal	See Tables 16 and 17 on next page for dose modifications
Serum ALT	Month 1, then every two to three months	Monitor when performing other tests
Pregnancy test	Monthly during therapy and for six months after completing therapy	Patients receiving IFN plus ribavirin therapy and their partners should use effective contraception throughout therapy and for six months afterward; if pregnancy occurs, therapy should be discontinued and the pregnancy monitored closely
TSH	Before treatment and at six and 12 months after therapy initiation	If TSH becomes elevated, confirm result and consider thyroid replacement therapy
HCV RNA by quantitative assay	At 12 weeks after therapy initiation	Consider discontinuing treatment in patients who remain viremic at 12 weeks and who have not achieved at least a 2 $\log_{10}$ reduction in viral load from the pretreatment level
HCV RNA by qualitative assay (minimum lower limit of detection of < 50 IU/mL)	End of therapy and six months following the completion of therapy	Essential for defining end-of-treatment and posttreatment response
Assessment for adverse effects and adherence	At each routine visit	Nonadherence impairs response
Depression screen	At each routine visit	For patients screening positive, consider antidepressant therapy or referral to mental health specialist
Substance abuse assessment (history of alcohol, cocaine, opiate, or amphetamine use)	Monthly	If positive, refer to addiction specialist
Liver biopsy	Baseline	Repeat after baseline rarely needed (see "Definition of Response" on page 13)

Abbreviations: ALT = alanine aminotransferase; Hb = hemoglobin; Hct = hematocrit; HCV = hepatitis C virus; IFN = interferon; TSH = thyroid-stimulating hormone; WBC = white blood cell count.

TABLE 16.

General Guidelines for Dose Reduction or Discontinuation of Pegylated or Standard IFN[8,9]

PARAMETER	RECOMMENDATION
WBC	
< 1.5 x 10^9/L	Reduce dose by 50% and reevaluate
< 1.0 x 10^9/L	Discontinue until resolution and reevaluation
Neutrophils	
< 0.75 x 10^9/L	Peginterferon alfa-2a: reduce dose by 25% and reevaluate; peginterferon alfa-2b: reduce dose by 50% and reevaluate; standard IFN alfa: reduce dose by 50% and reevaluate
< 0.5 x 10^9/L	Discontinue until resolution and reevaluation
Platelets	
< 80 x 10^9/L	Peginterferon alfa-2b: reduce dose by 50% and reevaluate
< 50 x 10^9/L	Peginterferon alfa-2a: reduce dose by 50% until resolution and reevaluation; peginterferon alfa-2b: discontinue until resolution and reevaluation; standard IFN alfa: reduce by 50% and reevaluate
< 25 x 10^9/L	Peginterferon alfa-2a: discontinue until resolution and reevaluation; standard IFN alfa: discontinue until resolution and reevaluation

Abbreviations: IFN = interferon; WBC = white blood cell count.

TABLE 17.

General Guidelines for Dose Reduction or Discontinuation of Ribavirin[8,9,*]

PARAMETER	RECOMMENDATION
Hb	
< 10.0 g/dL	Decrease to 600 mg/day in two divided doses
< 8.5 g/dL	Discontinue until resolution and reevaluation

Abbreviation: Hb = hemoglobin. *In patients with stable underlying cardiac disease, it's recommended that ribavirin be reduced to 600 mg/day for any 2-g/dL or greater drop in Hb over a four-week period. If the Hb level is less than 12 g/dL after four weeks of dose reduction, discontinue ribavirin until resolution and reevaluation.

treatment is sufficient for patients with genotype 2 or 3 HCV infection.[28] For patients with genotype 1 HCV infection, however, evidence supports continuing treatment for 48 weeks with a higher dose of ribavirin (1,000 to 1,200 mg/day, based on body weight). It's recommended that these ribavirin doses and

therapy durations also be applied to patients receiving peginterferon alfa-2b combination therapy.

Patients receiving combination therapy with either standard or pegylated IFN who have less than a 2 $\log_{10}$ drop from baseline HCV RNA levels after 12 weeks of treatment rarely attain viral eradication with additional treatment.[22] Therefore, treatment should be discontinued in these patients.

An exception to this is the patient with either moderate fibrosis or cirrhosis who appears to be benefiting in part from treatment (for example, serum ALT has normalized). Such patients clearly are in need of therapy and may derive benefit from its continuation. The risks and benefits of treatment beyond one year for patients who have not achieved viral clearance are under investigation.

SUMMARY

- Treatment duration should be 48 weeks in patients with genotype 1 infection who have an EVR to standard or pegylated IFN in combination with ribavirin.
- Treatment duration should be 24 weeks in patients with genotype 2 or 3 infection who have an EVR to standard or pegylated IFN in combination with ribavirin.
- Treatment generally should be discontinued in patients who have failed to achieve an EVR by 12 weeks.
- In patients who have significant hepatic fibrosis (stage 3 or 4 disease), treatment beyond 12 weeks can be considered, even in the absence of an EVR, particularly if a reduction in viral load has been observed.

POTENTIAL SUPPORTIVE THERAPY

A. Erythropoietin

The kidneys produce the hormone erythropoietin to stimulate erythrocyte production. Recombinant erythropoietin is FDA approved for treating anemia in patients taking zidovudine for HIV,[36] patients with nonmyeloid malignancies receiving chemotherapy,[37] patients with chronic renal failure,[38] and patients who are anemic prior to surgery and do not wish to be transfused.[39] Although erythropoietin is not approved for anemia associated with HCV therapy, some clinicians advocate using it to treat the hemolytic anemia observed in patients receiving ribavirin for chronic HCV infection.

The mean Hb decrease in patients taking ribavirin is 2 to 3 g/dL, a fall that should lead to a ribavirin dose reduction (see Table 17 on previous page). In contrast to drug discontinuation, this reduction appears to have only minor effects on therapeutic efficacy.[22] If erythropoietin can improve treatment response through its effects on ribavirin dosing, it seems that it would be most useful in preventing discontinuation of ribavirin in patients with profound hemolysis.

In one study, 17 patients taking IFN and ribavirin for chronic HCV infection became anemic (median Hb decrease, 3.6 g/dL) and were treated with recombinant erythropoietin 10,000 to 40,000 units SC once weekly.[40] Of these patients, 14 achieved a median Hb increase of 2.7 g/dL and were able to continue IFN plus ribavirin therapy. Fatigue and dyspnea either improved or resolved with erythropoietin treatment.

In an open-label, multicenter study, 44 patients taking IFN and ribavirin for chronic HCV infection became anemic (Hb less than 12 g/dL) during the first six months of treatment. The patients were randomized to receive either epoetin alfa (erythropoietin) 40,000 units SC once weekly for up to 36 weeks or "standard of care" treatment (ribavirin dose reduction for significant anemia). Epoetin alfa significantly increased Hb compared to standard of care treatment (mean change, 2.5 g/dL versus 0.3 g/dL). Alleviation of ribavirin-associated anemia also allowed for higher doses of ribavirin in the epoetin alfa group than in the standard of care group (982 mg/day and 678 mg/day, respectively, at week 16; $P = .003$). Adverse events were similar in both groups. The authors concluded that treatment with

epoetin alfa was well tolerated and permitted the maintenance of "optimal" ribavirin dosing in most patients.[41]

The cost-effectiveness of erythropoietin therapy and the impact on response rates and quality of life remain to be determined. Until such data are available, the routine use of erythropoietin for patients with chronic HCV who become anemic during treatment with IFN and ribavirin cannot be recommended. Dose reduction of ribavirin remains the first intervention in such patients. Administration of erythropoietin 40,000 units SC once weekly may benefit the subgroup of patients with severe symptomatic anemia (Hb below 10 g/dL) and those with persistent symptomatic anemia despite ribavirin dose reduction.

B. Growth Factors for Neutropenia and Thrombocytopenia

IFN causes neutropenia and thrombocytopenia by suppressing the bone marrow production of white blood cells and megakaryocytes, respectively. Both of these cytopenias are more common in patients receiving pegylated IFN than in those receiving standard IFN. (For guidance in modifying standard or pegylated IFN doses in patients who develop neutropenia or thrombocytopenia, see Tables 16 and 17 on page 26.)

Granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor stimulate neutrophil production and reduce infectious complications. Both growth factors have been used to treat neutropenia in patients infected with HIV and in those undergoing cancer chemotherapy.[36,42]

The limited data available on the use of recombinant G-CSF for managing IFN-induced neutropenia in chronic HCV disease and in patients undergoing liver transplantation for HCV suggest that G-CSF increases white blood cell count and may permit administration of full-dose IFN.[43–48] Typical dosing of G-CSF is 300 µg SC on Mondays and Thursdays.[48] The studies of G-CSF have been small and uncontrolled, however, and the treatment's efficacy, cost-effectiveness, and ability to improve HCV treatment responses are unproven. Until such data are available, routine use of G-CSF cannot be recommended for patients with HCV who become neutropenic during IFN therapy.

Thrombopoietin stimulates the production of platelets in the blood. As liver disease worsens, the liver produces thrombopoietin and serum levels decline.[49] Recombinant thrombopoietin is commercially available for the treatment of thrombocytopenia in patients undergoing cancer chemotherapy.[50] One in vitro study has suggested that thrombopoietin may be beneficial for treating IFN-induced thrombocytopenia.[51] Until safety and efficacy data are available, however, thrombopoietin cannot be recommended for patients with HCV who become thrombocytopenic during IFN therapy.

SUMMARY OF CURRENT TREATMENT RECOMMENDATIONS

See Table 18 on next page.

Concluding Comments

Through continued HCV research, response to treatments should improve, adverse effects should be reduced, and populations for whom treatment is appropriate should expand. As these advances occur, new recommendations will be made.

Therapy should be provided to those individuals who are most at risk for progressive liver disease and to those whose quality of life is impaired by HCV infection—as long as they lack contraindications to therapy.

Prospective data are needed on the risks and benefits of treatment in veterans. Much of the data reviewed for these recommendations have been derived from highly selected populations in clinical trials. Extrapolation of outcomes to the general veteran population is problematic.

Additionally, it's essential that safe and effective therapies be developed for those patients who have been served inadequately; those with contraindications to treatment with IFN or ribavirin; and those in whom treatment response is suboptimal. These in-

TABLE 18.

Summary of Current Treatment Recommendations

A. TREATMENT-NAÏVE PATIENTS

- **Patients with genotype 1 HCV and no contraindications to ribavirin:** Pegylated IFN weekly plus ribavirin 1,000 or 1,200 mg/day (in two divided doses) based on body weight, with a decision to continue or withdraw therapy based on virologic response at 12 weeks. In patients with an EVR, treatment should be continued for a total of 48 weeks.
- **Patients with genotype 2 or 3 HCV and no contraindications to ribavirin:** Pegylated IFN weekly plus ribavirin 800 mg/day (in two divided doses) or standard IFN plus ribavirin 1,000 or 1,200 mg/day (in two divided doses) based on body weight, with a decision to continue or withdraw therapy based on virologic response at 12 weeks. In patients with an EVR, treatment should be continued for a total of 24 weeks.
- **Patients with contraindications to ribavirin:** Pegylated IFN once weekly for 48 weeks, with a decision to continue or withdraw therapy based on the virologic response at 12 weeks, regardless of the infecting genotype.

B. RELAPSERS OR NONRESPONDERS TO COMBINATION THERAPY WITH STANDARD OR PEGYLATED IFN PLUS RIBAVIRIN

- **Relapsers to IFN alfa-2b plus ribavirin:** There are no approved therapies for this population. Retreatment with peginterferon plus ribavirin may be considered.
- **Nonresponders to IFN alfa-2b plus ribavirin:** There are no approved treatments for this population. Preliminary results suggest that retreatment with peginterferon plus ribavirin results in low SVR rates.[4]
- **Relapsers or nonresponders to pegylated IFN plus ribavirin:** There are no approved therapies for this population. Treatment with experimental therapies in a clinical trial should be considered.

Abbreviations: EVR = early virologic response; HCV = hepatitis C virus; IFN = interferon; SVR = sustained virologic response.

clude minority populations and patients who have uncontrolled psychiatric disease, use illicit injection drugs, have advanced and decompensated HCV disease, are receiving dialysis for renal failure, experience difficulty adhering to injection regimens, or are coinfected with HIV. These populations often are excluded from currently available treatment. It's likely that, for many, effective therapy will come from drugs in development. Meanwhile, optimization of HCV treatment in veterans requires knowledge of current therapeutic options, enhanced care delivery system, and ongoing clinical and basic research to evaluate the safety and efficacy of current and future treatments.

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NOTES

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