Chapter 4: Conclusions

Key Findings

Question 1b: 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 on 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 fibrosis 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 virologic response.

Question 1e: 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.
- These studies had some important limitations and varied widely in published evidence: they covered numerous tests and used a variety of methods for reporting results.
- These 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.

Question 2a: What is the overall 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 peginterferon alone for the treatment of chronic hepatitis C.
- These studies had relatively high study quality scores, but differed significantly in the distribution of patients by race/ethnicity, HCV genotype, and presence of cirrhosis.
- These studies were 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 plus ribavirin therapy for the treatment of chronic hepatitis C.
- A previous systematic review published 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 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 of naïve patients.

Question 2c: What is the efficacy and safety of current interferon based treatment options (including interferon alone) for chronic hepatitis C in subgroups of patients, especially those defined by the following patient characteristics: age less than 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 on 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 virologic response in *nonresponders* receiving combination therapy with standard interferon plus ribavirin.
- The additional studies reviewed were consistent in showing greater efficacy of combination therapy compared with standard interferon monotherapy in improving ETR in nonresponders; however, this response was not consistently sustained through follow-up.
- Evidence on the efficacy of standard interferon plus ribavirin in relapsers and nonresponders combined was heterogeneous and had methodologic limitations.
- A previous systematic review[66] reported that this type of combination therapy had a greater efficacy than standard interferon monotherapy for relapsers and nonresponders combined.
- The additional studies reviewed also were 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 do 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 significantly 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 on the efficacy of standard interferon in specific clinical subgroups was 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.

Question 2d: What are the long-term clinical outcomes of current treatment options for chronic hepatitis C?

Interferon- treated Patients

- The evidence on the effect of interferon-based therapy on long-term outcomes in hepatitis C was hetereogeneous and had 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 (with this information frequently missing), varying amounts of alcohol consumption, and little description of the population that was not treated.
- These studies nonetheless were 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 was very heterogeneous and had important methodologic limitations.
- These studies, however, were consistent in suggesting that older age, cirrhosis, hepatitis B co-infection, HIV infection, alcohol use, male gender, and initial fibrosis all predict worse long-term outcomes in hepatitis C.
- These studies were somewhat consistent in showing that HCV genotype does not increase the rate of fibrosis progression in patients with chronic hepatitis C.
- These studies were somewhat consistent in showing that HBV co-infection hastens the progression of liver disease in patients with chronic hepatitis C.
- Studies were also consistent in showing that patients with chronic hepatitis C who have a normal ALT have a lower incidence of HCC at five years.

Question 3a: What is the efficacy of using screening tests for hepatocellular carcinoma to improve clinical outcomes in patients with chronic hepatitis C?

- One prospective cohort study and no randomized controlled trials evaluated the efficacy of screening for HCC in patients with chronic hepatitis C.
- This 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.

Question 3b: 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 limitations and varied widely in study design and patient eligibility criteria.
- These 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, usually in no more than one study.
- 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.
- 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 were relatively consistent in demonstrating a high specificity of ultrasonography but variable sensitivity depending on the population screened.
- Combination screening with AFP and ultrasound demonstrated an increase in sensitivity in at least one trial with patients having 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.

Limitations

Limitations of the Studies on Question 1b (Relation of Initial Liver Biopsy Findings to Outcomes of Treatment)

The analyses in these trials were reported in many different ways. Some studies compared the presence and absence of cirrhosis while others used mean HAI or Knodell scores. The methods of statistical analysis were very heterogeneous across the studies, with few studies using multivariate analysis. Some studies used only univariate analysis or reported results stratified by treatment group or virologic outcome. In addition, most

studies presented results in terms of significance for a p value less than 0.05, but few presented adjusted parameter estimates and confidence intervals. While a p value of less than 0.05 indicates a greater chance of a significant relationship, a nonsignificant p value does not mean zero effect. In addition, none of the studies reported a multivariable analysis that examined the potential interaction between pre-treatment histology and the effects of different treatment regimens.

Another limitation is that many different treatment regimens were evaluated, and there tended to be few trials with each type of statistical analysis. Finally, there may be publication bias. Some authors may have evaluated the relation of initial histology to virologic outcomes, but they may not have reported data that did not show a significant relationship.

Limitations of the Studies on Question 1e (Tests for Predicting Fibrosis on Liver Biopsy)

The analyses in these trials were reported in many different ways. Some studies compared the presence and absence of cirrhosis while others used different staging systems including MHAI stage, HAI, METAVIR, Scheur, Desmet and other systems. None of the studies reported side effects or adverse outcomes after liver biopsy. Also, the methods of statistical analysis were very heterogeneous across the studies, with some studies presenting receiver operating characteristic analysis and other studies presenting test characteristics by predictive values of the test.

Limitations of the Studies on Questions 2a/2c (Treatment of Chronic Hepatitis C)

The reported evidence on the efficacy of different treatment options must be weighed against the information on the risk of adverse effects. This limitation is particularly important because the strongest evidence of efficacy is based on the rate of sustained virological response, which is only an intermediate outcome. Treatment studies often lacked variability in racial composition and gender, with most trials including predominately Caucasians and men. The proportion of patients with cirrhosis varied widely across trials. Most trials excluded women who were breast- feeding or pregnant and patients with HIV infection, a history of injection drug use or alcohol use, mental illness, or other significant co-morbidity. In addition, there was often variability in treatment regimens, particularly in trials with standard interferon and ribavirin. Finally, statistical analysis of these studies varied widely with trial results reported in many different ways.

Limitations of the Studies on Question 2d (Long-term Outcomes of Chronic Hepatitis C)

The studies evaluating long-term outcomes of patients with hepatitis C had varying lengths of follow-up both within the study subjects of any one particular study and between studies. In addition, the studies varied widely in the numbers of patients with cirrhosis, doses and duration of therapy, and amount of alcohol consumption reported. Many of the studies gave little description of the population not treated.

Limitations of the Studies on Question 3a (Efficacy of Screening for HCC in Chronic Hepatitis C)

The one study identified was not a randomized controlled trial and therefore had limited validity because of potential selection bias. Also, this study included patients with all forms of chronic liver disease, who may not be representative of patients with chronic hepatitis C.

Limitations of the Studies on Question 3b (Performance Characteristics of Screening Tests for HCC in Chronic Hepatitis C)

Many of the studies on this question included patients with hepatitis B as well as hepatitis C. The pathophysiology of these diseases and their relation to development of HCC is thought to be different; therefore, results of screening tests may be different in these populations. In addition, the heterogeneity of the studies made it difficult to synthesize results across studies and precluded performance of a quantitative meta-analysis of the studies. Finally, in studies evaluating the performance characteristics of hepatic ultrasound, the experience of the ultrasonographer had the potential to greatly influence the results of the study.

Overall Limitations of the Evidence Report

The potential scope of this systematic review of the literature was enormous because of the vast and highly heterogeneous nature of the literature on management of hepatitis C. The EPC team dealt with this challenge by trying to focus the review on the strongest studies on each of the defined key questions.

The EPC team also limited the literature review to articles published in English, thereby introducing potential publication bias. The exclusion of articles not published in the English language reflects the practical realities of obtaining and reviewing the details of non-English studies within the time frame and budget of the project. In addition, non-English studies are likely to be less relevant to the population of hepatitis C patients in the United States, and the Consensus Development Conference will be making recommendations primarily for the management of chronic hepatitis C in the United States. This limitation will be important to consider for clinicians and other groups who may be interested in extrapolating the findings to other populations.

The methods of evaluating diagnostic tests are complex and vary more than the methods of evaluating treatment questions. As a result, it was difficult to anticipate the information that would and would not be available before reviewing the details of all studies. The studies differed so much that it was difficult to extract and synthesize the information into the traditional table-based format of an evidence report. The evidence tables in this report focus on those key pieces of information that could be extracted from two or more studies.

For many of the studies reviewed, the presentation of data was incomplete or otherwise sub-optimal. In some cases, that left gaps in some of the columns of the evidence tables. In other cases, it led to the exclusion of entire studies because none of the results were presented in an extractable format.

Implications

Question 1b (Relation of Initial Liver Biopsy to Outcomes of Treatment)

As indicated in the causal pathway depicted in Figure 1, the evidence on the relation of initial liver biopsy results to outcomes of treatment for chronic hepatitis C has implications for the clinical decision about whether to obtain a liver biopsy before deciding on treatment. Clinicians may want to consider the lack of definitive evidence on this question when discussing the pros and cons of a liver biopsy with patients.

Future studies will need to be designed to address this question more directly. 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, randomized controlled trials of treatments for chronic hepatitis C should include plans for evaluating whether initial biopsy findings are independent predictors of the efficacy of treatment (measured in terms of virological and/or histological sustained response or other clinical outcomes) and should consider taking into consideration the potential interaction between histological stage of disease and the effects of each treatment strategy.

Question 1e (Tests for Predicting Fibrosis on Liver Biopsy)

As indicated in the causal pathway depicted in Figure 1, the evidence on the correlation of serologic or biochemical tests with liver histology has implications for the clinical decision about whether to obtain a liver biopsy before deciding on treatment. If an alternative, less invasive test could predict findings of liver biopsy, potential complications of the procedure could be avoided. Clinicians may want to consider the lack of definitive evidence on this question when discussing the pros and cons of serologic tests versus liver biopsy with patients infected with HCV.

Future 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.

Questions 2a/c (Treatment of Chronic Hepatitis C)

As indicated in the causal pathway depicted in Figure 1, the evidence on treatment regimens for hepatitis C and the possible virologic and histologic outcomes has significant implications for clinicians. Clinicians may want to consider the evidence on both virologic and histologic outcomes of different treatment regimens when discussing treatment options with patients infected with hepatitis C. For treatment-naive patients, the evidence indicates that peginterferon plus ribavirin is the most efficacious treatment option. For patients who did not respond to previous interferon treatment or who relapsed after treatment, the evidence suggests that there are options for achieving a response.

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 persons with end stage renal disease, HIV infection, hepatitis B, or mental illness. In particular, randomized controlled trials of treatments for chronic hepatitis C should include subgroup analysis by sex 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 key information from the studies performed to date.

Question 2d (Long-term Outcomes of Chronic Hepatitis C)

As indicated in the causal pathway depicted in Figure 1, the long-term sequelae of hepatitis C are significant, including cirrhosis, HCC, and death. If predictors of these complications can be identified, clinicians may be able to identify patients at higher risk and institute preventive measures, such as abstention from alcohol and increased screening for complications.

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. While some data have suggested that longer treatment is better for improving virologic outcomes, little is known about 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.

Questions 3a/b (Screening for HCC in Chronic Hepatitis C)

As indicated in the causal pathway depicted in Figure 1, the evidence on the efficacy of screening and on the performance characteristics of screening tests has implications for the clinical decision about whether to screen for HCC in patients with hepatitis C. Clinicians may want to consider the varying sensitivities and specificities of different tests, as well as the costs and potential complications of screening tests, when discussing the pros and cons of screening with patients. Screening strategies are most likely to be successful if they are based on the tests that have been shown to have at least moderate sensitivity and specificity.

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