Diagnosis, Management, and Treatment of Hepatitis C: An Update

Marc G. Ghany,[1] Doris B. Strader,[2] David L. Thomas,[3] and Leonard B. Seeff[4]

This document has been approved by the AASLD, the Infectious Diseases Society of America, and the American College of Gastroenterology.

Preamble

These recommendations provide a data-supported approach to establishing guidelines. They are based on the following: (1) a formal review and analysis of the recently published world literature on the topic (Medline search up to September 2008); (2) the American College of Physicians' *Manual for Assessing Health Practices and Designing Practice Guidelines*;[1] (3) guideline policies, including the American Association for the Study of Liver Diseases' (AASLD) Policy on the Development and Use of Practice Guidelines and the American Gastroenterological Association's Policy Statement on the Use of Medical Practice Guidelines;[2] and (4) the experience of the authors in regard to hepatitis C.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information. To more fully characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the AASLD requires a Class (reflecting benefit versus risk) and Level (assessing strength or certainty) of Evidence to be assigned and reported with each recommendation (Table 1, adapted from the American College of Cardiology and the American Heart association Practice Guidelines).[3,4]

Background

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease.[5] An estimated 180 million people are infected worldwide.[6] In the United States (U.S.), the prevalence of HCV infection between the years 1999 and 2002 was 1.6%, equating to about 4.1 million persons positive for antibody to hepatitis C (anti-HCV), 80% of whom are estimated to be viremic.[7] Hepatitis C is the principal cause of death from liver disease and the leading indication for liver transplantation in the U.S.[8] Some calculations suggest that mortality related to HCV infection (death from liver failure or hepatocellular carcinoma) will continue to increase over the next two decades.[9] The purpose of this document is to provide clinicians with evidence-based approaches to the prevention, diagnosis, and management of HCV infection.

Testing and Counseling

Testing. The optimal approach to detecting HCV infection is to screen persons for a history of risk of exposure to the virus, and to test selected individuals who have an identifiable risk factor.[10] Currently, injection drug use is the primary mode of HCV transmission in the U.S; thus, all persons who use or have used illicit injection drugs in the present or past, even if only once, as well as intranasal drug users who share paraphernalia, should be tested for HCV infection.[7,11,12] Individuals who have received a blood or blood component transfusion or an

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; ANC, absolute neutrophil count; anti-HCV, antibody to HCV; AST, aspartate aminotransferase; CKD, chronic kidney disease; CTP, Child-Turcotte-Pugh; EIA, enzyme immunoassay; ETR, end-of-treatment response; EVR, early virological response; FDA, U.S. Food and Drug Administration; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PCR, polymerase chain reaction; PEG, polyethylene glycol; RVR, rapid virological response; SVR, sustained virological response; ULN, upper limit of normal.

From the [1]Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, MD; [2]Division of Gastroenterology/Hepatology, Fletcher Allen Health Care, University of Vermont College of Medicine, Burlington, VT; [3]Infectious Disease, The Johns Hopkins University School of Medicine, Baltimore MD; [4]Liver Disease Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD.

Received November 21, 2008; accepted November 23, 2008.

Disclaimer Statement: The views expressed in these guidelines do not necessarily represent the views of the Department of Health and Human Services, the National Institutes of Health, the National Institute of Diabetes and Digestive and Kidney Diseases, or the United States Government.

Address reprint requests to: Leonard B. Seeff, M.D., Liver Disease Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Building 31, Room 9A27, Bethesda, MD 20892. E-mail: seeffl@extra.niddk.nih.gov; fax: 301-480-7926.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.22759

Potential conflict of interest: Drs. Marc Ghany, Leonard Seeff, and Doris Strader have no financial relationships to declare. Dr. David Thomas was on the Advisory Board of Merck, Sharpe and Dohme at the time of writing but has since resigned from this position.

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Table 1. Grading System for Recommendations

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful, and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment.
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful.
Level of Evidence	**Description**
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized trial, or nonrandomized studies.
Level C	Only consensus opinion of experts, case studies, or standard-of-care.

organ transplant before 1992 should also be tested. With the introduction of sensitive tests to screen blood donors for HCV antibodies in 1992, transfusion-transmission of HCV has become rare.[12,13] Persons with hemophilia should be tested for HCV infection if blood products were received before 1987, after which time, viral inactivation procedures were implemented.[14] Similarly, individuals with unexplained elevations of the aminotransferase levels (alanine and/or aspartate aminotransferase; ALT/AST), those ever on hemodialysis, children born to HCV-infected mothers, or those with human immunodeficiency virus (HIV) infection should be tested for the presence of HCV infection.[15-17]

Other potential sources of HCV transmission include exposure to an infected sexual partner or multiple sexual partners, exposure among health care workers to HCV-contaminated blood and blood products, and tattooing.[12,15,18-23] The prevalence of HCV infection is consistently higher among persons with multiple sexual partners, whereas sexual transmission of HCV between monogamous partners is uncommon.[11,18] Thus, although it is prudent to counsel HCV-infected persons to notify their current partners of their HCV status, they should be informed that the risk of sexual transmission is sufficiently low[19] that many authorities do not advise the use of barrier protection among monogamous couples.[18] Nevertheless, between 1% and 5% of monogamous sexual partners of index HCV cases test positive for anti-HCV. There is no need for HCV-infected persons to limit ordinary household activities except for those that might result in blood exposure, such as sharing a razor or toothbrush. The hepatitis C virus is not transmitted by hugging, kissing, sharing of eating utensils or breastfeeding.

Folk medicine practices, including acupuncture and ritual scarification, as well as body piercing, tattooing and commercial barbering are potential modes for transmission of HCV infection when performed without appropriate infection control measures.[24-28] Transmission of HCV infection by body piercing is, however, rare and many HCV infected persons who have undergone body piercing acquired their infection by other means.[23,29-33] Therefore, there is no need to routinely test persons who have received tattoos or undergone piercings in the absence of other risk factors, particularly if these procedures have taken place in licensed establishments. Because symptoms are generally absent in individuals with chronic HCV infection, recognition of infection requires risk factor screening, which should be done whenever it is possible to link with appropriate HCV testing and counseling.[10]

Table 2 outlines the list of persons who should be routinely screened for HCV infection.[15] For some groups, such as those with a history of injection drug use or persons with hemophilia, the prevalence of HCV is high (≈90%). For other groups (recipients of blood transfusions prior to 1992), the prevalence is moderate (≈10%). For still others, (persons with needle stick exposure, sexual partners of HCV-infected persons), the prevalence is low (1% to 5%).

Table 2. Persons for Whom HCV Screening is Recommended

- Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users.
- Persons with conditions associated with a high prevalence of HCV infection including:
  - Persons with HIV infection
  - Persons with hemophilia who received clotting factor concentrates prior to 1987
  - Persons who have ever been on hemodialysis
  - Persons with unexplained abnormal aminotransferase levels
- Prior recipients of transfusions or organ transplants prior to July 1992 including:
  - Persons who were notified that they had received blood from a donor who later tested positive for HCV infection
  - Persons who received a transfusion of blood or blood products
  - Persons who received an organ transplant
- Children born to HCV-infected mothers
- Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood
- Current sexual partners of HCV-infected persons*

Table adapted from "Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease." Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-19):1-39.

*Although the prevalence of infection is low, a negative test in the partner provides reassurance, making testing of sexual partners of benefit in clinical practice.

Table 3. Measures to Avoid Transmission of HCV

- HCV-infected persons should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound in order to prevent contact of their blood with others
- Persons should be counseled to stop using illicit drugs. Those who continue to inject drugs should be counseled to avoid reusing or sharing syringes, needles, water, cotton or other paraphernalia; to clean the injection site with a new alcohol swab; and to dispose of syringes and needles after one use in a safe, puncture-proof container
- HCV-infected persons should be advised to not donate blood, body organs, other tissue or semen
- HCV-infected persons should be counseled that the risk of sexual transmission is low, and that the infection itself is not a reason to change sexual practices (i.e., those in long-term relationships need not start using barrier precautions and others should always practice "safer" sex)

Table adapted from "Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease." Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-19):1-39.

Recommendation

1. As part of a comprehensive health evaluation, all persons should be screened for behaviors that place them at high risk for HCV infection. (Class I, level B).

2. Persons who are at risk should be tested for the presence of HCV infection (Table 2) (Class I, level B).

Counseling. Good clinical practice dictates that persons found to be HCV-infected are counseled regarding prevention of spread of the virus to others. Because exposure to infected blood is the primary mode of transmission, it is essential to inform HCV-infected individuals that precautions should be taken to avoid the possibility of exposing others to contact with their blood. This is particularly important for injection drug users who are the leading source of HCV infection, because their transmission route is primarily via sharing of needles and other infected implements. Table 3 outlines the measures to avoid HCV transmission.

Recommendation

3. Persons infected with HCV should be counseled on how to avoid HCV transmission to others, as indicated in Table 3 (Class I, level C)

Laboratory Testing

Two classes of assays are used in the diagnosis and management of HCV infection: serologic assays that detect specific antibody to hepatitis C virus (anti-HCV) and molecular assays that detect viral nucleic acid. These assays have no role in the assessment of disease severity or prognosis.

Serologic Assays. Tests that detect anti-HCV are used both to screen for and to diagnose HCV infection. Anti-HCV can be detected in the serum or plasma using a number of immunoassays. Two enzyme immunoassays (EIAs) are approved by the U.S. Food and Drug Administration (FDA) for clinical use, Abbott HCV EIA 2.0 (Abbott Laboratories, Abbott Park, IL) and ORTHO® HCV Version 3.0 ELISA (Ortho-Clinical Diagnostics, Raritan, NJ), as well as one enhanced chemiluminescence immunoassay (CIA) VITROS® Anti-HCV assay, (Ortho-Clinical Diagnostics, Raritan, NJ). The specificity of current EIAs for anti-HCV is greater than 99%.[34] False positive results are more likely to occur when testing is performed among populations where the prevalence of hepatitis C is low. False negative results may occur in the setting of severe immunosuppression such as infection with HIV, solid organ transplant recipients, hypo- or aggammaglobulinemia or in patients on hemodialysis.[35-37] The recombinant immunoblot assay, Chiron RIBA HCV 3.0 SIA (Chiron Corporation, Emeryville, CA) is also FDA approved. This assay was originally developed as a more specific, supplemental assay to confirm the results of EIA testing.[38,39] However, specificity is extremely high for third generation EIA results that exceed particular signal/cutoff ratios (e.g., >3.8 for the above mentioned Ortho and Abbott EIA tests). Given the widespread availability of nucleic acid testing, the role for RIBA testing in HCV diagnosis and management has all but disappeared.[40,41]

Molecular Assays. The list of commercial assays available for the detection (qualitative assays) or quantification (quantitative assays) of HCV RNA is shown in Tables 4 and 5. Historically, qualitative assays have been

Table 4. FDA Approved Qualitative Assays for Detection of HCV RNA

Assay and Manufacturer	Method	Lower Limit of Detection IU/mL	Setting
Amplicor HCV v2.0 (Roche Molecular Systems)	Manual RT-PCR	50	Diagnosis and monitoring
Cobas Amplicor HCV v2.0 (Roche Molecular Systems)	Semi-automated RT-PCR	50	Diagnosis and monitoring
Ampliscreen (Roche Molecular Systems)	Semi-automated RT-PCR	<50	Blood screening
Versant HCV RNA Qualitative Assay, (Siemens Healthcare Diagnostics)	Semi-automated TMA	10	Diagnosis and monitoring
Procleix HIV-1/HCV Assay (Chiron Corporation)	Manual TMA	<50	Blood screening

Abbreviations: RT-PCR, reverse transcription polymerase chain reaction; TMA, transcription-mediated amplification

Table 5. Available Assays for Quantification of HCV in Serum/Plasma

Assay (Manufacturer)	Method	IU/mL Conversion Factor	Dynamic Range (IU/mL)	FDA Approved
Amplicor HCV Monitor (Roche Molecular Systems)	Manual RT-PCR	0.9 copies/mL	600-500,000	Yes
Cobas Amplicor HCV Monitor V2.0 (Roche Molecular Systems)	Semi-automated RT-PCR	2.7 copies/mL	600-500,000	Yes
Versant HCV RNA 3.0 Assay (bDNA) (Siemens Health Care Diagnostics)	Semi-automated bDNA signal amplification	5.2 copies/mL	615-7,700,000	Yes
LCx HCV RNA-Quantitative Assay (Abbott Diagnostics)	Semi-automated RT-PCR	3.8 copies/mL	25-2,630,000	No
SuperQuant (National Genetics Institute)	Semi-automated RT-PCR	3.4 copies/mL	30-1,470,000	No
Cobas Taqman HCV Test (Roche Molecular Systems)	Semi-automated real-time PCR		43-69,000,000	Yes
Abbott RealTime (Abbott Diagnostics)	Semi-automated RT-PCR		12-100,000,000	No

more sensitive than quantitative assays. With the recent availability of real time polymerase chain reaction (PCR)-based assays and transcription-mediated amplification (TMA) assays, with sensitivities of 10-50 IU/mL, there is no longer need for qualitative assays.[42,43] A highly sensitive assay with this lower limit of detection is considered appropriate for monitoring during therapy. All currently available assays have excellent specificity, in the range of 98% to 99%. In 1997, the World Health Organization established the first International standard for HCV RNA nucleic acid technology,[44] and the IU rather than viral copies is now the preferred unit to report test results.[44,45] For monitoring purposes, it is important to use the same laboratory test before and during therapy.

Genotyping Assays. Genotyping is useful in epidemiological studies and in clinical management for predicting the likelihood of response and determining the optimal duration of therapy. The hepatitis C virus can be classified into at least 6 major genotypes (genotypes 1 to 6) based on a sequence divergence of 30% among isolates.[46] Genotype 1 (subtypes 1a and 1b) is the most common in the U.S., followed by genotypes 2 and 3. Less common genotypes (genotypes 4-6) are beginning to be observed more frequently because of the growing cultural diversity within the United States.[47] Several commercial assays are available to determine HCV genotypes using direct sequence analysis of the 5′ non-coding region, that include Trugene 5′NC HCV Genotyping kit (Siemens Healthcare Diagnostics Division, Tarrytown, NY), reverse hybridization analysis using genotype specific oligonucleotide probes located in the 5′ non-coding region, INNO-LiPa HCV II, (Innogenetics, Ghent, Belgium), and Versant HCV Genotyping Assay 2.0 (Siemens Healthcare Diagnostics Division, Tarrytown, NY). Incorrect typing among the major genotypes is rare (<3%) and mixed genotypes occur but are uncommon. Occasionally (<5%), tested samples cannot be genotyped. This usually results from low viral levels, issues with the PCR amplification step of the assay, or extreme nucleotide variability within the HCV genome.[48]

Diagnosis of Acute and Chronic HCV Infection and Interpretation of Assays

The diagnosis of acute or chronic HCV infection generally requires testing of serum for both antibody to HCV (anti-HCV) and for HCV RNA. A sensitive quantitative HCV RNA assay is recommended for diagnosis because it also provides information on the level of virus which is helpful in management.

The differentiation of acute from chronic HCV infection depends on the clinical presentation: namely the presence of symptoms or jaundice, and whether or not there was a prior history of ALT elevation and its duration. After acute exposure, HCV RNA is usually detected in serum before antibody; HCV RNA can be identified as early as 2 weeks following exposure whereas anti-HCV is generally not detectable before 8-12 weeks. These two markers of HCV infection may be present in varying permutations, requiring careful analysis for interpretation (Table 6).

Table 6. Interpretation of HCV Assays

Anti-HCV	HCV RNA	Interpretation
Positive	Positive	Acute or chronic HCV depending on the clinical context
Positive	Negative	Resolution of HCV; Acute HCV during period of low-level viremia.
Negative	Positive	Early acute HCV infection; chronic HCV in setting of immunosuppressed state; false positive HCV RNA test
Negative	Negative	Absence of HCV infection

Table 7. Comparison of Scoring Systems for Histological Stage

Stage	IASL[51]	Batts-Ludwig[52]	Metavir[53]	Ishak[54]
0	No fibrosis	No Fibrosis	No fibrosis	No fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion	Fibrous expansion of some portal areas with or without short fibrous septa
2	Moderate fibrosis	Rare bridges or septae	Periportal septae 1 (septum)	Fibrous expansion of most portal areas with or without short fibrous septa
3	Severe fibrosis	Numerous bridges or septae	Porto-central septae	Fibrous expansion of most portal areas with occasional portal to portal bridging
4	Cirrhosis	Cirrhosis	Cirrhosis	Fibrous expansion of most portal areas with marked bridging (portal to portal and portal to central)
5				Marked bridging (portal to portal and portal to central) with occasional nodules (incomplete cirrhosis)
6				Cirrhosis

One pattern is the identification of both anti-HCV and HCV RNA in a person with recent elevation of the ALT value. This scenario is consistent with either acute HCV infection when there is a recent known risk exposure, with exacerbation of chronic HCV infection, or with an acute hepatitis of another etiology in a patient with chronic HCV infection. Another pattern is the detection of anti-HCV but with a negative test for HCV RNA. This may represent acute HCV infection during a period of transient clearance of HCV RNA, a false positive or negative result or, more commonly, recovery from HCV infection. Re-testing for HCV RNA 4-6 months later is recommended to confirm the resolution of HCV infection. The reverse scenario — a negative anti-HCV test but a positive result for HCV RNA — is compatible with the early stage of acute infection prior to the development of antibody or may represent chronic infection in an immunosuppressed individual. Alternatively, it may represent a false positive HCV RNA result. In all circumstances, re-testing for anti-HCV and HCV RNA in 4-6 months should resolve the issue. Finally, if the patient has raised ALT values but the tests for anti-HCV and HCV RNA are negative, both acute and chronic hepatitis C may be excluded and another diagnosis should be considered. Antibody testing should be repeated in 4-6 months for confirmation purposes.

Recommendation

4. Patients suspected of having acute or chronic HCV infection should first be tested for anti-HCV (Class I, Level B.)

5. HCV RNA testing should be performed in:

a) Patients with a positive anti-HCV test (Class I, Level B)

b) Patients for whom antiviral treatment is being considered, using a sensitive quantitative assay (Class I, Level A)

c) Patients with unexplained liver disease whose anti-HCV test is negative and who are immunocompromised or suspected of having acute HCV infection (Class I, Level B).

6. HCV genotyping should be performed in all HCV-infected persons prior to interferon-based treatment in order to plan for the dose and duration of therapy and to estimate the likelihood of response (Class I, Level A)

Utility of the Liver Biopsy and Noninvasive Tests of Fibrosis

There are three primary reasons for performing a liver biopsy: it provides helpful information on the current status of the liver injury, it identifies features useful in the decision to embark on therapy, and it may reveal advanced fibrosis or cirrhosis that necessitates surveillance for hepatocellular carcinoma (HCC) and/or screening for varices. The biopsy is assessed for grade and stage of the liver injury, but also provides information on other histological features that might have a bearing on liver disease progression.[49] The grade defines the extent of necroinflammatory activity, while the stage establishes the extent of fibrosis or the presence of cirrhosis. Several scoring systems have been conceived, the most common being the French METAVIR, the Batts-Ludwig, the International Association for the Study of the Liver (IASL) and the Ishak Scoring systems.[50-54] (Table 7). The two more common non-HCV conditions that might affect disease progression and possibly impede treatment response are steatosis[49,55,56] and excess hepatocellular iron.[57] Identifying either of these two features does not preclude initiating treatment, but their presence provides additional information regarding the likelihood of response to treatment.[58-60]

The liver biopsy has been widely regarded as the "gold standard" for defining the liver disease status, but it has drawbacks that have prompted questions about its value.[61,62] The procedure is not without risks (including pain, bleeding and perforation of other organs),[63,64] it is

subject to sampling error,[65] it requires special expertise for interpreting the histopathology, it adds cost to medical care, and it is anxiety-provoking for the implicated person. Thus, efforts are underway to seek alternative means of establishing information on the extent of fibrosis by focusing on noninvasive blood marker panels.[66] These markers are useful for establishing the two ends of the fibrosis spectrum (minimal fibrosis and cirrhosis) but are less helpful in assessing the mid-ranges of fibrosis or for tracking fibrosis progression.[66] The recently developed transient elastography that uses ultrasound and low frequency elastic waves to measure liver elasticity[67] has improved the ability to define the extent of fibrosis without a liver biopsy, particularly when combined with other noninvasive markers.[68] However, it is not yet ready to replace the liver biopsy since it is not FDA approved, the failure rate is higher in obese patients, and there is now evidence that the transient elastography score can be unexpectedly increased in persons with acute hepatitis who have high necroinflammatory activity but no or minimal fibrosis.[69,70]

A liver biopsy may be unnecessary in persons with genotypes 2 and 3 HCV infection, since more than 80% of them achieve a sustained virlogical response (SVR) to standard-of-care treatment. There is, however, an ongoing debate about whether a biopsy is warranted for persons infected with HCV, genotype 1, whose response to such treatment approximates 50% among Caucasians and 30% among African Americans.[71-73] Even more uncertain is whether there is need for a liver biopsy in persons infected with the other less common genotypes (4 through 6).

Thus, although the liver biopsy was previously regarded as routine for defining the fibrosis stage in persons with genotype 1 infection,[62] the issue is now in a state of flux and possible transition. Supporters of a biopsy cite the difficult nature and high cost of current antiviral therapy and are therefore willing to withhold or delay treatment if liver histology displays minimal to moderate fibrosis stage ≤ 2 (Table 7), especially if the infection is known to have been long-standing. These individuals are regarded as having slowly progressive liver disease that may not be responsible for their ultimate demise[74-76] However, treatment is advised for those with more advanced fibrosis stage ≥ 3 (Table 7) It must be noted, however, that while information obtained from a biopsy is useful, the procedure is not mandatory for deciding on treatment. If performed and treatment is withheld, a common strategy is to repeat the liver biopsy 4 to 5 years later and to reconsider treatment should there be evidence of disease progression.[77]

The earlier views that persons with genotype 1 infection and persistently *normal* aminotransferase values did not require a liver biopsy because they were believed to have minimal liver disease, and that treatment may actually be harmful, are no longer valid.[78] It is now apparent that as many as a quarter of such individuals have significant fibrosis,[78-81] and that treatment response is similar to that of individuals with abnormal serum aminotransferase levels.[82-84] Therefore, the decision to perform a liver biopsy should be based on whether treatment is being considered, taking into account the estimated duration of infection and other indices of advancing liver disease (e.g., the platelet count), the viral genotype, and the patient's willingness to undergo a liver biopsy and motivation to be treated. If the biopsy is not performed and treatment not undertaken, the patient should continue to be monitored at least annually and a biopsy performed if the aminotransferase values become abnormal and other indicators of progressing liver disease become apparent.

Recommendations

7. A liver biopsy should be considered in patients with chronic hepatitis C infection if the patient and health care provider wish information regarding fibrosis stage for prognostic purposes or to make a decision regarding treatment (Class IIa, Level B)

8. Currently available noninvasive tests may be useful in defining the presence or absence of advanced fibrosis in persons with chronic hepatitis C infection, but should not replace the liver biopsy in routine clinical practice (Class IIb, Level C).

Initial Treatment of HCV Infection

Justification for Treatment. Natural history studies indicate that 55% to 85% of individuals who develop acute hepatitis C will remain HCV-infected.[76,85,86] Spontaneous resolution is more common among infected infants and young women than among persons who are older when they develop acute hepatitis.[86] Chronic HCV infection has relevance for the infected persons as well as for their contacts: the former are at risk for progression to cirrhosis and/or HCC, the latter are at risk of acquiring the infection through exposure to the virus. The risk of developing cirrhosis ranges from 5% to 25% over periods of 25 to 30 years.[87,88] Prospective studies of women and children infected at a young age and followed for 20 to 30 years report low rates of cirrhosis, 1% to 3%.[75,89-92] Retrospective studies of patients referred to tertiary care facilities document higher rates of cirrhosis, 20% to 25%, but this figure may be inflated by referral bias.[93,94] Progression to cirrhosis may be accelerated in persons who are of older

Table 8. Virological Responses During Therapy and Definitions

Virological Response	Definition	Clinical Utility
Rapid virological response (RVR)	HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay	May allow shortening of course for genotypes 2&3 and possibly genotype 1 with low viral load
Early virological response (EVR)	$\geq$ 2 log reduction in HCV RNA level compared to baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR)	Predicts lack of SVR
End-of-treatment response (ETR)	HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment	
Sustained virological response (SVR)	HCV RNA negative 24 weeks after cessation of treatment	Best predictor of a long-term response to treatment
Breakthrough	Reappearance of HCV RNA in serum while still on therapy	
Relapse	Reappearance of HCV RNA in serum after therapy is discontinued	
Nonresponder	Failure to clear HCV RNA from serum after 24 weeks of therapy	
Null responder	Failure to decrease HCV RNA by $<$ 2 logs after 24 week of therapy	
Partial responder	Two log decrease in HCV RNA but still HCV RNA positive at week 24	

age, who are obese, who are immunosuppressed (e.g., HIV co-infected), and who consume more than 50g of alcohol per day, although the precise quantity of alcohol associated with fibrosis progression is unknown. [95-98] Persons with HCV-related cirrhosis are at risk for the development of hepatic decompensation (30% over 10 years) as well as hepatocellular carcinoma (1% to 3% per year).[99]

Identifying individuals at risk for developing progressive disease is difficult. Presently, the preferred approach is to assess the degree of fibrosis on liver biopsy, using a validated staging system such as the Ishak, IASL, Metavir or Batts-Ludwig staging systems.[94,96,100] Persons with no or minimal fibrosis (Ishak stage 0-2; Metavir, IASL and Batts-Ludwig stage 0-1) have a low risk for liver-related complications and liver-related death (over the next 10 to 20 years). However, the presence of bridging fibrosis (for example Metavir stage 3, Table 7) is an important predictor of future progression to cirrhosis and therefore an indication for treatment.[101]

Infection with HCV can also cause extrahepatic diseases including mixed cryoglobulinemia, types II and III. Indeed, symptomatic cryoglobulinemia is an indication for HCV antiviral therapy regardless of the stage of liver disease. (See section on Treatment of Patients with Kidney Disease).

Treatment Objectives and Outcomes. The goal of therapy is to prevent complications and death from HCV infection. Because of the slow evolution of chronic HCV infection over several decades, it has been difficult to demonstrate that therapy prevents complications of liver disease. Accordingly, treatment responses are defined by a surrogate virological parameter rather than a clinical endpoint. Short-term outcomes can be measured biochemically (normalization of serum ALT levels), virologically (absence of HCV RNA from serum by a sensitive PCR-based assay), and histologically (>2 point improvement in necroinflammatory score with no worsening in fibrosis score).[71,72] Several types of virological responses may occur, labeled according to their timing relative to treatment. The most important is the sustained virological response (SVR), defined as the absence of HCV RNA from serum by a sensitive PCR assay 24 weeks following discontinuation of therapy (Table 8, Fig. 1). This is generally regarded as a "virological cure," although liver cancer has been identified years later, especially if cirrhosis existed at the time of achieving an SVR.[102]

Undetectable virus at the end of either a 24-week or 48-week course of therapy is referred to as an end-of-treatment response (ETR). An ETR does not accurately predict that an SVR will be achieved but is necessary for it to occur.

A rapid virological response (RVR), defined as undetectable HCV RNA at week 4 of treatment, using a sensitive test with a lower limit of detection of 50 IU/mL, predicts a high likelihood of achieving an SVR.[103,104] An early virological response (EVR) is defined as a $\geq$2 log reduction or complete absence of serum HCV RNA at week 12 of therapy compared with the baseline level. Failure to achieve an EVR is the most accurate predictor of not achieving an SVR.[72,105-107] Monitoring viral kinetics is thus useful for predicting whether or not an SVR is likely to develop.

Virological breakthrough refers to the reappearance of HCV RNA while still on therapy, while virological relapse is the reappearance of HCV RNA in serum after treatment is discontinued and an ETR was documented. Persons who fail to suppress serum HCV RNA by at least 2 logs after 24 weeks of therapy are null responders, while

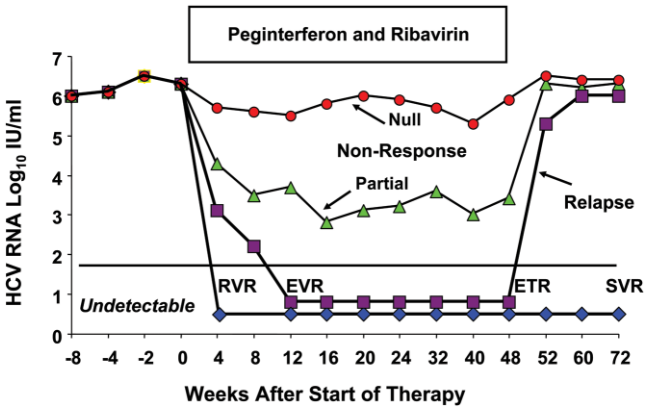

Fig. 1. Graphic display of virological responses. RVR, rapid virological response (clearance of HCV from serum by week 4 using a sensitive PCR-based assay); EVR, early virological response (≥2 log reduction in HCV RNA level compared to baseline HCV RNA level or HCV RNA negative at treatment week 12); SVR, sustained virological response (HCV RNA negative 24 weeks after cessation of treatment); relapse, reappearance of HCV RNA in serum after therapy is discontinued; nonresponder, failure to clear HCV RNA from serum after 24 weeks of therapy; partial nonresponder , 2 log decrease in HCV RNA but still HCV RNA positive at week 24; null nonresponder, failure to decrease HCV RNA by < 2 logs after 24 week of therapy.

those whose HCV RNA levels decrease by ≤2 logs IU/mL but never become undetectable are referred to as partial nonresponders.

The Optimal Treatment of Chronic HCV: Peginterferon Alfa and Ribavirin

The currently recommended therapy of chronic HCV infection is the combination of a pegylated interferon alfa and ribavirin. The choice of this regimen was based upon the results of three pivotal, randomized, clinical trials that demonstrated the superiority of this combination treatment over standard interferon alfa and ribavirin.[71-73] While not directly comparable, these three trials defined several key components of therapy, namely the appropriate dose of the drugs, the optimal duration of therapy and the need for a different regimen for patients with genotype 1 and genotype 2 and 3 infections.

There are two licensed pegylated interferons in the United States, peginterferon alfa-2b (Peg-Intron, Schering Plough Corp., Kenilworth, NJ), with a 12-kd linear polyethylene glycol (PEG) covalently linked to the standard interferon alfa-2b molecule, and peginterferon alfa-2a (Pegasys, Hoffmann-La Roche, Nutley, NJ) with a 40-kd branched PEG covalently linked to the standard interferon alfa-2a molecule.[108] The doses of these two forms of pegylated interferons differ.

The optimal dose of peginterferon alfa-2b, based on the original registration trial, is 1.5 μg/kg/week dosed according to body weight (Fig. 2). Although the dose of ribavirin used in the original registration trial was fixed at 800 mg daily, a subsequent community-based study of patients with genotype 1 infection demonstrated that weight-based ribavirin (800 mg for patients <65 kg; 1,000 mg for patients weighing 65 to 85 kg; 1,200 mg for patients weighing 85 to 105 kg; and 1,400 mg for patients weighing >105 kg but <125 kg) was more effective.[71,109]

Peginterferon alfa-2a is administered at a fixed dose of 180 μg/week given subcutaneously together with ribavirin 1,000 to 1,200 mg daily, 1,000 mg for those who weigh ≤75 kg and 1,200 mg for those who weigh >75 kg (Fig. 2).[72] The registration trial highlighted the two beneficial effects of ribavirin, an improvement in the ETR but, more importantly, a significant decrease in the relapse rate as compared to peginterferon monotherapy treatment.

A third randomized trial determined that the optimal duration of treatment should be based on the viral genotype. The study established that patients with genotype 1 should be treated for 48 weeks with peginterferon alfa-2a plus standard weight-based ribavirin, whereas patients with genotypes 2 and 3 could be treated with peginterferon alfa-2a plus low dose ribavirin (800 mg) for 24 weeks.[73]

For patients with HCV genotype 4 infection, combination treatment with pegylated interferon plus weight-based ribavirin administered for 48 weeks appears to be the optimal regimen, as concluded in a meta-analysis of six randomized trials.[110] While data from another randomized trial of treatment with combination peginterferon alfa-2b plus a fixed dose of ribavirin (10.6 mg/kg per day) has suggested that 36 weeks duration of therapy is sufficient provided an EVR is achieved, these results need to be confirmed.[111]

Patients with genotypes 5 and 6 are underrepresented in trials of peginterferon and ribavirin due to their limited worldwide frequency. A recent retrospective analysis of

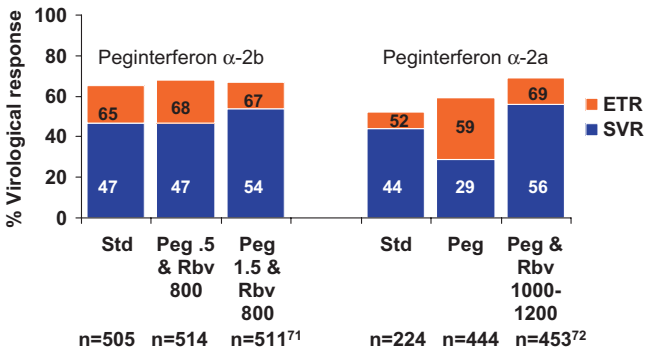

Fig. 2. Virological responses to pegylated interferon and ribavirin in the two U.S. Registration trials.[71,72] ETR, end-of-treatment response; SVR, sustained virological response.

the treatment of patients with HCV genotype 6 concluded that treatment with peginterferon alfa plus ribavirin for 48 weeks was effective and preferable to treatment for 24 weeks.[112] There are insufficient data to make recommendations on the specific doses of medications or durations of treatment for persons with genotype 5 infection.

Currently, the major challenge with regard to therapy is what new approaches are needed to increase the SVR rates in (1) patients with genotype 1 infection and a high viral load; (2) HCV-infected African-American patients (see below); and (3) persons who fail to achieve an SVR using the currently approved treatment regimens.

Pretreatment Predictors of Response. Pretreatment predictors of response are useful for advising patients on their likelihood of an SVR. Absence of favorable factors should not be used, however, to deny therapy. Data on predictors of an SVR come from several sources: registration trials which have strict inclusion and exclusion criteria and may not accurately reflect the general population infected with HCV; community-based trials that may not be conducted with the same rigor as registration trials; and Veterans Affairs databases which involve men predominantly and therefore do not reflect the general population with HCV infection. Despite these caveats, multivariate analyses have identified two major predictors of an SVR among all populations studied: the viral genotype and pretreatment viral load.[71-73] Sustained virological response rates were higher in patients infected with genotype non-1 infection (mostly genotype 2 and 3) and in those with a viral load of less than 600,000 IU/mL.[73] Other less consistently reported baseline characteristics associated with a favorable response include the doses of peginterferon (1.5 μg/kg/week versus 0.5 μg/kg/week) and ribavirin ($>$10.6 mg/kg), female gender, age less than 40 years, non–African-American race, lower body weight ($\leq$75 kg), the absence of insulin resistance, elevated ALT levels (three-fold higher than the upper limit of normal), and the absence of bridging fibrosis or cirrhosis on liver biopsy.[71,72,113]

Viral Kinetics

Measuring the rate of viral clearance from serum is helpful in predicting the likelihood of a response to therapy, for determining the optimal duration of therapy and as a stopping rule for patients with CHC. Accordingly, there has been intense interest in tailoring treatment regimens for individual patients using viral kinetics. This approach may have the benefit of limiting exposure to peginterferon and ribavirin, thus potentially leading to reduced toxicity and a cost savings.

Early Virological Response (EVR)

The absence of an EVR is the most robust means of identifying non-responders. Data from two retrospective analyses of multicenter trials indicated that failure to decrease serum HCV RNA by 2 logs or more at treatment week 12 correlated strongly with non-response in treatment-naive subjects with genotype 1 infection.[72,105] Ninety-seven to 100% of treatment-naive patients with HCV genotype 1 infection who did not reach an EVR failed to achieve an SVR. Thus, patients who do not have an EVR can discontinue therapy early without compromising their chance to achieve an SVR. In contrast, an EVR is less accurate in predicting an SVR since only 65% to 72% of subjects who achieved an EVR ultimately attained an SVR. A completely negative test for HCV RNA at week 12 (complete EVR) is a better predictor of an SVR than a 2-log reduction in HCV RNA, 83% versus 21%.[105] The clinical utility of an EVR is less helpful in persons with HCV genotype 2 and 3 infection since a majority of such individuals clear virus by week 12 and respond to therapy.

Rapid Virological Response (RVR)

Earlier time points have also been examined in the hope of limiting exposure to and the side effects of therapy. Achieving an RVR is highly predictive of obtaining an SVR independent of genotype and regardless of the treatment regimen.[107] However, only 15% to 20% of persons with HCV genotype 1 infection and 66% with HCV genotype 2 and 3 infections achieve an RVR.[107,114] In a retrospective analysis of the predictive value of an RVR in persons with HCV genotype 1 treated with peginterferon alfa-2a, those who achieved an RVR had an SVR rate of 91%, those who achieved a complete EVR had an SVR rate of 75%, and those who achieved an undetectable HCV RNA at week 24, had an SVR rate of 45%.[107]

Because of the rapid clearance of virus from serum, patients who achieve an RVR may be able to shorten the duration of treatment.[104,107] In contrast, because of a poor negative predictive value, the absence of an RVR should not be a basis for discontinuing treatment.

Utility of RVR in Patients with Genotype 1 Infection. Two analyses suggest that patients with HCV genotype 1 who achieve an RVR may be able to shorten the duration of therapy from 48 to 24 weeks. A *post hoc* analysis was conducted of a trial in which patients with chronic HCV infection were treated with peginterferon alfa-2a plus ribavirin either with a fixed dose (800 mg per day) or a weight-based dose (800-1,200 mg per day) for 24 or 48 weeks.[73] Overall, 24% of patients with HCV

Table 9. Summary of Studies Comparing Short Versus Standard Therapy Stratifying Based Upon RVR in Genotype 2 and 3 Patients

Trial/ Regimen	[a]PegIFN α-2b 1 μg/kg/wk & Rbv 1,000-1,2000 mg daily[117]			[b]PegIFN α-2a 180 μg/wk & Rbv 800-1,200 mg daily[118]			[c]PegIFN α-2a 180 μg/wk & Rbv 1,00-1,200 mg daily[119]		[d]PegIFN α-2a 180 μg/wk & Rbv 800 mg daily[114]	
N	283			153			150		1,469	
Gt 2	76%			26%			100%		50%	
Gt 3	24%			74%			0%		50%	
Rx duration/	12^{I} wks	24^{II} wks	24^{III} wks	16^{1} wks	24^{2} wks	24^{3} wks	16 wks	24 wks	16 wks	24 wks
n	113	80	70	71	71	11	50	100	732	731
RVR	100	0	64	100	100	0	86	87	67	64
ETR	95	68	79	94	85	72	100	98	89	82
SVR	85	64	76	82	80	36	94	95	62	70
REL	9	6	4	13	5	50	6	3	30	13

[a]Patients were randomized at baseline to a standard 24 week regimen (Group III), or a variable-duration regimen depending on results of HCV RNA testing at week 4: HCVRNA negative-treatment duration 12 weeks (Group I) or HCV RNA positive-treatment duration 24 weeks (Group II).

[b]All patients treated for 4 weeks, patients with an RVR (HCV RNA $<$ 600 IU/ml) were randomized to 16 (Group 1) or 24 weeks (Group 2). Patients with HCV RNA $\geq$600 IU/ml were treated for 24 weeks (Group 3).

[c]Patients randomized 1:2 to either 16 or 24 weeks.

[d]Patients randomized to 16 or 24 weeks.

Abbreviations: Gt, genotype; n, number; Rx, Treatment; REL, Relapser.

genotype 1 infection in the two 24-week treatment arms achieved an RVR. The SVR rate was 89% in patients who achieved an RVR and 19% in those who did not achieve an RVR, and was similar among those treated for 24 or 48 weeks.[104] Features predictive of an RVR were a low baseline viral load ($\leq$200,000 IU/mL) and HCV subtype 1b.

In another study, patients with HCV genotype 1 infection and a low viral load ($<$600,000 IU/mL) were treated with peginterferon alfa-2b, 1.5 μg/kg/week plus ribavirin 800 to 1,400 mg daily for 24 weeks.[115] Overall an SVR occurred in 50% of patients.[115] However, a subanalysis of patients who achieved an RVR, 47%, reported an SVR rate of 89% compared to 20% among those who did not achieve an RVR. These results suggest that HCV genotype 1 patients who achieve an RVR can be successfully treated with a 24-week course of therapy.

Utility of an RVR in Persons with Genotypes 2 and 3 Infections. Four trials have evaluated the usefulness of an RVR in shortening the duration of therapy from 24 weeks to 12 to 16 weeks in patients with chronic HCV genotypes 2 and 3 infection.[116-119] Although not directly comparable because of the use of different inclusion criteria, treatment regimens and trial designs, the data from these trials suggest that patients with genotypes 2 and 3 infection who achieve an RVR can shorten their treatment duration to 12 to 16 weeks, because the SVR rates at 12 to 16 weeks (62%-94%) were comparable to the SVR rates at 24 weeks (70%-95%), (Table 9). The one shortcoming of this approach is that the relapse rate more than doubles from 3% to 13% in those treated for 24 weeks, to 10% to 30% for those treated for 12 to 16 weeks. Importantly, patients with HCV, genotypes 2 and 3 who relapse after a short course of treatment almost always achieve an SVR when re-treated with a standard 24-week course of therapy. No predictors of an RVR were identified in multivariate analysis in the single study that performed this analysis.[117] Predictors of an SVR among these studies were HCV genotype 2 infection, a low baseline HCV RNA level ($\leq$800,000 IU/mL), and the absence of bridging fibrosis or cirrhosis.[118] Patients with genotype 2 and 3 infections who fail to achieve an RVR (mostly patients with HCV genotype 3 infection with high viral loads and bridging fibrosis or cirrhosis) have poor SVR rates with 24 weeks of therapy and may benefit from longer duration of treatment, but this has not been prospectively evaluated.

Based on these results, it appears that patients with HCV genotype 2 or 3 infections who achieve an RVR can shorten their duration of therapy to 12 to 16 weeks. However, a recent large multicenter, multinational trial that included 1,469 patients with genotype 2 and 3 infection has challenged this concept. Patients were randomized to receive peginterferon alfa-2a, 180 μg / week plus 800 mg of ribavirin for either 16 or 24 weeks without stratification based upon RVR. In contrast to previous studies, the results demonstrated that treatment for 24 weeks was superior to treatment for 16 weeks (SVR rate 76% versus 65%, respectively, $P < 0.001$), even in those who achieved an RVR (85% versus 79%, respectively).[114] One possible explanation for this varying result was that a fixed dose of ribavirin (800 mg) was used in this trial whereas weight-based ribavirin was used in the other trials.

Thus, patients with HCV genotypes 2 and 3 who are intolerant of a planned 24-week course of therapy can have their therapy discontinued between weeks 12 and 16 if they had achieved an RVR. However, patients should be informed of the higher relapse rate associated with this

strategy and be advised that re-treatment with a 24 to 48 week course of therapy may be required. Patients with HCV genotype 3 and a high viral load have lower response rates than do patients with HCV genotype 3 and a low viral load and patients with genotype 2 infections. Therefore, a longer duration of therapy should be considered for such patients. Comparable data are not available in difficult-to-treat populations such as African Americans, those with cirrhosis and those with HIV-HCV coinfection, and therefore this strategy cannot be recommended for these patient populations.

Utility of RVR in Persons with HCV Genotype 4 Infection. The role of RVR has also been assessed in patients with HCV genotype 4 infection. Patients with this genotype were treated with pegylated interferon, alfa-2b 1.5 μg/kg/week plus ribavirin 10.6 mg/kg/day for a fixed duration of 48 weeks or a variable duration based upon time to viral clearance (24 weeks if an RVR was achieved, 36 weeks if a complete EVR was achieved and 48 weeks for viral clearance beyond 12 weeks).[111] The SVR rate among those who achieved an RVR was 86%, 76% in those who achieved a complete EVR, 56% in those who had undetectable HCV RNA after 12 weeks, and 58% in those randomly assigned to 48 weeks. These results suggest that patients with HCV genotype 4 infection who achieve an RVR may be able to be treated for a shorter duration.

Effects of Higher Doses and Extended Duration of Treatment. Strategies to improve SVR rates in difficult-to-treat patients have included the use of higher doses of peginterferon and/or ribavirin or of longer durations of therapy. High dose interferon induction regimens have generally been unsuccessful. In one trial, high dose peginterferon alfa-2b induction therapy (3 μg/kg weekly for 1 week, 1.5 μg/kg/weekly for 3 weeks and 1 μg/kg weekly for 44 weeks) was compared to low dose peginterferon alfa-2b (0.5 μg/kg weekly for 48 weeks).[120] The high dose induction regimen was associated with a faster rate of viral clearance compared with the standard regimen, 22% versus 7% at week 4, but the proportion with undetectable HCV RNA was similar at the end of therapy, 71% versus 61.5%.[120] Unfortunately, SVR data were not provided.

High dose ribavirin (1,600 to 3,600 mg per day) given together with standard dose peginterferon was evaluated in a small pilot study of 10 patients with genotype 1 infection and a baseline viral load >800,000 IU/mL.[121] Ninety percent of patients achieved an SVR. While these results are compelling, safety issues are the major concern for this approach since significant anemia developed in all patients, requiring the use of growth factors in all and blood transfusions in two patients.

The strategy of extending therapy in naive subjects with delayed virological responses, defined as clearance of HCV RNA between weeks 12 and 24, was evaluated in two studies.[122,123] One study randomized subjects to either 48 or 72 weeks of treatment at week 12 if HCV RNA remained detectable,[123] and the other was a *post hoc* analysis of a study in which randomization of treatment duration occurred at baseline.[122] The study populations were not homogeneous, differing in their baseline characteristics and the regimens utilized were different. Nevertheless, the results showed a trend toward a higher SVR rate by extending therapy from 48 to 72 weeks. The SVR rate increased from 18% for 48 weeks treatment to 38% for 72 weeks of treatment in one study[123] and 17% to 29% in the other study.[122] The increased SVR was primarily due a lower relapse rate in the patients treated for 72 weeks. An additional study demonstrated that patients who failed to achieve an RVR (HCV RNA detectable at treatment week 4) also seemed to benefit from extending therapy from 48 to 72 weeks.[124] The SVR rates were significantly higher in patients who received treatment for 72 (45%) compared to those treated for 48 weeks (32%).[124] It is clear that not all patients will benefit from extended therapy judging from the results of the trial in which randomization to 48 or 72 weeks of therapy occurred at baseline.[122] No difference in SVR rates was observed between those treated for 48 compared to 72 weeks (53% versus 54%, respectively).[122] Thus, prolonging therapy can be considered in patients who are slow to respond (clearance of HCV RNA between weeks 12 and 24). Further studies are needed to determine whether extended therapy would be beneficial to patients who fail to clear virus between weeks 4 and 12.

Adverse Events. Almost all patients treated with peginterferon and ribavirin experience one or more adverse events during the course of therapy. Adverse events are a major reason that patients decline or stop therapy altogether. In the registration trials of peginterferon alfa-2a and 2b plus ribavirin, 10% to 14% of patients had to discontinue therapy due to an adverse event.[71,72] The most common adverse events in these trials were influenza-like side effects such as fatigue, headache, fever and rigors, which occurred in more than half of the patients, and psychiatric side effects (depression, irritability, and insomnia), which occurred in 22% to 31% of patients.

Laboratory abnormalities are the most common reasons for dose reduction. Among these, neutropenia (absolute neutrophil count [ANC] of 1500 mm^3) was a frequent laboratory abnormality, occurring in 18% to 20% in the two large phase III clinical trials where the dose was reduced 50% for an ANC of 750 mm^3 and permanently discontinued for an ANC of <500

mm^3.[71,72] Severe neutropenia, ANC <500 mm^3, occurred in 4% of subjects. Despite the decline in the neutrophil count, serious infections are uncommon[125] and granulocyte colony stimulating factor is rarely necessary except in patients with advanced cirrhosis. Anemia was observed in approximately one-third of patients, reaching a nadir within 6 to 8 weeks. Dose modification for anemia (hemoglobin level <10 g/dL) was required in 9% to 15% in the two phase III registration trials. Growth factors, such as erythropoietin and darbepoietin, have been used to counter the anemia associated with peginterferon and ribavirin. Although growth factors improve a patient's sense of well-being and have reduced the requirement for ribavirin dose reduction, their use has not been shown to improve SVR rates.[126-128] In one analysis, the use of a hematological growth factor nearly doubled the cost of treatment for chronic hepatitis C.[129] Although generally safe, erythropoietin and darbepoietin use has been associated with serious side effects including cardiovascular and thromboembolic events, pure red cell aplasia, progression of certain cancers, and death.[130]

There has also been a report of a new, orally active thrombopoietin-receptor agonist, called eltrombopag that stimulates thrombopoiesis.[131] Given for 12 weeks, it allowed successful therapy of HCV patients who had baseline thrombocytopenia (20,000 to 70,000 mm^3), but whether this product will permit patients to complete a full course of therapy has yet to be evaluated. Therefore, routine use of growth factors cannot be recommended at this time and dose reduction is the primary mode for managing cytopenias.

Neuropsychiatric side effects include depression, anxiety, insomnia, emotional lability, mood disorders, frank psychosis, suicidal ideation, actual suicide, and homicide. The most consistent risk factors for developing depression are the presence of mood and anxiety symptoms prior to therapy. A past history of depression and of receiving higher doses of interferon, as well as being female, have been identified as risk factors, but are less reliable ones.[132]

Interferon-induced depression appears to be composed of two overlapping syndromes — a depression-specific syndrome characterized by mood, anxiety, and cognitive complaints, and neurovegetative symptoms, characterized by fatigue, anorexia, pain and psychomotor slowing.[133-135] Depression-specific symptoms are highly responsive to serotonergic antidepressants whereas neurovegatative symptoms are not. These symptoms may be more effectively treated with agents that modulate catecholaminergic function. When selecting an agent, consideration should be given to drug–drug interactions, underlying hepatic function, the possibility of drug-induced hepatotoxicity and other adverse side effects. Consultation and follow up with a psychiatrist is advised (see section on Management of Psychiatric Illness).

Pegylated interferon may induce autoimmune disorders, such as autoimmune thyroiditis, or may worsen preexisting autoimmune disorders. Therefore, the presence of autoimmune conditions prior to treatment is a relative contraindication to therapy. A major dilemma, however, is that chronic HCV infection may present with features that simulate idiopathic autoimmune hepatitis, including the presence of a positive test for antinuclear antibodies. This poses the problem of distinguishing between chronic HCV infection with autoimmune features, for which treatment with antiviral therapy is appropriate, and persons with non-hepatitis C–related autoimmune hepatitis with superimposed chronic HCV infection which requires treatment with immunosuppressive drugs. A helpful distinction is a prior history of autoimmune hepatitis, the presence of other autoimmune conditions and the identification of specific HLA characteristics (See AASLD guidelines for Autoimmune Hepatitis).[136] A liver biopsy may also be helpful. An individualized approach with careful monitoring is recommended if treatment is initiated.

With regard to ribavirin, the most common side effect is hemolytic anemia. Since ribavirin is cleared by the kidney, the drug should be used with extreme caution in patients with renal disease and renal failure. Other side effects associated with ribavirin include mild lymphopenia, hyperuricemia, itching, rash, cough and nasal stuffiness. Ribavirin is reported to cause fetal death and fetal abnormalities in animals and thus it is imperative for persons who receive the drug to use strict contraceptive methods both during treatment and for a period of 6 months thereafter. The education of patients and caregivers about side effects and their management is an integral component of treatment and is important for a successful outcome.

Selection of Patients for Treatment. Current recommendations for treatment of persons with chronic HCV infection derive from data collected in the randomized registration trials. However these trials have usually been restrictive in their exclusion criteria and thus have not reflected the general population who require therapy. More data are needed in certain groups such as those with renal disease, depression and active substance abuse, children, and those with HIV/HCV co-infection. As with all decisions in medicine, a balance must be struck between the benefit and risk related to therapy. Application of these principles can be challenging and the relative strength of a recommendation will need to vary accordingly (Tables 10, 11 and 12).

Table 10. Characteristics of Persons for Whom Therapy Is Widely Accepted

- Age 18 years or older, and
- HCV RNA positive in serum, and
- Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher), and
- Compensated liver disease (total serum bilirubin <1.5 g/dL; INR 1.5; serum albumin >3.4, platelet count 75,000 mm and no evidence of hepatic decompensation (hepatic encephalopathy or ascites), and
- Acceptable hematological and biochemical indices (Hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1500 /mm^3 and serum creatinine <1.5 mg/dL, and
- Willing to be treated and to adhere to treatment requirements, and
- No contraindications (Table 12)

Table 12. Characteristics of Persons for Whom Therapy Is Currently Contraindicated

- Major uncontrolled depressive illness
- Solid organ transplant (renal, heart, or lung)
- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin
- Untreated thyroid disease
- Pregnant or unwilling to comply with adequate contraception
- Severe concurrent medical disease such as severe hypertension, heart failure, signioficant coronary heart disease, poorly controlled diabetes, chronic obstructive pulmonary disease
- Age less than 2 years
- Known hypersensitivity to drugs used to treat HCV

It must be re-emphasized that the recommendations on the selection of patients for treatment are guidelines and not fixed rules; management and treatment considerations should be made on a case-by-case basis, taking into consideration the experience of the practitioner together with the acceptance of risk by the patient.

Assessment Prior to Treatment and Monitoring During and After Therapy

It is advisable to assess the risk of underlying coronary heart disease, to control preexisting medical problems, such as uncontrolled diabetes and hypertension, and to pre-screen all candidates for symptoms of depression prior to iniating therapy. A number of validated self-rated or clinician-rated scales to assess depression are available.[137-140]

Patients should be monitored during therapy to assess the response to treatment and for the occurrence of side effects. A reasonable schedule would be monthly visits during the first 12 weeks of treatment followed by visits at 8 to 12 week intervals thereafter until the end of therapy. At each visit the patient should be questioned regarding the presence of side effects and depression. They should also be queried about adherence to treatment. Laboratory monitoring should include measurement of the complete blood count, serum creatinine and ALT levels, and HCV RNA by a sensitive assay at weeks 4, 12, 24, 4 to 12 week intervals thereafter, the end of treatment, and 24 weeks after stopping treatment. Thyroid function should be monitored every 12 weeks while on treatment.

Table 11. Characteristics of Persons for Whom Therapy Should Be Individualized

- Failed prior treatment (non-responder and relapsers) either interferon with or without ribavirin or peginterferon monotherapy
- Current users of illicit drugs or alcohol but willing to participate in a substance abuse program (such as a methadone program) or alcohol support program.
- Liver biopsy evidence of either no or mild fibrosis
- Acute hepatitis C
- Coinfection with HIV
- Under 18 years of age
- Chronic renal disease (either requiring or not requiring hemodialysis)
- Decompensated cirrhosis
- Liver transplant recipients

Patients who achieve an SVR usually have improvement in liver histology and clinical outcomes.[141,142] However, patients who achieve an SVR but who have cirrhosis are at risk for hepatic decompensation and HCC and death in the short term (5 years),[143] and therefore should continue to be monitored periodically, including screening for HCC (See AASLD guidelines on Management of Hepatocellular Carcinoma).[144] There is no role for a post-treatment liver biopsy among those who achieve an SVR.

Recommendations

9. Treatment decisions should be individualized based on the severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions, and the patient's readiness for treatment (Class IIa, Level C).

10. For patients in whom liver histology is available, treatment is indicated in those with bridging fibrosis or compensated cirrhosis provided they do not have contraindications to therapy (Class I, Level B).

11. The optimal therapy for chronic HCV infection is the combination of peginterferon alfa and ribavirin (Class I, Level A).

12. HCV RNA should be tested by a highly sensitive quantitative assay at the initiation of or shortly before treatment and at week 12 of therapy, (Class I, Level A).

<u>Genotypes 1 and 4 HCV Infection</u>

13. Treatment with peginterferon plus ribavirin should be planned for 48 weeks; the dose for peginterferon alfa-2a is 180 μg subcutaneously per week together with ribavirin using doses of 1,000 mg for those ≤75 kg in weight and 1,200 mg for those >75 kg; the

dose for peginterferon alfa-2b is 1.5 μg/kg subcutaneously per week together with ribavirin using doses of 800 mg for those weighing <65 kg; 1,000 mg for those weighing >65 kg to 85 kg, 1,200 mg for >85 kg to 105 kg, and 1,400 mg for >105 kg (Class I, Level A).

14. Treatment may be discontinued in patients who do not achieve an early virological response (EVR; ≥2 log reduction in HCV RNA at week 12 of treatment) (Class I, Level A).

15. Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued (Class I, Level A).

16. For patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks (Class IIa, Level B).

17. Patients with genotype 1 infection whose treatment continues through 48 to 72 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative at the end of treatment should be retested for HCV RNA 24 weeks later to evaluate for a sustained virological response (SVR; HCV RNA negative 24 weeks after cessation of treatment) (Class I, Level A).

Genotype 2 or Genotype 3 HCV Infection

18. Treatment with peginterferon plus ribavirin should be administered for 24 weeks, using a ribavirin dose of 800 mg (Class I, Level A).

19. Patients whose treatment continues through 24 weeks and whose measurement of HCV RNA with a highly sensitive assay is negative should be retested for HCV RNA 24 weeks later to evaluate for an SVR (Class I, Level A).

20. Patients with HCV-related cirrhosis who achieve an SVR, regardless of the genotype, should continue to be monitored at 6 to 12 month intervals for the development of HCC (Class IIa, Level C).

Retreatment of Persons Who Failed to Respond to Previous Treatment

The approach to patients who fail therapy depends on the nature of the initial response, on the potency of initial treatment and on host–viral factors. Twenty to fifty percent of patients treated with pegylated interferon and ribavirin will not achieve an SVR. Failure to achieve an SVR with a course of pegylated interferon and ribavirin can be a consequence of non-response, virological breakthrough, or relapse. Poor adherence to the prescribed treatment and inappropriate dose reductions can contribute to poor response rates. The induction of antibodies to peginterferon accounts for only a minority of cases.

Non-Responders. Approximately thirty percent of patients treated with pegylated interferon and ribavirin are unable to clear virus from the serum.[71,72] Options for non-responders to pegylated interferon and ribavirin are limited. Retreatment with the same regimen leads to an SVR in fewer than 5% of patients and therefore cannot be recommended.[145] There is no convincing evidence that switching to alternative interferons is effective.[146] Maintenance therapy with peginterferon with the goal of delaying or preventing progression to cirrhosis and/or hepatic decompensation is currently being assessed in two ongoing and one completed randomized trials in the U.S. and Europe.[147] Results of one of them, the HALT-C trial, have recently been reported.[148] In this trial, although serum ALT levels, HCV RNA and hepatic necroinflammation were statistically significantly reduced in the treated arm, the rates of clinical decompensation and progression to histologic cirrhosis were similar in both the treated and untreated groups, 34.1% and 33.8%, respectively (hazard ratio 1.01). Thus, based on the results of the HALT-C Trial, maintenance low dose peginterferon alfa-2a, 90 μg per week, is not indicated in patients with hepatitis C who have bridging fibrosis or cirrhosis and who have not responded to a standard course of peginterferon and ribavirin therapy. Until data become available from retreatment studies using alternate regimens, the decision to undergo retreatment should be individualized. Non-responders to peginterferon and ribavirin with advanced fibrosis should follow AASLD guidelines for screening for HCC and varices and be evaluated for liver transplantation if they are appropriate candidates. Patients with mild fibrosis (Metavir and IASL ≤1 or and Batts-Ludwig and Ishak ≤2) should be monitored without treatment.

For non-responders to standard interferon either with or without ribavirin, retreatment with peginterferon alfa-2a or 2b has been evaluated in three trials.[149-151] The SVR rates were higher among patients who had previously received interferon monotherapy, ranging from 20% to 40%, and were lower among non-responders to the combination of interferon and ribavirin, ranging from 8% to 10%. Persons more likely to achieve an SVR from retreatment included those with genotype non-1 infection, who had lower baseline HCV RNA levels, who had lesser fibrosis, who were of the Caucasian race, and whose prior treatment had consisted of interferon monotherapy.[150]

Relapsers. In the majority of instances, virological relapse occurs within the first 12 weeks and late relapse, beyond 24 weeks, is extremely uncommon. Patients with virological relapse are likely to respond to the same regi-

men given a second time but will still experience an unacceptable rate of relapse. For relapsers to standard interferon and ribavirin, two regimens have been evaluated — high dose peginterferon alfa-2b, 1.5 μg/kg/week with fixed dose ribavirin 800 mg daily, and low dose peginterferon alfa-2b, 1 μg/kg/week plus weight-based ribavirin, 1,000 to 1,200 mg daily.[151] The overall SVR rate was 42% and, although it was higher in the group treated with the higher dose of peginterferon (50%) than in those treated with the lower dose (32%), the number of treated patients was too few to draw meaningful conclusions. Data on retreatment of relapsers to peginterferon and ribavirin have not been published.

Recommendations

21. Retreatment with peginterferon plus ribavirin in patients who did not achieve an SVR after a prior full course of peginterferon plus ribavirin is not recommended, even if a different type of peginterferon is administered (for relapsers, Class III, Level C; for non-responders, Class III, Level B).

22. Retreatment with peginterferon plus ribavirin can be considered for non-responders or relapsers who have previously been treated with non-pegylated interferon with or without ribavirin, or with peginterferon monotherapy, particularly if they have bridging fibrosis or cirrhosis (Class IIa, Level B).

23. Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of peginterferon and ribavirin (Class III, Level B).

Special Patient Groups

Treatment of Persons with Normal Serum Aminotransferase Values. In the past, there has been uncertainty about how to manage persons infected with HCV who have *normal* aminotransferase levels, specifically the serum ALT.[152,153] One issue has been the question of what constitutes a normal ALT value; another had been whether or not persons with a normal ALT warrant treatment.

Regarding the former, the upper limit of normal (ULN) is generally established in individual laboratories by screening presumably healthy volunteers and defining a mean value ± 2 standard deviations. Not usually accounted for, however, is that the ALT value differs by age, race, and gender, and by body mass index.[154,155] Taking these items into consideration, it has recently been suggested that the ULN for ALT should in fact be 30 IU/L for men and 19 IU/L for women,[156] but many laboratories continue to set the ULN of ALT at about 40 IU/L. Therefore, since ALT values can fluctuate over time, a common definition for the existence of persistently normal aminotransferase levels is the identification of an ALT value of less than 40 IU/L on 2 to 3 occasions separated by at least a month over a period of six months.[156,157]

While on average, persons with persistently normal ALT values have significantly less liver fibrosis than persons whose ALT levels are abnormal,[78,155,158,159] there are reports of marked fibrosis (5%-30%) and even cirrhosis (1.3%) in persons with normal ALT values.[160-162] Thus, it is evident that HCV-infected persons with normal ALT values do warrant treatment if the liver biopsy shows significant fibrosis. Moreover, there are multiple studies that report SVR rates with standard-of-care treatment that do not differ from those achieved in persons with abnormal enzymes, and that treatment is equally as safe.[82-84,163-165]

Recommendations

24. Regardless of the serum alanine aminotransferase level, the decision to initiate therapy with pegylated interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential for serious side effects, the likelihood of response, and the presence of comorbid conditions (Class I, Level B).

25. The treatment regimen for HCV-infected persons with normal aminotransferase levels should be the same as that used for persons with elevated serum aminotransferase levels (Class I, Level B).

Diagnosis and Treatment of HCV-Infected Children. The exact prevalence of HCV infection among children in the U.S. is uncertain.[16] Recent national census results indicate that there are between 23,048 and 42,296 children in the U.S. who have chronic HCV infection with 7,200 new cases occurring yearly, most resulting from vertical transmission.[166] The seroprevalence increases with age: 0.2% of children 6 to11 years and 0.4% of children aged 12 to 19 years have positive HCV antibodies.[167] A subsequent study has reported a lower incidence of HCV infection (0.1%) among an urban population of HIV-negative children under the age of 6 years.[168]

Because of universal testing of blood donors for anti-HCV since 1992,[169,170] mother-to-child (vertical or perinatal) transmission has replaced transfusion-associated hepatitis C to become the most common mode of HCV transmission among children in the U.S. The prevalence of HCV infection among women of child-bearing age is 1.2%, and is higher in women who are injection drug users or who are HIV-coinfected.[167,171,172] However, routine screening of all pregnant women for HCV antibodies

is not recommended.[167] Selective testing based on high risk has been advocated by some, but does not detect all cases of HCV infection.[167]

The risk of perinatal HCV transmission is 4% to 6%, and is 2- to 3-fold higher for mothers with HIV/HCV co-infection.[173-180] Some pediatricians advise against the use of fetal scalp monitors and recommend delivery within 6 hours of rupture of membranes to avoid transmission when the mother is known to be HCV-infected.[17,181] Data supporting delivery of HCV-infected mothers by cesarean section is scant and most authorities do not recommend this approach.[167] Similarly, although HCV has been identified in breast milk of infected mothers,[182] there are no data to show that HCV is transmitted in breast milk; therefore breastfeeding is not prohibited in HCV-infected mothers.[183] Finally, in the U.S., horizontal transmission from child to child is rare. Therefore, the American Academy of Pediatrics does not recommend restricting children with chronic HCV infection from school attendance or participation in routine activities, including sports.[167]

Testing of infants born to HCV infected women should be preformed because of the risk of perinatal transmission. When to test can be challenging because maternal antibodies passively transferred to the newborn may persist for up to 18 months of age.[17,184] Therefore, current recommendations advocate postponing anti-HCV testing in exposed infants until 18 months of age.[167] If earlier diagnosis is desired, testing for HCV RNA may be performed at or after the infant's first well-child visit at 1 to 2 months of age. However, the sensitivity of HCV RNA testing at this time is low and a negative test should be repeated at a later date. Therefore it may be more prudent to defer HCV RNA testing until 6 months when sensitivity of the test is improved.[185]

There are several features of HCV infection that differ between children and adults. Children who are acutely infected with HCV, like adults, are generally asymptomatic, but they are more likely than infected adults to spontaneously clear the virus and are more likely to have normal ALT levels.[186] In a recent report of 157 children with HCV infection identified between 1990 and 2001, 28% cleared infection after 10 years of follow up.[187] Among neonatal cases, 25% had spontaneous clearance by 7.3 years. Younger age at follow up and a normal ALT value both favored spontaneous clearance ($P < 0.0001$).[187]

Children with chronic HCV infection, irrespective of mode of acquisition (vertical versus transfusion), have been shown to have minimal progression of their disease over 5 to 20 years.[188-191] Biopsy studies in children generally have demonstrated minimal fibrosis and rare cirrhosis 15 to 20 years after infection.[192-194] Nevertheless, significant disease can occur as reported in a study of 60 children, 12% of whom had bridging fibrosis on liver biopsy after a mean duration of infection of 13 years.[195] On follow up, two patients underwent liver transplantation, one of whom had an undiagnosed HCC.

To date, little is known about the potential for significant liver-related morbidity and mortality over the lifetime of the child. In one retrospective study of elderly Asian patients infected with HCV as children, 71% of those infected for greater than 60 years had cirrhosis on liver biopsy.[192] Unfortunately, no information was available regarding the presence of mitigating factors such as non-alcoholic fatty liver disease (NAFLD), diabetes, alcohol abuse or other viral hepatitis in these patients.

As with adults, the biggest challenge is identifying appropriate candidates for therapy. It may be concluded that the relatively mild disease experienced by most children early in the course of infection and the likelihood of improved future treatments argues against routine treatment. However, it is equally reasonable to accept that the average child is likely to be infected in excess of 50 years and therefore, routine treatment may still be warranted.

Early studies of therapy in children were restricted to interferon monotherapy because animal studies had suggested ribavirin was potentially teratogenic and embryocidal in humans.[196-201] The addition of ribavirin to interferon alfa resulted in higher SVR rates compared to interferon monotherapy.[199,200] Since pegylated interferon alfa together with ribavirin have become the standard of care for the treatment of HCV infection in adults, most recent studies of treatment of HCV-infected children have involved the use of pegylated interferon alfa together with ribavirin. In one such study, 59% of 62 infected children and adolescents treated with pegylated interferon alfa-2b, 1.5 μg/kg body weight once weekly together with ribavirin, 15 mg/kg per day for 48 weeks, achieved an SVR.[202] As with adults, the SVR rates were significantly higher in those children with genotypes 2 or 3 infections (100%) compared to those with infection due to genotype 1 (48%) on a per-protocol analysis. Adverse events led to dose modification in 31% and dose discontinuation in 7%. Similar results were obtained in a subsequent study documenting an overall SVR rate of 50%, 23% of whom required interferon dose reduction for neutropenia.[203]

Recent data indicate that treatment of HCV-infected children with peginterferon and ribavirin is safe and leads to SVR rates that are superior to those of standard interferon. Accordingly, the combination of peginterferon alfa-2b and ribavirin has been approved by the FDA for the treatment of children. The effectiveness of treating children with genotype 1 infection for 48 weeks using

Table 13. Four Pivotal Studies of Treatment of Chronic Hepatitis C in HIV-Infected Persons

Characteristic	APRICOT[217]	ACTG 5071[216]	RIBAVIC[218]	Barcelona[215]
Number enrolled	868	133	412	95
Peginterferon	2a	2a	2b	2b
Ribavirin	800 mg	600 up to 1g	800 mg	0.8 g, 1 g, 1.2 g[1]
HIV and CD4+ status	>200/mm^3 or 100-200/mm^3 and HIV RNA < 5000 c/mL	>100/mm^3 and HIV RNA <10,000 c/mL	>200/mm^3	>250/mm^3 and HIV RNA < 10,000 c/mL
ALT	"Elevated" twice	NA	NA	1.5 ULN
% Genotype 1[2]	60	77	48	55
% bridging fibrosis or cirrhosis[2]	12	11 (cirrhosis)	39	29
Genotype 1 peg-RBV SVR rate[3]	29%	14%	17%	38%

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal; c/mL, copies/mL; NA, not applicable. Table adapted from Thomas, HEPATOLOGY 2006;43:S221-S229.

[1]Based on body weight <65, 65-75, >75 kg.

[2]Taken from peginterferon and ribavirin arm; cirrhosis defined as F4-6 MHAI or F3-4 Metavir and Scheurer.

[3]Refers to the sustained virologic response (SVR) rate for HIV-infected persons taking peginterferon and ribavirin. Rates are for patients with genotype 1 hcv infection except for the RIBAVIC and Barcelona studies that grouped genotypes 1 and 4.

both drugs appears substantiated, but current data are insufficient to recommend using a 24 week course of treatment in children with genotype 2 or 3 infection.

Recommendation:

26. The diagnosis and testing of children suspected of being infected with HCV should proceed as for adults (Class I, Level B).

27. Routine testing for anti-HCV at birth of children born to HCV-infected mothers is not recommended because of the high rate of positive antibody due to passive transfer from the mother. Testing for anti-HCV may be performed at 18 months of age or older (Class I, Level B).

28. Testing for HCV RNA may be considered at 1-2 months of age in infants born to HCV-infected mothers if early diagnosis is desired (Class II, Level B).

29. Children aged 2-17 years who are infected with HCV should be considered appropriate candidates for treatment using the same criteria as that used for adults. (Class IIa, Level B).

30. Children should be treated with pegylated interferon alfa-2b, 60 μg/m^2 weekly in combination with ribavirin, 15 mg/kg daily for a duration of 48 weeks (Class 1, Level B).

Diagnosis, Natural History, and Treatment of Persons with HIV Coinfection. Approximately 25% of HIV-infected persons in the Western world have chronic HCV infection.[204] In the United States, up to 8% of those with chronic HCV infection may be HIV coinfected.[7,204,205] Since the advent of highly active antiretroviral therapy (HAART) in 1996, HCV-related liver disease has become an increasingly important cause of morbidity and mortality in HIV-infected persons.[205-207]

Because of the high prevalence of HIV/HCV coinfection, and because the management of each infection can differ in dually-infected persons, all HIV-infected persons should be tested for HCV and all HCV-infected persons with HIV risk factors should be tested for HIV. As in HIV-uninfected persons, the usual approach is to first test for anti-HCV and to confirm the positive results with a highly sensitive assay. However, approximately 6% of HIV-positive persons fail to develop HCV antibodies; therefore, HCV RNA should be assessed in HIV-positive persons with unexplained liver disease who are anti-HCV negative.[208,209]

The urgency for treatment of persons who are co-infected is greater than it is in those with HCV infection alone. Progression of liver disease is more rapid in HIV/HCV-co-infected persons, in whom there is an approximately twofold increased risk of cirrhosis.[210,211] Successful treatment of HCV also might improve the tolerability of HAART by reducing the risk of hepatotoxicity.[212,213]

The likelihood of achieving an SVR is lower in HIV/HCV co-infected persons than in those with HCV monoinfection.[214-218] The reduced SVR likelihood appears to be due in part to higher HCV RNA levels in HIV-infected persons compared to those with just HCV infection.

The combined use of peginterferon alfa and ribavirin is approved by the FDA for treatment of hepatitis C in HIV-infected persons. The superiority of peginterferon alfa and ribavirin treatment has been shown in four large studies (Table 13).[216-219] In the largest study (APRICOT), 868 persons were randomized to receive either

standard interferon alfa-2a (3 mU tiw) plus ribavirin (800 mg daily), peginterferon alfa-2a 180 μg per week plus placebo, or peginterferon alfa-2a, 180 μg weekly plus ribavirin 800 mg daily for 48 weeks; the overall SVR rates were 12%, 20%, and 40%, respectively.[217] For persons with genotype 1 infection, the SVR rate was 29% with peginterferon alfa and ribavirin, whereas an SVR was observed in 62% of those with genotype 2 or 3 infections. In addition to genotype, lower pretreatment HCV RNA levels (equivalent to $\leq$5.7 $\log_{10}$ IU/mL) were also associated with achieving an SVR. As in persons without HIV infection, those who took peginterferon alfa and ribavirin, but did not achieve an EVR (85 of 289), rarely attained an SVR (2 of 85). Medication was discontinued in 25% of those taking peginterferon alfa and ribavirin; in 15%, discontinuation was due to adverse events. Hepatic decompensation occurred in 14 of the 860 patients who received at least one dose of study medication. Each of the 14 subjects had cirrhosis and 7 subjects had Child-Turcotte-Pugh (CTP) scores of 7 or higher at baseline; also associated with decompensation were other markers of cirrhosis, such as low platelet counts, and didanosine use.[220] In general, similar response rates and toxicity were observed in the other three large studies including the two conducted with peginterferon alfa 2b.

Data on which to base definitive recommendations on the doses and duration of therapy for co-infected patients do not exist. Until such data become available, 48 weeks of ribavirin and peginterferon at doses used for HCV-monoinfected patients is recommended.

There are additional safety concerns in the treatment of HIV/HCV co-infected patients. Ribavirin-associated anemia is a greater problem in persons co-infected with HIV than in those with monoinfection.[221] Ribavirin-related anemia is especially common and severe in persons taking AZT.[222] Ribavirin inhibits inosine-5-monophosphate dehydrogenase, an effect that potentiates didanosine (ddI) toxicity.[223,224] Since symptomatic and even fatal lactic acidosis has been reported in some co-infected persons receiving ribavirin and ddI, ribavirin should not be used in persons receiving this drug.[220,224-226] Interferon alfa therapy causes a dose-related reduction in the white blood cell count and the absolute CD4 lymphocyte count, but the percentage of CD4 cells remains essentially unchanged, and its use is not associated with the development of opportunistic infections.[216-218,221,227-230] In fact, during therapy, peginterferon alfa use is associated with an approximately 0.7-log reduction in HIV RNA levels, suggesting a potential direct beneficial effect on HIV replication, although this effect is not sustained after peginterferon alfa is discontinued.

There continues to be controversy as to which HIV/HCV co-infected patients should undergo anti-HCV treatment since the greater risk of cirrhosis must be weighed against lower SVR rates and additional safety concerns. As is the case for HIV-uninfected patients, these decisions are influenced by the stage of liver disease, (see section on liver biopsy). In HIV/HCV co-infected persons newly initiating antiretroviral therapy, there is insufficient information to recommend a particular waiting period before commencing HCV treatment. In addition, there are very limited data on SVR rates in persons with CD4+ lymphocyte counts below 200/mm^3 and it is not clear which is more informative, the CD4+ lymphocyte nadir or the CD4+ count at the time that HCV therapy is started.[231,232] Most authorities wait at least several months before initiating therapy so that the adverse effects of the antiretroviral therapy are not confused with those caused by peginterferon or ribavirin. If indicated, HIV treatment should be optimized before providing HCV treatment. For HIV/HCV co-infected patients who do not meet one of the established criteria for HIV treatment (e.g., CD4+ lymphocyte count $>$350/mm^3), it is controversial whether antiretroviral therapy provides any advantage, either to improve the likelihood of SVR or to delay progression of HCV. Patients with decompensated liver disease (CTP class B or C) are not treatment candidates and should be considered for liver transplantation.

Outcomes with liver transplantation for patients who are HIV-infected are under evaluation.[233] Patients who are HIV/HCV coinfected appear to have more rapid progression of liver fibrosis and cirrhosis than those infected with just HCV alone. In addition, both drug interaction and mitochondrial toxicity were problematic issues.[234]

Recommendations

31. Anti-HCV testing should be performed in all HIV-infected persons (Class I, Level B).

32. HCV RNA testing should be performed to confirm HCV infection in HIV-infected persons who are positive for anti-HCV, as well as in those who are negative and have evidence of unexplained liver disease (Class I, Level B).

33. Hepatitis C should be treated in the HIV/HCV co-infected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy (Class I, Level A).

34. Initial treatment of hepatitis C in most HIV-infected patients should be peginterferon alfa plus ribavirin for 48 weeks at doses recommended for HCV mono-infected patients (see recommendation 13) (Class I, Level A).

35. When possible, patients receiving zidovudine (AZT) and especially didanosine (ddI) should be switched to an equivalent antiretroviral agent before beginning therapy with ribavirin (Class I, Level C).

36. HIV-infected patients with decompensated liver disease (CTP Class B or C) should not be treated with peginterferon alfa and ribavirin and may be candidates for liver transplantation (Class IIa, Level C).

Treatment of Patients with Kidney Disease. Hepatitis C affects the kidney in at least two ways. First, patients with chronic kidney disease (CKD) who undergo hemodialysis are at high risk of acquiring HCV infection,[235-237] the risk increasing the longer the patient is on hemodialysis.[236] Data from 8,615 patients in hemodialysis units screened for HCV in seven countries revealed the presence of the virus in a mean of 13.5%, ranging from 2.6% in the United Kingdom to 22.9% in Spain; the rate in U.S. units was 14.9%.[235] Even higher rates have been reported from dialysis units in some developing countries.[238,239] A national survey in U.S. dialysis centers in the year 2000 found anti-HCV to be present in 8.4% of patients and in 1.7% of staff.[237] This high rate of HCV transmission is due to direct percutaneous exposure to infectious blood because of inadequate infection control.[240] Its source is cross-contamination between patients because of lack of disinfection of commonly utilized medication equipment and supplies, the use of shared vials of heparin, and blood spills not immediately cleaned. Curbing transmission thus requires strict adherence to infection control measures together with monitoring of HCV-negative patients. If these principles are adhered to, there is no need to isolate HCV-positive patients or even to dialyze them separately on a dedicated machine.[240-242]

Second, infection with HCV may be associated with the development of a number of extrahepatic disorders, one of the most serious being essential mixed (type II) cryoglobulinemia.[243-246] Its cardinal feature is a systemic vasculitis, presenting clinically as palpable purpura, arthralgias and arthritis, fatigue, peripheral neuropathy, and glomerulonephritis,[243-246] The most common histologic patterns are diffuse membrano-proliferative glomerulonephitis,[246] and less commonly, non-cryoglobulinemic membrano-proliferative glomerulonephritis, focal and segmental glomerulosclerosis, and fibrillary and immunoactoid glomerulopathies.[243-248] The majority of persons with essential mixed cryoglobulinemia are infected with HCV. Since the early presentation of cryoglobulinemia may consist simply of proteinuria and renal dysfunction without symptoms of either cryoglobulinemia or liver disease, all persons with proteinuria and cryoglobulinemia should be screened for HCV RNA even if they lack clinical and/or biochemical evidence of liver disease

HCV infection has a significant effect on the health of persons with CKD. Hemodialysis patients infected with HCV have a higher mortality rate than non-infected hemodialysis patients, a result of an increased rate of progression to cirrhosis and/or hepatocellular carcinoma.[249-251] Moreover, patients with HCV infection who undergo kidney transplantation have reduced survival rates, as do their grafts.[252-254] In addition, kidney transplant recipients who remain HCV-infected are at high risk of developing post-transplant diabetes mellitus[255-257] as well as *de novo* membranous glomerulonephritis post-transplantation.[258-260] Accordingly, there is general belief that persons with CKD who are infected with hepatitis C should be treated before they reach the need for kidney transplantation.[261]

Despite the serious impact of HCV infection on persons with CKD, ALT levels are often lower in these patients than in persons with an equivalent grade of liver injury without kidney disease, and the values may even be normal.[262-264] In one study, a wide discrepancy was noted between the level of the ALT and the extent of histologic damage.[265] Accordingly, a liver biopsy is as important for these individuals as it is for persons who do not have CKD. There is some concern that, because platelet dysfunction is increased in persons with uremia, performing a liver biopsy in persons with CKD increases the risk of bleeding.[266-268] Nevertheless, liver biopsies have been performed frequently in persons with CKD undergoing hemodialysis without leading to an increase in bleeding complications.[265,269-271] A liver biopsy may therefore be performed in persons with renal insufficiency using the same guidelines as those used for persons without CKD.[272]

Testing for HCV infection should start with anti-HCV, followed by a highly sensitive assay for HCV RNA.[273] Because of the high prevalence of HCV infection and its deleterious effects in these individuals, all persons with CKD should be tested for HCV infection regardless of the severity of the kidney disease or of the ALT level, in order to plan management and treatment.[261] If not already done, CKD patients should be tested for serum HCV RNA before the start of hemodialysis and both pre- and post-kidney transplantation. Screening for HCV infection should also be performed in hemodialysis patients with unexplained abnormalities of liver-related biochemical tests, and in all patients with possible nosocomial exposure to hepatitis C.[273] Hemodialysis patients should be tested monthly for ALT and 6-monthly for anti-HCV followed by re-testing for HCV

Table 14. Treatment According to Stages of Chronic Kidney Diseases[273]

Stage	Description	GFR (ml min^{-1} 1.73 m^{-2})	Recommended Treatment
1.	Kidney damage with normal or increased GFR	≥90	A
2.	Kidney damage with mild decrease GFR	60-90	A
3.	Moderate decrease GFR	30-59	B
4.	Severe decrease GFR	15-29	B
5.	Kidney failure	<15	B
5D.	Dialysis (hemo- or peritoneal)		C

A: Routine combination therapy according to viral genotype.

B: Peginterferon alfa-2b, 1 μg/kg subcutaneously once weekly, or Peginterferon alfa-2a, 135 μg subcutaneously once weekly plus Ribavirin, 200-800 mg/day in two divided does starting with low dose and increasing gradually

C: Controversial: Standard interferon (2a or 2b) 3mU three times weekly, or Pegylated interferon alfa-2b, 1 μg/kg/week, or Pegylated interferon alfa-2a, 135 μg/kg/week ± Ribavirin in markedly reduced daily dose.

Abbreviation: GFR, glomerular filtration rate.

RNA if these parameters raise suspicion of a new infection.[273]

When HCV infection is identified in persons with CKD, interferon-based antiviral treatment must be considered, but the regimen will vary depending upon the expression of the kidney disease. For this purpose, CKD can be subdivided into four broad categories; (1) persons with early stage CKD identified by a decreased glomerular filtration rate (GFR) but not sufficient to warrant dialysis; (2) patients who require hemodialysis; (3) patients listed for and who undergo kidney transplantation, and (4) persons with HCV-related glomerulonephritis, most with associated cryoglobulinemia.

The decision to treat must take into account the competing severities of the CKD and the chronic liver disease, the risks of the treatment itself, whether or not hemodialysis is being contemplated, and whether there are comorbid conditions that may affect morbidity and mortality, such as cardiovascular disease. Of relevance is that the kidney plays a role in the catabolism and filtration of both interferon[274,275] and ribavirin[276,277] and thus their clearances may be affected in persons with kidney failure.[278,279] The clearance of pegylated interferon is reduced in persons with kidney failure, although hemodialysis does not appear to affect clearance.[280,281] Ribavirin is filtered by the kidneys, and therefore its clearance is impaired in persons with advanced kidney disease and it is not removed by dialysis. The result is an increased severity of hemolytic anemia among persons in whom anemia is already a problem.[276,277] Consequently, as the kidney function begins to deteriorate, the concentration of both drugs must be reduced; indeed, ribavirin should be used with caution when the creatinine clearance falls to below 50 mL/minutes.[282] In limited research studies, reduced doses of ribavirin have been used, even when the creatinine clearance is low, together with both standard interferon,[283] and pegylated interferon.[282] These regimens are associated with a very high rate of adverse events and hence such treatment requires extremely close monitoring and often the added use of growth factors. Treatment regimens and their doses will therefore need to be considered in light of the severity of the CKD.

The therapeutic regimen varies with the severity of the kidney disease. Persons with slight to mild kidney disease (GFR >60 mL/minute), referred to as CKD stages 1 and 2 (Table 14), can be treated with the same regimen routinely administered to HCV-infected persons without kidney disease. For patients with worsening kidney function who are still pre-hemodialysis (CKD stages 3-5), treatment trials have been limited, with little available information to guide recommendations. Nevertheless, most experts support the cautious use of pegylated interferon alfa, adjusting the dose to the level of kidney dysfunction. The recommended doses for this group are peginterferon alpha-2b, 1 μg/kg subcutaneously once weekly or peginterferon alfa-2a, 135 μg subcutaneously once weekly, together with ribavirin, 200 to 800 mg per day in 2 divided doses, starting with the low dose and increasing gradually as long as side effects are minimal and manageable.[273]

There have been numerous, mostly small, studies of treatment of patients with HCV infection who are on hemodialysis (CKD stage 5D).[283-299] These have included monotherapy with standard interferons [285-290] leading to overall SVR rates of 33% to 37% with rates of 26% to 31% in persons with genotype 1 infection[285,286] but associated with high dropout rates.[285,288] Of note is that these SVR rates are higher than occurs in persons without kidney disease treated with standard interferon alone. Higher response rates have been reported in hemodialysis patients treated with standard interferon and reduced doses of ribavirin,[283,289-291] with peginterferon alone,[292-296] or peginterferon together with ribavirin,[283,297] but these have been associated with very high frequencies of side effects, requiring growth factors to treat the anemia and neutropenia, high dropout rates, and high rates of relapse

on completion of treatment.[283,289-291] Clearly, treatment of patients on hemodialysis is fraught with difficult and requires meticulous attention to side effect management.

An international group of experts in both kidney and liver disease have recommended that if HCV-infected hemodialysis patients are considered for treatment, it should consist of standard interferon, alpha 2a or 2b, in preference to pegylated interferons, without the addition of ribavirin.[273] The rationale for this recommendation is that standard interferon has appeared as effective as pegylated interferon in persons on hemodialysis because its excretion is reduced in these patients, its adverse effects are lower, and management of adverse effects is more difficult with pegylated than with standard interferons. The dose recommended is 3mU given subcutaneously three times a week.[273] However, in a recently reported study, treatment of dialysis patients with peginterferon alfa-2a (135 μg per week) and low-dose ribavirin (200 mg/day) led to an SVR in 29% of HCV monoinfected patients (one-half with genotype 1) and in one-third of those coinfected with HIV.[300] The dropout rate was high (71.4%) due largely to the development of severe anemia, but the authors called for larger prospective, controlled clinical trials using combination therapy.[300]

There have also been small studies of treatment for patients with HCV infection who have undergone kidney transplantation because of their higher mortality rate than transplant patients not infected with HCV. Trials have included interferon alone,[301] interferon with low dose ribavirin,[302-304] and ribavirin alone.[304-306] Response rates have been low and graft rejection a consistent problem. Accordingly, routine interferon-based antiviral treatment post-kidney transplant is not recommended and should be considered only for persons who develop post-transplantation fibrosing cholestatic hepatitis.[307]

Treatment of cryoglobulinemia-associated glomerulonephritis also is challenging. Treatment with interferon may exacerbate the vasculitis,[308,309] and therefore should be restricted to those with overt symptoms, with careful monitoring of renal function to ensure that the kidney disease is not worsened.[245] Persons with progressive renal failure generally require treatment with immunosuppressive therapy with cyclophosphamide or rituximab, as well as plasmapheresis and pulsed steroids.[310,311] The role of interferon-based antiviral therapy for hepatitis C in persons with cryoglobulinemia is still being defined but is considered useful for those with mild to moderate kidney disease or after the acute flare has been controlled with immunosuppressive agents.[312] Trials with interferon alone,[313,314] interferon with ribavirin,[315,316] and pegylated interferon with ribavirin,[317-319] have yielded mixed results. Because most of these studies have been small and uncontrolled trials, there is no evidence-based data on which to base firm recommendations. Thus, it is suggested that persons with moderate proteinuria and slowly progressive kidney disease can be treated for 12 months either with standard interferon or with reduced doses of peginterferon, as described above.[273] Treatment leads commonly to disappearance of the cryoglobulinemia and, in those treated with pegylated interferon plus ribavirin, to a high SVR (62.5%).

Recommendations

37. All persons with chronic kidney disease awaiting renal replacement therapy, namely hemodialysis or kidney transplantation, should be screened for hepatitis C in order to plan for management and treatment (Class I, Level B).

38. The decision to perform a liver biopsy in patients with kidney disease should be individualized, based upon the clinical assessment for the need for therapy and the need to establish the severity of the liver disease (Class IIa, Level C).

39. Persons with chronic HCV infection and mild kidney disease (GFR > 60 mL/minute) can be treated with the same combination antiviral therapy as that used in persons without kidney disease (Class IIa, Level C).

40. Persons with chronic HCV infection and severe kidney disease not undergoing hemodialysis can be treated with reduced doses of both peginterferon (alpha-2a, 135 μg/week; alpha-2b, 1 μg/kg/week) and ribavirin (200-800 mg/day) with careful monitoring for adverse effects (Class IIa, Level C).

41. Treatment of HCV in patients on dialysis may be considered with either standard interferon (2a or 2b) in a dose of 3 mU t.i.w. or reduced dose pegylated interferon 2a, 135 ug/week or 2b 1 ug/kg/week. (Class IIa, level C). Ribavirin can be used in combination with interferon in a markedly reduced daily dose with careful monitoring for anemia and other adverse effects. (Class IIb, level C).

42. Treatment is not recommended for patients with chronic HCV infection who have undergone kidney transplantation, unless they develop fibrosing cholestatic hepatitis (Class III, Level C).

43. Patients with cryoglobulinemia and mild to moderate proteinuria and slowly progressive kidney disease can be treated with either standard interferon or reduced doses of pegylated interferon alfa and ribavirin (Class IIa, Level C).

44. Patients with cryoglobulinemia and marked proteinuria with evidence of progressive kidney disease or an acute flare of cryoglobulinemia can be

treated with rituximab, cyclophosphamide plus methylprednisolone, or plasma exchange followed by interferon-based treatment once the acute process has subsided (Class IIa, Level C).

Treatment of African Americans. The prevalence in the U.S. of anti-HCV is higher in African Americans (3%) than in non-Hispanic whites, (1.5%) and Hispanics (1.3%).[7] Compared to Caucasians, African Americans tend to have lower ALT levels for similar histologic activity, and milder liver histology but a higher rate of development of hepatocellular carcinoma.[320] Especially concerning is that African Americans are less likely than non-Hispanic whites to respond to interferon-based therapies.

Two published studies using pegylated interferon and ribavirin were designed specifically to compare response rates between African Americans and non-Hispanic whites.[321,322] In these two trials, SVR rates in African American with genotype 1 infections were 19% and 28% respectively, while both reported an SVR rate of 52% in non-Hispanic whites.[321,322] The study reporting the lower SVR rate in African American subjects utilized a lower dose of ribavirin (1000 mg daily for 12 weeks, followed by 800 mg daily) than the second study, which used weight-based ribavirin dosing.[321] A third, community-based randomized trial was designed to compare a flat (800 mg/day) ribavirin dose to weight-based ribavirin in combination with pegylated interferon, and included sufficient African American subjects that permitted a subanalysis of treatment response in this population.[323] In the treatment arm receiving weight-based ribavirin, SVR rates were 21% and 37% in African Americans and Caucasian patients, respectively.[323] SVR rates were also reported to be lower among African American compared to Caucasian patients with HCV genotypes 2 and 3 infections.[324]

The reasons for this marked difference in response rates between African Americans and non-Hispanic Whites are unclear; in the NIH-sponsored study, the low response rate was independent of BMI, the presence of diabetes, viral subtype (1a versus 1b), viral levels, severity of liver disease, dose of peginterferon and ribavirin received or compliance.[322] Early virological kinetics and ETR were poorer in African Americans, suggesting perhaps a defect in antiviral response to either interferon or ribavirin.[322]

Baseline constitutional neutropenia is a more common finding in African Americans than Caucasians and may be a safety concern. In spite of this, African Americans do not appear to be at increased risk for serious infections or adverse events during peginterferon and ribavirin combination therapy.[321,322,325] Since maintenance of full dose peginterferon is important for achieving an SVR, some experts recommend not to reduce the initial or on-treatment dose of peginterferon in African-American patients unless the absolute neutrophil count is below 500 mm^3.[3,125,322]

Despite the diminished response in African Americans, their management should not differ from that of Caucasian patients. Because of the higher prevalence of HCV infection and lower response rates in African Americans, it is vital that this group of patients be adequately represented in future trials evaluating new agents for chronic HCV infection.

Table 15. Modified Child-Turcotte-Pugh Score for Grading Severity of Liver Disease

Variable	1	2	3
Serum bilirubin, mg/dL	<2.0	2.0-3.0	>3.0
Serum albumin, g/dL	>3.5	2.8.0-3.5	<2.8
Prothrombin time INR	<1.7	1.7-2.3	>2.3
Ascites	None	Easily controlled	Poorly controlled
Encephalopathy	None	Minimal	Advanced coma

The score is calculated as the sum of the scores for albumin, bilirubin, prothrombin time, acites and encephalopathy (range 5-15). Class A is defined as 5-6, class B as 7-9, and class C as 10-15.

Recommendations

45. African Americans infected with HCV who are appropriate treatment candidates should be treated with the current optimal regimen consisting of pegylated interferon and ribavirin (Class I, Level A).

46. African Americans with baseline neutropenia (ANC ≤1500 mm^3) should not be excluded from hepatitis C treatment (Class IIa, Level B).

Treatment of Persons with Compensated and Decompensated Cirrhosis. Compensated cirrhosis is generally distinguished from decompensated cirrhosis by means of the CTP scoring system (Table 15). In the early registration treatment trials, patients who had HCV-related compensated cirrhosis did achieve SVRs but at lower rates than did those without cirrhosis.[71-73] Two subsequent treatment studies focused exclusively on persons with compensated cirrhosis.[326,327] In the first, an SVR was reached in 30% of those treated with peginterferon alfa-2a alone although 10% developed neutropenia, reversible after treatment discontinuation.[326] In the second that used peginterferon alfa-2a together with two different doses of ribavirin (1,000 to 1,200 mg per day or 600 to 800 mg. per day), an SVR was achieved in 52% of patients who received the standard ribavirin dose and in 38% of those treated with the low dose.[327] Serious adverse events developed in 14% and 18% of recipients of the standard and low ribavirin doses, respectively, while dose

reduction was necessary in 78% and 57% of the two groups, respectively. Thus, patients with HCV-related compensated cirrhosis can be successfully treated but with an anticipated higher rate of developing adverse effects of treatment.

Treatment of patients with decompensated cirrhosis, defined as one or more of the clinical complications of chronic liver disease — ascites, encephalopathy, variceal bleeding, and/or impaired hepatic synthetic function — is more problematic. Their treatment of choice is liver transplantation, although variceal bleeding can be successfully managed without surgery, following which such patients can remain stable for a prolonged period before the need for transplantation arises. For those undergoing liver transplantation, reinfection of the allograft with HCV is the rule and progressive post-transplantation disease of the grafted liver is common.[328,329] Accordingly, since eradication of HCV pre-transplantation is associated with a lower likelihood of post-transplantation infection, there is a strong incentive to treat the HCV infection before transplantation, provided the risks of treatment are acceptable. However, treatment commonly leads to serious adverse events, such as life-threatening infection and the possible acceleration of hepatic decompensation.

At least five groups have evaluated treatment for patients with decompensated cirrhosis preliminary to liver transplantation.[330-334] In the earliest reported study, 32 patients awaiting liver transplantation were considered for antiviral treatment, but over one-half were found ineligible because of cytopenias.[330] Among those treated with standard or low doses of interferon alfa-2b or low doses of both interferon alfa-2b and ribavirin, 33% became HCV RNA negative. Almost all developed adverse effects, most of which was graded as severe. In a second study, 30 patients with HCV-related cirrhosis destined for liver transplantation (half graded as CTP class A) were treated with interferon alfa-2b, 3 mU daily and ribavirin, 800 mg/day if their presumed time to liver transplantion was less than 4 months.[331] After a median treatment duration of 12 weeks, 30% responded to treatment and then underwent liver transplantation, 2/3 of whom remained HCV RNA negative over a median follow-up period of 46 weeks. Sixty percent developed neutropenia. Reported in the same year was a study of 20 patients, most with genotype 1 infection, who were treated before transplantation for a mean of 14 months with interferon alfa-2b in a dose of 5 mU daily.[332] At transplantation, 60% were HCV RNA negative, but only 20% remained negative after transplantation. A fourth study involved 124 patients with advanced cirrhosis (CTP classes A, B and C) treated mainly with interferon alfa-2b plus ribavirin, and less frequently, with pegylated interferon plus ribavirin.[333] Treatment began with half doses that were increased incrementally as tolerated at 2 week intervals (referred to as a low accelerating dose regimen), and growth factors were used as needed. An SVR developed in 13% of patients with genotype 1 and in 50% with non-genotype 1 infections. Adverse events were frequent, requiring dose reductions or treatment termination, but among those who did become HCV RNA negative before transplantation, 80% remained negative 6 or more months after transplantation. The most recent study is the only one to include non-treated controls but these consisted of patients unwilling to participate in the study.[334] The treatment administered was peginterferon alfa-2b, 1.0 μg/kg body weight given weekly and ribavirin, 800 to 1000 mg daily for 24 weeks. An SVR developed in 44% of the patients with HCV genotypes 2 or 3, and in 7% of those with genotypes 1 or 4. Treatment had to be discontinued in 20%, was reduced in 39%, and was tolerated in 41%. Over a 30-month follow-up period, decompensated events occurred in 83% of the controls, 62% of the nonresponders, and in 23% of the patients who had developed an SVR. The conclusion of this study was that antiviral therapy can be life-saving, improves hepatic function, and that treatment seems appropriate for persons with genotype 2 and 3 infections particularly in those with cirrhosis, CTP classes A and B.

Hematologic adverse events, including anemia, neutropenia and thrombocytopenia are more common in persons with than without cirrhosis, particularly those with clinically decompensated liver disease (See section on Adverse Events).

Recommendations

47. Patients with HCV-related compensated cirrhosis (CTP class A), can be treated with the standard regimen of pegylated interferon and ribavirin but will require close monitoring for adverse events (Class I, Level A).

48. Patients with HCV-related decompensated cirrhosis should be referred for consideration of liver transplantation (Class I, Level B).

49. Interferon-based therapy may be initiated at a lower dose in patients with decompensated cirrhosis (CTP class B and C), as long as treatment is administered by experienced clinicians with vigilant monitoring for adverse events preferably in patients who have already been accepted as candidates for liver transplantation (Class IIb, Level B).

50. Growth factors can be used for treatment-associated anemia and leukopenia to improve quality of life and may limit the need for antiviral dose reduc-

tions in patients with decompensated cirrhosis (Class IIb, Level C).

Treatment of Patients After Solid Organ Transplantation. The prevalence of hepatitis C infection in recipients of solid organ transplants varies depending on the organ received. Currently, 40% to 50% of liver recipients are infected with HCV, whereas the proportion of cardiac, lung, and kidney transplant recipients with HCV infection is lower. Recipients of heart, lung, or kidney transplants with post-transplantation HCV infection may have had HCV infection that predated transplantation or acquired their infection as a result of infected grafts, blood, or blood products, particularly before 1992, prior to the introduction of screening for HCV.[15] Since then, the risk of acquiring HCV infection during the peri-transplant period has been very low. Hepatitis C viremia persists in most transplant recipients with pre-transplantation infection and progressive liver disease may affect survival post-solid organ transplantation.[335,336] Immunosuppression administered to prevent allograft rejection likely plays a role in the accelerated liver disease observed in the post-transplantation setting.

Heart and Lung Transplantation. Reports are conflicting on the short-term outcome of graft and patient survival among recipients of hearts from anti-HCV positive donors compared to those who received hearts from anti-HCV negative donors. Early studies reported similar 5-year survival rates, 71% to 86% among heart transplant recipients who received anti-HCV positive donor hearts or acquired post-transplantation HCV infection compared with anti-HCV negative donors or those without post-transplant HCV infection.[337,338] However, later studies report an increased rate of mortality from liver disease and the development of accelerated graft damage due to coronary vasculopathy in anti-HCV positive donors in heart transplant recipients compared with anti-HCV negative donors.[339,340] Differences in reported outcome may be related to different immunosuppressive regimens, donor-recipient HLA mis-match, recipient age and severity of liver disease (in those transplanted with preexisting HCV infection).

Information on the outcome of lung transplantation in anti-HCV positive recipients comes from case reports only. In one report, 6 patients with chronic HCV infection (1 with cirrhosis on liver biopsy) underwent lung transplantation. Two deaths occurred, one at 8 months and the other at 2 years, none of which were liver-related.[341]

Data on therapy of HCV infection in heart and lung recipients are derived from small case series.[342,343] These reports indicate that interferon can be safely administered and tolerated but response rates are poor. Until more data become available, administration of antiviral therapy should be made on an individual basis in anti-HCV positive heart and lung transplant recipients.

Liver Transplanatation. Chronic HCV infection is the leading indication for liver transplantation in the adult U.S. population. Graft re-infection is almost universal and graft loss due to recurrent HCV occurs in approximately 25% to 30% of patients.[344,345] Fibrosis progression may be accelerated in patients with recurrent HCV infection post-liver transplantation, with 6% to 23% of patients developing cirrhosis after a median of 3.4 years.[328,346,347] Survival of patients with recurrent HCV infection post-liver transplantation is lower than in patients transplanted for other indications.[348] Since HCV-related liver disease in this group is typically more progressive and survival reduced, as compared to the outcome among immune-competent individuals, many experts have advocated interferon-based antiviral therapy. However, the indications for treatment, the optimal timing, dose and duration of treatment for patients with recurrent HCV infection post-transplantation are not clear.

Therapy may be initiated preemptively, before the development of histological and biochemical recurrent hepatitis, or may be started once recurrent clinical disease is evident. Analyses of studies examining the efficacy of treatment for recurrent HCV infection are hampered by the enrollment of small numbers of patients at single centers, the use of different immunosuppressive regimens (which may play a role in the accelerated liver disease following liver transplantation), different criteria for initiating and stopping therapy, and finally, different treatment regimens among the various centers.

A preemptive strategy would seem attractive because treatment is begun while viral levels are low and before the graft is damaged and theoretically may lead to higher SVR rates. However, in practice, only 40% to 60% of patients are candidates because of the high doses of immunosuppression used, underlying cytopenias, mild renal dysfunction and the presence of other medical problems during this early period post-liver transplantation. The use of standard interferon or pegylated interferon monotherapy is not advised because of poor SVR rates, 0% and 8%, respectively as reported in randomized controlled trials.[349-351] Although the addition of ribavirin was associated with improved response rates, ribavirin is not well tolerated in the early peri-transplant period and dose reduction is common.[352,353] Small, uncontrolled, trials of peginterferon plus ribavirin report SVR rates of 18% to 19%. In all studies, pre-emptive therapy was associated with high rates of side effects, including rejection and unrelated deaths, and a large proportion of patients re-

Table 16. Summary of Post–Liver Transplant Treatment Trials

Trial / Reference	N	Regimen	SVR (%)	Histological Response	D/C (%)	Dose Reduction (%)	Rejection
IFN vs RBV MonoRx RCT (1998[355])	30	IFN-α 3MU tiw $\times$ 24 weeks RBV up 10 1.2 g qd	0	No difference	0	21	
			0	Lobular inflammation improved	24	50	
IFN&RBV OL (2002[356])	54	IFN 1.5-3MU tiw RBV 800-1000 mg qd $\times$ 48 weeks	30		6	72	6
IFN &RBV vs no Rx RCT (2003[357])	52	IFN-α 3 MU tiw RBV 800-1200 mg qd $\times$ 48 weeks	21	No difference in histology at end of follow-up	43		4
		control	0				
IFN&RBV OL (2003[358])	54	IFN-α 3 MU tiw RBV 1000 mg qd $\times$ 48	26		11		2
IFN/PegIFN&RBV OL (2006[359])	31	IFN/RBV	13		40*	57*	3
	36	PegIFN/RBV	50				14
IFN&RBV OL (2004[360])	24	IFN-α 3 MU tiw RBV 1000 mg qd $\times$ 12 months RBV 600-1200 mg $\times$ 6 months	13		29	88	
IFN&RBV OL (2005[361])	38	IFN-α 3 MU tiw RBV 800-1200 mg qd $\times$ 48 weeks		No change in fibrosis	37	71	
PegIFN/RBV OL (2005[362])	32	PegIFN 180 μg q week RBV 1000-1200 mg qd $\times$ 12 months	34		16	65	
PegIFN/RBV OL (2004[363])	20	PegIFN 0.5-1 μg q week RBV 400-800 mg qd	45	Improved	20	65	25
PegIFN/RBV OL (2005[364])	24	PegIFN 1.5 μg q week RBV 400-800 mg qd $\times$ 48 weeks	35		13	58	
PegIFN/RBV OL (2006[365])	25	PegIFN 1 μg q week RBV 600 mg qd $\times$ 48 weeks	36	Worsened fibrosis	4	52	0
PegIFN/RBV OL (2006[366])	55	PegIFN 180/1.5 μg/kg q week RBV 11 mg/kg/d $\times$ 48 weeks	44	Inflammation improved. No change in fibrosis	7	29	2
PegIFN/RBV OL (2007[367])	35	PegIFN 90-180 μg/0.5-1.5 μg/kg/week RBV 800 mg qd $\times$ 48 weeks	37		43	74	11

*Total for both groups

quired dose reductions. Thus, given these adverse effects, the low SVR rates and the lack of improvement in graft loss or mortality, preemptive therapy cannot be universally recommended at present.

Most transplant centers prefer to delay therapy until recurrent disease is confirmed, either by persistently raised ALT levels unexplained by other causes, or by the demonstration of significant fibrosis on liver biopsy (Metavir and IASL stage $\geq$2 or Batts-Ludwig and Ishak stage $\geq$3).[354] Therefore, unlike the non-transplant population, there is a lower threshold for performing liver biopsies in transplanted patients. The decision to initiate therapy must consider the benefits of achieving an SVR, including the potential for histologic improvement, versus the risk of precipitating acute cellular rejection and side effects of therapy. The early experience of interferon-based therapy post-liver transplantation was derived from small, uncontrolled, observational studies using either interferon monotherapy or its combination with ribavirin, results of which were generally disappointing (Table 16).

The combination of pegylated interferon alfa and ribavirin has not been shown to be superior to peginterferon monotherapy in the post-transplantation setting.[368] The SVR rates were similar with monotherapy (38%) compared to combination therapy (33%). This is likely due to the poor tolerance of ribavirin in the post-transplant setting, the requirement for reduced initial doses and the frequent need for dose reduction. Studies suggest that patients with mild histological disease respond better compared to those with more advanced liver disease. In one study, HCV-infected patients with mild, recurrent hepatitis C (Metavir F0-F2) were randomized to receive peginterferon alfa-2b plus ribavirin for 48 weeks or to no treatment.[369] Patients with severe recurrence (Metavir F3, F4 and cholestatic hepatitis) were treated. Forty-eight percent of patients with mild recurrent and 19% with severe recurrent HCV infection achieved an SVR compared to 0% of untreated controls. Accordingly, close monitoring of patients post-liver transplant by liver biopsy is

advised and if progressive fibrosis is noted, treatment should be instituted.

Predictors of response to treatment post-transplantation have not been well studied. A retrospective analysis of 35 patients with recurrent HCV infection post-liver transplantation who were treated with peginterferon alfa and ribavirin for a planned duration of 48 weeks identified lower baseline HCV RNA level, negativity for HCV RNA at week 12, and adherence to the treatment regimen as predictors of an SVR.

Adverse events were common in all trials of patients with recurrent HCV post-liver transplantation, cytopenias being the most common reported. The risk of acute cellular rejection is an important concern that has been difficult to estimate. Uncontrolled trials report rates of 11% to 30%,[370-372] but randomized trials report lower rates (0% to 5%).[369,373,374] Profound graft dysfunction may occur after viral clearance, but this is not common and mangement needs to be elucidated. Efforts should be made to define criteria for diagnosis, therapy and to define the optimal timing, duration and dose to treat recurrent HCV post-liver transplant before the disease becomes severe. Once cirrhosis develops, hepatic decompensation is common,[375] and results of re-transplantation are generally poor.[376,377]

Recommendations

51. Treatment of HCV-related disease following liver transplantation should be initiated in appropriate candidates after demonstration of recurrent histologic disease but should be undertaken with caution and under the supervision of a physician experienced in transplantation (Class IIa, Level A).

52. Peginterferon alfa either with or without ribavirin should be the preferred regimen when treating patients with hepatitis C after liver transplantation (Class IIa, Level B).

53. Interferon-based therapy should not be used in recipients of heart, lung, and kidney grafts, except for patients who develop fibrosing cholestatic hepatitis (Class III, Level C).

Treatment of Persons with Acute Hepatitis C

The response rate to treatment is higher in persons with acute than with chronic HCV infection. However, the optimal treatment regimen and when it should be initiated remains uncertain.

There is consistent evidence that treatment reduces the risk that acute hepatitis C will evolve to chronic infection. Studies using high doses of interferon (5-10 million units per day) for at least 12 weeks, or until serum enzymes normalized, report sustained viral response rates of 83% to 100%, which are much higher than any estimates of spontaneous clearance,[378,379] or of response rates in persons with chronic HCV infection. One meta-analysis considered results of 16 trials that compared interferon therapy with spontaneous resolution of acute hepatitis C.[380] There is remarkable consistency in the superiority of treatment in preventing evolution to chronic HCV infection when compared to observation. Overall, the pooled estimate of the treatment effect was a risk difference of 49% (95% CI 33-65), making it clear that treatment of acute hepatitis C reduces the risk of developing chronic infection.

The optimal regimen to treat acute HCV infection has not been definitively established. In one study from Germany, the most effective regimen at the time was administered to 60 patients diagnosed with acute hepatitis C.[381] The majority (85%) presented with symptomatic disease. None of those with asymptomatic acute hepatitis C spontaneously cleared virus, whereas 52% of those with symptomatic onset lost virus spontaneously, usually within 12 weeks. Treatment given to those who did not spontaneously lose virus, beginning 3 to 6 months after onset of disease, led to an SVR rate in 81%. Overall, 91% cleared virus either spontaneously or through treatment. The authors concluded that for those with symptomatic acute hepatitis, treatment should be delayed for the first 12 weeks. Further support for delaying treatment for up to 12 weeks came from another multi-center study of acute hepatitis C in which SVR rates >90% were reported for patients randomized to 12 weeks of peginterferon alfa-2b after delaying 8 or 12 weeks after diagnosis.[382] In contrast, a lower SVR rate (76%) was found for those randomized to delay peginterferon 20 weeks after diagnosis. In another study from Japan, 13 of 15 persons randomized to start within 8 weeks had an SVR compared to 8 of 15 in whom treatment was delayed by 12 months.[383] Collectively, these data suggest that it is reasonable to start treatment within 8-12 weeks after identified acute hepatitis C, and thus patients should be monitored monthly for this purpose. Within this range, treatment might be delayed longer in persons presenting with jaundice and those with fluctuating viremia patterns that are associated with spontaneous clearance, while earlier treatment might be favored in persons with genotype 1 infection who have high (>800,000 $\log_{10}$ IU/mL) viral loads.

There are few studies that address the regimen, dose, or duration. Several case series using variable doses of peginterferon alfa-2b for 12 weeks reported higher SVR rates in persons who received higher doses (>1.2-1.33 μg/kg/wk).[384,385] However, aside from a trend toward a higher peginterferon dose, as of this time there are no definitive answers to whether concurrent use of ribavirin improves

SVR rates with acute HCV treatment, nor are there data establishing the benefit of peginterferon alfa or the comparability of 12 weeks to longer courses. Although HCV RNA in patients with acute infection generally is cleared from the blood by 8 to 16 weeks in most persons who recover spontaneously, viremia has been observed as late as 48 weeks after acute infection in injection drug users who ultimately clear.[386-388] Thus, what is offered is an interim set of recommendations that will need modification as more data accumulate.

Recommendations

54. Patients with acute HCV infection should be considered for interferon-based anti-viral therapy (Class I, Level B).

55. Treatment can be delayed for 8 to 12 weeks after acute onset of hepatitis to allow for spontaneous resolution (Class IIa, Level B).

56. Although excellent results were achieved using standard interferon monotherapy, it is appropriate to consider the use of peginterferon because of its greater ease of administration (Class I, Level B).

57. Until more information becomes available, no definitive recommendation can be made about the optimal duration needed for treatment of acute hepatitis C; however, it is reasonable to treat for at least 12 weeks, and 24 weeks may be considered (Class IIa, Level B).

58. No recommendation can be made for or against the addition of ribavirin and the decision will therefore need to be considered on a case-by-case basis (Class IIa, Level C).

Treatment of Active Injection Drug Users

Illicit injection drug use is the predominant mode of HCV transmission, accounting for more than 60% of new cases in Western countries. Many individuals who acquired HCV infection from injection drug use discontinued the practice years before medical management of their infection began, and the standard guidelines outlined above apply. However, there is a wide spectrum of illicit drug use that includes persons of all socioeconomic strata and that varies in many respects: whether use is ongoing or took place in the distant past; whether illicit drug use is occasional or an uncontrollable daily need; whether heroin, cocaine, or other substances are used; and whether use is by injection or other modes. In addition, many who use illicit drugs transition between these stages. Thus, it is important to consider the individual issues that may affect the risks and benefits of treatment of HCV infection in persons who use illicit drugs, rather than to make categorical recommendations.[389]

The use of methadone, naltrexone, or buprenorphine is an effective means of reducing illicit drug use and its complications.[390] Although some *in vitro* studies have suggested that opiates diminish endogenous interferon alfa production,[391] there are several studies of persons taking methadone that suggest that the drug does not significantly reduce the likelihood of an SVR, nor does it alter the dosing of interferon alfa or ribavirin.[392,393] Therefore, methadone use does not directly affect the management of HCV infection.

The benefits of treatment would be diminished substantially if a person were reinfected, which has been reported after spontaneous recovery both in humans and in experimental studies of chimpanzees.[394,395] The risk of reinfection following an SVR in persons who use illicit drugs is not well established. In one study, 18 injection drug users who acquired SVR were followed and HCV RNA was detected again in two.[396]

For many individuals who are actively injecting illicit drugs, there is low willingness to undergo HCV treatment and diminished ability to adhere to treatment and precautions regarding contraception, and to maintain regular follow-up visits. For example, in one multicenter study, almost one half of young HCV-infected injection drug users had moderate or severe depression.[397] Some illicit drug users, however — even those who use by injection — are willing and able to undergo treatment for HCV infection.[393,398-400] For example, in one study, 76 persons taking methadone for heroin addiction were treated in a setting established to diminish treatment barriers.[392,401] Of 76 treated, 21 achieved an SVR, an outcome that was less likely for those with pretreatment psychiatric disease but not active drug use.

Thus, there are a number of factors that determine the benefits and risks of HCV treatment in illicit drug users, and treatment decisions will need to be individualized accordingly. Many factors, such as the stage of liver disease and HCV genotype, are similar to persons who do not use illicit drugs. Special concerns include an increased risk of reinfection and, for select individuals, concerns about use of needles causing relapse into drug use. For persons who continue to inject illicit drugs, especially if they share needles and other drug-use equipment, efforts should generally be focused on providing addiction treatment. Ideally, HCV management is integrated with addiction treatment and delivered by multidisciplinary teams, including experienced drug abuse and psychiatric counseling services.

Recommendations

59. Treatment of HCV infection can be considered for persons even if they currently use illicit drugs or who are on a methadone maintenance program, provided they wish to take HCV treatment and are able and willing to maintain close monitoring and practice contraception (Class IIa, Level C)

60. Persons who use illicit drugs should receive continued support from drug abuse and psychiatric counseling services as an important adjunct to treatment of HCV infection (Class IIa, Level C).

Treatment of Persons with Psychiatric Illnesses

Patients with chronic HCV infection have a higher prevalence of psychiatric illness compared to the general U.S. population. The prevalence of chronic HCV infection in patients with mental or psychiatric diseases ranges from 8% to 31%, which is 4 to 20 times that of the U.S. population (1.8%). Mental or psychiatric disease represents a significant barrier to treatment in patients with chronic HCV infection. The argument against treatment of this population stems from the neuropsychiatric side effects associated with interferon and ribavirin therapy such as depression, irritability, suicidal ideation, mania, mood swings and relapse of drug or alcohol abuse.[389,402] Persons with mental or psychiatric disorders are felt to be at higher risk for these side effects.[402] Significant depressive symptoms occur in 21% to 58% of interferon-treated patients. However, a recent prospective controlled trial demonstrated that these patients may be successfully treated with a multidisiplinary approach to management of adherence and neuropsychiatric side effects. Using this approach, they can achieve SVR rates that are similar to patients without psychiatric disorders.[403]

Most psychotropic agents are thought to be safe for use in the management of patients with chronic HCV infection and psychiatric disease. However, consideration should be given to drug–drug interactions and dose modification in patients with advanced liver disease. Despite the clinical challenges of HCV treatment in patients with mental and psychiatric disease, the available evidence is that interferon and ribavirin can be safely administered provided there is comprehensive pretreatment psychiatric assessment, a risk benefit analysis is conducted, and there are provisions for ongoing follow-up of neuropsychiatric symptoms during antiviral therapy by a multidisciplinary team.

Recommendations

61. Patients with HCV infection and concomitant mental and psychiatric disorders can be considered for treatment using the currently approved regimens. (Class IIa, Level C).

62. Treatment of hepatitis C infection in patients with psychiatric disorders should be undertaken only with the support of a multi-displinary team that should include psychiatric counseling services (Class IIa, Level C).

General Management Issues

An important adjunct to the therapy of HCV is to advise chronically affected persons of measures that might be helpful in reducing or even preventing further fibrosis progression, independent of treatment. Most important is the issue of the potential deleterious effect of alcohol.

There are numerous studies that have reported a strong association between the use of excess alcohol and the development or progression of liver fibrosis and even the development of HCC.[96,97,404-407] Moreover, excess alcohol intake may increase HCV RNA replication and interfere with response to treatment.[408,409] Controversy exists, however, about the level of alcohol intake that is clearly harmful to the HCV-infected person. It is widely believed that the daily consumption of more than 50 grams of alcohol has a high likelihood of worsening the fibrosis, but there are reports of levels of alcohol intake of less than that amount having a deleterious effect on the liver disease.[410]

Clearly, for heavy alcohol users, efforts should be undertaken to treat the alcohol abuse and dependence before starting treatment, but treatment is not contraindicated for persons who have an occasional drink of alcohol or who have a past history of alcoholism. Although no consensus opinion exists, it seems reasonable to recommend either the complete suspension of alcohol intake while on treatment or restricting its use to an occasional drink during the course of the treatment.

Obesity and its associated nonalcoholic fatty liver disease are believed to play a role in the progression of fibrosis in HCV-infected individuals and response to treatment.[411,412] It is therefore appropriate to counsel those who are overweight (defined by a raised body mass index of >25 kg/m^2 or more) to attempt to lose weight. Additionally, weight reduction and improvement in insulin resistance may improve the response to peginterferon plus ribavirin therapy. This is sound advice for its potentially positive impact not only on the liver disease but also on the other conditions associated with being overweight.

A single report has suggested that superimposition of hepatitis A virus infection in persons with chronic liver disease, particularly those with hepatitis C, was associated with fulminant hepatitis.[413] Therefore, it is recommended that persons with chronic HCV infection who lack evidence of preexisting antibody to hepatitis A be

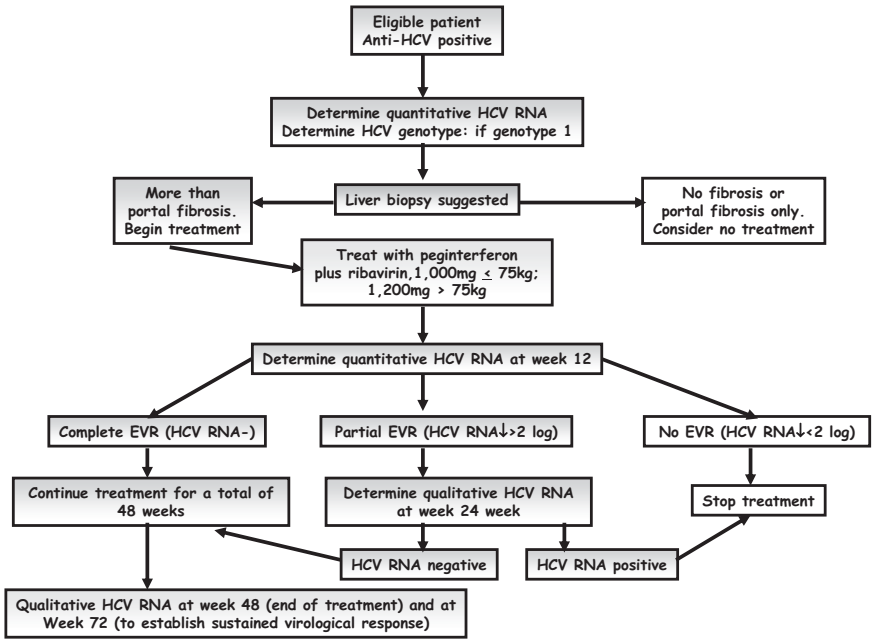

Fig. 3. Treatment algorithm for managing and treating patients with chronic HCV infection, genotype 1. SVR, sustained virologic response; EVR, early virologic response. RVR is omitted from this treatment algorithm because it has not yet been adequately evaluated. HCV RNA should be quantitated using a sensitive assay (10-50 IU/mL).

administered the hepatitis A vaccine.[414] Although no specific recommendation has been advanced for vaccination against hepatitis B, the evidence that persons co-infected with hepatitis B and C have a worse prognosis than those with HCV infection alone[415] suggests that hepatitis B vaccination should be offered to persons who are at risk for exposure to hepatitis B if they lack preexisting antibody to hepatitis B.

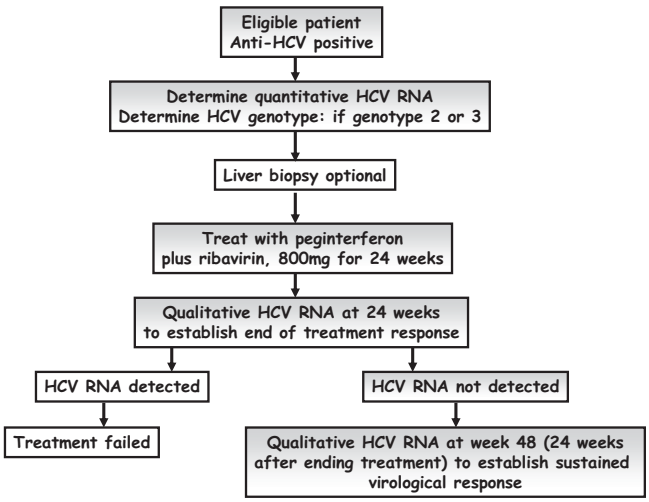

Fig. 4. Treatment algorithm for managing and treating patients with chronic HCV infection, genotype 2 or 3. EVR, early virologic response; ETR, end of treatment response; SVR, sustained virologic response. RVR is omitted from this treatment algorithm because it has not yet been adequately evaluated. HCV RNA should be quantitated using a sensitive assay (10-50 IU/mL).

Persons with chronic liver disease including those with hepatitis C frequently use herbal remedies.[416] In a prospective study, 42% of patients with chronic HCV infection reported using at least one herbal product.[417] Silymarin (milk thistle extract) was the most frequently reported herbal remedy used representing 72% of all herbals taken.[417] Similarly, approximately 40% of patients with advanced chronic hepatitis C and prior nonresponse to antiviral therapy who entered the long-term HALT-C treatment trial were found at the baseline visit to have either used herbal products in the past or were continuing to use them even while committing themselves to long-term peginterferon treatment.[418] Once again, silymarin was by far the preferred herbal. The benefit of silymarin or other herbal therapies for patients with chronic HCV infection has not been well studied or established. Currently, the NIH is conducting a well-designed scientific study of a standardized formulation of silymarin to determine its effectiveness in persons with chronic hepatitis C who had not responded to conventional medication, as well as among persons with nonalcoholic steatohepatitis (NASH). Of concern is that some herbals, particularly herbal mixtures have been associated with severe hepatotoxicity, fulminant hepatitis and death.[419] Accordingly, patients with chronic HCV infection should seek advice from their physician prior to initiating any herbal preparation. Similarly, prescription medications should be limited to the absolute minimum, particularly in those with cirrhosis.

Persons with chronic HCV infection should not share items of personal hygiene such as razors and toothbrushes.

Recommendations

63. All persons with chronic HCV infection who lack antibodies to hepatitis A and B should be offered vaccination against these two viral infections (Class IIa, Level C).

64. Persons with chronic HCV infection should be advised to abstain from alcohol consumption (Class IIb, Level C).

65. No recommendation can be made for the use of herbal products. There is no current evidence that herbal products have a role in the treatment of patients with acute or chronic HCV infection, (Class III, level C).

Conclusions

Described above are the current data on testing, diagnosis, decisions regarding whom to treat, and the recommended treatments of patients with chronic HCV infection. Figures 3 and 4 summarize the sequential steps recommended for managing and treating persons chronically infected with hepatitis C for whom treatment is considered clearly appropriate. As noted earlier, these represent currently acceptable guidelines; it is recognized that reasonable physicians may deviate from the strategy and remain within acceptable standards of treatment.

The issue of treatment of chronic HCV infection is in constant flux. There is highly active clinical research in this area, and new information appears with increasing frequency. Presented here is the current state of the art for management and treatment of persons with chronic HCV infection. However, these recommendations will need to be revised and updated in the future as additional critical and pivotal information becomes available.

Acknowledgment: This update of a previously published practice guideline was produced in collaboration with the Practice Guidelines Committee of the American Association for the Study of Liver Diseases. This committee supplied extensive peer-review of the manuscript. Members of the AASLD Practice Guidelines Committee include Margaret C. Shuhart, M.D., M.S., (Committee Chair), Gary L. Davis, M.D. (Board Liaison), Kiran Bambha, M.D., Andres Cardenas, MD, MMSc., Timothy J. Davern, M.D., José Franco, M.D., Steven-Huy B. Han, M.D., Stephen A. Harrison, M.D., Charles D. Howell, M.D., Simon C. Ling, MBChB, MRCP, Lawrence U. Liu, M.D., Paul Martin, M.D., Robert S. O'Shea, M.D., Nancy Reau, M.D., Bruce A. Runyon, M.D., Jayant A. Talwalkar, M.D., MPH, John B. Wong, M.D., and Colina Yim, RN. M.N. The authors and the committee would like to acknowledge the contributions of Teresa L. Wright, MD to the previous version of this guideline.

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