Diagnosis Management and Treatment of Hepatitis C

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Preamble

These recommendations provide a data-supported approach. They are based on the following: (1) a formal review and analysis of the recently-published world literature on the topic [Medline search]; (2) the American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines[1]; (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the AGA Policy Statement on Guidelines[2]; the guideline procedures of the Infectious Diseases Society of America[3]; (4) and the experience of the authors in the specified topic.

These recommendations are fully endorsed by the American Association for the Study of Liver Diseases, and the Infectious Diseases Society of America.

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. In an attempt to characterize the quality of evidence supporting recommendations, the Practice Guidelines Committee of the AASLD requires a category to be assigned and reported with each recommendation (Table 1).

Table 1

QUALITY OF EVIDENCE ON WHICH RECOMMENDATION IS BASED

Grade	Definition
I	Randomized, controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology[4]

Introduction

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease. In the United States (U.S.), the Centers for Disease Control and Prevention estimates that there are more than 2.7 million people with ongoing HCV infection[5]. HCV is the leading cause of death from liver disease in the U.S.[6] The purpose of this document is to provide clinicians with approaches to the diagnosis, management and prevention of HCV infection.

Testing and Counseling

Testing

The optimal method of detecting HCV infection is to screen populations for history of risk, and to test selected individuals with an identifiable risk factor. With careful questioning, an HCV risk factor can be identified in more than 90% of cases[7]. The primary source of HCV transmission is HCV-infected blood or blood products. In the United States, injection drug use is the chief mode of transmission, and anyone who has ever injected illicit drugs should be tested[5, 7]. Persons should also be tested if they had received a blood or blood component transfusion or organ transplant before 1992, when sensitive tests were first used to screen donors for HCV antibodies. Since that time, HCV infection is rarely transmitted by transfusion[8]. Other potential sources of HCV transmission include exposure to an infected sexual partner or multiple sexual partners, frequent exposure to infected blood among health care workers and perinatal exposure[9-11].

Although HCV prevalence rates are consistently higher in persons with multiple sexual partners, sexual transmission of HCV between monogamous partners is rare[7]. Thus, while it is common to counsel HCV-infected persons to notify their current partners of their HCV status, they should be told that the risk of sexual transmission is sufficiently low[12] that many authorities do not advise use of barrier precautions (that is, latex condoms). Testing of sexual partners, therefore, is done chiefly for reassurance. There is no need to curtail ordinary household activities except those that might result in blood exposure, such as sharing a razor or toothbrush. HCV is not transmitted by hugging and the sharing of eating utensils. Although a monogamous sexual relationship carries a low risk of transmission of HCV infection, as noted above, the risk is higher in persons involved with multiple sexual partners. Persons with hemophilia should be tested for HCV infection if blood products were received before 1987, when viral inactivation procedures were implemented. It is also advisable to test persons for HCV infection if they have evidence of otherwise unexplained elevations of aminotransferase levels (alanine and/or aspartate aminotransferases; ALT/AST), have ever been on hemodialysis, or have human immunodeficiency virus (HIV) infection[10].

Other situations that have been suggested to carry a risk for HCV transmission include certain folk medicine practices (acupuncture, ritual scarification), body piercing, tattooing and even commercial barbering[13-17]. Some studies of hepatitis C infection have reported associations with commercial tattooing, suggesting possible acquisition of HCV infection in this set-

ting[18-20]. Most studies of body piercing have not differentiated between ear piercing and piercing of other body parts[18-20]. As a result of discrepancies in study design, definitive conclusions regarding risks associated with these forms of percutaneous exposures are problematic, although the risk, if present, is likely to be low. Thus, there is no need to test routinely persons who have received tattoos or have undergone piercing, particularly if these procedures have taken place in licensed establishments. Finally, it is appropriate to test immigrants, both children and adults, who come from areas where HCV infection is common, such as Egypt. Table 2, adapted from recommendations published by the Centers for Disease Control, Atlanta Georgia,[10] outlines the list of persons who should be routinely tested for HCV infection. For some of these categories, the HCV prevalence is high (e.g., injection drug users, persons with hemophilia; ~90%), for others, the prevalence is moderate (e.g., recipients of blood transfusions prior to 1992; ~10%), while for still others, it is quite low (e.g., persons exposed by needle stick, sexual partners of HCV-infected persons; 2-5%).

Table 2

PERSONS FOR WHOM HCV TESTING 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 before 1987
  - Persons who were ever on hemodialysis
  - Persons with unexplained abnormal aminotransferase levels
- Prior recipients of transfusions or organ transplants 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 before July 1992
  - Persons who received an organ transplant before July 1992
- Children born to HCV-infected mothers
- Healthcare, 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*

Adapted from MMWR, October 16, 1998[10]

*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.

Recommendation

1. Persons who should be tested for HCV infection are listed in Table 2 (III)

Counseling

Persons found to be HCV-infected need to be counseled regarding prevention of spread of the virus to others. Good clinical practice dictates that all persons identified as infected with HCV be informed that transmission to others occurs through contact with their blood and that they should therefore take precautions against the possibility of such exposure. Although this advice applies to all HCV-infected persons, it has particular importance for injection drug users who are the leading source of HCV infections. Circumstances requiring counseling are shown in Table 3.

Table 3

COUNSELING TO AVOID TRANSMISSION OF HCV

- HCV-infected persons should be counseled to avoid sharing toothbrushes, dental or shaving equipment and be cautioned to cover any bleeding wound in order to keep their blood away from 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 safely of syringes and needles after one use
- 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 (that is, those in long-term relationships need not start using barrier precautions and others should always practice 'safer' sex)
- HCV-infected persons should be advised to not donate blood, body organs, other tissues, or semen

Adapted and modified from MMWR October 16, 1998 [10]

Recommendation

2. Persons infected with HCV should be counseled on how to avoid HCV transmission to others, as indicated in Table 3 (III)

Laboratory Testing

Testing Strategy

Utilizing the tests described below, several strategies can be employed to detect HCV infection. In clinical practice, the usual approach is to test initially for antibodies to HCV (anti-HCV) with an enzyme immunoassay (EIA), then to use HCV RNA to document viremia. Because most persons with ongoing HCV infection have HCV RNA levels in the range of the quantitative assays and because the quantity of HCV RNA is useful to know before providing and monitoring HCV treatment[21], many experts routinely obtain quantitative rather than qualitative HCV RNA testing to confirm the presence of viremia[22]. However, quantitative HCV RNA tests are generally not as sensitive, and therefore some experts prefer a qualitative HCV RNA test to confirm a positive HCV antibody result, either as the primary test or in patients with a negative result by quantitative assay[23, 24]. A negative sensitive RNA test in a person with HCV antibodies by EIA most likely indicates that the HCV infection has resolved. Other interpretations are that the anti-HCV immunoassay is falsely positive, the HCV RNA test is falsely negative, or rarely, that a person has intermittent or low-level viremia.

The recombinant immunoblot assay (RIBA) has limited usefulness in clinical practice but may establish the cause of a positive anti-HCV immunoassay in a person with undetectable HCV RNA[24]. A negative immunoblot result indicates that a positive anti-HCV immunoassay result represented a false positive result and that no further testing is needed. A positive immunoblot result followed by two or more instances in which HCV RNA cannot be detected using a licensed, qualitative assay suggest that HCV infection has resolved and no further HCV testing is indicated.

There are instances in which a negative anti-HCV does not exclude HCV infection in patients with suspected liver disease. These include acute HCV infection or immunosupressed states. HCV RNA testing can be used to establish acute HCV infection after an exposure because HCV RNA can be detected in 1 to 2 weeks while antibodies to HCV are detectable an average of 8 weeks later[25-27]. HCV RNA testing can also be used to test for HCV infection in persons with negative HCV antibody results who are known to have conditions associated with diminished antibody production, such as HIV infection and chronic hemodialysis [23].

Assays for HCV RNA

Qualitative Assays

HCV RNA can be detected in the blood using amplification techniques such as polymerase chain reaction (PCR) or transcription-mediated amplification (TMA)[28]. The FDA has approved two PCR-based tests for qualitative detection of HCV RNA: (1) AMPLICOR® Hepatitis C Virus (HCV) Test, version 2.0, and (2) COBAS AMPLICOR® Hepatitis C Virus Test, version 2.0 (Roche Molecular Systems, Branchburg, New Jersey), which have lower limits of detection of approximately 50 IU/mL. Other commercially-available non-approved assays are used by some diagnostic laboratories.

Quantitative Assays

These assays ascertain the quantity of HCV RNA in blood using either target amplification (PCR, TMA) or signal amplification techniques (branched DNA assay) (Table 4). The level of HCV RNA in blood helps in predicting the likelihood of response to treatment, and the change in the level of HCV RNA during treatment can be used to monitor response. The results should be reported in international units to standardize data[29], although the dynamic ranges differ and the results can be difficult to compare between assays, as noted in Table 4. Because a change in the HCV RNA level is used to monitor treatment response (see later), it is important at the outset of treatment to obtain the *actual* level rather than simply a report indicating that the level exceeds an upper limit of detection, since HCV RNA levels sometimes are above the linear range of currently available assays. In addition, the same quantitative test should be used while on therapy to avoid confusion. The only quantitative test that has currently received FDA approval is VERSANT® HCV RNA version 3.0. (Bayer Diagnostics, Tarrytown, NY)(Table 4).

HCV Genotyping

There are six major HCV genotypes[30]. Although genotype does not predict the outcome of infection, it does predict the likelihood of treatment response, and in many cases, determines the duration of treatment[31-33]. Genotyping can be performed by direct sequence analysis, by reverse hybridization to genotype-specific oligonucleotide probes, or by the use of restriction fragment length polymorphism. Two tests, not yet FDA approved, are currently available for clinical use; the Trugene HCV 5'NC Genotyping kit (Visible Genetics, Toronto, Ontario, Canada), based on direct sequencing followed by comparison with a reference sequence database, and the line-probe assay (Inno LiPA HCV II, Innogenetics, Ghent, Belgium), based on reverse hybridization of PCR amplicons on a nitrocellulose strip coated with genotype specific oligonucleotide probes[34-36]. Once the genotype is identified, the test need not be repeated. Current commercial tests fail to identify the genotype in a small proportion (<3 %) of HCV-positive persons[37], and a similarly low proportion (1-4%) may display mixed genotypes[37, 38].

Recommendations

3. Patients suspected of having chronic HCV infection should be tested for HCV antibodies. (II-2)

4. HCV RNA testing should be performed in:

a . Patients with a positive anti-HCV test (II-2).

b. Patients for whom antiviral treatment is being considered, using a quantitative assay (II-2)

c. Patients with unexplained liver disease whose anti-HCV test is negative and who are immune compromised or suspected of having acute HCV infection (II-2).

5. HCV genotype should be determined in all HCV-infected persons prior to treatment in order to determine the duration of therapy and likelihood of response (I).

Table 4

ASSAYS FOR QUANTITATION OF HCV RNA IN SERUM

Assay	1 IU/L Conversion	Technique	Dynamic Range (IU/L)
Amplicor HCV Monitor V2.0 (Roche Molecular Systems)	0.9 copies/ml	Manual competitive reverse transcriptase PCR (rtPCR)	600-500,000
Cobas Amplicor Monitor HCV V2.0 (Roche Molecular Systems)	2.7 copies/ml	Semi-automated competitive rtPCR	600-500,000
Versant HCV RNA 3.0 Quantitative Assay (Bayer Diagnostics)	5.2 copies/ml	Semi-automated 'branched DNA' assay	615-700,000
LCx HCV RNA Quantitative Assay (Abbott Diagnostics)	3.8 copies/ml	Semi-automated competitive rtPCR	25-2,630,000
SuperQuant (National Genetics Institute)	3.4 copies/ml	Semi-automated competitive rtPCR	30-1,470,000

Adapted and modified from Pawlotsky[23]

Roche Molecular Systems, Branchburg, NJ; Bayer Diagnostics, Tarrytown, NY; Abbott Diagnostics, Chicago, IL; National Genetics Institute, Los Angeles, CA

Utility of Liver Biopsy

The role of liver biopsy in the management of patients with chronic hepatitis C is currently being debated. In the initial treatment trials of hepatitis C, a liver biopsy was regarded as an important parameter in helping to guide management and treatment, particularly at a time when response to treatment was low. More recently, with the improvement of treatment effectiveness, the value of the liver biopsy has begun to be questioned because of the potential risks of the procedure and the concern of sampling error[39]. This has prompted some to challenge the need for biopsy and to suggest that the procedure may not be necessary as a prelude to treatment. However, since current therapy is effective in clearing virus in only about one-half of those treated, and since treatment is associated with costs and adverse events, there are likely many individuals in whom therapy can be safely deferred.

The liver biopsy furnishes information about the staging of fibrosis and the degree of hepatic inflammation, histopathological features that are helpful to both the patient and the provider for predicting the natural history of disease and thus the relative urgency of therapy[40-42]. Three scoring systems for defining the degree of inflammation (grading) and the extent of fibrosis (staging) have been devised, two of which – the Metavir scoring system[43] and the Ishak grading system[44] – have received the greatest attention. The components of these systems are shown in Table 5. Using the degree of fibrosis as one component of the basis for therapy, treatment is generally advised if the liver biopsy displays a Metavir score of ≥ 2 or an Ishak score of ≥ 3. Some experts, in considering the need for treatment, also assess the intensity of liver inflammation. However, there are no established guidelines for how to combine the degrees of liver fibrosis and inflammation. Moreover, measurement of liver fibrosis and especially liver inflammation can be compromised by sampling error and by difficulties in the histopathologic interpretation. In most studies, the extent of liver fibrosis is an independent predictor of treatment response. Patients with milder degrees of fibrosis generally respond more favorably to treatment than do patients with more advanced fibrosis (bridging fibrosis or cirrhosis)[45, 46]. However, the need for treatment in such patients is lower than it is for those with advanced fibrosis. The cost effectiveness of treating patients with no liver fibrosis has been questioned, since the prognosis even without therapy is excellent, further underscoring the importance of accurately staging the severity of liver disease[47]. Clinical, laboratory and radiological findings can identify many patients with cirrhosis, but not those with lesser degrees of fibrosis[48]. Thus, in persons without strong clinical evidence of cirrhosis, a liver biopsy is useful in providing information about the extent of liver damage associated with chronic infection, the feature that remains the best predictor of prognosis. Although liver fibrosis markers are commercially available, they are currently insufficiently accurate to support their routine use[49]. Until sensitive serum markers can be developed that will define all stages of fibrosis and mirror the information derived from liver biopsy, the procedure remains the only means of defining the severity of damage from HCV infection in many patients.

Table 5

HISTOLOGIC SCORING SYSTEMS

Stage	Metavir System [43]	Ishak System [44]
0	No fibrosis	No fibrosis
1	Periportal fibrosis expansion	Fibrous expansion of some portal areas, with or without short fibrous septa
2	Portal-portal septae (>1 septum)	Fibrous expansion of most portal areas, with or without short fibrous septae
3	Portal-central septae	Fibrous expansion of most portal areas with occasional portal-portal (P-P) bridging
4	Cirrhosis	Fibrous expansion of portal areas with marked bridging (P-P or portal-central P-C)
5	–-	Marked bridging (P-P or P-C) with occasional nodules (incomplete cirrhosis)
6	–-	Cirrhosis

After weighing the risks, benefits and costs of existing HCV treatments and of liver biopsy, most experienced clinicians routinely obtain a liver biopsy in patients with HCV genotype 1 infection to guide recommendations for treatment (see below). Patients infected with HCV, genotypes 2 and 3, however, have a high likelihood of response and, therefore some advocate treating all such patients regardless of severity of liver disease without resorting to liver biopsy. For patients with no or little fibrosis (i.e., Metavir score < 2 or Ishak score < 3), in whom treatment is often deferred, liver biopsy can be used to monitor progression of liver disease. An interval of 4 to 5 years between biopsies may be needed to measure change in such patients[50].

Although the spectrum of liver fibrosis tends to be worse in persons with elevated blood levels of aminotransferases than in those with normal aminotransferase levels[51], 14-24% of persons with persistently normal values have more than portal fibrosis on liver biopsy. Such individuals may have progressive liver disease over time despite persistence of normal aminotransferase values[51, 52]. In individuals with normal aminotransferase values and extensive hepatic fibrosis (bridging fibrosis or cirrhosis), treatment should be considered, and liver biopsy is the only available method to obtain the necessary information to guide this decision. Among patients with chronic infection and clinical signs of advanced cirrhosis, liver biopsy may add little to the clinical impression and may be riskier than in healthier patients.

Recommendations

6. Regardless of the level of ALT, a liver biopsy should be done when the results will influence whether treatment is recommended, but a biopsy is not mandatory in order to initiate therapy (III).

7. A liver biopsy may be obtained to provide information on prognosis (III).

Initial treatment of HCV infection

Justification for Treatment

Natural history studies indicate that 55% to 85% of persons who develop acute hepatitis C will remain HCV-infected. Among these individuals, 5% to 20% are reported to develop cirrhosis over periods of approximately 20 to 25 years[53, 54]. The higher percentage figure of 20% may not reflect the cirrhosis rate in the general population of HCV-infected persons since these data originate largely from studies in tertiary care settings, and hence may represent referral bias. Persons with HCV-related cirrhosis are at risk for developing end-stage liver disease (a risk of approximately 30% over ten years) as well as hepatocellular carcinoma (HCC) (a risk of approximately 1% to 2% per year)[55]. The 15-45% of persons with acute hepatitis C who do recover (HCV RNA not detected in their blood) are not subject to long-term complications and do not need treatment. In general clinical practice, however, acute hepatitis C is uncommonly recognized; the majority of patients already have chronic hepatitis C. Among individuals with persistent infection, evolution to cirrhosis is the primary concern, usually requiring the passage of two or more decades, and occurring more often in persons infected at older ages, particularly men, those who drink more than 50 grams of alcohol each day, those who are obese or have substantial hepatic steatosis, or those with HIV co-infection[56-58]. More than portal fibrosis on liver biopsy (Metavir ≥ 2 or Ishak ≥ 3) is an important predictor of future progression of liver disease and the need for HCV treatment[40, 41, 57].

Infection with HCV can also be associated with a variety of extra-hepatic manifestations, chief of which is the induction of abnormal circulating proteins called cryoglobulins. The pathologic consequence, termed mixed cryoglobulinemia, is the development of vasculitis, which is associated with certain skin manifestations and internal organ damage that predominantly affects the kidney. The presence of symptomatic cryoglobulinemia is an indication for HCV antiviral therapy, regardless of the stage of liver disease.

Treatment Objectives and Outcomes

The goal of treatment is to prevent complications of HCV infection, which is principally achieved by eradication of infection. Accordingly, treatment responses are frequently characterized by the results of HCV RNA testing. Infection is considered eradicated when there is a *sustained virologic response (SVR)*, defined as the absence HCV RNA in serum by a sensitive test at the end of treatment and six months later. As discussed below, persons who achieve an SVR almost always have a dramatic earlier reduction in the HCV RNA level defined in some studies as a 2 log drop or loss of HCV RNA twelve weeks into therapy, referred to as an *early virologic response (EVR)*. Continued absence of detectable virus at termination of treatment is referred to as *end of treatment response (ETR)*. A patient is considered to have *relapsed* when HCV RNA becomes undetectable on treatment but is detected again after discontinuation of treatment. Persons in whom HCV RNA levels remain stable on treatment are considered *non-responders*, while those whose HCV RNA levels decline (for example by >2 logs) but never become undetectable, are referred to as *partial responders*. Improvement in liver histology, including improvement in fibrosis, has been observed in patients receiving interferon or peginterferon in combination with ribavirin, particularly in those with a sustained virological response to therapy[59].

Figure 1

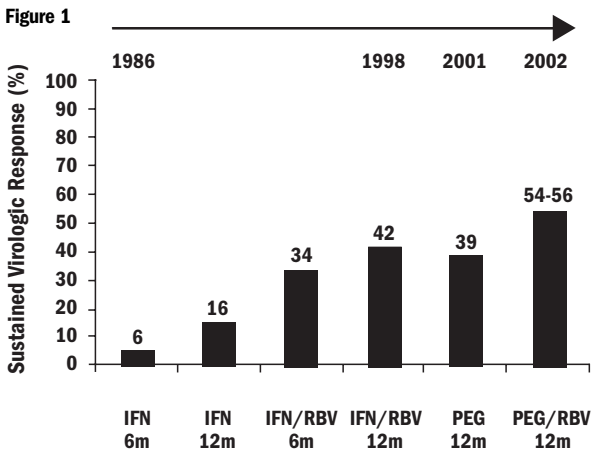

Figure1: Milestones in therapy of chronic hepatitis C (IFN, interferon; RBV, ribavirin; PEG, pegylated interferon; m, months)

The Optimal HCV Treatment

There have been substantial improvements in the success of HCV treatment (Figure 1), and there are currently several treatments approved by the Food and Drug Administration

Table 6

DRUGS USED IN THE TREATMENT OF CHRONIC HEPATITIS C

Generic (Trade Name)	Recommended Dose
Combination Peginterferon Regimens with Ribavirin	
Peginterferon alfa-2a (40 kD) (Pegasys™)	180 μg SQ once weekly regardless of weight
Peginterferon alfa-2b (12 kD) (Peg-Intron®)	1.5 μg/kg SQ once weekly
Ribavirin (Rebetol®, Copegus®)	800-1200 mg po daily (in two divided doses), dose depending on infection, genotype and patient weight (see text)
Regimens Used in Certain Clinical Circumstances (see text)	
Peginterferon alfa-2a (40 kD) (Pegasys®)	180 μg SQ once weekly as monotherapy regardless of weight
Peginterferon alfa-2b (12 kd) (Peg-Intron®)	1.0 μg/kg SQ once weekly as monotherapy
Interferon alfa-2b plus ribavirin (Rebetron®)	Interferon alfa-2b SQ 3 mU tiw. Ribavirin 1,000 mg po daily ≤ 75 kg or 1,200 mg daily if > 75 kg (in two divided doses)
Interferon	
• alfa-2a (Roferon-A®)	3 mU SQ tiw
• alfa-2b (Intron-A®)	3 mU SQ tiw
• consensus (Infergen®)	9 μg SQ tiw; but 15 μg tiw in non-responders

Abbreviations: kd, kilodaltons, μg, micrograms; SQ, subcutaneously; kg, kilograms; mU, million units; tiw, three times per week; po, per mouth, mg, milligrams

Pegasys, Hoffmann-La Roche, Nutley NJ; Peg-Intron, Schering-Plough Corporation, Kenilworth, NJ; Rebetol; Schering-Plough Corporation, Kenilworth, NJ; Copegus, Hoffmann-La Roche, Nutley NJ; Rebetron, Schering-Plough Corporation, Kenilworth, NJ; Roferon-A, Hoffmann-La Roche, Nutley NJ; Intron-A, Schering-Plough Corporation, Kenilworth, NJ; Interfergen, InterMune, Brisbane, CA

(FDA) (Table 6). In randomized clinical trials, the highest overall SVR rates have been achieved with the combination of weekly subcutaneous injections of long-acting peginterferon alfa and oral ribavirin, which represents the current standard of care.

Peginterferon Alfa and Ribavirin

Peginterferons are produced by binding of the inert polyethylene glycol moiety to interferon molecules, thus decreasing renal clearance, altering metabolism and increasing the half life of the peginterferon molecule[60]. There are two licensed products in the United States, the 12-kd peginterferon alfa-2b (Peg-Intron; Schering-Plough, Kenilworth, NJ), and the 40-kd peginterferon α-2a (Pegasys; Hoffmann-La Roche, Nutley, NJ). Because of their prolonged half lives, they can be administered by subcutaneous injection once weekly. In large, randomized, controlled trials, higher SVR rates have been achieved with the combination of weekly injections of peginterferon alfa plus oral ribavirin given twice daily than with interferon alfa given by injection three times a week together with ribavirin or peginterferon alfa used alone[31, 32]. In these trials, peginterferon alfa-2b was dosed by weight (1.5 μg/kg was FDA approved) and coupled with 800 mg of ribavirin, while peginterferon alfa-2a was given as a fixed dose of 180 μg along with a weight-adjusted, higher dose of ribavirin (1,000 mg if ≤ 75 kg and 1,200 mg if > 75 kg). In a third randomized controlled trial, 180 μg of peginterferon alfa-2a was used with either 800 mg or the higher, weight-adjusted doses of ribavirin[33]. Since the two peginterferon alfa compounds have not been compared in a randomized controlled trial using similar ribavirin doses, their relative efficacies cannot be assessed. However, there were similar indicators of treatment response and adverse events that are discussed below. It should be noted that data believed to be useful for establishing treatment recommendations were not always replicated for both forms of peginterferon. For example, the design of the peginterferon alfa-2a study was the only one capable of determining that a treatment duration of 6 months is sufficient for persons infected with HCV genotypes 2 or 3[33]. Nevertheless, recommendations have been broadened to encompasss both peginterferon preparations.

Efficacy and Predictors of Response

Overall response rates to peginterferon plus ribavirin and response according to genotype and pre-treatment HCV RNA levels are shown in Figures 2-4. The likelihood of achieving an SVR can be predicted by pre-treatment patient characteristics, as well as by the early virologic response. In all prospective treatment studies, genotype is the strongest predictor of response. In the above-mentioned randomized, controlled studies of peginterferon alfa-2b and ribavirin, SVR rates were higher in patients who had genotype 2 or 3 HCV infections, lower pretreatment HCV RNA levels (Figure 2), younger ages, lower body weights, and absence of bridging fibrosis and cirrhosis[31-33]. In persons who were treated with peginterferon alfa-2a together with ribavirin, the independent variables associated with an SVR included genotype non-1 (Figure 3), age

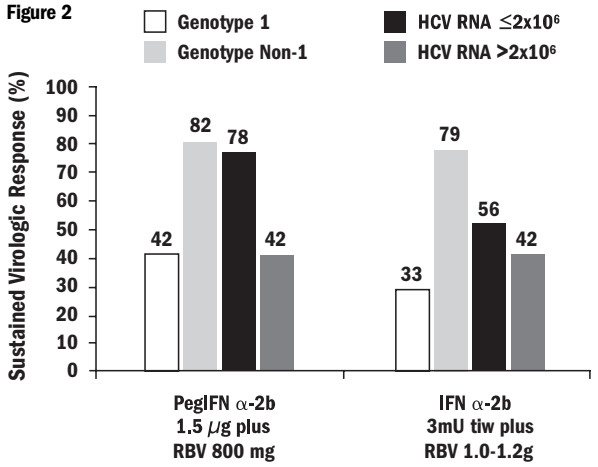

Figure 2: Sustained virologic response rates with peginterferon a-2b (PegIFN) and ribavirin (RBV) therapy for 48 weeks according to the genotype and viral concentration[31]

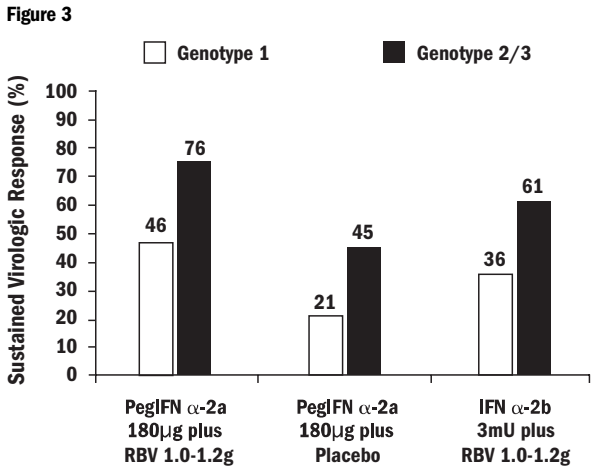

Figure 3: Sustained virologic response rates with peginterferon a-2a (PegIFN) or interferon a-2b (IFN) and ribavirin (RBV) according to genotype[32]

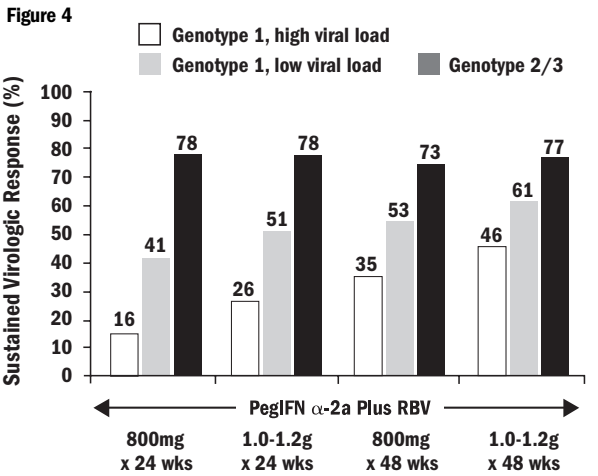

Figure 4: Sustained virologic response rates in recipients of peginterferon a-2a (PegIFN) and two different doses of ribavirin (RBV) for 24 or 48 weeks[33]

less than 40 years and body weight less than 75 kg[32]. The majority of patients in the first two peginterferon combination trials who had genotype non-1 infection[31, 32], were infected with genotypes 2 or 3, but a small number were infected with genotypes 4, 5 and 6. In these two registration trials, among patients with genotype 1 infections, SVRs were 42-46%, while the response rates in those with genotype 2 or 3 were higher, 76-82%. In the study that evaluated peginterferon alfa-2a, the data were analyzed further by combining genotype and viral load[32]. Persons with genotype 1 and a *high viral load* (>2 x 10^6 copies/ml, equivalent to ~800,000 IU/mL) who received the combination of peginterferon alfa-2a and ribavirin had an SVR of 41%, whereas the rate among those with genotype 1 and a *low viral load* (≤2 x 10^6 copies/ml), treated with the same regimen was 56%. In contrast, among persons with genotypes 2 and 3 and a *high viral load* given peginterferon alfa-2a and ribavirin, the SVR rate was 74%, while those with genotypes 2 and 3 and a *low viral load*, treated similarly, had an SVR of 81%.

In African American patients with genotype 1 infection, SVR rates are typically lower than in Caucasians[61, 62], although precise estimates are not currently available for the combination of peginterferon alfa and ribavirin.

Early Virological Response (EVR)

In the study of peginterferon alfa-2a with ribavirin, the predictability of an SVR based on the EVR was assessed[32]. Defined at week 12 as an at least 2-log decline from baseline of the HCV RNA level, 65% of patients with an early virologic response (EVR) subsequently achieved an SVR. Conversely, among those who did not have an early virologic response, 97% failed to develop an SVR. Similar data were noted in the study that used peginterferon alfa-2b together with ribavirin[63]. Among treated persons who had an EVR, as described above, 72% ultimately achieved an SVR, whereas among those who did not have an EVR, none developed an SVR.

Effects of Treatment Duration and Ribavirin Dose

The optimal treatment duration and ribavirin dose were investigated in a multi-center randomized, controlled trial in which all persons received peginterferon alfa-2a at a dose of 180µg while patients in the four arms received either 24 or 48 weeks of ribavirin at doses of either 800mg or the higher weight-based dose of 1,000 or 1,200mg daily (Figure 4)[33]. Data were analyzed taking into account not only the HCV genotype, but also the pre-treatment viral load (> or ≤ 2 x 10^6 copies/ml) among those with genotype 1. In patients with genotype 1 with low level viremia, the SVR was highest in persons who had received the higher ribavirin dose and who were treated for 48 weeks (61%). This regimen was also optimal for patients with genotype 1 and a high viral load in whom 46% achieved an SVR. In contrast, in patients with genotypes 2 or 3, regardless of the pre-treatment viral load, no differences were detected with the four treatment regimens, suggesting that peginterferon alfa-2a plus ribavirin at a dose of 800mg given for 24 weeks is adequate[33].

Adverse Events

In general, the incidence and types of side effects of peginterferon alfa plus ribavirin are similar to those identified for interferon plus ribavirin. Approximately 75% of those treated experience one or more systemic side effects, including:

(i) those typically associated with interferon alfa, such as: neutropenia, thrombocytopenia, depression, hypo- and hyperthyroidism, irritability, concentration and memory disturbances, visual disturbances, fatigue, muscle aches, headaches, nausea and vomiting, skin irritation, low-grade fever, weight loss, insomnia, hearing loss, tinnitus, interstitial fibrosis and hair thinning. "Flu-like" symptoms and depression appeared to occur significantly less frequently with peginterferon alfa-2a plus ribavirin than with interferon alfa-2b plus ribavirin[32].

(ii) those typically associated with ribavirin, such as: hemolytic anemia, fatigue, itching, rash, sinusitis, birth defects or gout. Because of the concern of birth defects from the use of ribavirin, it is imperative that persons who receive the drug use strict contraception methods both during treatment and for a period of 6 months after treatment.

Deaths reported in association with the use of interferon alfa and ribavirin include suicide, myocardial infarction, sepsis, and stroke.

Growth factors, such as epoetin and granulocyte colony stimulating factor (GCSF) have been used to counteract the adverse events of ribavirin and interferon, respectively. However, there are insufficient data currently to recommend their routine use to avoid or ameliorate peginterferon and ribavirin dose reductions in clinical practice.

Adverse events tend to be more severe in the initial weeks of treatment and often can be managed with analgesics (e.g., acetaminophen [< 2.0 grams/day] or non-steroidal anti-inflammatory drugs), anti-depressants (e.g., serotonin uptake inhibitors), and occasionally, growth factors.

Selection of Patients for Treatment

Current recommendations for treatment of persons with chronic hepatitis C are derived from data gathered in the randomized, controlled registration trials described above. Persons who entered these trials, however, were carefully selected so as to exclude those with conditions that might potentially compromise treatment response. Much less information is available for HCV-infected persons who have co-morbid conditions such as depression and active substance abuse, conditions that are frequent among persons with chronic hepatitis C, as well as for special groups not yet involved in controlled trials, such as infants and children. As with all clinical decisions, selection of patients for HCV treatment requires accurate assessment of both therapeutic risk and benefit, a determination that is complicated by exclusion from registration trials of persons with conditions that might increase risk and diminish benefit. Application of these principles to individual patients can be challenging and the relative strength of recommendation of treatment varies accordingly. This variability is displayed in Tables 7-9.

There is insufficient experience to provide recommendations

Table 7

PERSONS FOR WHOM THERAPY IS WIDELY ACCEPTED

Individuals with detectable HCV RNA who meet all the criteria listed below:

- are at least 18 years of age
- have abnormal ALT values
- have a liver biopsy showing chronic hepatitis with significant fibrosis (more than portal fibrosis: Metavir score ≥2; Ishak score ≥3)
- have compensated liver disease (total serum bilirubin <1.5g/dL; INR <1.5; albumin >3.4 g/dL; platelet count >75,000 k/mm^3 , and no evidence of hepatic encephalopathy or ascites)
- have acceptable hematological and biochemical indices (hemoglobin >13 g/dL for men and > 12 g/dL for women; neutrophil count >1.5 k/mm^3; creatinine < 1.5 mg/dL)
- have not been treated previously for HCV infection
- may have a history of depression, but the condition is well-controlled
- are willing to be treated and to conform to treatment requirements

Table 8

PATIENTS FOR WHOM THERAPY SHOULD BE INDIVIDUALIZED

Individuals with detectable HCV RNA who:

- have persistently normal ALT values
- have failed prior treatment (non-responders and relapsers) consisting of either interferon given alone or in combination with ribavirin, or with peginterferon given alone
- are current modest users of illicit drugs or alcohol but are willing to participate in a substance abuse or alcohol support program, such as a methadone program or an alcohol support program
- have liver biopsy evidence of either no or only mild fibrosis (portal fibrosis: Metavir score <2; Ishak score <3)
- have acute hepatitis C
- are co-infected with HIV
- are under 18 years of age
- have chronic renal disease whether or not they are on hemodialysis
- have decompensated cirrhosis
- have undergone liver transplantation

Table 9

PERSONS FOR WHOM THERAPY IS CURRENTLY CONTRAINDICATED

Individuals with detectable HCV RNA who:

- have a major, uncontrolled depressive illness
- have undergone renal, heart or lung transplantation
- have conditions known to be exacerbated by interferon and ribavirin, such as autoimmune hepatitis
- have untreated hyperthyroidism, are currently pregnant or are unwilling or unable to comply with adequate contraception, have severe concurrent disease such as severe hypertension, heart failure, significant coronary artery disease; poorly controlled diabetes, obstructive pulmonary disease, etc.
- are under 3 years of age
- have known hypersensitivity to the drugs used to treat HCV

for treatment of persons with genotypes 4, 5 and 6. Experienced providers would need to make treatment judgments on a case-by-case basis.

Recommendations for treatment of persons with HCV-related liver disease

8. The treatment of choice is peginterferon plus ribavirin (I)

9. For patients in whom liver histology is available, treatment is indicated in those with more than portal fibrosis (III)

10. Treatment decisions should be individualized based on the severity of liver disease, the potential of serious side effects, the likelihood of treatment response and the presence of co-morbid conditions (III).

<u>Genotype 1 HCV Infection:</u>

11. Treatment with peginterferon plus ribavirin should be planned for 48 weeks, using a ribavirin dose of 1,000 mg. for those ≤ 75 kg in weight and of 1,200 mg for those > 75 kg (I).

12. Quantitative serum HCV RNA should be performed at the initiation of or shortly before treatment and at week 12 of therapy. (I)

13. Treatment may be discontinued in patients who do not achieve an early virological response at 12 weeks, although the decision should be individualized according to the tolerability of therapy, severity of underlying liver disease and demonstration of some degree of biochemical and/or virological response (I, III)

14. Persons whose treatment continues through 48 weeks and whose qualitative measurement of HCV RNA at that time is negative, should be re-tested for HCV RNA 24 weeks later to document a sustained virological response (II-1)

<u>Genotypes 2 or 3 HCV infection:</u>

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

16. Persons whose treatment continues for the full 24 weeks and whose qualitative measurement of HCV RNA at that time is negative, should be re-tested for HCV RNA 24 weeks later to document a sustained virological response (II-1)

Re-treatment of Persons who Failed to Respond to Previous Treatment

The approach to persons who failed to respond to initial treatment depends on the nature of the initial response, the potency of the initial treatment, and on host-viral factors. Two categories of patients have been identified: non-responders and relapsers.

Non- and Partial Responders

Overall, an SVR can be achieved by re-treatment with peginterferon alfa and ribavirin in 25% to 40% of persons who failed to respond to interferon alfa monotherapy and about 10% who failed to respond to interferon alfa and ribavirin[64, 65].

In one study that carefully evaluated on-treatment responses, an SVR was only achieved in those who were partial responders[64]. There were no SVRs in non-responders. As noted in the trials involving persons previously naïve to treatment, factors associated with a higher likelihood of response to re-treatment included genotype non-1, lower baseline HCV RNA levels, lesser degrees of fibrosis, and Caucasian race[65].

Relapsers

Persons who relapse after an initial response will generally achieve another on-treatment response. In one study of patients who relapsed after a regimen of interferon without ribavirin, almost half achieved an SVR following re-treatment with interferon alfa and ribavirin for 24 weeks[66]. The same factors as those identified in previous studies, genotype 2 and 3 and a low HCV RNA load, predicted a favorable outcome. Although studies using peginterferon alfa and ribavirin to treat relapsers have not been completed, it stands to reason that the optimal re-treatment responses will be achieved with the most potent regimen available.

Maintenance therapy

While eradication of HCV RNA is the primary goal for treatment of persons with chronic hepatitis C, there is accumulating evidence that treatment may have a secondary benefit of reducing progression of fibrosis and thereby delaying evolution to cirrhosis or possibly reversing early cirrhosis. Some studies have demonstrated that, despite an absence of virological response to treatment, histological improvement can occur[31, 59]. In addition, studies have also shown that in treated patients who fail to clear virus, the rate of progression to cirrhosis may be decreased or reversed[67], and there may be a lower frequency of development of HCC[68, 69]. Although these are interesting and suggestive data, the hypothesis that treatment will delay disease progression even if it does not eradicate the actual hepatitis C virus has not been tested in well-controlled trials. Such studies are in progress, but until they are completed and the treatment regimen established, no recommendation can be offered with regard to the value of maintenance therapy.

Recommendations

17. Retreatment with peginterferon plus ribavirin should be considered for non-responders or relapsers who have significant fibrosis or cirrhosis and who have undergone previous regimens of treatment using non-pegylated interferon (II-3)

18. Retreatment with peginterferon plus ribavirin with the aim of eradicating HCV is not indicated in patients who have failed to respond to a prior course of peginterferon plus ribavirin, even if a different type of peginterferon is administered (III)

Special Patient Groups

The majority of HCV treatment trials were conducted among highly selected patient populations making it difficult to predict the safety and efficacy of existing therapy in many settings. While it is hoped that future research focusing on these 'understudied' populations will provide additional information regarding the natural history and optimal therapy for these patients, some general recommendations based on expert opinion are provided.

Treatment of Persons with Normal Serum Aminotransferase Values

Management of persons with normal serum aminotransferase values is important since up to 60% of HCV-infected first-time blood donors and injection drug users have been reported to have normal values[70-72]. One problem in developing guidelines for management of persons with normal aminotransferase levels is ascertaining the optimal upper limit of normal (ULN), a value that must be established for each individual laboratory. Also, ALT values differ by age, race, gender, and body mass, further underscoring the challenge of establishing what is considered to be "normal"[73]. Nonetheless, for purposes of this discussion, a person is considered to have normal ALT levels when there have been two or more determinations identified to be in the normal range of a licensed laboratory over six or more months.

Currently, there is disagreement in regard to whether HCV-infected persons with established normal ALT values warrant treatment[51, 74-76]. On the one hand, individuals with persistently normal ALT values generally have less severe liver disease than that observed in those with abnormal aminotransferase values. Thus, some believe that liver disease progression is uncommon in most such individuals and the adverse events associated with current therapy outweigh the probability that existing treatment will be successful. On the other hand, biopsies of those with normal aminotransferase values have revealed bridging fibrosis or cirrhosis in 1% to 10% of cases, and at least portal fibrosis in a greater proportion (see Liver Biopsy section)[42, 51, 52, 77]. Even though the majority of HCV-infected persons with minimal fibrosis rarely develop progressive disease, histological and clinically advancing liver disease has clearly been documented despite persistently normal aminotransferase values[52, 78]. In addition, the response rate in this group to interferon alfa and ribavirin appears to be similar to that of individuals with abnormal values, and an early report of ALT flares resulting from interferon monotherapy has not been confirmed[79].

Recommendation

19. Regardless of the serum aminotransferase levels, the decision to initiate therapy with interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential of serious side effects, the likelihood of response, and the presence of co-morbid conditions (III).

Diagnosis and Treatment of HCV-infected Children

An estimated 240,000 children in the United States have antibodies to hepatitis C[11]. The seroprevalence is 0.2% for children under 12 years of age, and 0.4% for those 12 to 19 years of age[80]. Cross-sectional studies indicate that viremia is present in 50%-75% of children. Children at risk for HCV

infection include those born to HCV-infected mothers and those who received blood or blood products prior to 1992. The rate of spontaneous viral clearance varies by age at acquisition, and generally occurs within the first year after acute infection. At present, new HCV infections in children are primarily the result of vertical (perinatal) transmission[81].

There are a number of differences in HCV infection between children and adults. Children are less likely to have symptoms, more likely to have spontaneous viral clearance, more likely to have normal or near-normal aminotransferase values, and have a slower rate of advancement to end-stage liver disease[82-86]. Data show that the characteristic histological lesions of HCV occur with the same frequency in children as in adults[87-89]. However, periportal fibrosis is relatively common, occurring in approximately 70% of children in two studies, and appears to progress with age and duration of infection[88, 89]. Of particular interest is the natural history of HCV in children infected via the perinatal route. Despite the data indicating only mild liver disease in the majority of children during the first two decades of infection, little is known about the potential for significant liver-related morbidity and mortality over the lifetime of the perinatally infected child. As in adults, the biggest challenge is identifying appropriate candidates for therapy. While it may be suggested that the relatively mild disease experienced by most children early in infection and the likelihood of better future treatments argues against routine treatment, it is equally reasonable to accept that the average child is likely to be infected in excess of 50 years and therefore, routine treatment is warranted.

The FDA has approved the use of Rebetron for the treatment of hepatitis C in children 3 to 17 years of age. This approval was based on data from several treatment trials demonstrating comparable tolerance and efficacy of interferon alone, and of interferon together with ribavirin, among HCV-infected children as compared with adults. Initial studies evaluated interferon as monotherapy. SVRs in the range of 33% to 45% were achieved, as good as or even better than that seen among adults treated with monotherapy[90-93]. An analysis of 11 published studies revealed an overall SVR of 35%, ranging from 25% for persons with genotype 1 to 70% for persons with non-1 genotype infection[94]. Side effects were surprisingly uncommon. Indeed, children appear to tolerate interferon well without overt serious adverse effects. There may be an adverse effect of interferon on weight; weight gain appears to accelerate once treatment is terminated[95, 96].

There have been a few studies that utilized combination therapy to treat children. In one study, children aged 5 to 11 years were treated with 3mU/m^2 of standard interferon thrice weekly and either 8, 12, or 15mg/kg body weight of ribavirin daily. Preliminary results indicated that the sustained viral response rate was 31% among those with genotype 1, and 38% overall[97]. Dose-dependent hemolytic anemia in the cohort is less than that reported among adults. A 15mg/kg dose of ribavirin has been evaluated in a larger efficacy trial because it was associated with the highest SVR and comparable side effects when compared with lower dose ribavirin[98]. This study is encouraging, suggesting an increased SVR and fewer adverse events when standard combination therapy is used to treat children as compared with adults. A liquid formulation of ribavirin has recently been approved for children, useful particularly for those too small to swallow capsules. Capsules should *never* be opened in order to access their contents.

Given the fact that the risk of HCV transmission at the time of delivery is 1%- 5%, and that the prevalence of HCV infection among women of childbearing age is 1.2%, it is important to consider means of reducing transmission to the newborn. Accordingly, 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. Since there are few data that support delivery of an HCV-infected mother by Caesarean section as a means of reducing perinatal HCV transmission, most authorities do not recommend this procedure. Also, there is little evidence that HCV is transmitted by breast milk and, therefore, HCV-infected mothers need not avoid breast-feeding. Finally, horizontal transmission of HCV from child to child is rare. The American Academy of Pediatrics does not recommend restricting school attendance or participation in routine activities, including contact sports.

Recommendations

20. Diagnosis and testing (including liver biopsy) of children suspected of having chronic HCV should proceed as with adults (II-2)

21. Because of the high rate of clearance of the HCV virus within the first year of life, and the level of anxiety that may be caused by an early positive test, routine testing for HCV RNA among infants born to HCV-infected mothers is not recommended. Testing with anti-HCV may be performed at 18 months or later. If an earlier diagnosis is desired, PCR for HCV RNA may be performed at or after the infant's first well-child visit at 1 to 2 months (I)

22. Children aged 3-17 years infected with hepatitis C who are considered appropriate candidates for treatment may receive therapy with interferon alfa-2b and ribavirin, administered by those experienced in treating children (I, III).

23. Treatment of children under the age of 3 years is contraindicated (III)

Diagnosis, Natural History and Treatment of Persons with Human Immunodeficiency Virus-1 (HIV) Co-Infection

Approximately 25% of HIV-infected persons in the western world have chronic hepatitis C[99]. In the U.S., up to 10% of those with chronic hepatitis C may be HIV co-infected, an estimate based on assumptions that there are 2.7 million persons infected with HCV, and that of those with HIV infection, approximately 250,000 are also infected with HCV[5, 99]. Since the advent of effective antiretroviral treatments in 1996, liver disease has become an increasingly important cause of morbidity and mortality among HIV-infected persons[100-102].

Because of the high prevalence of HIV/HCV co-infection

and because the management of each infection can differ in dually-infected persons, all HIV-infected individuals 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 HCV antibodies and confirm positive results with RNA tests. However, approximately 6% of HIV-positive persons fail to develop HCV antibodies, and therefore HCV RNA should be tested in HIV-positive persons with unexplained liver disease who are anti-HCV negative[103, 104].

The urgency for treatment of persons who are co-infected is greater than it is in those with HCV infection alone. The course of liver disease is more rapid in HIV/HCV co-infected persons, in whom there is an approximately two-fold increased risk of cirrhosis[105, 106]. Treatment of HCV might improve the tolerability of highly active antiretroviral therapy (HAART), since HCV infection increases the risk of hepatotoxicity from HAART[107].

Although there is much less published information on treatment outcomes among HIV/HCV co-infected than in HCV mono-infected patients, the likelihood of achieving an SVR is lower in HIV/HCV co-infected persons[108-110]. Since factors associated with a poor treatment response (such as a high viral load, cirrhosis, and African American race) are disproportionately found in HIV infected populations, it is not clear to what extent HIV infection itself diminishes the SVR rate, and to what extent advancing immunosuppression (e.g., CD4 lymphocyte count <200/mm^3) further reduces response.

Treatment

There are no FDA-approved medications for the treatment of hepatitis C in HIV-infected persons, and as of February 2004, no studies had been published using the most potent anti-HIV regimen (peginterferon alfa plus ribavirin) in HIV/HCV co-infected persons. Nonetheless, preliminary data from three large studies convincingly show that SVR rates are higher in HIV-infected persons who receive peginterferon alfa and ribavirin than in those who receive standard interferon and ribavirin[110, 112]. In an AIDS clinical trials group study, 133 adults were randomized to receive either interferon, 3mU tiw or peginterferon alfa-2a, 180 µg weekly plus ribavirin (600 mg daily initially, then increased if tolerated).[110] SVR rates in this study, in recipients of peginterferon versus standard interferon, were: genotype 1, 14% versus 6%; genotype non-1, 73% versus 33%. Liver histologic activity was observed in 35% of persons who failed to achieve a virologic response at 24 weeks. No adverse effect on control of HIV replication was observed and treatment was discontinued in only 12%. In a similar study from Europe, 416 patients with HIV/HCV co-infection were randomized to receive either peginterferon alfa-2b (1.5 µg/kg weekly) plus ribavirin (800 mg daily) or interferon alfa-2b (3mU tiw) in combination with the same dose of ribavirin.[111] SVR was achieved in 27% and 19% of persons in the peginterferon alfa and standard interferon alfa arms, respectively. Genotype 1 specific responses were not reported for intent-to-treat analysis. In this study in which approximately 40% had cirrhosis or bridging fibrosis, serious adverse events were reported by 31% of subjects and 16% developed hepatic failure.

In a third study, 868 persons were randomized to receive either standard interferon alfa-2b (3mU 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; the SVR rates were 12%, 20%, and 40%, respectively.[112] 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 infection. Medication was discontinued in 25%; 15% due to adverse events. The median CD4+ lymphocyte percent did not decline. Differences in the persons enrolled in these studies probably contributed to differences in the reported efficacy and safety, and results will need to be reconsidered when published in detail. Nonetheless, these preliminary data, derived from studies of both peginterferon alfa-2a and alfa-2b, suggest that peginterferon plus ribavirin is currently the optimal therapy for most HIV/HCV co-infected persons.

In HIV-infected persons, the optimal doses of ribavirin and peginterferon alfa and optimal duration of HCV therapy may differ from those recommended for HIV-uninfected persons, but data on which to base definitive recommendations do not exist. Until there are data to indicate otherwise, ribavirin and peginterferon doses derived from trials of HCV mono-infected patients are recommended for co-infected patients when clinically tolerated. Most existing studies have treated HIV-infected persons for 48 weeks, and some ongoing studies are evaluating longer courses of treatment (e.g., 18 months). Abbreviated, 24-week courses of peginterferon alfa and ribavirin therapy for persons with genotype 2 or 3 have not been adequately studied in persons co-infected with HIV.

An issue of uncertainty is whether the level of the CD4+ lymphocyte count should dictate the decision to treat the HCV infection. Although in some studies the likelihood of HIV/HCV co-infected persons achieving an SVR was higher in persons with higher CD4+ lymphocyte counts (e.g., >350-500/mm^3) compared with those with lower counts, and although persons with counts <100-200/mm^3 were excluded from many trials, there is no absolute CD4+ lymphocyte count threshold below which treatment is contraindicated.

There are additional safety concerns in the treatment of HIV/HCV co-infected patients. Ribavirin-associated anemia may be a greater problem in persons co-infected with HIV than in those with mono-infection, because of the high prevalence of pre-existing anemia and limited myeloid reserves[113]. Ribavirin inhibits inosine-5-monophosphate dehydrogenase, an effect that potentiates didanosine (ddI) anti-HIV activity and increases toxicity[114, 115]. Since symptomatic and even fatal hyperlactatemia have been reported in some co-infected persons receiving ribavirin and didanosine, the manufacturer does not recommend the use of ribavirin in persons taking ddI if there are equivalent therapeutic options[115-117]. Although *in vitro* ribavirin may antagonize 2', 3'-dideoxynucleotides, such as zidovudine, zalcitabine, and stavudine, clinically important interactions have not been shown[118-120]. If these agents are used with ribavirin, treat-

ed patients should be carefully monitored for potential problems.

Interferon alfa therapy causes a dose-related reduction in white blood cell count and 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[119-122]. In fact, in some persons, peginterferon alfa use is associated with an approximately 0.4 log reduction in HIV RNA level, suggesting a potential direct beneficial effect on HIV replication.

Selection of patients

It remains controversial as to which HIV/HCV co-infected person 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 non-infected persons, these decisions are influenced by the results of the liver biopsy interpreted in light of other factors that might reduce the benefits of treatment (such as the stage of HIV infection or alcohol use) and co-morbid conditions (such as depression) that might increase treatment toxicity. If indicated, HIV treatment should be optimized before providing HCV treatment. Patients with decompensated liver disease (Child's 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[123].

Recommendations

24. Anti-HCV testing should be performed in all HIV-infected persons (III).

25. 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 (III).

26. Hepatitis C should be treated in the HIV/HCV co-infected person 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 (III).

27. Initial treatment of hepatitis C in most HIV-infected persons is peginterferon alfa plus ribavirin for 48 weeks (III).

28. Given the high likelihood of adverse events, HIV/HCV co-infected patients on HCV treatment should be monitored closely (III).

29. Ribavirin should be used with caution in persons with limited myeloid reserves and in those taking zidovudine and stavudine. When possible, patients receiving didansosine should be switched to an equivalent anti-retroviral before beginning therapy with ribavirin (III).

30. HIV-infected patients with decompensated liver disease may be candidates for orthotopic liver transplantation(II-2; III).

Treatment of Persons with Renal Disease

There is a well-recognized relationship between HCV infection and the kidney. Hepatitis C infection has been associated with cryoglobulinemia that may lead to membrano-proliferative glomeruloneprhritis[124, 125]. Also, persons with renal disease have historically been at increased risk of acquiring HCV through blood transfusions, exposure to HCV-contaminated equipment during hemodialysis or, rarely, at the time of renal transplantation. Hepatitis C is thus the most common liver disease among renal dialysis patients, but the exact prevalence of HCV infection among this population is unknown. Data from the National Surveillance of Dialysis Associated Disease in the United States conducted in 2001 revealed an average HCV antibody prevalence of 8.6% with some centers reporting prevalences as high as 40% [CDC, unpublished data,[126]]. Similarly, studies from individual dialysis centers in other parts of the world have reported prevalences ranging between 5% and 50%[127]. Among patients on dialysis, HCV infection is associated with a modest increase in risk of death[128]. There is an additional concern that hepatitis C has an adverse effect on long-term patient and graft survival after renal transplantation[129-133]. As a result, current treatment efforts focus on eliminating the virus in dialysis patients who may be candidates for renal transplantation.

There are several circumstances in which treatment of HCV infection in patients with renal disease might be considered. These include (1) persons with HCV-induced glomerulonephritis not on dialysis (most of whom have associated cryoglobulinemia); (2) persons on hemodialysis who are HCV-infected; (3) persons with milder degrees of renal disease who develop superimposed HCV infection; and (4) persons who are infected peri- or post-renal transplantation. The latter category will be discussed in a later section.

Although treatment of persons with cyroglobulinemia-related glomerulonephritis has led to improvement in the renal disease as defined by decreased levels of cryoglobulin, rheumatoid factor and creatinine[134, 135], relapse is common, even with the use of combination therapy[136, 137]. There are even reports of worsening of cryoglobulinemia due to interferon treatment[138], as well as of worsening of the renal disease itself[139, 140]. Combination therapy with peginterferon and ribavirin has not been reported. Other therapeutic approaches have included the use of corticosteroids, cyclophosphamide, plasmapheresis and the use of monoclonal antibody to B cells (rituximab)[141].

Also problematic are decisions to treat patients with renal disease undergoing hemodialysis. These decisions are complicated by the concern of an increased risk in performing liver biopsies in order to define the need for therapy, as well as the increased toxicity from treatment because of impaired renal clearance of the therapies used for HCV. The goals of treating patients on dialysis as well as those with less severe degrees of renal impairment are to reduce progression of liver disease and/or to clear HCV infection in those who might later need to undergo renal transplantation. There are, however, few studies that help discriminate which patients are most likely to need therapy. Potentially severe liver disease cannot be excluded because of the presence of normal ALT values. Individuals on hemodialysis, with significant fibrosis on liver biopsy are less likely to have abnormal ALT values than HCV-infected persons with similar histologic findings who do not have renal disease[142, 143]. There is a theoretical increased risk of bleeding in

patients on hemodialysis who undergo liver biopsy, but studies involving liver biopsy in such patients have rarely reported severe side effects from the procedure[142,143]. Accordingly, a liver biopsy may be performed in persons with renal insufficiency for whom treatment is believed to be a high priority.

Ribavirin is contraindicated in this patient population because the drug is not removed during conventional dialysis and its accumulation causes a dose-dependent hemolytic anemia[144]. In one study in which low dose ribavirin was administered, severe hemolysis occurred[145]. The likelihood of hemolysis during treatment with ribavirin has been shown to correlate with baseline creatinine clearance[146,147]. Consequently, ribavirin is contraindicated in patients with renal failure, and if treatment is undertaken, therapy should be with interferon alfa monotherapy. Numerous small studies have been reported, involving 6 to 37 patients, using different formulations of interferon[148-153]. Rates of SVR in these studies ranged from a low of 14% to a high of 71%. Furthermore, treatments were associated with high rates of serious adverse effects (26% of treated patients), requiring dose reduction or total drug withdrawal. Pegylated interferon, which is more effective than interferon in persons with normal renal function, may also play a role in the treatment of HCV-infected persons on dialysis, but the dose should be reduced. Studies using this product are still ongoing.

Treatment of patients with mild to moderate impairment in renal function (i.e., not on dialysis) must be individualized. The closer that the renal function is to normal, the safer is it to use ribavirin. Ribavirin is currently not recommended in persons with creatinine clearances of less than 50 mL/min, and treatment of persons with mild to moderate renal impairment remains investigational. With regard to the use of peginterferon, a dose recommendation for persons on dialysis (135µg SQ/week) is available only for peginterferon alfa-2a[141].

Recommendations

31. The decision to perform a liver biopsy in patients with renal disease should be individualized based on the clinical assessment of the need for therapy and the need to establish the severity of liver disease (III).

32. Eligible patients with renal insufficiency or end-stage renal disease and HCV may be treated with interferon (II-2.)

33. Treatment with peginterferon alfa-2a monotherapy at a dose of 135µg SQ/week for patients on hemodialysis may be considered, with close monitoring for interferon toxicity. However, a firm recommendation regarding the use of peginterferon monotherapy must await results of ongoing controlled trials (III).

34. Patients with renal failure should not be treated with ribavirin (II-2).

Treatment of Persons with Decompensated Cirrhosis

Liver transplantation is the treatment of choice for patients with decompensated cirrhosis, defined as one or more of the clinical complications of liver diseases, such as ascites, encephalopathy, bleeding from varices secondary to portal hypertension and/or impaired hepatic synthetic function. Re-infection of the transplanted liver with the hepatitis C virus is the rule and progressive post-transplantation disease of the allograft is common. Eradication of virus prior to transplantation has been associated with a low likelihood of post-transplantation infection, providing a strong incentive to treat HCV infection prior to transplantation, as long as the risks of pre-transplantation treatment are acceptable[154]. There is a desire to slow the progression of cirrhosis and even improve the degree of decompensation of the patient, as has been demonstrated with effective pre-transplantation viral suppression in patients with hepatitis B cirrhosis[155, 156]. In contrast to the patient with decompensated cirrhosis, hepatitis C antiviral therapy is clearly indicated in patients with compensated HCV-related cirrhosis, with preserved hepatic synthetic function who also have sufficient platelet and white blood cell counts to tolerate therapy (Table 7). Such patients have typically been included in registration trials of HCV therapies, although there have been few studies focused specifically on this population.

There is little published information regarding the risks and benefits of antiviral therapy in patients with *decompensated* cirrhosis who have clinical complications of liver disease and/or who have more profound thrombocytopenia and/or leukopenia than those defined in Table 7. In these groups, therapy is potentially dangerous because of the increased likelihood of life-threatening infection. There is also concern that treatment might accelerate hepatic decompensation, as has been described with interferon alfa in patients with decompensated hepatitis B-related cirrhosis[157]. Two groups of investigators have focused specifically on risks and benefits of antiviral therapy in this population. In the first, treatment was initiated with interferon alfa and ribavirin, beginning with half doses of each and then increasing the drugs incrementally as tolerated at two week intervals[154, 158]. Although there was a high rate of adverse effects (27%), 39% had a favorable on-treatment response and 21% developed an SVR (11% in genotype 1 and 50% in genotype 2 and 3), all of whom remained virus-free post-transplantation. Approximately one-half of the 102 patients studied had Child's A, namely clinically compensated cirrhosis, although the other half included in the study had greater degrees of hepatic decompensation. The mean Child's Pugh Turcotte score of studied patients was 7. The second study was far less encouraging[159]. Many potential candidates were excluded from therapy because of severe hematologic abnormalities, and many of those who actually did receive therapy had poor outcomes including severe, life-threatening treatment-related side effects. Patients enrolled in the second study generally had more severely decompensated liver disease (predominantly Child's B and C cirrhosis) than those included in the first study, likely accounting for some of the differences in outcome. Neither study included a comparison group that would allow careful evaluation of the safety and efficacy of treating this population.

Hematological adverse events, including anemia, neutropenia, or thrombocytopenia are more common in persons *with* than in those *without* cirrhosis, and especially in those with

clinically *decompensated* disease[158-160]. Treatment requires vigilance and close monitoring, and dose modifications will be more common, which may in turn compromise treatment response. This has led to increased utilization of growth factors such as epoetin, granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) to help counter these adverse effects, although the data supporting this position are limited. Although the use of epoetin seems appropriate in order to maintain a reasonable hemoglobin in the face of the anemia induced by ribavirin, there have been no studies to assess the effect on the SVR rate[161-164]. As a result, effectiveness of this intervention cannot be determined. Similarly, studies have not been designed to assess the impact of G-CSF or GM-CSF in reducing infections in patients with HCV infection who are receiving treatment[164-166].

Recommendations

35. Patients with clinically decompensated cirrhosis should be referred for consideration of liver transplantation (I, III).

36. Antiviral therapy may be initiated at a low dose in patients with mild degrees of hepatic compromise, 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 (II-3).

37. Growth factors should be used for treatment-associated anemia (epoetin) and leukopenia (G-CSF, GM-CSF) and may limit the need for antiviral dose reductions in patients with decompensated cirrhosis (III).

Treatment of Patients following Solid Organ Transplantation

The prevalence of hepatitis C infection among the recipients of solid organ transplants depends upon the organ received. Currently, forty to fifty percent of liver recipients are infected with HCV, whereas the proportion of cardiac, lung and kidney transplant recipients with HCV infection is lower. Among recipients of liver allografts, the majority with pre-transplantation infection have persistent virus post-transplantation, and persistent infection is often associated with progressive liver disease[167]. Likewise, HCV viremia persists in other organ transplant recipients with pre-transplantation infection and may result in rapid progression of liver disease in those with advanced fibrosis[168]. In addition, recipients of heart, lung, or bone marrow transplants with post-transplantation HCV infection may have acquired their infection as a result of infected grafts, blood or blood products, particularly prior to 1992, when routine screening for HCV was introduced[10]. Since then, the risk of acquiring HCV during the peri-transplant period is very low.

Immunosuppression administered to prevent allograft rejection likely plays a role in the accelerated liver disease observed in HCV-infected patients following transplantation. Graft survival is reduced in HCV-infected versus non-infected liver transplantation recipients and may also be diminished in kidney transplant recipients after 10 years[131, 132, 169]. The long-term outcome of heart or lung transplant recipients with HCV is unknown, but there are case reports of severe and even fatal liver disease, suggesting that, as in other solid organ transplant recipients, immunosuppression is deleterious. Interferon can precipitate rejection of kidney grafts[148, 170, 171]. Therefore, in the absence of clear benefit from therapy, and with the concern of precipitating rejection, HCV infection should not be treated in recipients of heart, lungs and kidneys.

The risk of precipitating rejection with interferon in liver transplantation recipients appears to be low. Since HCV-related liver disease in this group is typically more progressive than that observed in immune competent individuals, many experts advocate antiviral therapy. Therapy may either be initiated pre-emptively before the development of histological and biochemical recurrent hepatitis, or may be begun once recurrent disease is established. Preliminary information using pre-emptive therapy within a few days or weeks of transplantation suggests that toxicity is unacceptable[172]. The majority of reported experience with anti-viral therapy post-transplantation comes from uncontrolled observational studies rather than from prospective randomized controlled trials[173-175]. As such, it is difficult to define clearly the risks and benefits of therapy.

Despite the clear need for effective HCV treatments post-liver transplantation, results of interferon-based treatments have in general been disappointing. Most published trials have used interferon as monotherapy or in combination with ribavirin, and published experience with pegylated interferon is quite limited. As in other immune compromised populations, such as those with HIV/HCV co-infection, interferon and ribavirin is less well tolerated and efficacy is lower than in immune competent patients. Although undetectable levels of HCV RNA can be achieved during treatment, rates of SVR are reduced[176, 177]. An early, non-randomized study reported a 25% SVR after 6 months of combination therapy followed by ribavirin monotherapy[176]. Safety and tolerability were acceptable. Histological improvement appears to be less frequently associated with virological response than in immune competent patients[178]. Low response is due in part to over-representation in patients following liver transplantation of predictors of non-response, predictors such as genotype 1 and high viral load. As is the case for immune competent patients, response to therapy is more effective in patients with genotype 2 or genotype 3 infection than in those with genotype 1 infection.

Adverse events are frequent, particularly ribavirin-associated anemia[179], most likely a result of calcineurin inhibitor-induced renal insufficiency. Once patients develop cirrhosis, hepatic decompensation is common[180]. Results of re-transplantation for HCV disease are generally poor[181]. Studies using pegylated interferon and ribavirin are ongoing to refine further the appropriate post-transplantation therapies.

Recommendations

38. Treatment of HCV-related disease following liver transplantation should be undertaken with caution because of the increased risk of adverse events and should be performed under the supervision of a physician experienced in transplantation (II-2).

39. Antiviral therapy is generally contraindicated in recipients of heart, lung and kidney grafts (III).

Treatment of Persons with Acute Hepatitis C

Because hepatitis C so frequently progresses to chronic hepatitis, and because, at best, only 50% of those with chronic hepatitis respond to therapy, there has been interest in identifying and treating persons with acute hepatitis C. Unfortunately, efforts to conduct studies on treatment of patients with acute hepatitis C have been hampered by the fact that the majority of acutely infected persons do not develop symptoms and therefore do not seek medical attention, so that the numbers included in case series have been small. Moreover, those who do have symptoms are more likely to resolve the infection spontaneously[25, 182]. In addition, there is no specific diagnostic test for acute hepatitis C, further hampering the ability to make a specific diagnosis. These issues contribute to the limitations of the currently available literature to guide recommendations regarding management of persons with acute hepatitis C, a literature that consists of studies of uncontrolled case series receiving a variety of treatment regimens administered at varying times after acute infection.

Combined data from 17 studies, using different forms of interferon alfa monotherapy showed that 62% of those treated achieved an SVR, whereas 12% of untreated patients spontaneously recovered over the follow up period[183]. Similar data from a meta-analysis revealed a 32% SVR rate among treated patients, compared with a 4% spontaneous resolution rate among those not treated[184]. Studies using higher doses of interferon (5 to 10 million units daily) for at least 12 weeks or until serum enzymes normalized report sustained viral response rates of 83% to 100%[185-187]. These are clearly remarkable results, but there are several important qualifications. Most studies were not controlled; many chiefly included persons with icteric disease who have greater spontaneous rates of resolution; in some, treatment was started shortly after diagnosis leaving no opportunity for spontaneous resolution; and the treatment regimens differed from the current standard of care.

Issues that require resolution with regard to treatment of acute hepatitis C therefore are: (1) what is the optimal time to initiate treatment given the fact that spontaneous resolution of acute HCV infection is not uncommon?; (2), what is the optimal treatment regimen since various treatment regimens were used in the reported studies?; and (3) what is the appropriate duration of treatment?.

Some helpful although incomplete information in this regard comes from a recent published study from Germany[188]. Various forms of treatment, the most effective regimen at the time – interferon alone, interferon plus ribavirin, peginterferon alone, peginterferon plus ribavirin – were administered to 60 patients diagnosed with acute hepatitis C. The majority (85%) presented with symptomatic disease. Treatment was begun immediately on diagnosis in 6 patients, with interferon alone or in combination with ribavirin. Among the remaining 54 who were not treated immediately, 37 (68%) spontaneously cleared HCV RNA within a mean of 8.4 weeks after diagnosis. Thirteen of them later relapsed, leaving 24 (44%) persistently HCV RNA negative. 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 a sustained virological response in 81% of them. 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 twelve weeks to permit spontaneous resolution and avoid unnecessary treatment, but for those with asymptomatic hepatitis, treatment should begin as early as possible. While awaiting confirmation of this uncontrolled study using various treatment combinations, the clear evidence that the response rate of treatment with acute hepatitis is extremely high, even with interferon alone, is sufficient justification to consider seriously treatment in most instances after 2 to 4 months of waiting for spontaneous clearance. What is offered is an interim set of recommendations that will need modification as more data are generated.

Recommendations

40. The diagnosis of acute hepatitis C in patients with new onset, unexplained liver disease should be confirmed by measuring HCV RNA in serum (II-2)

41. Although excellent results were achieved in reported uncontrolled studies using standard interferon monotherapy, it is appropriate to consider the use of peginterferon because of its improved ease of administration (III)

42. No recommendation can be made about the addition of ribavirin and the decision will therefore need to be considered on a case by case basis (III)

43. In the absence of controlled study data, no definitive recommendations can be made in regard to the timing of treatment initiation, but it seems reasonable to delay treatment for 2 to 4 months after acute onset to allow for spontaneous resolution (II-3)

44. In the absence of controlled study data, no definitive recommendations can be made in regard to the duration of treatment needed to treat acute hepatitis C, but it seems reasonable to continue treatment for at least 6 months(II-3).

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 from injection drug use discontinued the practice years before medical management of their infection begins, 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, such as 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 among persons who use illicit drugs, rather than making categorical recommendations[189].

Methadone. The use of methadone or buprenorphine is an effective means of reducing illicit drug use and its complications[190]. Although some in vitro studies have suggested that opiates diminish endogenous interferon alfa production[191], there are several studies of persons taking methadone that suggest that the drug does not significantly reduce the likelihood of an SVR, nor alter the dosing of interferon alfa or ribavirin[192, 193]. Therefore, methadone use does not directly effect the management of HCV infection.

Re-infection. The benefits of treatment would be diminished substantially if a person were re-infected, which has been reported after spontaneous recovery (versus treatment) both in humans and in experimental studies of chimpanzees[194, 195]. There is evidence that re-infection is less likely to become chronic in humans and chimpanzees who previously spontaneously cleared infection[194, 196]. However, it is not known whether this benefit would be expected after treatment-associated viral clearance[197].

Willingness, Adherence, and Tolerability. 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, as well as to maintain regular follow-up visits. For example, in one multi-center study, almost one-half of young HCV-infected injection drug users had moderate or severe depression[198]. Concern has also been raised that use of needles for interferon alfa (as well as exacerbations of depression) will cause relapse into injection drug use. Collectively, these factors may diminish the benefit and increase the risk of treatment. Some illicit drug users, however, even those who use by injection, are willing and able to undergo treatment for HCV infection[192, 193, 199, 200].

Selection of Patients for Treatment. There are a number of factors that determine the benefits and risks of HCV treatment in illicit drug users. Many, such as the stage of liver disease and HCV genotype, are similar to persons who do not use illicit drugs. Likewise, regardless of drug use, treatment of HCV is only considered for those who are willing to take it, able to maintain close monitoring, and observe contraception. For persons who continue to inject illicit drugs, especially if they share needles and other drug-use equipment, it is likely that the risks of treatment will outweigh the benefits even if they are "willing and able." This is true despite the potential public health benefit of reducing transmission to others. In such individuals, efforts should generally be focused on providing addiction treatment. However, there may be individual exceptions, and it is important to continue to monitor persons because most factors that determine treatment readiness, such as the intensity and nature of drug use and the severity of depression, change over time. On the other hand, there are no data to indicate that long-term, 'controlled' use of illicit drugs directly affects the risk or benefit of HCV treatment, which therefore should be considered based on the HCV genotype, stage of the disease, and other factors, as in persons not using illicit drugs.

The likelihood that a person will remain in recovery from drug use, or remain willing and able to take medication, is related to the duration of recovery and improves substantially with time. Given the slow natural history of HCV infection, it is certainly reasonable to hold off treatment until recovery from drug use seems likely and to conduct pre-treatment counseling to improve the likelihood that HCV treatment will be beneficial. The complexity of HCV treatment and treatment decisions in persons using illicit drugs underscores the value of multidisciplinary management that include experienced drug abuse and psychiatric counseling services that are willing to monitor carefully and regularly for possible negative effects of the treatment for HCV.

Recommendations

45. Treatment of HCV infection should not be withheld from persons who 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 observe contraception (III)

46. The decision regarding whether to treat should be made considering the anticipated risks and benefits for the individual (III).

47. Continued support from drug abuse and psychiatric counseling services is an important adjunct to treatment of HCV infection in persons who use illicit drugs (III)

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 hepatocellular carcinoma [57,58,201-204]. Moreover, excess alcohol intake may increase HCV RNA replication and interfere with response to treatment[205,206]. Controversy exists, however, in regard to 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[207]. 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 history of alcoholism. Although no consensus opinion exists, it seems reasonable to recommend either the complete suspension of alcohol intake while on treatment or to restrict the use of alcohol to an occasional drink during the course of the treatment.

Obesity and its accompaniment – non-alcoholic fatty liver disease – are believed to play a role in the progression of fibrosis in HCV-infected individuals[208,209]. It is therefore appropriate to counsel those who are overweight, as defined by a raised body mass index (BMI) of greater than 25 kg/m^2, to attempt to lose weight. This is sound advice not only for its potentially positive impact on the liver disease, but also on the other conditions

Figure 5

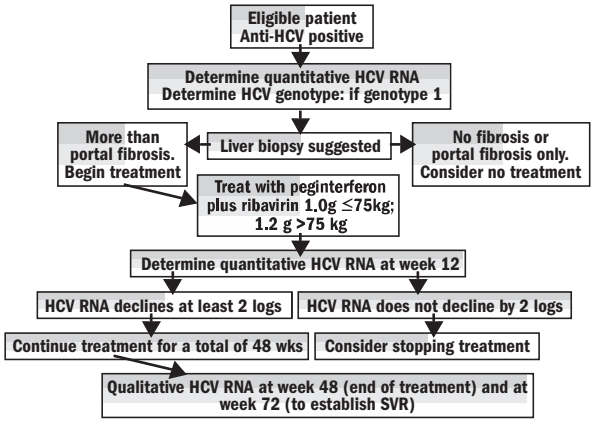

Figure 5: Sequential steps in managing and treating patients with chronic HCV infection, genotype 1 (SVR, sustained virologic response)

Figure 6

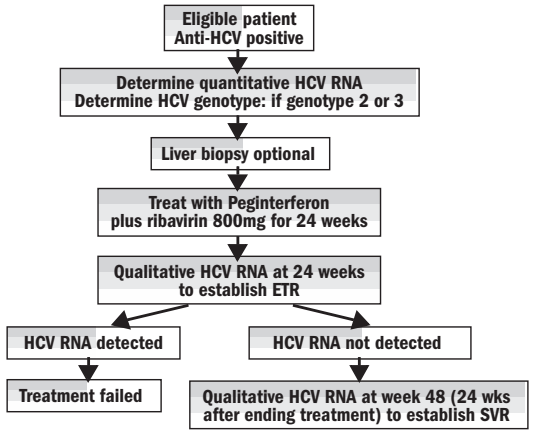

Figure 6: Sequential steps in managing and treating patients with chronic HCV infection, genotypes 2 or 3 (ETR, end of treatment response; SVR, sustained virologic response)

associated with being overweight.

There are reports that superimposition of hepatitis A virus infection in persons with chronic liver disease, particularly those with hepatitis C, has been associated with fulminant hepatitis[210,211]. Accordingly, it is recommended that persons with chronic hepatitis C who lack evidence of pre-existing antibody to hepatitis A (anti-HAV) be administered the hepatitis A vaccine[212]. 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 do those with HCV infection alone[213] suggests that hepatitis B vaccination should be offered to persons who are at risk for exposure to hepatitis B if they lack pre-existing antibody to hepatitis B (anti-HBs).

Conclusion

Described above are the current data on testing, diagnosis, decisions regarding whom to treat, and the recommended treatments of patients with chronic hepatitis C infection. Shown above are two figures (Figures 5 and 6) summarizing the sequential steps recommended in managing and treating persons chronically infected with hepatitis C for whom treatment is considered to be clearly appropriate. As noted earlier, these represent currently acceptable 'guidelines,' but it is recognized that reasonable physicians may deviate from the strategy and remain within acceptable standards of treatment.

Also, as must be evident from the preceding, the issue of treatment of chronic hepatitis C 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 hepatitis C. However, these recommendations will need to be revised and updated in the future as additional critical and pivotal information becomes available.

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Conflict of Interest Statement

Authors

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Practice Guidelines Committee

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