American Gastroenterological Association Technical Review on the Management of Hepatitis C

In the United States, hepatitis C virus (HCV) infection accounts for approximately 40% of all chronic liver disease, results in an estimated 8000–10,000 deaths annually, and is the most frequent indication for liver transplantation.[1–7] The Third National Health and Nutrition Examination Survey, conducted between 1988 and 1994 among 21,000 adults, revealed antibodies to HCV (anti-HCV) in 1.8%, three fourths of whom had detectable serum HCV RNA levels.[8] Generalized to the population of the United States, these findings suggest that approximately 4 million persons have been infected and that 3 million have chronic HCV infection. Among those aged 40–59 years and among black subjects, the prevalence of anti-HCV was even higher. Moreover, the results of such serologic surveys may actually provide conservatively low estimates, failing to include representative proportions of high-risk populations such as injection drug users, incarcerated persons, and homeless persons. Projections based on the current prevalence of infection and anticipated rates of progression raise concerns over the potential impact of HCV during the next 2 decades. A computer cohort simulation of the US population for 2010–2019 suggests that the morbidity and mortality associated with chronic hepatitis C will increase dramatically, resulting in 165,900 deaths from chronic liver disease, 27,200 deaths from hepatocellular carcinoma (HCC), and $10.7 billion in direct medical expenditures related to HCV.[5,9–12] On a global scale, based on current estimates that as many as 175 million persons are infected with HCV, the morbidity, mortality, and current and projected health care costs associated with HCV infection are staggering.

These alarming statistics and projections focus attention on the critical need to prevent and control HCV infection. Although effective vaccines to prevent HCV infection are not likely to be practical, virtual elimination of HCV from the blood supply by donor screening and changes in behavior to prevent HCV infection associated with injection drug use have reduced dramatically the frequency of new infections.[13–19] Still, because of the residua of several decades of high-incidence acute hepatitis C in at-risk populations, a large reservoir of chronic HCV infection persists.[20] Fortunately, substantial progress in antiviral therapy has taken place; this chronic viral disease can be cured in a substantial proportion of patients, and the ultimate impact of hepatitis C is likely to be minimized by these and future advances in management.[21]

To support this technical review,[22] a comprehensive search of electronic databases (including MEDLINE, the Cochrane Database of Systematic Reviews Database of Abstracts of Reviews of Effectiveness, American College of Physicians Journal Club, *British Medical Journal* Clinical Evidence, EMB Reviews, CINAHL, EMBASE, and HealthSTAR) was performed by a professional evidence-based medicine company to identify relevant articles from 1990 to 2003. The search was restricted to articles involving human studies that were available in English. Additional relevant articles published after the search was completed that were identified by the authors were also included.

Screening

In the United States, of the anticipated 3–4 million persons with hepatitis C, only approximately half a million have been treated, and the majority have not been identified. Most diagnoses of chronic hepatitis C are made by medical serendipity, when persons with asymptomatic hepatitis C attempt to donate blood or when they have blood drawn as part of routine medical evaluations or during insurance physical examinations. Because the frequency of hepatitis C in the general population is low (<2%) and because screening tests for anti-HCV, like any other diagnostic test, have a fixed frequency of nonspecificity, routine screening of all asymptomatic adults (who have a low prior probability of HCV infection) is not recommended. For example, among asymptomatic blood donors with an anti-HCV prevalence of 1%–2%, a screening test that is 98%–99% specific is likely to identify as many persons with false-positive as true-positive reactivity. In contrast, among high-risk groups with a high prior probability of true infection (eg, persons who underwent transfusion before 1992 [when donor screening for anti-HCV was intro-

Abbreviations used in this paper: CI, confidence interval; EVR, early virologic response; HAART, highly active antiretroviral therapy; HAI, histologic activity index; HIV, human immunodeficiency virus; IFN, interferon; MU, million units; OR, odds ratio; PEG, pegylated; RCT, randomized controlled trial; SVR, sustained virologic response.

0016-5085/06/$32.00
doi:10.1053/j.gastro.2005.11.010

duced], those with a past or recent history of injection drug use, those with hemophilia who received clotting factors before 1987 [when processing to inactivate viruses was introduced], those with frequent percutaneous exposures, those with clinical or biochemical evidence for chronic liver disease, or immigrants from countries with a high prevalence of HCV infection),[23] true-positive results outweigh false-negative results so substantially that a positive test result is highly predictive of the presence of infection. In such populations, even among asymptomatic persons, diagnostic testing for HCV infection has been recommended by the US Public Health Service, expert panels, and professional medical specialty societies.[23–26]

Recently, the US Preventive Services Task Force concluded, based on a literature-based analysis, that even among high-risk groups and even though antiviral therapy is effective in treating hepatitis C, insufficient data exist to demonstrate that screening in this setting improves long-term outcomes.[27,28] Although such long-term outcome data have yet to be developed, other professional societies and the American Gastroenterological Association take issue with the conclusion of the US Preventive Services Task Force that data do not warrant a recommendation for screening of high-risk persons for hepatitis C. Based on many factors (the documented progression, albeit slow in most cases, of chronic hepatitis C to cirrhosis, hepatic decompensation, HCC, liver transplantation, and/or death[7,29–39]; the documented benefits of antiviral therapy in curing this viral disease in half of treated persons [side effects notwithstanding][40–42]; the slowing among treated persons in progression of fibrosis and even the reversal of fibrosis and cirrhosis among treated patients[43–47]; the potential suggested by some reports for a reduction in HCC among those who achieve sustained virologic responses [SVRs] to antiviral therapy[48,49]; and the impact of antiviral therapy on prolonging survival[50]), the American Gastroenterological Association advocates strongly the position that members of such high-risk groups, even those who are asymptomatic, should be screened for evidence of hepatitis C infection. Patients in these high-risk groups, and especially those with an established diagnosis of hepatitis C, should be counseled about the natural history of hepatitis C; availability, effectiveness, and side effects of therapy; avoidance of alcohol; risk of sexual transmission; and US Public Health Service recommendations for hepatitis A and B vaccination.[23]

Recommendation category: III[22,51] *(Table 1)*

Table 1. Coding System for Hierarchy of Evidence Adopted by the American Gastroenterological Association

Level of evidence	
I	Well-designed RCTs
II-1a	Well-designed controlled trials with pseudo-randomization
II-1b	Well-designed controlled trials with no randomization
II-2a	Well-designed cohort (prospective) study with concurrent controls
II-2b	Well-designed cohort (prospective) study with historical controls
II-2c	Well-designed cohort (retrospective) study with concurrent controls
II-3	Well-designed case-control (retrospective) study
III	Large differences from comparisons between times and/or places with and without intervention (in some circumstances these may be equivalent to level II or I)
IV	Opinions of respected authorities based on clinical experience; descriptive studies; reports of expert committees

NOTE. In an attempt to standardize recommendations, the American Gastroenterological Association Practices Guidelines Committee has developed categories of evidence based on the quality of the data supporting specific recommendations,[22] as adapted from CRD report #4.[51] These are noted at the end of each guideline. When studies of different hierarchical levels support a recommendation, the highest level is cited.

Natural History

After acute HCV infection, most of which is asymptomatic or only mildly symptomatic,[52,53] recovery is the exception; persistent infection occurs in approximately 85% of cases. Among those with chronic hepatitis C, however, the rate of disease progression is variable, and, to some extent, assessments of the natural history of chronic hepatitis C are colored by selection and referral biases; hepatitis C appears to be a more progressive disease in liver specialty clinics and tertiary care centers[30] but much less so in community practices.[29] Retrospective and prospective studies have suggested that progression to cirrhosis during the first 20 years of infection occurs in approximately 20% of patients with transfusion-associated hepatitis and of patients seen in liver clinics[30,54] but in only 7% of patients with community-acquired hepatitis C, only 4% of blood donors with HCV infection, and 2%–4% of young children with transfusion-associated chronic hepatitis C.[29,55] A dramatic dichotomy in progression rates, not explained by demonstrable differences in HCV genotype or other viral factors, is reflected by the 0–2% progression to cirrhosis among young women followed up for 17–20 years after acquiring HCV infection from contaminated anti-D Rh globulin[56,57] versus the 30% progression rate in less than 11 years among patients with agammaglob-

ulinemia who received HCV-contaminated intravenous immunoglobulin.[58]

Estimates based on serial histologic assessments over time or single histologic assessments coupled with assumptions about the duration of HCV infection have suggested that the rate of fibrosis in hepatitis C can be slow, moderate, or rapid[32,59–61]; however, progression of fibrosis may not be linear,[60–62] and determinants of the rate of progression are not known definitively. Potential contributing factors to progressive fibrosis include excessive alcohol intake, concomitant diseases associated with liver injury (eg, hepatitis B, hemochromatosis, steatohepatitis), concomitant human immunodeficiency virus (HIV) infection, advanced histologic grade (ie, necroinflammatory activity), persistently elevated aminotransferase activity, male sex, older age, ethnicity (in some studies, not others), obesity, hepatic steatosis, immunosuppression, and certain HLA haplotypes.[32,54,59,61,63–79]

Among patients with chronic hepatitis C and compensated cirrhosis, the 10-year survival rate is approximately 80%[35] but is lower in other experiences (eg, 8-year survival of 67%[80]); however, the 10-year survival rate decreases to 50% after the first clinical episode of hepatic decompensation (eg, ascites, bleeding esophageal varices, hepatic encephalopathy).[35] In compensated cirrhotic patients with chronic hepatitis C, the annual rate of hepatic decompensation is 4%–5% and of death is 2%–6%.[35,81] Ominously, the risk of HCC is increased after approximately 3 decades of HCV infection, almost exclusively in the group with cirrhosis. Patients with HCV-associated cirrhosis experience an annual incidence of HCC that ranges between 1% and 4% and is up to 7% in some extreme experiences.[35–37,81,82] Currently, one third of all cases of HCC in the United States and 90% of cases of HCC in Japan are associated with chronic hepatitis C; the incidence of HCV-associated HCC has tripled over the past decade in the United States and quadrupled over the past 4 decades in Japan.[37,52,83]

Ultimately, chronic hepatitis C progresses gradually, slowly in some and more rapidly in others. Ideally, with the current limitations and associated side effects of antiviral therapy, treatment should be advised for patients with progressive disease but foregone or postponed in those with early or inactive disease.[26] Of all clinical variables, histologic grade and stage are the most helpful in distinguishing between those who need therapy and those who do not. Because, currently, almost all patients in whom hepatitis C is identified have had the disease for 2–3 decades, liver biopsy provides an assessment of the degree of severity and stage of progression during the previous decades. In addition, histologic analysis of a baseline liver biopsy specimen is valuable not only to estimate the degree of liver injury during previous decades but also prognostically to predict the rate of histologic progression over the future 1–2 decades.[84]

Pretreatment Diagnostic Considerations

Persons with a reactive enzyme immunoassay for anti-HCV and the presence of HCV RNA should be considered as potential candidates for antiviral therapy.[26,69] Because, currently, antiviral therapy is not recommended for patients with hepatic decompensation, patients who have decompensated cirrhosis (Child–Turcotte–Pugh score $\geq$7, history of ascites, bleeding esophageal varices, hepatic encephalopathy) should be excluded.[24,26] A history of severe, uncontrolled psychiatric disorder (eg, severe depression, suicidal ideation) should trigger misgivings about introducing antiviral therapy that can precipitate or aggravate these conditions; however, mild to moderate depression should not be a contraindication.[85] In such cases, antidepressant medication and psychiatric monitoring usually suffice to support a patient through antiviral therapy. Substance abuse and excessive alcohol use have been associated with limited treatment compliance and outcome; therefore, decisions about antiviral therapy in injection drug users and alcoholic persons should be linked with counseling, substance withdrawal programs, and, preferably, a sustained period of abstinence.[26,85–87] Finally, patients with marked leukopenia or thrombocytopenia may not tolerate interferon (IFN), and patients with marked anemia, cardiovascular or cerebrovascular disease, or renal failure may not tolerate ribavirin, which causes dose-dependent hemolytic anemia.[85]

When antiviral therapy was introduced initially, all supporting clinical trials had been conducted in patients with elevated aminotransferase activity; although persons with sustained, normal aminotransferase levels are less likely to progress histologically than those with elevated serum aminotransferase levels,[61,88–91] this group responds to antiviral therapy as well as do patients with elevated aminotransferase activity (see following text).[92,93] Testing for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels is an important component of the diagnostic evaluation in patients with chronic hepatitis C, but elevation of ALT and AST levels is not a requirement for therapy.

Virologic Tests for Monitoring Therapy

All candidates for antiviral therapy should be tested for HCV RNA with a quantitative amplification assay, which provides both a baseline level against which

to monitor virologic response and a prognostic indicator of the likelihood of response. Patients with very high levels of HCV RNA respond less well to antiviral therapy than do those with lower levels. Both target amplification polymerase chain reaction and signal amplification branched DNA assays are available with ranges of quantitation between 10^1 and 10^6 IU/mL.[94,95] These assays are valuable for demonstration of early virologic response (EVR), that is, a $\geq$2-$\log_{10}$ reduction in HCV RNA levels within 12 weeks of initiating therapy (see following text).[41,96] Because these quantitative assays differ in sensitivity and dynamic range, the same assay should be used before and during antiviral therapy.[94,95] For documentation of a virologic response at the end of therapy (end-of-treatment response) or an SVR $\geq$6 months after completing therapy, a more sensitive quantitative HCV RNA assay (such as real-time TaqMan polymerase chain reaction, with a sensitivity threshold of $\leq$50 IU/mL) or a qualitative HCV RNA assay (based on polymerase chain reaction or transcription-mediated amplification, with lower quantitation limits of $\leq$50 IU/mL[94,95]) is recommended.

All candidates for antiviral therapy should be tested for HCV genotype by serologic immunoassay or molecular determination.[42,94,95] Among the 6 known HCV genotypes, most patients in the United States have either genotype 1 (approximately 70%–80%) or genotypes 2 and 3 (20%–30%).[97–100] For patients with the more treatment-refractory (SVR $\leq$40%–50%) genotype 1, a full 48 weeks of therapy with maximum doses of ribavirin (1000–1200 mg/day) is recommended; for patients with the more treatment-favorable (SVR $\geq$80%) genotypes 2 and 3, 24 weeks of therapy with lower-dose ribavirin (800 mg/day) suffices.[26] Patients with genotype 4, uncommonly encountered in the United States but common in Egypt, are intermediate in responsiveness to therapy between that of genotype 1 and genotypes 2 and 3 and are treated for a full 48 weeks with full-dose ribavirin, like patients with genotype 1.[100–103]

Liver Biopsy

Neither clinical nor laboratory markers, individually or in combination, predict accurately the degree of necroinflammatory activity or the level of fibrosis in the liver. Therefore, despite sampling error, liver biopsy remains the gold standard for determining histologic grade and stage.[84] Patients in whom antiviral therapy is being considered are candidates for liver biopsy to assess the current status of the liver and to provide prognostic information for future disease progression.[26,84] If the biopsy specimen documents the presence of moderate to severe fibrosis (Ishak stage $\geq$3, METAVIR stage $\geq$F2; see Table 2),[104,105] progressive fibrosis is likely and antiviral therapy is recommended. If, however, the biopsy specimen demonstrates milder histologic disease, progression may be sufficiently slow to justify monitoring without imminent therapeutic intervention in a proportion of these patients (see Treatment Recommendations).[26] Percutaneous liver biopsy is associated with potential complications, including bleeding (1%–3%), pain (20%–30%), bile peritonitis (<1%), pneumothorax (<1%), punctured viscera (<1%), and death.[84,106–108] Therefore, the threshold for performing liver biopsy may vary with potential for complications (eg, higher in persons with coagulopathy). Furthermore, for patients with genotypes 2 and 3, the likelihood of response is so high and the duration of therapy so much shorter than for genotype 1 that the benefits of treatment may outweigh considerations of disease severity and future potential for progression. Therefore, because of these considerations, some authorities forego a baseline liver biopsy in patients with genotypes 2 and 3, whereas others obtain biopsy specimens before therapy in patients with all genotypes because baseline histology is a predictor of response to therapy that is independent of genotype.[84]

Table 2. Histologic Scoring Systems for Fibrosis

Fibrosis	METAVIR[105]	Ishak[104]
None	0	0
Portal fibrosis (some)	1	1
Portal fibrosis (most)	1	2
Bridging fibrosis (occasional)	2	3
Bridging fibrosis (marked)	3	4
Incomplete cirrhosis	4	5
Cirrhosis	4	6

Finally, obesity[109] and/or the presence of hepatic steatosis[67,68,110] requires histologic evaluation, and steatosis has been shown to be a negative predictor of response to antiviral therapy, especially in patients with genotype 3[111] but also in patients with genotype 1.[110]

Liver biopsies can be performed under ultrasound guidance or by traditional percussive and auscultative localization. Similarly, the procedure can be performed by needle aspiration or by automated biopsy gun. Data to support one approach over another are insufficient to justify mandating a single approach in all cases and by all practitioners, regardless of levels of skill and experience. Every attempt should be made to yield a nonfragmented biopsy core of at least 1 cm in length.

Treatment of Chronic Hepatitis C

Therapy for chronic hepatitis C infection has evolved substantially during the past decade. Initial ther-

apy with IFN alfa had limited success, but the addition of ribavirin and later the pegylation of IFN led to marked improvements in response rates. The current standard of care, therefore, is pegylated IFN (PEG-IFN) and ribavirin,[26] and the rationale for this selection will be reviewed. In addition, the experience with earlier regimens will be reviewed.

IFN Alfa

Initially, when treatment with IFN was first introduced, a 6-month course of thrice weekly injections of 3 million units (MU) was approved. In early studies, the primary end point was a biochemical response, defined as normalization of ALT levels.[112,113] Two meta-analyses, one of 52 randomized controlled trials (RCTs) of treatment with IFN for 3–6 months[114] and another of 33 RCTs of treatment for a full 6 months,[115] showed that IFN monotherapy resulted in normalization of ALT levels by the end of treatment in 51.2% and 45% of subjects, respectively, but in only 21.7% and 21% of subjects, respectively, 3–6 months after discontinuing therapy.

When virologic assays became available to detect HCV RNA, response rates were observed to be lower than those reported with less stringent biochemical end points. In a meta-analysis of 32 RCTs between 1986 and 1996 among patients with chronic hepatitis C receiving IFN alfa-2b (at least 2 MU 3 times weekly for 24 weeks), IFN compared with placebo or no treatment was evaluated in 20 trials, and different doses, durations, or strategies of treatment were compared in 12 trials.[116] Normalization of ALT levels at the end of treatment was seen in 47% of treated patients compared with 4% of controls (odds ratio [OR], 25.1; $P < .0001$) and 6 months after stopping treatment in 23% of treated patients compared with 2% of controls (OR, 17.8; $P < .0001$). End-of-treatment virologic responses, however, were observed in only 29% of treated patients compared with 5% of controls (OR, 9.4; $P < .001$), and 6-month posttreatment SVRs were documented in 8% of treated patients compared with 1% of controls (OR, 8.6; $P < .001$). Higher doses, more frequent injection schedules, different preparations, and induction therapy with high initial doses failed to improve virologic responsiveness. In contrast, a doubling of the duration of therapy to 12 months increased the frequency of SVR to approximately 20%.[116] In addition, several studies demonstrated lower response rates among patients infected with genotype 1, cirrhotic patients, and previous nonresponders to IFN.[117] Among patients who achieved an SVR after IFN monotherapy, biochemical, virologic, and histologic responses were maintained for up to 7–10 years in almost all cases[118,119] and HCV RNA levels were undetectable in the liver in 27 of 27 patients tested, suggesting that SVR is tantamount to cure.[118]

IFN Alfa and Ribavirin

The addition of the synthetic guanosine analogue ribavirin to IFN was a major breakthrough in the treatment of HCV infection. Although ribavirin monotherapy was shown to be ineffective,[120–122] pilot studies had suggested that combination therapy with IFN and ribavirin was more effective than IFN alone.[117,123] A small, double-blind, placebo-controlled RCT showed an SVR in 18 of 50 patients (36%) in the IFN alfa-2b and ribavirin group compared with 9 of 50 patients (18%) in the IFN and placebo group ($P = .047$).[124]

Several landmark studies then followed that consistently demonstrated the dramatically improved responses to combination therapy, especially for patients with genotypes 2 and 3.[125–129] The studies by McHutchison et al and Poynard et al also reinforced the importance of longer-duration therapy for 48 weeks in patients with genotype 1 infection.[126,127] As noted previously, although rare in the United States, genotype 4 HCV infection is common in other parts of the world (eg, Egypt) and, like genotype 1, genotype 4 is more refractory to treatment.[101–103] Predictors of response to therapy in large RCTs are displayed in Table 3.

A systematic review by Kjaergard et al in 2001 for the Cochrane Collaboration included data from 6 trials in which patients received IFN monotherapy or IFN/ribavirin combination therapy.[130] Compared with IFN monotherapy, combination therapy reduced the nonresponse rate (absence of SVR) by 26% in naive patients (relative risk, 0.74; 95% confidence interval [CI], 0.70–0.78). This systematic review also summarized the clinical outcomes for the patients in these 6 trials. In 6 recipients of combination therapy and in 12 recipients of IFN monotherapy, cirrhosis developed despite therapy, as assessed histologically by posttreatment liver biopsy specimens; however, not surprisingly given the brief duration of monitoring in these trials, clinical features of decompensated cirrhosis did not occur in any of the patients. HCC developed in 1 patient who received IFN monotherapy, but none of the patients in either group underwent liver transplantation. One recipient of IFN monotherapy committed suicide, and 1 accidental death occurred in both intervention arms. No significant difference was observed in liver-related morbidity or all-cause mortality after treatment in the combination therapy group versus the IFN monotherapy group, whether cirrhotic subjects were included or excluded from the analysis (Peto OR, 0.45 [95% CI, 0.19–1.06] and Peto

Table 3. Predictors of Response to Antiviral Therapy of Chronic Hepatitis C

Regimen	Non-genotype 1	Low HCV RNA level	Absence of cirrhosis	Female sex	48 weeks of therapy	Age 40 years or younger	Body surface area ≤2 m^2	ALT level ≥3 times the upper limit of normal	Lighter body weight
IFN alfa-2b/ribavirin[126]	✓	✓	✓	✓	✓				
IFN alfa-2b/ribavirin[127]	✓	✓	✓	✓					
PEG-IFN alfa-2a 180 μg[142]	✓	✓	✓			✓	✓	✓	
PEG-IFN alfa-2b 1.5 μg/kg[145]	✓	✓							
PEG-IFN alfa-2b 1.5 μg/kg + ribavirin[40]	✓	✓	[a]			✓			✓
PEG-IFN alfa-2a 180 μg + ribavirin[41]	✓					✓			✓
PEG-IFN alfa-2a 180 μg + ribavirin[42]	✓	[b]			[b]				

[a]Absence of cirrhosis and bridging fibrosis.
[b]For genotype 1 (not for genotype 2 and 3).

OR, 0.29 [95% CI, 0.04–2.10], respectively). Of course, these studies were performed in patients with well-compensated hepatitis C, and the duration of follow-up monitoring in these time-limited trials is much too short to expect a difference in hepatic decompensation or death in a disease whose evolution usually requires decades, not months.

Despite the established contribution of ribavirin to the efficacy of IFN therapy, the mechanism of action of ribavirin in chronic hepatitis C remains controversial. Among the suggested, but not proven, roles for ribavirin in the treatment of chronic hepatitis C are an immunologic modulation (shift from a Th2 to a Th1 response, suppression of interleukin-10 synthesis), inhibition of host inosine monophosphate dehydrogenase activity, depletion of intracellular guanosine triphosphate pools, induction of mutational catastrophe, or a moderate, transient, early direct antiviral effect.[131–140] When used with PEG-IFN, ribavirin has been shown to yield a very short-lived, <1-$\log_{10}$ reduction in HCV RNA levels early during therapy[140] and to increase the slope of the second-phase decline, not influencing the first-phase decline (see Antiviral Therapy and Viral Kinetics) in treatment-associated levels of HCV RNA.[141] Antiviral kinetic modeling supports a direct antiviral effect and excludes an immunomodulatory role for ribavirin.[141]

PEG-IFN Alfa Monotherapy

The attachment of polyethylene glycol to the IFN molecule is the most recent innovation in the treatment of HCV infection. Pegylation reduces the degradation and clearance, prolonging the half-life, of IFN, permitting less frequent, weekly dosing while maintaining higher, sustained IFN levels. In the initial studies of PEG-IFN, including dose-ranging studies, monotherapy was evaluated.[142–145] The two PEG-IFNs were studied: (1) PEG-IFN alfa-2b, a 12-kilodalton linear molecule with a mean terminal half-life of 40 hours and a mean clearance of 94 $mL \cdot h^{-1} \cdot kg^{-1}$, administered on the basis of weight (1.5-μg/kg dose), and (2) PEG-IFN alfa-2a, a 40-kilodalton, branched molecule with a terminal half-life of 80 hours and a mean clearance of 22 $mL \cdot h^{-1} \cdot kg^{-1}$, administered at a fixed, 180-μg dose. These 2 PEG-IFNs each doubled the SVR achieved with their nonpegylated counterparts.[142,144,145] These studies were encouraging, because they demonstrated not only improvement over nonpegylated IFN monotherapy but also, in some studies[142,144] but not all,[146] similarity to SVRs achieved with nonpegylated IFN/ribavirin combination regimens. Thus, these studies set the stage for clinical trials to follow and the anticipation that combination therapy with PEG-IFN and ribavirin would be even more effective. Predictors of response to therapy in the large RCTs of PEG-IFN are displayed in Table 3.

Of note, one of the PEG-IFN monotherapy trials was the first substantive prospective study confined to patients with compensated cirrhosis or advanced fibrosis.[143] Post hoc analyses of data from previous studies had suggested that cirrhosis was a predictor of reduced responsiveness,[126,127,142] and safety concerns had been expressed over treating cirrhotic patients who had leukopenia and thrombocytopenia associated with hypersplenism. This study, however, showed that PEG-IFN monotherapy was both well tolerated and effective (yielding an SVR in 30%) in cirrhotic patients with chronic hepatitis C.[143]

The current role of PEG-IFN monotherapy is imprecisely defined. Although PEG-IFN monotherapy has been recommended for patients with contraindications to ribavirin (eg, those with renal insufficiency, hemoglobinopathies, and ischemic cardiovascular or cerebrovascular

Table 4. Relative Weighting of Predictors of Response to PEG-IFN Plus Ribavirin Therapy Identified by Multivariable Logistic Regression Analyses in RCTs Conducted in Previously Untreated, Immunocompetent Patients With Compensated Chronic Hepatitis C

Clinical trial of PEG-IFN/ribavirin	Alfa-2b[40]	Alfa-2a[41]	Alfa-2a[42]
Non-genotype 1	(<.0001)	3.25 (<.001)	5.4 (<.001)
HCV RNA ≤2 million copies/mL	(<.0001)	NS	1.71[a] (.034)
Absence of cirrhosis/bridging fibrosis	(<.01)	NS	NS
Duration of therapy (for genotype 1)	NA	NA	2.19 (<.0001)
Age 40 years or younger	(<.01)	2.60 (<.001)	NS
Lighter body weight (≤75 kg)	NS	1.91 (.002)	NS

NOTE. Values are expressed as CIs (*P* values).
NS, not significant; NA, not applicable (ie, variable not studied).
[a]Low HCV RNA level was a significant predictor for the subset analysis of 48-week versus 24-week therapy but not for the subset analysis of standard-dose versus low-dose ribavirin therapy (OR, 1.53; 95% CI, 0.93–2.52; $P = .10$).

disease), no clinical trials have been reported to date in these populations. For patients with contraindications to ribavirin but who have indications for antiviral therapy, PEG-IFN represents the best available treatment. Dosing of PEG-IFN should be reduced in patients on dialysis (see End-Stage Renal Disease).

PEG-IFN and Ribavirin

The most recent large clinical trials have focused on treatment with PEG-IFN and ribavirin.[40–42] The earlier two of these studies, involving a uniform 48 weeks of therapy for all patients, have yielded the highest SVRs reported.[40,41] At a weight-based, 1.5-μg/kg dose of PEG-IFN alfa-2b and a fixed, 180-μg dose of PEG-IFN alfa-2a, the overall response rate in clinical trials was 54%–56%; response rates for genotype 1 infection exceeded 40% for the first time and were recorded to be as high as 42%–46%. SVR rates of 76%–82% for genotypes 2 and 3 were also impressive; although these response rates were not necessarily higher than those achieved in these favorable genotypes with nonpegylated IFN plus ribavirin, reduced injection frequency favors PEG-IFN and ribavirin, even for patients with genotypes 2 and 3. Therefore, the combination of PEG-IFN and ribavirin has become the standard of care for the treatment of previously untreated patients with chronic hepatitis C.[26] Predictors of response to therapy in these large RCTs are displayed in Table 3, and the relative weights of the predictors of response in the 3 RCTs of PEG-IFN plus ribavirin are displayed in Table 4. Unfortunately, neither of the PEG-IFN preparations in combination with ribavirin is more effective than standard IFN plus ribavirin in patients weighing ≥85 kg.[147] Now that 2 Food and Drug Administration–approved PEG-IFN preparations are available, comparisons have been made between the results of the initial 2 studies with these 2 drugs in an attempt to determine the better therapy. To date, however, the results of contemporaneous head-to-head comparisons have not been reported; therefore, no definitive conclusions can be drawn. Although comparisons are tempting, the 2 initial trials differed substantially in methodological details and in the composition of the patient populations studied. The best treatment arm in the PEG-IFN alfa-2b study involved a weight-based PEG-IFN dose but a low, fixed 800-mg daily dose of ribavirin.[40] In the trial of PEG-IFN alfa-2a, a fixed dose of PEG-IFN was used but the daily dose of ribavirin was higher (1000–1200 mg), depending on weight <75 kg or ≥75 kg.[41] In the PEG-IFN alfa-2b study, a post hoc analysis demonstrated that an SVR of 61% was achieved in the subgroup whose dose of ribavirin exceeded 10.6 mg/kg.[40] Although the study was not prospectively designed or sufficiently powered to address the contribution of more optimal ribavirin weight-based dosing (in fact, the optimal ribavirin dose has not been defined), another retrospective analysis highlighted the potential importance of higher doses of ribavirin and adherence to treatment,[148] and a suboptimal dose of ribavirin may have had an impact on response rates in the original PEG-IFN alfa-2b/ribavirin trial. In the realm of tolerability, a reduced frequency of depression was observed when PEG-IFN alfa 2a and ribavirin (22%) were compared with non–PEG-IFN alfa-2b and ribavirin (30%).[41] Although the differences in depression between the 2 arms were statistically significant, these data have been criticized because evaluations of depression were subjective, not based on a validated depression instrument. In the PEG-IFN alfa-2b study, depression recorded with a validated instrument was indistinguishable from that observed in patients in the standard IFN alfa-2b plus ribavirin arm.[40]

Similarly, some of the systemic side effects of therapy were less frequent in the PEG-IFN arm than in the standard IFN arm of the PEG-IFN alfa-2a trial but not the PEG-IFN alfa-2b trial[41]; however, again, the fact

that slightly different populations were enrolled in these trials could have accounted for differences in the experience or reporting of such side effects. A considerably larger proportion of subjects with bridging fibrosis or cirrhosis were enrolled in the PEG-IFN alfa-2b/ribavirin trial (29%)[40] than in the PEG-IFN alfa-2a/ribavirin trial (12%).[41] In addition, a larger proportion of patients in the PEG-IFN alfa-2b/ribavirin trial were from the United States (68%)[40] than in the PEG-IFN alfa-2a/ribavirin trial (41%).[41] As has been noted previously in studies including American patients, the mean weight of the patients was slightly higher in the PEG-IFN alfa-2b/ribavirin trial (82 kg)[40] than in the PEG-IFN alfa-2a/ribavirin trial (79.8 kg)[41]; theoretically, this could have favored PEG-IFN alfa-2a/ribavirin. Similarly, the proportion of patients with genotype 1 and high-level HCV RNA levels was imbalanced between the 2 trials, favoring PEG-IFN alfa-2a/ribavirin.[41] Whether one of these PEG-IFN/ribavirin regimens or weight-based modifications of the 2 regimens will prove to be superior is the focus of ongoing trials.

In both of these initial studies, all patients were treated for 48 weeks[40,41]; neither trial addressed the potential for shorter-duration therapy in patients with HCV genotypes 2 and 3. Moreover, PEG-IFN plus ribavirin had proven so effective in preliminary trials that, potentially, full-dose ribavirin might not be necessary and shorter-duration therapy might suffice even for patients with genotype 1. Therefore, in a subsequent registration trial reported by Hadziyannis et al, both the duration of treatment and the dose of ribavirin were evaluated.[42] In this RCT of PEG-IFN alfa-2a (180 μg once a week) plus ribavirin, patients were randomized into 4 groups to be treated for either 24 or 48 weeks and to receive either 800 mg daily or 1000–1200 mg daily (based on weight) of ribavirin. In this study, a high frequency of SVR occurred in patients with genotypes 2 and 3 regardless of the regimen, but optimal frequencies of SVR in genotype 1 (52%, the highest recorded to date) required longer-duration and full-dose ribavirin, independent of the level of HCV RNA (Table 5). Among participants in this trial of PEG-IFN/ribavirin combination therapy, levels of HCV RNA had little impact on frequency of SVR in patients with genotypes 2 and 3, but SVR in patients with genotype 1 treated for a full 48 weeks and with full-dose ribavirin was only 47% for those with HCV RNA levels >2 million copies/mL but as high as 65% for those with HCV RNA levels ≤2 million copies/mL. Therefore, this study supports published recommendations[26,69] that patients with genotype 1 require 48 weeks of therapy with higher doses of ribavirin, while patients with genotypes 2 and 3 can be treated for only 24 weeks and with only 800 mg daily of ribavirin. An RCT of 24 versus 48 weeks of treatment with PEG-IFN alfa-2b plus ribavirin limited to patients with genotypes 2 and 3 demonstrated that 24 weeks of therapy suffices for this PEG-IFN preparation as well.[149] Moreover, in some patients with genotypes 2 and 3, 12 weeks of combination treatment (albeit with full-dose, weight-based ribavirin) may suffice.[150]

Table 5. SVR Rates in the Trial Conducted by Hadziyannis et al[42] in Which Duration of Therapy and Dose of Ribavirin Were Evaluated in Patients Receiving PEG-IFN Alfa-2a/Ribavirin Combination Therapy

PEG-IFN alfa-2a plus ribavirin (*mg/day*)	No.	No. of weeks	SVR (%)	
			Genotype 1	Genotypes 2 and 3
800	207	24	29	84
1000/1200	280	24	42	81
800	361	48	41	79
1000/1200	436	48	52[a]	80[b]

[a]For patients with genotype 1, 48 weeks of therapy was significantly more effective than 24 weeks of therapy ($P < .001$), and standard-dose ribavirin was significantly more effective than reduced-dose ribavirin ($P = .005$).
[b]For patients with genotypes 2 and 3, 48-week duration and standard-dose ribavirin therapy were no more effective than 24-week duration and low-dose ribavirin therapy ($P > .2$).

Included in the large study by Hadziyannis et al[42] of duration of PEG-IFN therapy and dose of ribavirin was a small cohort of 36 patients with genotype 4. None of 5 responded to low-dose ribavirin/short-duration combination therapy, 8 of 12 (67%) responded to full-dose ribavirin/short-duration combination therapy, 5 of 8 (63%) responded to low-dose ribavirin/long-duration combination therapy, and 9 of 11 (82%) responded to full-dose ribavirin/long-duration combination therapy. Thus, although genotype 4 appeared to be more responsive than genotype 1, full-course/full-dose therapy, which can yield SVR rates comparable to those achieved in patients with genotypes 2 and 3, is recommended.

Antiviral Therapy and Viral Kinetics

Pharmacokinetic studies have shown that the reduction in HCV RNA levels during IFN therapy follows a 2-phase pattern. Levels decrease rapidly, declining steeply during the first 2–3 days, consistent with inhibition of HCV replication and/or release; thereafter and lasting for many months, the slope of HCV reduction becomes less steep, which is believed to reflect a different antiviral mechanism (ie, the loss of infected hepatocytes).[151–155] Because SVR has been shown to be more likely after favorable early viral kinetics (ie, a more rapid and profound reduction in HCV RNA levels), induction

therapy (high-dose, more frequent IFN injections for the first several months) was postulated as an approach to achieve higher SVR rates; however, as noted previously, induction therapy is not more effective than standard therapy in achieving SVR.[116,154] As a predictor of SVR, however, an EVR is a valuable clinical milestone, as demonstrated convincingly for data from individual studies and for data pooled from the registration trials of PEG-IFN plus ribavirin.[41,96,156] Achieving an SVR is confined to the subgroup who demonstrate an EVR, defined as a $\geq$2-log$_{10}$ reduction in HCV RNA levels during the first 12 weeks of therapy. Among those with an EVR, the likelihood of an ultimate SVR is approximately 70%. As a negative predictor, EVR is an even more robust predictor. In the absence of an EVR, the likelihood of an SVR is approximately 0–2%.[156] Furthermore, Davis et al[96] reported that, among 380 patients with a $\geq$2-log$_{10}$ reduction in HCV RNA levels during the first 12 weeks of therapy, an SVR was achieved ultimately in 84% of those in whom the 12-week HCV RNA level was undetectable by polymerase chain reaction, compared with in only 21% of those in whom the 12-week HCV RNA level was still detectable.

Another important determinant of responsiveness to antiviral therapy is adherence (especially important in patients with genotype 1). In a retrospective analysis of data collected in the large registration trials of standard IFN and ribavirin, McHutchison et al[148] found that SVR was more likely in patients who had taken at least 80% of all projected IFN injections and at least 80% of all ribavirin capsules for at least 80% of the anticipated duration of treatment.

Histologic Response to Antiviral Therapy

A favorable effect of antiviral therapy on hepatic histology, including fibrosis, has been demonstrated in most studies of IFN monotherapy,[43,45,46,157] and improvement in histologic necroinflammatory activity was not confined to biochemical and virologic responders.[116] This observation suggests that IFN therapy may have a beneficial effect on liver histology even in the absence of an SVR. Similarly, in clinical trials of IFN/ribavirin combination therapy, histologic improvement was documented; in compiled data from 1509 patients included in 3 RCTs, the progression of fibrosis was reduced significantly among IFN/ribavirin-treated patients.[44] SVR, duration of treatment, and baseline fibrosis stage were all predictors of fibrosis reduction in a proportional hazards regression analysis. In a combined database of RCTs of PEG-IFN alfa-2b with or without ribavirin, Poynard et al[158] also found that antiviral therapy was associated with a reversal of cirrhosis. In a recent meta-analysis of 3 RCTs of PEG-IFN alfa-2a versus standard IFN alfa-2a involving 1013 patients with and without cirrhosis,[142,143,146] Cammà et al[47] found that PEG-IFN alfa-2a reduced fibrosis significantly more effectively than IFN alfa-2a and that the improvement in fibrosis was confined to patients with an SVR. In reports by Shiffman et al,[159,160] even nonresponders with reductions in HCV RNA levels demonstrated improvements in necroinflammatory activity and/or fibrosis, while in other analyses, histologic improvement did not correlate with improvements in HCV RNA levels.[44]

Similarly, in a systematic review of the histologic response to IFN/ribavirin combination therapy compared with IFN monotherapy, Kjaergard et al[130] for the Cochrane Collaboration found that combination therapy significantly increased the likelihood of histologic response, expressed as a reduction in the necroinflammatory component of the histologic activity index (HAI) in prior treatment-naive patients (relative risk, 0.83; CI, 0.74–0.93; reported in 5 trials). IFN/ribavirin combination therapy, however, provided no significant benefit compared with IFN monotherapy on the fibrosis score in prior treatment-naive patients (relative risk, 0.93; CI, 0.86–1.02; reported in 4 trials) or in relapsers and nonresponders (relative risk, 0.85; CI, 0.66–1.08; reported in 1 trial).

Such analyses of histologic outcomes in studies of antiviral therapy have been hampered somewhat, but not invalidated, by reduced posttreatment biopsy compliance, consistent among trials. In the most recent pivotal trials of antiviral therapy, rates of biopsies at the end of follow-up ranged from 58%[145] to 67%[144] to 68%[40,127,143] to 73%.[126] (The 2 trials of PEG-IFN alfa-2a plus ribavirin[41,42] did not include assessments of the histologic response to therapy.) Although the low frequency of second biopsies detracts somewhat from confidence in conclusions about histologic outcome of antiviral therapy, in these pivotal trials, for those patients with paired biopsy specimens, Knodell HAI scores[161] improved relatively consistently, necroinflammatory HAI scores in 48%–69% and fibrosis HAI scores in 14%–21% (Table 6).

Effect of Antiviral Therapy on Clinical Outcomes

For the most part, clinical trials of antiviral therapy for chronic hepatitis C have been confined to observations during finite, $\leq$1-year courses of therapy and 6-month posttreatment observation periods.[40–42,112,113,115,116,126,127]

Table 6. Histologic Outcome in Large RCTs of Antiviral Therapy for Chronic Hepatitis C

Regimen	% with improved inflammation (mean change from baseline in HAI)			% with improved fibrosis (mean change from baseline in HAI)		
	All patients	SVR	No SVR	All patients	SVR	No SVR
PEG-IFN alfa-2b 1.5 μg/kg + ribavirin[40]	68 (−3.4)	90 (−5.2)	38 (−0.8)	21 (−0.1)	26 (−0.3)	14 (+0.2)
IFN alfa-2b/ribavirin[40]	69 (−3.4)	91 (−5.3)	44 (−1.1)	20 (−0.2)	21 (−0.2)	19 (−0.1)
PEG-IFN alfa-2b 1.5 μg/kg[145]	48 (−1.5)	77 (−4.0)	36	15 (+0.1)	21 (−0.1)	12
IFN alfa-2b ribavirin for 24 wk[126]	57 (−1.8)	88 (−4.4)	41 (−0.6)	16 (0.0)	24 (−0.2)	12 (+0.2)
IFN alfa-2b/ribavirin for 48 wk[126]	61 (−2.4)	86 (−4.5)	39 (−0.5)	14 (0.0)	16 (−0.1)	12 (+0.2)
IFN alfa-2b/ribavirin for 24 wk[127]	52 (−2.7)			22 (−2.0)		
IFN alfa-2b/ribavirin for 48 wk[127]	63			19		

NOTE. Improvement in inflammation was defined as a decrease of ≥2 in the Knodell[161] necroinflammatory score. Improvement in fibrosis was defined as a decrease of ≥1 in the Knodell[161] fibrosis score.

In addition, except for the earliest of trials in the late 1980s,[112,113,162] the primary end point in most trials has been SVR, a virologic rather than clinical end point. Because of the limited duration of follow-up in these trials, and because the natural history of chronic hepatitis C evolves relatively slowly over many years and even decades in most patients, studies of antiviral therapy have not been designed to address the potential benefits of antiviral therapy on clinical outcomes such as mortality or morbidity. In the systematic review by Kjaergard et al for the Cochrane Collaboration,[130] no significant difference could be detected in liver-related morbidity and all-cause mortality after treatment with IFN/ribavirin combination therapy versus IFN monotherapy. These investigators focused their review on trials of standard IFN therapy and did not include experience with the current standard of care of PEG-IFN and ribavirin. Certainly, trials of antiviral therapy have shown an improvement in quality of life, a measure of improved morbidity, after successful IFN therapy.[163–165] Moreover, Yoshida et al[50] and Kasahara et al[166] have reported prolonged survival and a reduction in complications of liver disease after successful IFN therapy. Based on literature-derived projections of the natural history of chronic hepatitis C and the demonstrated efficacy of antiviral therapy in clinical trials, several groups have performed decision analyses demonstrating that antiviral therapy is cost-effective, not only for patients typically included in clinical trials but also for patients with milder chronic hepatitis C.[21,107,167–169] In these analyses, when the cost of therapy is weighed against the expected clinical outcomes of chronic hepatitis C, treatment can be calculated to reduce direct medical care costs, a model that supports the value of antiviral therapy in reducing the ultimate clinical complications of chronic hepatitis C.

Quite controversial is the potential effect of antiviral therapy on the occurrence of HCC. More than a dozen reports, as reviewed by El-Serag,[37] have appeared in the literature purporting to show a reduction in the incidence over time of HCC in IFN-treated versus untreated or in IFN-responsive versus IFN-nonresponsive subjects.[48,49,81,170,171] Only one of these reports was described as being a prospective RCT[49]; however, in this trial, the extraordinarily high (38%) frequency of HCC in the untreated control group and the reduction in HCC even in IFN nonresponders generated reservations about the conclusions of the study. The rest of these studies were either not randomized or retrospective and therefore were potentially influenced by lead-time bias favoring treatment of patients with earlier-stage disease. Thus, the observed reduction in HCC among treated patients may have reflected the inclusion in treated groups of patients with earlier-stage disease in whom the risk of HCC was lower, rather than reflecting the benefits of treatment.[37,172,173] In contrast, several retrospective and prospective trials failed to detect any reduction in HCC among cirrhotic patients with chronic hepatitis C treated with IFN.[35,174,175] Currently under way are at least 3 prospective, randomized trials of maintenance PEG-IFN therapy among patients with chronic hepatitis C and advanced fibrosis designed to determine the impact of such protracted treatment in the subset of patients at increased imminent risk of decompensation and HCC.[176]

Side Effects of Therapy

Side effects during therapy for chronic hepatitis C with IFN or PEG-IFN include the following: (1) flu-like systemic symptoms; (2) marrow suppression (primarily leukopenia and thrombocytopenia); (3) emotional effects such as irritability, difficulty concentrating, disturbed memory, and depression; and (4) autoimmune reactions, the most common of which is autoimmune thyroiditis.[40–42,112,126,142,143,145,177–179] Neutropenia is more likely in patients receiving PEG-IFN than in those receiving standard IFN; in combination IFN/ribavirin trials, dose reductions associated with neutropenia were

more likely in PEG-IFN recipients (18%–20%) than in standard IFN recipients (5%–8%).[40,41,177] Although neutropenia is common in IFN recipients, the risk of infection remains low, even for patients with absolute neutrophil counts $<500/mm^3$ [179,180]; therefore, although careful monitoring and clinical vigilance is indicated for severe neutropenia, granulocyte colony-stimulating factor therapy is required very rarely. In addition to these 4 broad categories of adverse events, treated patients may experience hair thinning and loss, insomnia, visual disorders (including, rarely, retinal hemorrhages, which are more likely in patients with preexisting vascular disorders such as diabetes and hypertension), fatigue, weight loss, hearing impairment, interstitial pneumonitis, pancreatitis, colitis, and exacerbation of inflammatory diseases such as psoriasis.[177] Flu-like symptoms respond to acetaminophen or nonsteroidal anti-inflammatory drugs, sleep-promoting agents are used for insomnia, and antidepressants can be used to counter symptoms of depression.[177]

Ribavirin contributes additional side effects, the most important of which is hemolytic anemia.[181] A meta-analysis of data from 17 studies revealed an overall increased risk (ribavirin versus no ribavirin) for anemia of 9% (CI, 4%–13%),[182] which was higher in 2 Asian studies with risk differences of 29% and 22% than the pooled risk difference of 7% (CI, 3%–12%) for the 15 non-Asian studies in the meta-analysis. Not surprisingly, the risk associated with ≥1000 mg of ribavirin daily was higher (risk difference, 9%; CI, 4%–14%) than that for 800 mg of ribavirin daily (risk difference, 1%; CI, 4%–6%).

In a systematic review, IFN/ribavirin combination therapy was found to increase the risk not only of anemia but also of other adverse events over those observed in recipients of IFN monotherapy.[130] In the combination therapy versus monotherapy group, the relative risk of anemia was 16.67 (CI, 5.68–48.89; reported in 17 trials), of cough was 1.66 (CI, 1.19–2.31; reported in 3 trials), of dyspepsia was 1.72 (CI, 1.17–2.54; reported in 4 trials), of dyspnea was 2.03 (CI, 1.49–2.77; reported in 2 trials), of leukopenia was 4.52 (CI, 1.55–13.23; reported in 1 trial), of pharyngitis was 1.55 (CI, 1.14–2.12; reported in 2 trials), of pruritus was 2.32 (CI, 1.75–3.08; reported in 9 trials), and of rash was 2.37 (CI, 1.58–3.56; reported in 7 trials). Sinusitis is also associated with ribavirin. Dose reductions were more likely in the combination therapy group (relative risk, 2.44; CI, 1.58–3.75; reported in 19 trials), as was treatment discontinuation (relative risk, 1.28; CI, 1.07–1.52; reported in 25 trials). Precipitation of gout has also been observed in ribavirin-treated patients, and, because the drug is renally excreted, ribavirin should be avoided in patients with renal insufficiency. Similarly, because ribavirin is teratogenic in animals, the drug is contraindicated in pregnancy, necessitating strict precautions and rigorous contraceptive practices in women of childbearing potential and their male sexual partners. In registration trials of PEG-IFN/ribavirin combination therapy, side effects and laboratory abnormalities led to dose reductions in 36%–45% and to drug discontinuation in 5%–16%.[40–42]

Complicated as it is by anemia, ribavirin should be avoided in patients with severe anemia and in populations who cannot tolerate the onset of anemia, such as those with ischemic cardiovascular and cerebrovascular disease. If symptomatic anemia occurs during ribavirin therapy, the dose of ribavirin can be reduced or erythropoietin can be added. Preliminary studies suggest that erythropoietin injection therapy improves some of the symptoms of anemia, improves quality-of-life and fatigue scores, and allows the maintenance of higher doses of ribavirin[183–185]; however, to date, an increase in EVR or SVR rates has not been evaluated or demonstrated. Currently under investigation are second-generation ribavirins such as the ribavirin prodrug viramidine, which is "targeted" to the liver by the requirement for hepatic metabolism to the active ribavirin metabolite[186,187]; in preliminary trials, viramidine plus PEG-IFN has been associated with less frequent and less severe anemia.[188] If confirmatory trials demonstrate a similar efficacy and safety of viramidine, the need for ribavirin dose reductions and/or red blood cell growth factors will likely be minimized.

Although severe depression and suicide attempts are rare among treated patients, these psychiatric side effects merit special concern. In the large randomized trials of standard IFN plus ribavirin, PEG-IFN monotherapy, and PEG-IFN plus ribavirin, depression was the most likely cause for premature discontinuation of therapy[126] and the most severe psychiatric side effect[142]; deaths resulting from suicide occurred in 1 patient in an IFN/ribavirin re-treatment trial of nonresponders[178] and in 1 patient in 1 of the 3 trials of PEG-IFN/ribavirin combination therapy.[42]

In the study of PEG-IFN monotherapy in patients with cirrhosis (or advanced fibrosis) by Heathcote et al,[143] 2 liver failure deaths and 1 HCC-associated death occurred half a year to more than 1 year after therapy, and 1 death resulting from a cerebral hemorrhage after a suspected methadone overdose occurred 24 days after the completion of treatment. Generally, patients with compensated cirrhosis tolerate antiviral therapy well, but extra vigilance is required in this subpopulation.[26,101,143,189,190] For patients with de-

compensated cirrhosis, IFN-based antiviral therapy has been linked to life-threatening adverse events[189,191] and is not recommended routinely.[26,190] Instead, such patients should be referred for assessment as candidates for liver transplantation. In selected liver transplantation centers, prospective trials of "gingerly" administering low-dose, progressively escalated IFN are in progress in an attempt to reduce the HCV burden before transplantation and to minimize the risk of posttransplantation reinfection.[192–196]

Management of side effects is especially critical to improve adherence to therapy.[148] Patients are more likely to complete therapy when substantial support is provided by the clinical team, and support personnel lend substantially to this effort.[26,177]

Treatment Recommendations

For previously untreated patients with chronic hepatitis C, circulating HCV RNA, elevated aminotransferase levels, evidence on liver biopsy of moderate to severe hepatitis grade and stage (METAVIR stage ≥F2, Ishak stage ≥3, septal or bridging fibrosis), and compensated liver disease, PEG-IFN and ribavirin are recommended.[26,69] A combination of weight-based PEG-IFN alfa-2b (1.5 μg/kg) or fixed-dose PEG-IFN alfa-2a (180 μg) by subcutaneous injection once a week plus daily oral ribavirin is the treatment of choice. The results of a single, large RCT[42] support a recommendation that patients with more treatment-refractory genotype 1 require 48 weeks of therapy with higher daily doses of ribavirin (in divided doses administered twice daily; 1000–1200 mg, depending on weight <75 kg or ≥75 kg), while patients with the more treatment-favorable genotypes 2 and 3 can be treated for only 24 weeks and with only 800 mg daily of ribavirin (in divided doses administered twice daily). Moreover, 12 weeks of therapy suffices in patients with genotypes 2 and 3 in whom HCV RNA levels are undetectable at week 4.[150] In the group of patients with genotypes 2 and 3, patients with genotype 2 are more likely than those with genotype 3 to achieve an SVR[149]; for patients with genotype 3 who have high levels of HCV RNA or advanced fibrosis on liver biopsy, many authorities recommend treatment for 48 weeks. For patients with genotype 4, 48 weeks of PEG-IFN plus full-dose ribavirin (1000–1200 mg) is recommended. (Based on data in the registration trial of PEG-IFN alfa-2b plus ribavirin,[40] a ribavirin dose of only 800 mg/day was approved for routine use of this combination regimen, regardless of genotype; however, the consensus of most authorities is that the higher, weight-based dose of ribavirin should be used in patients with genotype 1.[26,69,197])

Recommendation category: I

For patients with milder histologic changes (METAVIR stage F1, Ishak stage <3) (and normal serum aminotransferase activity; see following text), the risk of disease progression is lower.[32,61,91] Although trials designed to demonstrate the efficacy of contemporary combination antiviral therapy were not powered to address patients with mild histology specifically, such patients appear to respond as well as, or even better than, patients with more advanced histologic changes.[92] Therefore, decisions about this subgroup of patients can be individualized; such patients can be counseled about the low risk of progression but still can be offered therapy (see following text). If a decision is made to defer therapy in patients with mild disease, periodic laboratory and histologic monitoring should be pursued.[26] Some authorities have suggested repeat liver biopsies at 3-year intervals[26]; however, data to support a recommendation on the frequency of histologic monitoring are wanting. Current contraindications to therapy include decompensated cirrhosis, pregnancy, uncontrolled depression or severe mental illness, active substance abuse in the absence of concurrent participation in a drug treatment program, advanced cardiac or pulmonary disease, severe cytopenias, poorly controlled diabetes, retinopathy, seizure disorders, immunosuppressive treatment, autoimmune diseases, or other inadequately controlled comorbid conditions.[24,26,198] Although these contraindications excluded a large proportion of potential candidates in the clinical trials that validated antiviral therapy,[198] efficacy and tolerability of antiviral therapy in clinical practice are very similar to those reported in multicenter, registration trials.[199]

Recommendation category: I

Before therapy, baseline quantitative HCV RNA levels should be determined, and the same quantitative assay should be repeated at 12 weeks. Failure to achieve a ≥2-$\log_{10}$ reduction in HCV RNA levels (EVR) predicts ultimate failure to achieve an SVR with almost 100% certainty.[41,96,156] Therefore, and especially for persons who tolerate therapy poorly, many authorities discontinue therapy after 12 weeks for patients who have failed to achieve an EVR.[26] Because histologic benefit may accrue even in the absence of an SVR,[116,159,160] some authorities treat beyond 12 weeks even in patients who have not achieved an EVR. Testing for HCV RNA with a qualitative assay or a more sensitive quantitative assay is helpful at the completion of therapy to determine whether an end-of-treatment response has occurred and at 24 weeks after completing therapy to establish whether an SVR has occurred.[26,156] Achieving an SVR at 6 months posttreatment is likely to be maintained indefinitely in ≥98% of patients, and a 2-year SVR represents a cure in all cases.[43,45,118,119,200]

In the absence of contraindications, liver biopsy is recommended before therapy to assess the degree of inflammation and fibrosis.[24,26,84,201] Because most patients with chronic hepatitis C have had the disease for several decades before coming to medical attention, a baseline biopsy specimen provides information on the histologic toll of HCV infection in the past. In addition, histologic grade and stage are the best predictors of future progression of hepatitis C to cirrhosis[32] and good predictors of response to therapy.[40,126,127,142,202] Patients with moderate to severe hepatitis C are candidates for therapy, while those with mild hepatitis (METAVIR stage <2, Ishak stage <3) may progress sufficiently slowly to justify withholding or postponing therapy and reliance on monitoring alone[26] (see following text). Because the response to antiviral therapy is so high in patients with genotypes 2 and 3, some authorities treat this subgroup without a baseline biopsy.[84]

Clinical and virologic monitoring during therapy should be conducted at intervals ranging from once a month to once every 3 months. Frequent hematologic monitoring is necessary to identify marked anemia, neutropenia, and thrombocytopenia; monitoring of thyroid-stimulating hormone levels is indicated to identify hypothyroidism or hyperthyroidism. Dose reductions of PEG-IFN and ribavirin are recommended for hematologic thresholds reviewed in Table 7. Clinicians treating patients with hepatitis C should monitor carefully for clinical signs of depression and intervene appropriately (eg, frequent in-person or telephone contacts for mild depression, more frequent/intense monitoring, dose reductions of 25%–50%, and/or the addition of antidepressant medications for moderate depression, and discontinuation of antiviral therapy and psychiatric consultation/therapy for severe depression).

Recommendation category: I

Recommendations and their rationale for other populations, most of whom were not addressed in registration trials, are reviewed in the following text.

Table 7. Recommended Thresholds for Drug Dose Reductions in Patients Treated With PEG-IFN and Ribavirin for Chronic Hepatitis C

Hematologic threshold	Dose reduction[a]
Absolute neutrophil count (/mm^3)	
500–750	Reduce PEG-IFN dose[b]
<500	Withhold PEG-IFN
Platelet count (/mm^3)[c]	
25,000–50,000	Reduce PEG-IFN dose[c]
<25,000	Withhold PEG-IFN
Hemoglobin (g/100 mL)	
≤10	Reduce ribavirin dose[d]
≤8.5	Discontinue ribavirin[d]

NOTE. These recommendations may be useful in monitoring therapy but do not represent absolute guidelines; those who treat patients with chronic hepatitis C rely on discretion and close monitoring of their patients. Attempts can be made to reinstitute therapy or to resume full/higher-dose therapy after cytopenias improve or resolve.
[a]The magnitude of dose reductions differs between the 2 PEG-IFN preparations, as noted in the following footnotes.
[b]For PEG-IFN alfa-2b, reduce dose by 50%; for PEG-IFN alfa-2a, reduce dose to 135 μg.
[c]The platelet thresholds cited appear in the product insert for PEG-IFN alfa-2a (dose reduction to 90 μg); in the product insert for PEG-IFN alfa-2b, the platelet threshold for dose reduction is 80,000/mm^3 (dose reduction 50%) and for drug discontinuation is 50,000/mm^3.
[d]For PEG-IFN alfa-2b, a dose reduction of 200 mg is recommended; for PEG-IFN alfa-2a, reducing the dose to 600 mg/day is recommended. Alternatively, erythropoietin can be administered.

Other Patient Populations

Patients with mild hepatitis C and/or normal ALT levels. Several studies have shown that patients with persistently normal ALT levels demonstrate less evidence of histologic progression than patients with elevated ALT levels, as documented by serial liver biopsy specimens, during intervals of up to 5 years.[61,88–91] Therefore, some clinicians choose to monitor such patients without therapy. In fact, among patients with normal ALT levels monitored for 5 years, levels of ALT become elevated in approximately one fifth to one fourth,[89] reinforcing the importance of close monitoring in this population. Similarly, as noted previously, histologic progression is much less likely in patients with histologically mild chronic hepatitis C.[32] Finally, in early trials of IFN monotherapy among patients with normal ALT levels, response rates were low, and elevations of ALT levels during therapy were a cause for concern.[24] Histologic stability notwithstanding, however, in patients with mild disease (low grade and stage)[203] and/or normal ALT levels,[92,93,204–207] IFN/ribavirin combination therapy and PEG-IFN/ribavirin combination therapy have been shown to achieve response rates comparable to those seen in patients with more biochemically active and histologically advanced disease, and elevations of ALT levels during combination therapy have not been observed.[92,93,204–208] Similarly, decision analyses in patients with biochemically and histologically mild chronic hepatitis C have led to the conclusion that, even in this population, antiviral therapy is cost-effective.[168,169,209] Therefore, many clinicians choose to include patients with persistently normal ALT levels and/or histologically mild chronic hepatitis C as candidates for antiviral therapy. Given the borderline indication for therapy in this group and the factors weighing for and against treatment, clinicians may rely in their decision making on individual patient features, including patient motivation and perspective, genotype,

relative histologic activity and fibrosis, duration of HCV infection, age, occupation, symptoms, and so on. As therapy becomes more effective and better tolerated, the threshold for treating will be lowered; inevitably, highly effective therapy with few side effects will be offered routinely even to patients with very mild disease.

Recommendation category: I

Fibrosis/cirrhosis. Although their likelihood of responding is lower than that identified in large-scale registration trials involving primarily noncirrhotic patients, patients with compensated cirrhosis or advanced fibrosis who can tolerate and respond to therapy are candidates for treatment.[40,126,127,142,143,189,210] As response rates have increased overall with IFN/ribavirin combination regimens, the response rates observed in the subgroups of patients with bridging fibrosis and cirrhosis have also increased and are now approximately 40%, depending on HCV genotype.[42] In patients with advanced fibrosis or cirrhosis included in registration trials of PEG-IFN plus ribavirin, however, SVR rates for PEG-IFN/ribavirin combination therapy (43%–44%) were no higher than response rates for standard IFN/ribavirin combination therapy (41%).[40,190] Still, and baseline cytopenias in cirrhotic patients notwithstanding, PEG-IFN plus ribavirin is a more convenient and no less effective regimen and is recommended in this subpopulation, as it is in noncirrhotic patients.

Recommendation category: I

In patients with decompensated cirrhosis (bilirubin level >1.5 mg/100 mL; prothrombin time >15 seconds [international normalized ratio, ≥1.7]; albumin level <3.4 g/100 mL; history of ascites, bleeding esophagogastric varices, or hepatic encephalopathy), antiviral therapy is not recommended[191]; these patients should be referred for evaluation as liver transplantation candidates.[26]

Recommendation category: IV

Previous relapse and nonresponder patient populations. A recent analysis of 624 patients with end-of-treatment responses to IFN-based therapy showed that 98% of all relapses occur within the first 12 weeks after cessation of therapy.[211] Patients who experience a relapse (ie, in whom HCV RNA becomes undetectable during and at the end of therapy but reappears again after completion of therapy) are likely to respond and experience a relapse again with a subsequent course of the same therapy. The chance of achieving an SVR in relapsers, however, may be as high as 40%–50% if re-treatment is pursued with more effective therapy.[178] If this group of patients is to be re-treated, ideally, a different, more effective regimen should be used.[130,173,178,210,212–214] For example, in the largest trial reported among relapsers to standard IFN, a course of standard IFN plus ribavirin resulted in an SVR in 50% of patients.[178] Similar findings have been reported in other studies.[215–220] In the same vein, relapsers after a course of standard IFN monotherapy or of standard IFN/ribavirin combination therapy are candidates for PEG-IFN plus ribavirin. One supportive prospective trial demonstrated an SVR in 42% of patients who, having experienced a relapse previously after being treated with standard IFN and ribavirin, were re-treated subsequently with PEG-IFN and ribavirin for 48 weeks.[221]

Among prior nonresponders to standard IFN, re-treatment with standard IFN/ribavirin combination therapy yields only a small increment in SVR (≤15%), as determined in randomized trials or in meta-analyses of published trial results, regardless of which IFN preparation is used.[130,173,204,212,216,218,219,222–224] For nonresponders to a previous course of standard IFN, with or without ribavirin, re-treatment with PEG-IFN plus ribavirin increases the frequency of responsiveness.[204] This approach has been shown in a trial involving 604 patients with advanced fibrosis to result in an end-of-treatment response in 35% but an SVR in only 18%.[176,212] The likelihood of achieving an SVR was increased (as determined by multivariable regression analysis) in previous IFN monotherapy recipients (28%), those with genotypes 2 (65%) and 3 (54%), noncirrhotic patients (23%), patients with an AST/ALT ratio ≤1 (23%), and patients with a baseline HCV RNA level <1.5 million IU/mL (27%).[176] One third of those who achieved an EVR eventually achieved an SVR, while the SVR rate in the absence of an EVR was only 1%.[176] Perhaps the most relevant observation in this study was the fact that, among patients who had failed in the past to respond to a course of standard IFN plus ribavirin, only 12% achieved an SVR when re-treated with PEG-IFN plus ribavirin. Among those whose dose of ribavirin during the first 20 weeks of therapy was ≥80% of the target dose, compared with those whose doses were reduced to ≤60% of the target dose, SVRs occurred in 21% and 11%, respectively.[176] These factors, in addition to a patient's tolerance to previous therapy and severity of underlying liver disease, should be taken into consideration when making individualized decisions about the re-treatment of prior nonresponder patients.

Recommendation category: I

Acute hepatitis C. Acute HCV infection is usually asymptomatic and, consequently, primarily clinically inapparent.[18,52,53] This observation and the markedly reduced annual incidence of cases of acute hepatitis

C reported over the past decade[17] have limited attempts to conduct clinical trials in patients with acute hepatitis C. Most of the early literature included multiple, small, uncontrolled trials of differing design, some with biochemical and others with biochemical and virologic end points, but several controlled trials have been subjected to meta-analyses. One meta-analysis included data from 4 randomized, placebo-controlled but not blinded trials[115] that included an enrollment range of 25–48 patients. Patients were treated with either 3 MU of IFN alfa-2b 3 times per week for 3 months in 3 trials or 3 MU daily of IFN beta for 5 days followed by 3 MU 3 times per week for 3 weeks in the fourth trial. An SVR, as measured 12 months after stopping therapy, occurred in 41% of treated patients compared with 4% of control patients ($P < .001$). Another meta-analysis included these 4 trials plus 5 others (total of 9 studies, 5 randomized and 4 nonrandomized, 8 involving IFN versus no treatment and 1 involving different IFN schedules)[225] identified by a MEDLINE search; however, an SVR was reported in only 5 trials. In these 5 trials, SVR was 44% more frequent in treated than in untreated groups, a marked effect in favor of treatment ($P < .0001$; 95% CI, +33% to +56%). In another meta-analysis that included both RCTs and nonrandomized trials, patients treated with IFN alfa and IFN beta were analyzed separately.[226] Among the studies involving treatment with 3 MU of IFN alfa-2b 3 times a week for 6–24 weeks, SVR was increased by 33% in treated patients (95% CI, +8% to +58%; $P < .001$). The analysis of studies involving daily intravenous IFN beta for 4–7 weeks favored treatment by a gain in SVR of 83% (95% CI, 61%–100%; $P < .001$); however, the use of such an intensive intravenous approach to therapy and reliance on IFN beta have been confined to Japan, are not available in the United States or Europe, and can be matched in efficacy by less invasive approaches (see following text). These early meta-analyses, however, do appear to support a role for antiviral therapy during acute hepatitis C.

Others have reported the results of small trials in which short-course, high-dose (ie, daily) therapy was initiated during acute hepatitis C, but results were mixed and the efficacy of treating for limited periods (eg, until normalization of ALT levels[227] or for approximately 1 month[228,229]) was unconvincing. The most compelling study reported was a prospective, multicenter, open-label, uncontrolled German trial in which 44 patients with acute hepatitis C were treated, beginning at a mean of 89 days after infection, with 5 MU of IFN alfa-2b daily for 4 weeks and then 3 times per week for another 20 weeks, which was well tolerated; SVR assessed 6 months after completion of therapy was achieved in 43 patients (98%).[230] Although no untreated control group was included in this trial, in another German study, spontaneous clearance of HCV infection occurred in 52% of patients with acute hepatitis C, predominantly in those with symptomatic acute infection.[231] The excellent results of the German treatment trial,[230] despite the approximately 3-month delay in initiating treatment, suggest that a period of observation to allow for potential spontaneous viral clearance before initiating antiviral therapy may not affect response rates adversely. Similarly, because the likelihood of acute HCV infection after an accidental needlestick is only approximately 3% and because antiviral therapy initiated after the onset of hepatitis C viremia is so effective, treatment to prevent HCV infection need not be initiated prophylactically after needlestick exposure.[23]

A recent study of antiviral therapy in patients with acute hepatitis C revisits the concept of high-dose, short-term therapy. Nomura et al[232] reported the results of an RCT of short-term, early treatment versus late treatment in Japan. Thirty patients with acute hepatitis C were randomized to receive 6 MU of lymphoblastoid IFN administered intramuscularly daily for 4 weeks, beginning either 8 weeks after the onset of acute hepatitis or after 1 year of observation. In the early intervention group, 13 of 15 (87%) achieved an SVR; in the other 2 patients, who experienced a relapse after the initial 4 weeks of therapy, an additional 20 weeks of treatment (this time with 6 MU intramuscularly 3 times weekly) resulted in an SVR (total, 100% SVR). In the 1-year delayed-treatment group, an SVR was achieved in only 40% after 4 weeks of daily therapy and in an additional 2 patients only after 20 more weeks of thrice-weekly therapy (total, 53% SVR). These findings suggest that a brief course of antiviral therapy may suffice in the majority of patients with acute hepatitis C, an observation that reinforces the importance of relatively early intervention. On the other hand, daily intramuscular injections limit the appeal of this approach.

Based on available data, patients with acute hepatitis C are candidates for antiviral therapy.[26,69,233] Because of the dramatic effect of standard IFN monotherapy in patients with acute hepatitis C, some have argued that monotherapy suffices and that ribavirin is not required.[234] Preliminary data suggest that PEG-IFN monotherapy for 24 weeks results in SVR rates comparable to those observed with the intense IFN regimen used in the German trial described previously.[234] In another study of 40 patients with acute hepatitis C, half received PEG-IFN monotherapy and half received PEG-IFN/ribavirin combination therapy for 24 weeks; an SVR occurred in 80% of the monotherapy group and 85% of

the combination therapy group.[235] Given the enhanced efficacy of PEG-IFN/ribavirin combination therapy in patients with chronic hepatitis C, conventional doses of such combination therapy may represent a reasonable approach to treatment of patients with acute hepatitis C. In fact, the optimal regimen, dose, time to initiate therapy, duration of therapy, or benefit of adding ribavirin to IFN therapy have not been established, and the infrequency of acute hepatitis C will likely confound the prospective comparison of different treatment regimens. Based on available data, many authorities would initiate treatment within no later than 2–3 months after the onset of acute hepatitis and would extend combination therapy for at least 24 weeks.[233]

Recommendation category: II-2b

Injection drug use. In the past, injection drug use was considered a contraindication to antiviral therapy of hepatitis C[24]; however, currently, injection drug users represent one of the largest groups with chronic hepatitis C and the subpopulation most likely to be infected acutely with HCV.[17,66,86,198,236] During the 2002 National Institutes of Health Consensus Development Conference on Management of Hepatitis C, attention was focused on this overlooked patient group, previously excluded from most clinical trials.[26,85,86] For active injection drug users, compliance is a concern, as are psychiatric side effects of IFN-based therapy and the risk of HCV reinfection. Similarly, for recovered injection drug users, which includes those in methadone maintenance programs, the psychiatric side effects of antiviral therapy and the availability of syringes and needles required for therapy were considered potential barriers.[86,237]

Experience in treating both active and recovered injection drug users has been very limited; however, in preliminary trials, both groups have been treated, with SVR rates comparable to those achieved in non-drug users.[238–241] Compliance has been reduced substantially in some studies but not in others, particularly in those with recent injection drug use; psychiatric comorbidity, as anticipated, is more common than in patients without a history of injection drug use, but these patients can be treated effectively. Decisive ingredients for success in this patient population, however, are participation of health professionals experienced in addiction medicine in their treatment and linkage of antiviral therapy with ongoing drug treatment programs.[26,86,237]

These early, encouraging data indicate that injection drug users with hepatitis C can be treated successfully; therapy is recommended for recovered drug users, including those on methadone maintenance, and, based on a case-by-case review, for active drug users, especially when in conjunction with drug treatment programs.[26,86,237] Additional randomized trials will be required to evaluate the safest and most effective treatment regimens; the levels of and factors favoring compliance; the risk of recidivism; side effect profiles, including the risk of depression; and the impact of antiviral therapy on methadone requirements.

Recommendation category: I

Alcoholism. Active, excessive alcohol use, which has been shown to be associated with progressive liver disease in patients with chronic hepatitis C,[59,242–245] had been considered a contraindication to antiviral therapy.[24] Therefore, patients who were not abstinent from alcohol for at least 1–2 years were excluded from most of the large clinical trials of antiviral therapy for chronic hepatitis C. Clinical trials including patients who were actively consuming alcohol are very limited but suggest that excessive alcohol use reduces the likelihood of a response to therapy.[87,246–248] During the 2002 National Institutes of Health Consensus Development Conference on Management of Hepatitis C, the consensus panel concluded that continued alcohol abuse affected the response to therapy adversely, that abstinence should be recommended before and during antiviral treatment, that treatment of alcohol abuse should be linked with efforts to treat hepatitis C in alcoholic patients, that a safe level of alcohol consumption in patients with hepatitis C has not been established, and that even moderate alcohol consumption can have a deleterious effect on the progression of liver disease in patients with chronic hepatitis C.[26,87]

Recommendation category: II-1b

Black patients. Black patients have a higher rate of HCV infection[8] and a lower response rate to antiviral therapy (and less favorable antiviral kinetics) than white patients,[77,101,155,245,249–254] and these disparities remain to be explained. Recognition of a lower response rate among black patients emerged from retrospective analyses of data from large RCTs of IFN monotherapy (SVR of 2% in 40 patients)[249] and IFN/ribavirin combination therapy (SVR of 11% in 53 patients).[253] Although the latter analysis suggested that an increased prevalence of genotype 1 accounted for the low response rate among black patients,[253] response rates remain lower in black patients with genotype 1 than in white patients with genotype 1,[254,255] and genotype does not explain the differences adequately. Poor response rates in black patients were confirmed in additional retrospective analyses of IFN monotherapy[251,252] and in 2 prospective trials of PEG-IFN/ribavirin combination therapy in treatment-naive patients[254,255] as well as in a prospective trial of

PEG-IFN/ribavirin re-treatment of prior IFN or IFN/ribavirin nonresponders.[176] These studies suggest also that the constitutional neutropenia observed frequently in black patients is not a barrier to treatment.[254] Thus, while contemporary PEG-IFN/ribavirin regimens have improved response rates among black patients, their response rates remain substantially lower than those in their white counterparts. Although expectations for success are lower, black patients should be offered antiviral therapy for chronic hepatitis C.[26] Before therapy, treating physicians should explain the reduced response rate observed in black patients, and those who fail to respond should be encouraged to participate in clinical trials designed to improve responsiveness.

Recommendation category: I

Hematologic disorders. Patients with thalassemia or other hemoglobinopathies and patients with hemophilia and other inherited coagulation disorders were at greater risk of acquiring HCV infection as a consequence of repeated transfusions of blood and clotting factors, respectively, before the introduction of blood donor screening for hepatitis C.[256–261] Because of their hematologic disorders, however, they were excluded from registration trials of antiviral therapy, and their response to contemporary PEG-IFN/ribavirin combination therapy has not been reported.

Thalassemia. For thalassemic patients with chronic hepatitis C, chronic anemia represents a potential contraindication for antiviral regimens that include ribavirin. A concern in this population is the exacerbation of chronic anemia by the dose-dependent hemolytic anemia associated with ribavirin.[181,182] Moreover, many thalassemic patients have concomitant, severe hemosiderosis and iron-related liver disease, including cirrhosis. The application of therapy for hepatitis C has been studied in only a small number of trials, and the numbers of patients studied are too low to provide meaningful conclusions. In several trials with small numbers of subjects, rates of SVR after IFN monotherapy were comparable to those achieved in nonthalassemic patients.[85,262–267] After IFN/ribavirin combination therapy, an SVR rate as high as 72% was reported in a group of 18 thalassemic patients, but confidence in these results is limited by the small number studied, and therapy was complicated by a substantial increase in transfusion requirements during therapy.[268] Therefore, this chronically anemic, iron-overloaded subpopulation can be treated effectively, but the toll of adverse effects is higher than in those without thalassemia. For thalassemic patients with substantial hemosiderosis, primary therapy, before considerations of antiviral therapy, should be focused on reducing iron overload.

Hemophilia. Frequencies of SVR among hemophiliac patients treated with IFN monotherapy or IFN/ribavirin combination therapy have been reported in a limited number of clinical trials, each involving only small numbers of subjects. Response rates tend to be similar to or appreciably lower than those in the nonhemophiliac population; approximately 30% have been reported to respond to 1 year of combination therapy.[259,269–277] For example, in the largest reported RCT,[259] 113 patients with inherited coagulation disorders were treated with IFN alfa-2b (3 MU 3 times weekly) plus ribavirin (1000 mg/day) or IFN monotherapy. The SVR rate in the combination therapy arm was 29% compared with 7% in the monotherapy arm. Adolescents treated with the combination had a significantly higher response rate than adults (59% vs 15%; $P < .001$).[259]

In general, these patients should receive care similar to that recommended for other HCV-infected patients. Although data based on clinical trials do not exist on the use of PEG-IFN and ribavirin in hemophiliac patients, the safety and efficacy profiles are likely to be similar to those of the more general population of patients with hepatitis C. The duration of therapy should be guided by genotype, and liver biopsies can be performed safely by experienced teams working in conjunction with hematologists. Thus, until data are available, treatment options and recommendations should be adapted from the nonhemophiliac population.[85,274]

Recommendation category: II-2b

Children. Only a small proportion of patients infected with hepatitis C are children. Like adults, children with chronic hepatitis C are usually asymptomatic, and their biochemical profiles and histologic findings are similar to those in adults; however, rates of disease progression during childhood appear to be slower than for adults.[55,221,278,279] Whether the lifetime risk of progression will turn out to be lower remains to be determined, and more long-term data are awaited. For children, the general principles of management are the same as those for adults. Treatment is generally well tolerated by children, and response rates to IFN monotherapy and IFN/ribavirin combination therapy are similar to those reported in adults.[26,69,278–281] Ribavirin is also available as a pediatric liquid (40 mg/mL), and the approved dose of IFN alfa-2b for pediatric use is 3 MU/m^2. The duration of therapy is determined by genotype, and therapy is not recommended for patients younger than 3 years.

Trials of PEG- IFN in combination with ribavirin are in progress.

Recommendation category: I

End-stage renal disease. The higher prevalence of HCV infection in patients with end-stage renal disease and the increased risk of disease progression and diminished graft and patient survival following renal transplantation and immunosuppression[282–285] highlight the serious nature of this infection in patients with renal failure.[85] Ideally, an effective therapy for hepatitis C before renal transplantation would be desirable; however, ribavirin is excreted renally (and not cleared by dialysis) and therefore is currently contraindicated in this population, and pharmacokinetic studies have shown that the clearance of IFN is lower in patients on dialysis compared with patients who have normal renal function.[286]

Still, studies of antiviral therapy in patients with end-stage renal disease suggest that IFN monotherapy is generally well tolerated and that SVR rates are higher than those observed in patients with normal renal function.[283,287,288] Generally, however, the number of study subjects in these trials, individually and even collectively, was too low to support confident conclusions, side effects and serious adverse events were more common in this population, and, in some studies, the vast majority of patients discontinued therapy prematurely because of adverse events.[289–295] The role of therapy in this population and the safety and utility of smaller doses of ribavirin[85,296] in combination with PEG-IFN remain unclear and are currently under investigation. Therefore, currently, the role of antiviral therapy in this population remains undefined. For individual patients, the potential benefit of therapy should be weighed against the higher risk of toxicity, and treatment should be undertaken in centers with experienced clinicians, ideally in clinical trials.

For PEG-IFN alfa-2a, a dose reduction from 180 to 135 μg is recommended by the manufacturer for patients with renal failure; for PEG-IFN alfa-2b, the manufacturer makes no specific recommendation about dose reduction for patients with renal failure, but 50% dose reductions are recommended for other clinical indications (eg, hematologic).

If an HCV-infected patient with end-stage renal disease is being considered for kidney transplantation, the degree of hepatic fibrosis should be evaluated; advanced fibrosis and cirrhosis in this population are associated with reduced graft and patient survival.[283]

Recommendation category: II-2a

Extrahepatic disease. Although the frequency of circulating immune complex activity is high in patients with chronic hepatitis C,[297] symptomatic extrahepatic manifestations of chronic HCV infection occur only rarely in these patients. In patients with cutaneous vasculitis or glomerulonephritis resulting from HCV-associated essential mixed cryoglobulinemia, the response to antiviral therapy is variable and often disappointing. In a small number of trials involving small numbers of patients, improvements in cutaneous vasculitis and glomerulonephritis have been reported to occur during therapy, but SVRs were unlikely,[298–303] the promising results of 1 recent study notwithstanding.[304] Therefore, many such patients require indefinite maintenance of antiviral therapy.[24,305–307] In refractory cases, plasmapheresis and/or cytotoxic chemotherapy may be required. Non-Hodgkin's B-cell lymphoma has been reported, albeit rarely, among patients with chronic hepatitis C.[308] A promising report indicated that HCV-associated B-cell lymphoma responded to antiviral therapy with IFN.[309]

Recommendation category: IIb

HIV and HCV coinfection. Approximately one fourth to one third of all persons infected with HIV are coinfected with HCV, presumably because of shared routes of transmission.[310] HCV/HIV coinfection is particularly common in injection drug users with HIV infection, in whom up to 90% may be coinfected with HCV. With the introduction of highly active antiretroviral therapy (HAART) and the improved survival that followed in HIV-infected patients, hepatitis C and its complications (acceleration of liver disease, progression of fibrosis, frequency of cirrhosis, and occurrence of end-stage liver disease, liver failure, and HCC) have become a substantial source of mortality and morbidity in persons with HIV infection.[73–76,310–317] Because HIV infection has such a detrimental effect on the natural history of HCV infection, all HIV-infected patients should be screened for HCV infection; among those with HCV infection, evaluation of candidacy for antiviral therapy should be undertaken (including liver biopsy).[310,318] Ideally, the HIV infection should be well controlled with antiretroviral therapy before treatment of the HCV infection is initiated.

Unfortunately, patients with HIV/HCV coinfection respond less favorably to antiviral therapy than patients with HCV infection alone,[310,319] and the US Food and Drug Administration has not approved antiviral therapy for HCV infection in HIV-infected patients. Still, 4 recent clinical trials have documented the safety and efficacy of PEG-IFN and ribavirin in this patient population (Table 8).[320–323] In the Adult AIDS Clinical Trials Group trial 5071 conducted in the United States,[320] 133 adult patients were randomized to receive 48 weeks of

Table 8. RCTs of PEG-IFN Plus Ribavirin Versus Standard IFN Plus Ribavirin in Patients With HIV/HCV Coinfection

Trial	ACTG 5071[320]	RIBAVIC[321]	APRICOT[322]	Barcelona[323]
Duration (*wk*)	48	48	48	48/24[a]
Type of PEG-IFN	alfa-2b	alfa-2b	alfa-2a	alfa-2b
SVR genotypes 1–4 (%)[b]	14	17	29	38
SVR genotypes 2–3 (%)[b]	73	44	62	53
Discontinued therapy (%)[c]	12	39	25	15

[a]Forty-eight weeks for genotypes 1–4; 24 weeks for genotypes 2–3 with HCV RNA level <800,000 IU/mL.
[b]Data are presented for only the PEG-IFN/ribavirin arm, statistically superior to the standard IFN/ribavirin arm.
[c]Data for both treatment arms combined (statistically indistinguishable frequency of discontinuation between the 2 arms).

combination therapy with either IFN alfa-2b 3 MU 3 times a week or PEG-IFN alfa-2a 180 μg once a week plus ribavirin 600 mg/day initially (increased if tolerated). Although PEG-IFN was superior to standard IFN, the efficacy of PEG-IFN/ribavirin therapy was well below that reported in HCV-monoinfected patients with HCV genotype 1. The frequency of SVR in the PEG-IFN/ribavirin group was only 14% for genotype 1. In contrast, for coinfected patients with genotypes 2 and 3, the frequency of SVR was 73% following a full 48 weeks of therapy, comparable to that reported in HCV-monoinfected patients (treated for only 24 weeks). Treatment was well tolerated, requiring discontinuation in only 12% of patients, and antiviral therapy for hepatitis C did not affect control of HIV replication.[320]

In a European study, 416 patients with HCV/HIV coinfection (approximately 40% of whom had bridging fibrosis or cirrhosis on baseline liver biopsy) were randomized to receive 48 weeks of treatment with PEG-IFN alfa-2b (1.5 μg/kg weekly) or IFN alfa-2b (3 MU 3 times a week) plus ribavirin (800 mg/day). In the PEG-IFN group, 27% achieved an SVR, compared with only 20% in the standard IFN group ($P = .047$). In the superior PEG-IFN group, an SVR was achieved in only 17% of patients with genotypes 1 and 4; in those with non-1 genotypes (genotypes 2, 3, and 5), an SVR occurred in 44%. Serious adverse events were reported by 35% of patients, equal in both treatment groups, and therapy was discontinued in 39% of patients, again equal in both treatment groups. In the PEG-IFN/ribavirin group, doses of PEG-IFN were reduced in 33% and doses of ribavirin reduced in 23%; for the standard IFN/ribavirin group, doses of IFN were reduced in 21% and doses of ribavirin reduced in 15%.[321]

In a large international trial, the AIDS Pegasys Ribavirin International Coinfection Trial,[322] 868 HCV/HIV-coinfected patients were randomized to receive 48 weeks of treatment with standard IFN alfa-2a (3 MU 3 times a week) plus ribavirin (800 mg/day), PEG-IFN alfa-2a (180 μg/wk) plus placebo (monotherapy), or PEG-IFN alfa-2a (180 μg/wk) plus ribavirin (800 mg/day). Again the PEG-IFN/ribavirin combination regimen proved superior, and in this trial SVR rates as high as 29% were achieved in patients with HCV genotype 1 and 62% in those with genotypes 2 or 3. Treatment was discontinued in 25% of patients despite the allowance of growth factor use in this trial.[322]

Finally, in a single-site, open-label RCT in 95 patients (30% with bridging fibrosis/cirrhosis) conducted in Barcelona, patients were randomized to PEG-IFN alfa-2b (100 μg/wk for weight <75 kg or 150 μg/wk for weight ≥75 kg) plus ribavirin versus standard IFN alfa-2b plus ribavirin (in both arms, the dose of ribavirin was weight based; 800 mg/day for weight <60 kg, 1000 mg/day for weight between 60 and 75 kg, and 1200 mg/day for weight >75 kg). Patients with genotypes 1 and 4 were treated for 48 weeks, while patients with genotypes 2 and 3 who had HCV RNA levels <800,000 IU/mL were treated for 24 weeks. In patients with genotypes 1 and 4, an SVR was achieved in 38% of the PEG-IFN group versus 7% of the standard IFN group ($P = .007$); in patients with genotypes 2 and 3, an SVR was accomplished in 53% of the PEG-IFN group versus 47% of the standard IFN group ($P = .73$). Treatment was discontinued for adverse effects in 17% of the PEG-IFN group and 12% of the standard IFN group ($P = .565$); treatment doses were reduced for adverse events in 42% of the PEG-IFN group and 37% of the standard IFN group ($P = .667$).[323]

Three of these 4 trials support a recommendation of a full 48 weeks of PEG-IFN/ribavirin combination therapy (at least 600–800 mg daily, more if tolerated) for patients with HCV/HIV coinfection, regardless of genotype. (Alternatively, some may choose to follow the recommendation of a European Consensus Conference jury, which suggested full-dose [1000–1200 mg], weight-based ribavirin therapy for coinfected patients with genotypes 1 and 4 and 800 mg for patients with genotypes 2 and 3.[324]) Data from these randomized trials, however, demonstrate that the most advanced treatment regimen for HCV infection (ie, PEG-IFN/ribavirin combination therapy), while safe and effective in HCV/HIV-coinfected patients, is substantially inferior in efficacy (especially in patients with HCV genotype 1) to that achieved in HCV-monoinfected patients. Thus, the majority of coinfected patients do not respond to

contemporary therapy. Whether the short-term histologic benefits observed during IFN treatment, even in virologic nonresponders,[320] would translate into a postulated benefit of maintenance therapy in nonresponders remains to be determined. In the absence of randomized trials linking histologic and clinical benefits to longer-term treatment in coinfected patients, a maintenance treatment strategy cannot be recommended at this time.

Although antiviral therapy for HIV and HCV can be administered together safely,[325] one exception has been reported. Ribavirin, which has been shown to increase the activity and potentiate the toxicity of didanosine, should not be used in patients receiving didanosine for HIV infection.[326] Because of the potential drug-drug interactions in patients on HIV treatment regimens that include didanosine, HIV treatment regimens should be altered in those starting combination therapy for HCV infection. If didanosine is critical to the HIV regimen, ribavirin should be avoided. In addition, management of chronic hepatitis C in HCV/HIV-coinfected patients can be confounded by the difficulty in distinguishing among the effects of HCV, HAART hepatotoxicity, and opportunistic infections involving the liver.[327] Finally, reactivation of HCV-associated liver inflammatory activity has been reported after initiation of HAART in patients with HCV/HIV coinfection, attributed to immunologic reconstitution after HAART and restoration of cytolytic T-cell activity against HCV-infected hepatocytes.[328]

Recommendation category: I

Liver transplantation. Hepatitis C–associated end-stage liver disease represents the most frequent indication for liver transplantation.[7,329–331] Recurrent HCV infection in the new liver, as documented by detectable viremia, is universal following transplantation; however, during the early years after transplantation, clinical progression of liver disease may be limited, and, generally, early graft and host survival are unchanged.[332,333] Nevertheless, histologic progression is accelerated during the half decade following transplantation, by which time more than half of patients have moderate to severe hepatitis and 10% have advanced fibrosis or cirrhosis.[332,333] The favorable clinical outcome during the first 5 years notwithstanding, ultimately, recurrent hepatitis C results in impaired posttransplantation survival.[334–336] Moreover, the frequency of early acute rejection appears to be increased in patients undergoing liver transplantation for hepatitis C.[337]

Even during the early posttransplantation period, a small proportion of patients with chronic hepatitis C experience reactivation of hepatitis, often associated with difficult-to-manage rejection.[338] The need for extra immunosuppressive therapy in such patients increases HCV replication and, in turn, HCV-associated liver injury.[338–340] Thus, treated episodes of acute rejection (eg, with methylprednisolone pulses, polyclonal antilymphocyte globulin, or monoclonal antibodies to T cells) represent a risk factor for accelerated progression of hepatitis C after liver transplantation.[341,342] The most aggressive and fortunately the rarest form of recurrent hepatitis C following liver transplantation is fibrosing cholestatic hepatitis, severe and relentlessly progressive liver injury characterized by fibrosis, cholestasis, and severe jaundice with only limited necroinflammatory activity.[343,344] Neither antiviral therapy (see following text) nor retransplantation has been effective in this setting.

Results of antiviral therapy for hepatitis C after liver transplantation have been disappointing, and results of clinical trials are mixed at best. Whether begun prophylactically immediately after transplantation to prevent reinfection or initiated after posttransplantation hepatitis C becomes clinically evident, antiviral therapy, even with the combination of PEG-IFN and ribavirin, may suppress HCV replication but results in an SVR in $<20\%$ of treated patients.[345–349] Moreover, IFN, PEG-IFN, and ribavirin have not been well tolerated after liver transplantation, necessitating dose reductions for adverse events such as anemia and serious infections. An increase in acute rejection, however, as reported in renal allograft recipients treated with IFN, is recognized much less commonly but remains a risk in liver allograft recipients treated with IFN.[337,342,345,348,350] Therefore, after liver transplantation, the risks and benefits of antiviral therapy should be weighed carefully for each patient, and treatment should be initiated with caution by transplantation teams experienced in the treatment of hepatitis C.[342] Because immunosuppression increases HCV replication, which is associated with increased HCV-associated liver injury and may contribute to disease progression, doses of immunosuppressive drugs should be kept to a minimum in patients who undergo liver transplantation for chronic hepatitis C. Although candidates for liver transplantation (ie, patients with decompensated cirrhosis) are not candidates for IFN-based antiviral therapy, attempts to eradicate hepatitis C viremia with progressively escalated, low-dose antiviral therapy before transplantation have met with early success[192–196]; additional data are awaited.

In patients undergoing liver transplantation for hepatitis C, the development of new classes of potent, well-tolerated antiviral agents merits a high priority.

Recommendation category: I

Other Medical Therapies

An association between high levels of hepatic iron deposition and nonresponse to IFN-based antiviral therapy led to the hypothesis that iron removal by phlebotomy would enhance responsiveness to IFN; however, RCTs failed to show any benefit of phlebotomy,[351,352] which therefore has no role in the treatment of chronic hepatitis C.

A variety of other medical therapies have been evaluated; however, to date, none have been shown to be effective in enhancing SVR rates. None of these therapies have been approved, and they are not recommended for patients with chronic hepatitis C.

Included among them is amantadine, which has been studied as monotherapy and in combination with IFN and with IFN and ribavirin. Although amantadine appeared to provide benefit in a few trials in naive[353] and nonresponder[354] patient cohorts, most RCTs showed no benefit associated with amantadine therapy.[355–359] Therefore, amantadine cannot be recommended as a component of antiviral therapy for chronic hepatitis C.

As discussed previously in reference to acute hepatitis C, IFN beta has properties similar to IFN alpha and therefore has been studied as therapy for HCV infection. Studies of treatment with IFN beta, however, show no advantage over treatment with IFN alfa[360–363]; IFN beta has not been approved for treatment of hepatitis C and cannot be recommended. IFN gamma, which has potential antifibrotic effects resulting from inhibition of stellate cell activation and proliferation, has also been evaluated in patients with chronic hepatitis C. Preliminary, promising data notwithstanding,[364,365] a recent multicenter RCT (the results of which have not yet been published) failed to confirm an antifibrotic effect of IFN gamma in patients with chronic hepatitis C. Similarly, interleukin-10, evaluated in a preliminary, 3-month trial, was found to have no antiviral effect[366,367] but possibly an antifibrotic effect.[367] Subsequently, a multicenter RCT of interleukin-10 versus placebo for a full year failed to show an antifibrotic effect in patients with chronic hepatitis C.[368] Thymosin α-1 is an immunoregulatory peptide that influences T-cell maturation, antigen recognition, and cytokine production. The results of 2 RCTs to assess the efficacy of IFN and thymosin combination therapy[369,370] suggested a marginal enhancement of biochemical and virologic responses, but a conclusive benefit of thymosin has not been observed to date. Large-scale trials to assess combination PEG-IFN/thymosin therapy are in progress.

Recommendation category: I

Maintenance therapy. Although contemporary antiviral therapy can result in an SVR in more than half of all treated patients, a sizable proportion of treated patients fail to achieve durable responses. Given the difficulty of clearing hepatitis C viremia, these nonresponder patients have been considered as candidates for long-term maintenance therapy. Among patients treated with IFN, histologic improvement has been recorded at the end of therapy in three fourths of patients, despite the fact that a minority experienced an SVR.[116] In addition, antiviral therapy with IFN has been shown to result in reduced hepatic fibrosis.[43–45,157,371] These observations suggest that antiviral therapy may have a beneficial impact on hepatic histology even in the absence of a virologic response. The potential benefit of maintenance therapy to achieve histologic benefit in previous IFN nonresponders was tested in 2 small, preliminary, randomized studies. In 1 study, 53 nonresponders were randomly assigned to continue IFN for 24 months or to discontinue treatment.[160] In the untreated group, the fibrosis score did not decline and histologic deterioration was recorded. In contrast, in the treated group, mean fibrosis score declined from 2.5 to 1.7 (out of 4), 80% of patients had histologic improvement ($P < .03$), and none demonstrated histologic deterioration; histologic improvement was confined to patients in whom HCV RNA was suppressed. In another study, 57 patients with normal ALT levels and persistent HCV RNA after 1 year of IFN treatment were assigned randomly to no treatment or treatment with IFN continued for 1 year with gradual reduction of the dose to keep serum ALT activity below the upper limit of normal.[372] In 6-month posttreatment biopsy specimens, the histologic grade (necrosis and inflammation) was significantly lower in the treated than in the untreated group (mean ± SD grade, 0.7 ± 0.2 vs 1.1 ± 0.3; $P < .05$). In the treated group, fibrosis scores decreased slightly (mean ± SD fibrosis score, 1.3 ± 0.4 decreasing to 1.1 ± 0.2); in the untreated group, fibrosis scores increased (mean ± SD fibrosis score, 1.3 ± 0.4 increasing to 1.6 ± 0.4). The results of these studies generated the hypothesis that maintenance IFN therapy in prior nonresponders might retard the progression of fibrosis or even limit the progression of cirrhosis to end-stage liver disease. Therefore, several large, multicenter RCTs of long-term (2–4 years) therapy with low-dose PEG-IFN are in progress to assess the impact of maintenance therapy on histologic and clinical end points in patients with chronic hepatitis C and advanced fibrosis.[176,373–375] The results of these trials will be required before recommendations can be made for long-term maintenance therapy in those who fail to achieve an SVR.

Recommendation category: I

Alternative Therapies

The basis for the major treatment recommendations outlined previously are adequately sized and powered, scientifically controlled trials. Yet, many patients with chronic hepatitis C choose to rely on so-called "alternative and complementary" medicines that have not been proven to be effective. Very few of the "natural" and herbal preparations patients take for hepatitis C have ever been subjected to clinical trials; of those that have, most of the trials fell far short of acceptable trial methodology.[376–378] Even among the few herbal preparations subjected to placebo-controlled trials, none have been proven to affect HCV RNA levels or to result in an SVR.[378] Alternative therapies have no role in the treatment of chronic hepatitis C.

Recommendation category: I

Concluding Remarks

Chronic hepatitis C is recognized to be a potentially progressive disorder with a 20% 2-decade incidence of cirrhosis and, among cirrhotic patients, a 1%–4% annual incidence of HCC. Over the course of the past decade and a half, antiviral therapy for hepatitis C has progressed considerably. The frequency of SVRs to antiviral therapy, tantamount to a cure, has increased from <10% when the only therapy available was a 6-month course of IFN monotherapy to approximately 55% (80% in patients with HCV genotypes 2 and 3) with the contemporary standard of combination PEG-IFN plus ribavirin. Indeed, the fact that more than half of all patients with this chronic viral infection can be cured is precedent-setting; detracting somewhat from this success is the high burden of side effects and intolerability of available drugs. In addition, virologic assays have advanced in parallel with advances in antiviral therapy and, currently, standardized amplification assays, with sensitivities as low as 10^2 virions/mL and a broad dynamic range, can be used for monitoring early, end-of-treatment, and SVRs during and after therapy.

Successful antiviral therapy has been shown to have a beneficial effect on hepatic necroinflammatory activity and fibrosis, quality of life, mortality, and complications of liver disease. The impact of successful antiviral therapy on preventing HCC is controversial; prospective controlled trials are in progress to address this issue.

When antiviral therapy was introduced originally, clinical trials had been confined to patients with chronic hepatitis C, elevated aminotransferase levels, histologic features of moderate to severe necroinflammatory activity and fibrosis, and absence of any comorbidities or contraindications. As therapy has improved and experience has increased, several of the contraindications of the early years have become acceptable indications today. Data derived from clinical trials support the application of antiviral therapy, not necessarily universally, but certainly in selected patients with biochemically and histologically mild chronic hepatitis, acute hepatitis, advanced fibrosis and cirrhosis, hematologic disorders, children, end-stage renal disease, extrahepatic manifestations of hepatitis C, HIV/HCV coinfection, and after liver transplantation. Even in patients who continue to use injection drugs and alcohol, antiviral therapy can be administered when provided in association with abstinence and drug treatment programs by health care teams experienced in addiction medicine. For prior nonresponders, application of a more advanced treatment regimen has a high success rate; for prior nonresponders, even the most advanced regimen has only a marginal impact on increasing the frequency of SVR. Several large RCTs are in progress to assess the potential value of chronic maintenance therapy in prior nonresponders with advanced fibrosis. After a frustrating period of investigative drought, early successes in the development of protease and polymerase inhibitors have raised expectations for even more effective antiviral therapies.

JULES L. DIENSTAG
Gastrointestinal Unit (Medical Services)
Massachusetts General Hospital
Department of Medicine and Office of
the Dean for Medical Education
Harvard Medical School
Boston, Massachusetts

JOHN G. MCHUTCHISON
Duke Clinical Research Institute
Division of Gastroenterology
Duke University Medical Center
Durham, North Carolina

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Address requests for reprints to: Chair, Clinical Practice and Economics Committee, AGA National Office, c/o Membership Department, 4930 Del Ray Avenue, Bethesda, Maryland 20814. Fax: (301) 654-5920.

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Clinical Practice and Economics Committee. It was approved by the Committee on September 17, 2005, and by the AGA Governing Board on November 6, 2005.

Dr. Dienstag serves currently on scientific advisory boards and/or data monitoring committees for Achillion Pharmaceuticals, Bristol-Myers Squibb, Genzyme, Gilead Sciences, Idenix Pharmaceuticals, Metabasis Therapeutics, Nucleonics, Oxxon Therapeutics, SciClone, and Vertex. Dr. McHutchison has served on scientific advisory boards, speakers bureaus, or as a consultant for Amgen, Anadys Pharmaceuticals, Centocor, GlaxoSmithKline, Idenix, InterMune Pharmaceuticals, Isis Pharmaceuticals, National Genetics Institute, Novartis Pharmaceuticals, Pfizer Pharmaceuticals, Prometheus Laboratories, Ribozyme Pharmaceuticals, Schering-Plough Corporation, Vertex Pharmaceuticals, and XTL; he has received research support from Akros Pharma, Amgen, Bayer Pharmaceuticals, Bio-Medicines, Bristol-Myers Squibb, Coley Pharmaceuticals, Fujisawa, Gilead Sciences, Human Genome Sciences, IDUN, Isis Pharmaceuticals, Ortho Diagnostic Systems, Prometheus Laboratories, Ribozyme Pharmaceuticals, Roche Pharmaceuticals, Schering-Plough Corporation, SciClone, Triangle Pharmaceuticals, and Vertex Pharmaceuticals.

The Clinical Practice and Economics Committee acknowledges the following individuals whose critiques of this review paper provided valuable guidance to the authors: Robert L. Carithers, MD, Jason Dominitz, MD, Ira Jacobson, MD, and Teresa L. Wright, MD.