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Number 60

Management of Chronic Hepatitis C

Summary

Overview

Hepatitis C, a viral disease, is the most common blood-borne infection in the United States, affecting more than 4 million Americans. Approximately 36,000 cases of acute hepatitis C infection occur each year in the United States and 85 percent of those with acute hepatitis C develop a chronic infection. Chronic hepatitis C is often asymptomatic but may lead to cirrhosis of the liver as well as hepatocellular carcinoma (HCC). The natural history is variable, and progression to cirrhosis is estimated to occur in approximately 20 percent of patients. Prognosis of those with hepatitis C-related cirrhosis often depends on the development of hepatic decompensation or HCC. The 10-year survival of those with chronic hepatitis C is approximately 50 percent for those with uncomplicated cirrhosis and the median survival for HCC is approximately 6-20 months. Chronic hepatitis C is the leading cause of liver transplants and HCC in the United States and accounts for between 8,000 and 10,000 deaths per year. Without advances in treatment, the number of deaths could triple in the next 10 to 20 years.

The National Institutes of Health (NIH) conducted a Consensus Development Conference in 1997 on the management of hepatitis C. Missing from the conclusions and recommendations of the 1997 conference was discussion of the utility of liver biopsy in determining the appropriateness of treatment or the best protocols for screening for hepatocellular carcinoma. In addition, medical research has made significant progress in the past 5 years regarding treatment modalities for chronic hepatitis C, with pegylated (peg) interferon and ribavirin showing promising results. Recent research has shown that certain subgroups of patients may be more or less likely to benefit from treatment based on clinical factors such as ethnicity, hepatitis C virus (HCV) genotype, or initial response to therapy. In addition, a substantial number of patients treated with initial therapies either relapsed after treatment or never responded. The NIH is convening another Consensus Development Conference on the management of hepatitis C to update the recommendations on prevention, diagnosis, and treatment of hepatitis C. The purpose of this Evidence Report is to review and synthesize the recent literature on several key questions on the management of chronic hepatitis C that will be addressed at the Consensus Development Conference.

Reporting the Evidence

This report addresses the following key questions in the management of chronic hepatitis C.

Role of Initial Liver Biopsy

- **Q1b: How well do the results of initial liver biopsy predict outcomes of treatment in patients with chronic hepatitis C, taking into consideration patient characteristics such as viral genotype?**

  Initial biopsy means the biopsy that occurs at initial evaluation before treatment decisions are made. The main outcomes of interest were virologic and histologic measures of disease activity and progression.

- **Q1e: How well do biochemical blood tests and serologic measures of fibrosis predict the findings of liver biopsy in patients with chronic hepatitis C?**

  The focus was on biochemical and serologic tests that clinicians could use to estimate the likelihood of fibrosis in patients with chronic hepatitis C.

Treatment Options

- **Q2a: What is the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients, including: peginterferon plus ribavirin, peginterferon alone, standard interferon plus ribavirin, and standard interferon plus amantadine?**

  Efficacy was assessed in terms of virologic and histologic response to treatment as well as other clinical outcomes including the incidence of cirrhosis, hepatic decompensation, HCC, death, and adverse effects of treatment.

- **Q2c: What is the efficacy and safety of current interferon-based treatment options (including interferon alone) for chronic hepatitis C in selected subgroups of patients, especially those defined by the following characteristics: age less than or equal to 18 years, race/ethnicity, HCV genotype, presence or absence of cirrhosis, minimal versus decompensated liver disease, concurrent hepatitis B or HIV infection, nonresponse to initial interferon-based therapy, and relapse after initial interferon-based therapy?**

  Efficacy was assessed in terms of virologic and histologic response to treatment as well as other clinical outcomes.

- **Q2d: What are the long-term clinical outcomes (greater than or equal to 5 years) of current treatment options for chronic hepatitis C?**

  The main outcomes of interest were the incidence of cirrhosis, hepatic decompensation, HCC, and death. This question included studies of the natural history of chronic hepatitis C because observation is an option.

Screening for Hepatocellular Carcinoma

- **Q3a: What is the efficacy of using screening tests for hepatocellular carcinoma to improve clinical outcomes in patients with chronic hepatitis C?**

  The review on this question focused on alpha-fetoprotein, other serological markers, ultrasonography, computerized tomography, and other imaging studies. The outcomes of interest were mortality and the rate of resectable versus nonresectable HCC.

- **Q3b: What are the sensitivity, specificity, and predictive values of tests that could be used to screen for hepatocellular carcinoma (especially resectable carcinoma) in patients with chronic hepatitis C?**

  The review on this question focused on the same screening tests listed above.

Methodology

The Evidence-based Practice Center (EPC) team recruited 20 technical and community experts to provide input into the definition of the key questions and to review a draft of the report. These included hepatitis specialists from academic settings and experts from relevant professional organizations and other settings. The EPC team also recruited representatives from a range of other stakeholder organizations to serve as peer reviewers of the draft Evidence Report. The reviewers included an allied health professional, experts in assessment of diagnostic technologies, and other clinical specialists drawn from academic and government settings.

Several literature sources were used to identify all studies potentially relevant to the research questions. Eight electronic databases were searched through DIALOG (a commercial database vendor) for the period from January 1, 1996 to September 30, 2001: MEDLINE®; Biological Abstracts-BIOSIS Previews®; Science Citation Index-SciSearch®; Manual, Alternative and Natural Therapy-MANTIS; the Allied and Complementary Medicine Database; CAB Health; PsycINFO; and Sociological Abstracts. To ensure a comprehensive literature search and identification of all relevant articles, the EPC team updated the search in March 2002, examined the reference lists from material identified through the electronic searching and discussion with experts, and reviewed the tables of contents of recent issues of journals that were cited most frequently (between October 2001 and March 2002).

Two members of the study team independently reviewed the titles and abstracts identified by the search to exclude those that did not meet the following eligibility criteria: 1) written in English; 2) includes human data; 3) original data; 4) information relevant to the management of hepatitis C; 5) reports basic sciences as well as clinical data; 6) applies to one of the key questions. Also excluded were meeting abstracts (no full article for review). Citations deemed not relevant by both reviewers were excluded. To focus the search on the studies that would be most valuable in addressing the key questions, the following types of studies were excluded: 1) studies in which all data was reported in a subsequent publication; 2) studies that may have contained some data related to a key question but the study was not designed to address the question; 3) studies that addressed management of hepatitis C in liver transplant patients only; 4) studies in which the total number of participants was less than 30; and 5) studies in which the outcomes/results were not measured with an appropriate objective standard (i.e., virologic and/or histologic measures of treatment response, or histologic or pathologic evidence of HCC for the screening questions).

Focus of Key Questions

For key question 1b, we included only randomized controlled trials because they provide the strongest evidence on whether the findings on initial liver biopsy are independent predictors of the greater efficacy of one treatment strategy compared to another. Although cohort studies could provide evidence of the relation between initial histology and the response to a given treatment regimen, they are susceptible to selection bias because patients could be excluded from a cohort on the basis of histological findings. We also required at least 24 weeks of follow-up for key question 1b.

For key question 1e, we included only studies that evaluated biochemical blood tests or serological tests that could serve as measures of liver fibrosis. These studies could include other tests, but we did not include studies that examined only other tests such as hematologic tests or radiologic imaging studies.

For key questions 2a and 2c, we included only randomized controlled trials that had a planned length of follow-up that was at least 24 weeks after the end of treatment.

For key question 2d, we included only studies that had at least 5 years of follow-up, including studies of natural history without treatment.

For key question 3a, we looked for studies on patients with chronic hepatitis C that had at least 6 months of follow-up for comparing one screening strategy to another screening strategy or to no screening.

For key question 3b, we included only studies that reported data on patients with hepatitis C although these studies could include some patients with only hepatitis B or patients co-infected with HCV and hepatitis B virus (HBV). We excluded studies that focused solely on hepatitis B because the pathophysiology and natural history of hepatitis C differs from that of hepatitis B.

Review Process

Paired reviewers assessed the quality of each eligible study in terms of representativeness of the study population (5 items), bias and confounding (4 items), description of therapy/management (4 items), outcomes and follow-up (5 items), and statistical quality and interpretation (4 items). The score for each category of study quality was the percentage of the total points available in each category for that study and could range from zero to 100 percent. The total quality score was the average of the five categorical scores. In addition, the reviewers also completed an item on potential conflict of interest. At least one reviewer in a pair had clinical training and at least one reviewer had training in epidemiology and clinical research methods. One reviewer in the pair was responsible for completing both the quality assessment and content abstraction, and the second reviewed and confirmed the material abstracted.

Findings

Q1b: How well do the results of initial liver biopsy predict outcomes of treatment in patients with chronic hepatitis C, taking into consideration patient characteristics such as viral genotype?

- A moderate number of randomized controlled trials addressed this question.
- These studies varied widely in how they reported the relation of initial histological findings to the outcomes of treatment.
- The analyses for this question had important limitations including frequent lack of reporting of parameter estimates and confidence intervals.
- The studies that used multivariate analysis were relatively but not entirely consistent in suggesting that the presence of advanced fibrosis or cirrhosis on initial liver biopsy may predict a modest decrease in the likelihood of having a sustained virological response to treatment. The studies suggested that there is no interaction between pre-treatment liver histology and the effect of different treatment regimens on the rate of sustained virological response.

Q1e: How well do biochemical blood tests and serologic measures of fibrosis predict the findings of liver biopsy in patients with chronic hepatitis C?

- Numerous studies evaluated the value of biochemical tests and serologic measures of fibrosis in predicting fibrosis on liver biopsy in chronic hepatitis C.
- The studies had some important limitations and varied widely in published evidence: they covered numerous tests and used a variety of methods for reporting results.
- The studies were relatively consistent in showing that 1) serum liver enzymes have only modest value in predicting fibrosis on liver biopsy, 2) the extracellular matrix tests hyaluronic acid and laminin have modest value in predicting fibrosis on liver biopsy, 3) cytokines have less value than the extracellular matrix tests in predicting fibrosis on liver biopsy, and 4) panels of tests may have the greatest value in predicting the absence of more than minimal fibrosis on liver biopsy and in predicting the presence versus absence of cirrhosis on biopsy.

Q2a: What is the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients, including peginterferon plus ribavirin, peginterferon alone, standard interferon plus ribavirin, and standard interferon plus amantadine?

Peginterferon Plus Ribavirin

- Two published trials evaluated the efficacy of peginterferon plus ribavirin for the treatment of

hepatitis C. The results of an additional large trial have not yet been published.

- The largest of these two trials had a relatively high score in all five categories of study quality, but generalizability was limited by the exclusion of patients with HIV infection, previous interferon treatment, mental illness, or other significant co-morbidity (among other exclusions).
- The studies were consistent in showing a significant increase in efficacy with peginterferon plus ribavirin compared with standard interferon plus ribavirin or peginterferon alone.

Peginterferon Alone

- A few randomized controlled trials evaluated the efficacy of standard peginterferon alone for the treatment of chronic hepatitis C.
- The studies had relatively high study quality scores, but differed significantly in the distribution of patients by race/ethnicity, HCV genotype, and presence of cirrhosis.
- The studies were somewhat consistent in showing a large relative increase in virological sustained response and a modest increase in histological response with peginterferon compared with standard interferon.

Standard Interferon Plus Ribavirin

- A large number of trials evaluated the efficacy of standard interferon and ribavirin therapy for the treatment of hepatitis C.
- A previous systematic review demonstrated an increased efficacy of standard interferon plus ribavirin compared with standard interferon alone in treatment-naive patients.
- The additional studies reviewed were somewhat consistent in showing at least a modest increase in virological sustained response with standard interferon plus ribavirin compared with standard interferon alone.
- The magnitude of the relative treatment effect may depend on the dose and duration of treatment as each study used a different treatment regimen.

Standard Interferon Plus Amantadine

- A moderate number of trials evaluated the efficacy of standard interferon plus amantadine therapy for the treatment of chronic hepatitis C.
- Evidence on the efficacy of standard interferon and amantadine was fairly homogeneous with relatively high study quality scores and some variation in treatment protocols.
- The studies were relatively consistent in showing that standard interferon plus amantadine is not more effective than standard interferon monotherapy and is not more effective than standard interferon plus ribavirin in treatment-naive patients.

Q2c: What is the efficacy and safety of current interferon-based treatment options (including interferon alone) for chronic hepatitis C in selected subgroups of patients, especially those defined by the following characteristics: age less than or equal to 18 years, HCV genotype, presence or absence of cirrhosis, minimal versus decompensated liver disease, concurrent hepatitis B or HIV infection, nonresponse to initial interferon-based therapy, and relapse after initial interferon-based therapy?

Standard Interferon Plus Ribavirin: Relapsers and Nonresponders

- A moderate number of trials evaluated the efficacy of standard interferon plus ribavirin for the treatment of chronic hepatitis C in patients who previously failed to respond to interferon or who relapsed after interferon treatment.
- Evidence of the efficacy of standard interferon plus ribavirin in nonresponders is heterogeneous and has methodologic limitations including differences in HCV genotype, gender, and treatment protocols among the studies.
- Efficacy data was stronger for sustained virological response than for clinical outcomes like cirrhosis and hepatitis C specific mortality.
- Previous systematic reviews suggested a small but significant increase in sustained virological response in nonresponders receiving combination therapy with standard interferon plus ribavirin.
- The additional studies reviewed were consistent in showing combination therapy has greater efficacy than standard interferon monotherapy in improving end-of-treatment response in nonresponders; however, this response was not consistently sustained through follow-up.
- Evidence of the efficacy of standard interferon plus ribavirin in relapsers and nonresponders combined was heterogeneous and had methodologic limitations.
- A previous systematic review reported that this type of combination therapy had a greater efficacy than standard interferon monotherapy for relapsers and nonresponders combined.
- The additional studies reviewed were relatively consistent in demonstrating that longer duration of interferon and ribavirin therapy has a greater efficacy than shorter duration in both interferon relapsers and nonresponders. Furthermore, the evidence was consistent in showing that

interferon relapsers have a better response to therapy than previous nonresponders.

Standard Interferon Plus Amantadine

- Two studies evaluated the efficacy of standard interferon plus amantadine for treatment of chronic hepatitis C in patients who did not respond to previous interferon treatment. These studies were small but one had a high study quality score.
- The studies suggested that amantadine plus standard interferon is not more effective than standard interferon alone.
- Only one small study evaluated the efficacy of standard interferon in combination with ribavirin and amantadine compared to interferon and ribavirin in nonresponders.

Interferon Monotherapy

- A moderate number of studies evaluated the efficacy of standard interferon therapy for the treatment of chronic hepatitis C in selected subgroups of clinical interest.
- The evidence of the efficacy of standard interferon in specific clinical subgroups is heterogeneous and had important limitations.
- Few randomized controlled trials of standard interferon therapy focused on HIV-infected patients, renal patients, hemophiliacs, or intravenous drug users.
- The studies that have been done were consistent in showing that standard interferon monotherapy is relatively ineffective in the retreatment of nonresponders and relapsers.

Q2d: What are the long-term clinical outcomes (greater than or equal to 5 years) of current treatment options for chronic hepatitis C?

Interferon-treated Patients

- The evidence of the effect of interferon-based therapy on long-term outcomes in hepatitis C is heterogeneous and has important methodologic limitations, including variable lengths of follow-up within and among studies, variable numbers of patients with cirrhosis, different doses and durations of therapy (and this information is frequently missing), varying amounts of alcohol consumption, and little description of the population that was not treated.
- These studies were nonetheless somewhat consistent in suggesting that treatment with interferon-based therapy decreases the risk of HCC and cirrhosis in complete responders.
- The evidence also suggested that biochemical responders may also have a decreased risk of HCC and decreased progression of liver disease.
- The data were inconsistent regarding the impact of interferon therapy in nonresponders and relapsers compared with each other and with untreated controls. One long-term randomized trial suggested that all patients treated with interferon, regardless of response, derive long-term benefits; other studies suggested that relapsers but not nonresponders or controls derive long-term benefit from interferon therapy.

Natural History

- The evidence on the natural history of hepatitis C is very heterogeneous and has important methodologic limitations. The studies, however, were consistent in suggesting that older age, cirrhosis, hepatitis B coinfection, HIV infection, alcoholism, male sex, and initial fibrosis all predict worse long-term outcomes in hepatitis C.
- The studies were somewhat consistent in showing that HCV genotype does not increase the rate of fibrosis progression in patients with chronic hepatitis C.
- Studies were somewhat consistent in showing that HBV coinfection hastens the progression of liver disease in patients with chronic hepatitis C.
- Studies were consistent in showing that patients with chronic hepatitis C who have a normal ALT have a lower incidence of HCC at 5 years.

Q3a: What is the efficacy of using screening tests for hepatocellular carcinoma to improve clinical outcomes in patients with chronic hepatitis C?

- Only one prospective cohort study and no randomized controlled trials evaluated the efficacy of screening for HCC in patients with chronic hepatitis C.
- The prospective cohort study had important limitations, especially the fact that it included patients with chronic liver disease—primarily due to hepatitis B or C, but also due to other causes—and thus may not be representative of the development of HCC in patients with hepatitis C.
- This study suggested that HCC was detected earlier and was more often resectable in patients who underwent routine screening with AFP and hepatic ultrasound than in those who had usual care.

Q3b: What are the sensitivity, specificity, and predictive values of tests that could be used to screen for hepatocellular carcinoma (especially resectable carcinoma) in patients with chronic hepatitis C?

- Numerous trials evaluated the performance characteristics of serum AFP in screening for HCC in patients with chronic hepatitis C.
- These studies had important methodologic weaknesses and varied widely in study design and patient eligibility criteria.

- The studies were relatively consistent in suggesting that a serum AFP level of greater than 10 ng/mL has a moderate sensitivity of 75 to 80 percent and a specificity of approximately 95 percent in screening for HCC, and that a serum AFP level of greater than 400 ng/mL has a low sensitivity with a specificity of nearly 100 percent.
- Several other serologic and urinary screening tests have been evaluated, but none of these has been evaluated in more than two studies.
- Few of these studies had a large enough population of patients with chronic hepatitis C to provide reliable estimates of the performance characteristics of the tests.
- The studies on use of soluble interleukin-2 receptor level and protein induced in vitamin K absence (PIVKA-II) suggested that these tests could be useful in screening for HCC if combined with serum AFP or ultrasonography.
- A few studies evaluated the performance characteristics of ultrasonography in screening patients with hepatitis C.
- These studies had some limitations in that they varied by screening frequency, experience of the ultrasonographer, and extent of liver disease in the screened patients.
- The studies using ultrasonography were relatively consistent in demonstrating high specificity but variable sensitivity depending on the population screened.
- Combination screening with AFP and ultrasonography demonstrated an increase in sensitivity in at least one trial of patients with hepatitis B or C.
- Two studies reported on the performance characteristics of computerized tomography and magnetic resonance imaging.
- These studies were limited in that they were not designed to assess the efficacy of screening, but to evaluate the incidence of HCC.
- The studies were consistent, however, in demonstrating both a high sensitivity and specificity in patients with hepatitis C.

Future Research

Relation of Initial Liver Biopsy Findings to Outcomes of Treatment

Future treatment studies need to be designed to appropriately answer this question using initial liver biopsy findings in analysis of factors associated with a virologic or histologic response to therapy. These studies should use standard techniques for obtaining adequate liver biopsy samples and standardized reporting of liver biopsy results. The studies also should report the details of both univariate and multivariate analyses of the relation of initial biopsy findings to outcomes, including adjusted and unadjusted parameter estimates of the relation of each histological variable to the outcome variable, and whether the analysis considered potential interaction effects. Such studies would help to provide better estimates of the independent value of liver biopsy in predicting outcomes of treatment options.

Tests to Predict Fibrosis on Liver Biopsy

Future studies will need to be designed to more directly address this question. Such studies should give attention to the methodologic limitations we encountered in trying to extract meaningful information from the studies performed to date. In particular, the studies should provide enough details about the liver biopsy methods to convince readers of the adequacy of the reference standard. Future studies also should give more attention to the potential value of a panel of tests for predicting fibrosis on liver biopsy.

Treatment of Chronic Hepatitis C

Future studies will need to further address the questions of the optimal doses and duration of therapies. In addition, randomized controlled trials should include traditionally understudied populations with high rates of hepatitis C, such as blacks, injection drug users, alcoholics, and those with renal disease or HIV. In particular, randomized controlled trials of treatments for chronic hepatitis C should include subgroup analysis by gender and race/ethnicity, as some studies have suggested different response rates between women and men, and between different racial/ethnic groups. Such studies should give attention to the methodologic limitations we encountered in trying to extract meaningful information from the studies performed to date.

Long-term Outcomes of Chronic Hepatitis C

Future studies will need to assess the long-term outcomes of current treatment options, particularly studies with standard interferon plus ribavirin, as well as new studies with peginterferon. Although some data has suggested that longer treatment is better for improving virologic outcomes, little is known regarding the long-term outcomes of different treatment durations. Finally, although natural history studies may no longer be practical in the current treatment era, following certain subgroups at high risk for complications, such as patients co-infected with HIV or HBV, injection drug users, and alcoholics, will be useful in making clinical recommendations regarding follow-up for these patients.

Efficacy of Screening for HCC

Randomized controlled trials of screening of patients with hepatitis C will be most useful in helping to determine screening recommendations for these patients; however, it is difficult to conduct large, randomized controlled trials of

screening strategies. Therefore, conducting trials on the patients at greatest risk may yield the most significant results. At the present time, serum AFP and ultrasonography appear to hold the most promise.

Performance Characteristics of Screening Tests

Future studies should include randomized controlled trials of screening for HCC in patients with chronic hepatitis C. Although it may be difficult to conduct randomized controlled trials in all patients with hepatitis C, including patients at highest risk for HCC in screening trials makes it more likely that future research will determine definitively the benefits of screening. Future studies should consider the use of a combination of screening tests and should consider examining the relative cost-effectiveness of alternative strategies.

Future studies also should consider examining promising new tests such as soluble Interleukin-2 receptor compared to and possibly combined with the currently most sensitive screening options, including serum AFP and ultrasonography.

Overall Areas of Future Research

Most studies reviewed provided limited information on the type and degree of involvement of the funding source. Consistent with new reporting guidelines accepted by many major journals, this information should become part of the standard data report in future trials.

In addition, to improve the quality of publications on these study questions, standardized methods should be developed and disseminated to investigators. Journals should encourage standardized approaches to presenting data on these questions. For published articles, full copies of protocols should be made available, perhaps on the Web. This is important because the pressure to shorten manuscripts often results in reduced descriptions of study methods.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Johns Hopkins University Evidence-based Practice Center, Baltimore, MD, under contract number 290-97-0006. It is expected to be available in summer 2002. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 60, *Management of Chronic Hepatitis C*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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