Chapter 3: Results

Literature Search and Abstract Review

The literature search process identified 3,349 unique potentially relevant citations. The first complete set of searches was completed in September 2001, with updated searches carried out in March of 2002.

Through the review of titles of the identified citations, 1,745 citations were determined eligible for abstract review. Of these, 24 had been included in previous systematic reviews, and were dropped from further review. Of the remaining 1,721 citations, 72 percent (1,237 articles) did not meet the criteria for article review. Abstracts were excluded for the following reasons: the article was not in English (1); the article did not include human data (8); the article did not present any original data (180); the article did not contain information relevant to the management of hepatitis C (54); the article reported only on basic science (66); the article did not address one of the EPC's key questions (555); the article related only to key question 2a or key question 2c, and was not a randomized controlled trial (389); the article addressed only key question 2a, and reported on treatment with interferon alone, without an analysis of any patient subgroups of interest (5); the article addressed only key question 2d, and did not have at least 60 months of followup (6); the study did not use appropriate objective outcomes (1); the total study population of the article was less than 30 patients (59); the article did not include at least 24 weeks of follow-up (2); the article was a case report (14); the article presented only editorial material (6); the article was a cost-effectiveness analysis (1); the article reported on therapies that were not treatment options of interest (5); the article addressed only key question 1e, but the test used was not biochemical or serologic (15); the article dealt only with patients after liver transplant (1); the article answered only key question 1b and did not meet the team's methodology requirements (3); or no copy of the article could be obtained (1). The total number of reasons for exclusion exceeded the number of abstracts reviewed because the paired reviewers did not have to agree on the reason for the exclusion, only that the citation was excluded.

Article Review

Following the abstract process, 486 articles remained eligible for review. Of these, 150 articles were tagged for key question 1b (relation of initial biopsy results to treatment outcomes) or key question 1c (relation of follow-up biopsy results to outcomes of treatment), 108 pertained to key question 1e (use of tests to predict biopsy findings), 163 addressed key questions 2a or 2c (current treatment options), 73 addressed key question 2d (long-term outcomes of current treatment options), and 52 addressed either key question 3a or key question 3b (screening for HCC). The total number of articles pertaining to key questions exceeded the number of articles reviewed because some articles were identified as relevant for more than one key question.

At article review, 129 articles were excluded from the 150 articles originally identified for possible relevance to key question 1b. Of these, 15 were not relevant to any of the EPC team's key questions, two were related to HIV rather than HCV, one included fewer than 30 HCV

patients, one did not use suitably objective outcomes, seven had a total study population of less than 30 patients, and four did not have at least 24 weeks of follow-up. Thirty-two articles did not apply to key question 1b, and were recorded as being excluded for reasons relevant to other key questions. Seventy-eight articles did not meet the EPC team's previously described methodology requirements for articles relevant to key question 1b. Following article review, 21 articles remained eligible for the review on key question 1b.

At article review, 42 articles were excluded from the 108 articles originally identified for possible relevance to key question 1e. Of these, 8 were not relevant to any of the EPC team's key questions, 11 were not designed specifically to answer one of the team's key questions, four contained no data that could be extracted systematically. Seven reported on tests were were not biochemical nor serological, not intended to measure fibrosis, or not regularly available to clinicians. Five articles had a total study population of fewer than 30 patients, and five studies were not relevant to key question 1e and were excluded for reasons relevant to other key questions. Following article review, 66 articles pertaining to key question 1e remained.

At article review, 117 articles were excluded from the 163 articles originally identified for possible relevance to key question 2a or 2c. Of these, one did not apply to any key question, 31 did not report on therapies of interest, one study's data was all reported in a subsequent publication, two were not randomized controlled trials, 64 reported on interferon monotherapy and did not include subgroups of interest , four did not use suitably objective outcomes, nine articles had a total study population of less than 30 patients, and five articles were not relevant to key question 2a or key question 2c and were excluded for reasons pertaining to other key questions. Of the remaining 46 articles, 16 pertained to key question 2a, and 30 pertained to key question 2c.

At article review, 33 articles were excluded from the 73 initially identified for possible relevance to key question 2d. Of these, one was not in English, two contained no original data, five did not pertain to any of the EPC team's key questions, one had no data that could be extracted, one study had fewer than 30 HCV patients, 16 did not have at least 60 months of follow-up, one did not have suitable objective outcomes, one article had a total study population of less than 30 patients, and five articles were not relevant to key question 2d and were excluded for reasons pertaining to other key questions. Following article review, 40 articles remained relevant to key question 2d.

At article review, 28 articles were excluded from the 52 initially identified for possible relevance to key question 3a or 3b. Of these, ten were not relevant to any key question, four contained no data that was extractable, five reported on screening tests that are not routinely available to clinicians, two articles had a total study population of less than 30 patients, one study had fewer than 30 HCV patients, one did not use suitably objective outcomes, one study did not have at least 24 weeks of follow-up and two studies were not relevant to questions 3a or 3b and were excluded for reasons pertaining to other key questions. Following article review, one study was identified as relevant to key question 3a, and 23 studies were relevant to key question 3b.

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?*

Results of Literature Search

As indicated above, we identified 21 studies that were eligible for our review on key question 1b. Of these 21 studies, 14 were also included in our review of studies on key questions 2a and 2c, and seven were studies of interferon-based therapies not included in key question 2a or 2c. We did not include studies that were included in the previous systematic reviews that we reviewed for questions 2a and 2c.

Characteristics of Studies on the Relation of Initial Liver Biopsy Results to Outcomes of Treatment

Evidence Table 1 summarizes the specific aims and patient eligibility criteria of the 21 studies that met our criteria for key question 1b. Most studies were conducted in the United States or Europe, but one study was in Asia and a few studies recruited patients from Australia. Almost all studies were at least co-sponsored by the pharmaceutical industry. Almost all studies excluded patients with other forms of liver disease, including hepatitis B, and several excluded patients with decompensated liver disease. Most also excluded women who were pregnant or breast feeding, patients with active intravenous drug use, heavy alcohol use, anemia, HIV infection, or other significant co-morbidity.

Evidence Table 2 summarizes the demographic and clinical characteristics of the study populations. In all of the studies, the majority of participants were men with the mean age ranging between 34 and 59 years. The mean serum alanine aminotransferase (ALT) was between 65 and 200 mg/dl with the duration of infection ranging from 5.5 to nearly 20 years. The distribution of the initial liver biopsy findings was varied with many studies using different reporting methods; however, there were both cirrhotics and noncirrhotics included in all treatment groups. Genotypes were obtained routinely and varied according to the country in which the study was performed.

Quality of Studies on the Relation of Initial Liver Biopsy Results to Outcomes of Treatment

All studies pertaining to this question were randomized controlled trials. As shown in Evidence Table 3, the median overall quality score for the studies was 64 percent with a range of 31 to 75 percent. The 25 percent and 75 percent interquartile ranges were 56 percent and 70 percent. Most of the studies had a representativeness score, outcomes score and statistical analysis score greater than or equal to 75 percent. Although these studies generally used appropriate methods for measuring outcomes, very few reported on the incidence of complications from the liver biopsy. Also, the bias and description scores tended to be lower than the scores in the other categories. For question 1b, the assessment of potential bias and

confounding was based on a question about whether the study performed an independent and blind comparison of the outcomes to the biopsy results. Only a minority of studies met this criterion fully. Some studies reported that the outcome assessment was independent of the biopsy readings but did not indicate whether it was blinded (yielding a score of 50 percent). Other studies did not report either element explicitly (yielding a score of 0 percent). The description score for question 1b was based on the adequacy of the study's description of the technique and size of the liver biopsy. Surprisingly few studies provided this important information. Finally, only a few studies identified both the source of funding and the type and degree of involvement of the funding agency.

Results of Studies on the Relation of Initial Liver Biopsy Results to Outcomes of Treatment

Results were presented in several ways (see Evidence Table 4). Twelve studies presented multivariate analysis with pretreatment histologic results considered as an independent variable in predicting virologic or histologic outcomes. Eight studies presented univariate analyses of baseline histologic results and their association with outcomes, and three studies presented data on pretreatment histologic results stratified by treatment group or virologic or histologic outcome. Only six studies reported enough data to permit us to perform a multivariate logistic regression analysis of the effects of pre-treatment histological abnormalities on the efficacy of treatment options.

Multivariate analysis Among the studies that used multivariate analysis, one compared pegylated (peg) interferon and ribavirin with standard interferon alpha-2b and ribavirin,[18] four evaluated standard interferon in combination with ribavirin versus standard interferon alone,[19-21] one evaluated peginterferon versus standard interferon alpha-2b,[13] one evaluated peginterferon versus standard interferon alpha-2a,[22] three evaluated different doses of interferon alone, or different types of interferon treatment,[23,24] one study evaluated standard interferon and amantadine versus standard interferon alone,[25] and one study evaluated standard interferon with colchicine.[26] In the study with peginterferon and ribavirin, the absence of cirrhosis was associated with sustained virologic response to therapy in both univariate and multivariate analyses.[18] In one of the studies with ribavirin and standard interferon, the multivariate analysis did not show a significant association between sustained viral response and initial histologic grade, initial histologic stage, or initial presence or absence of cirrhosis.[19] In another study with ribavirin and standard interferon alpha-2b, the multivariate analysis showed a significant association between pretreatment fibrosis and virologic nonresponse to treatment, but the p values and parameter estimates were not provided in the text of the article.[20] The third study with standard interferon and ribavirin found no significant association between pretreatment grade and ultimate response to therapy in multivariate analysis.[21] This study did demonstrate a significant association between pretreatment fibrosis and virologic response in univariate analysis. In the study evaluating peginterferon versus standard interferon alpha-2b, baseline histologic results were not associated with sustained virologic response, although the histologic response rates were higher than the virologic response rates.[13] In contrast, in the study with peginterferon compared to interferon alpha-2a, there was a significant association between virologic response and the absence of cirrhosis or fibrosis.[22]

In one study evaluating different doses of interferon, the pretreatment Knodell index was a significant predictor of treatment response.[23] In another study, the histologic activity index (HAI) was not a predictor of response.[24]

Finally, in the study evaluating standard interferon and amantadine, there was no significant association between pretreatment histologic findings and virologic response to therapy.[25] In the study of standard interferon and colchicine, however, lower stage on pretreatment biopsy did predict a virologic response to treatment in both univariate and multivariate analysis. Interestingly, in this study lower grade did not predict virologic response to treatment.[26]

Univariate analysis Multiple studies performed univariate analyses to assess the association between initial liver biopsy results and virologic or histologic outcomes. Five studies evaluated standard interferon alone in univariate analysis,[27-31] two evaluated standard interferon with ribavirin,[32,33] and one study evaluated standard interferon with amantadine versus standard interferon alone.[34]

The results of the studies with standard interferon alone were mixed, with two studies demonstrating a significant association between baseline histology and response to treatment,[28,29] two studies demonstrating no association between pretreatment biopsy findings and response to treatment,[27,31] and one study demonstrating a significant association of pretreatment biopsy findings with biochemical response but not with virologic or histologic outcomes.[30]
In the study with standard interferon and amantadine[34] and the studies of interferon and ribavirin, [32,33] pretreatment biopsy findings did not predict virologic response to treatment.

Analysis stratified by outcome When the analysis of the relation between biopsy results and outcome was stratified by outcome, results were mixed. Some studies performed univariate analysis of pretreatment stage by treatment group. One study that stratified by outcome evaluated three different types of interferon (recombinant, leukocyte, and fibroblast).[35] In this study, sustained responders had lower baseline HAI scores than did nonresponders, both within each treatment group and compared to other groups, but the actual HAI scores were presented only as graphical data.[35]

Analysis stratified by treatment In two studies, results were stratified by treatment group. One study examined standard interferon with and without ribavirin,[36] and the other compared standard interferon with peginterferon.[37] In the interferon and ribavirin study, pretreatment histologic results did not predict response in the group treated with standard interferon and ribavirin, but fibrosis stage did predict response in the interferon-alone group.[36] In the study comparing standard interferon with peginterferon the virologic response was similar in those patients with bridging fibrosis and those with cirrhosis. In addition, HAI scores were not predictive of virologic response.[37]

Other Data on Relation of Biopsy Results to Outcomes of Treatment

Six studies reported enough data to permit a multi-variate logistic regression analysis of the relation of pre-treatment liver histology to the effect of the treatment regimens on the SVR rate (see Table 1 at end of chapter). The resulting analyses indicated that pre-treatment histology was not consistently associated with an independent effect on SVR rate and the studies were

relatively consistent in finding no interaction between pre-treatment histology and the effect of different treatment regimens.

Summary of the Relation of Initial Liver Biopsy Results to Outcomes of Treatment

The published evidence on the relation of pretreatment liver biopsy findings to outcomes of treatment is extremely heterogeneous and has important methodologic limitations. Specific limitations are lack of reporting of parameter estimates and confidence intervals from univariate and multivariate analysis as well as limited evaluation of interaction effects between baseline histology and treatment. Recognizing these limitations and using the studies with the strongest type of analysis for this key question (i.e., multivariate analysis), we found that these studies were relatively, but not entirely, consistent in suggesting that the presence of advanced fibrosis or cirrhosis may predict a modest decrease in the likelihood of having a sustained virologic response to treatment [Evidence Grade B].

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

Results of Literature Search

As indicated in the previous section, we found 66 studies that met all of our eligibility criteria for this key question.

Characteristics of Studies on Tests for Predicting Biopsy Findings

Evidence Table 5 summarizes the specific aims, patient eligibility criteria, geographic location, and funding source of the studies that met our criteria for key question 1e. The main inclusion criterion was evidence of chronic hepatitis C. A common method for documenting HCV was the presence of viral RNA in serum. Several studies reported the distribution of patients by HCV genotype with the percentage of patients with genotype 1b ranging from 26 to 92 percent.

The most common exclusion criteria were evidence of hepatitis B infection (24 studies), heavy alcohol use (21 studies), presence of other liver diseases (18 studies), previous antiviral treatment (17 studies), immune system disorders (16 studies), and HIV infection (12 studies).

Evidence Table 6 shows selected demographic and clinical characteristics of the study groups in each study. Most of the studies used a cross-sectional or diagnostic test design, but a few studies used a prospective cohort design. In a few studies, a first set of patients was used to develop a statistical model predicting fibrosis, and the results were validated in an independent second set of patients.[38-40] The mean age of the study populations ranged from 17 to 65 years. The percentage of subjects that were male ranged from 30 to 58 percent with a median of 48 percent. The mean fibrosis score by the HAI ranged from 34 percent to 94 percent. Histological

evidence of liver fibrosis was evaluated with several different staging systems including the MHAI stage, HAI, METAVIR, Scheur, Desmet, and other systems.

Quality of Studies

The median overall quality score for the studies on question 1e was 62 percent with a range from 11 to 88 percent (see Evidence Table 7). Most of the studies had scores greater than or equal to 75 percent for the study quality categories of representativeness, bias and confounding, and statistical analysis. The scores for description of the liver biopsy methods were low because very few studies reported details on the type of needle biopsy and size of the liver core. Few studies had scores greater than or equal to 75 percent for the category of outcome assessment, and none of the studies reported on side effects or adverse outcomes after liver biopsy.

Results of Studies on Tests for Predicting Biopsy Findings

Nineteen studies investigated a single serum test as a measure of liver fibrosis and the remainder used two or more markers. The results of these studies are summarized in Evidence Table 8.

Serum ALT and AST. Serum ALT was the most commonly investigated marker.[40-54] It was statistically associated with fibrosis stage in 11 of 15 studies,[40,45-54] with sensitivity ranging from 61 to 76 percent,[50,52] and specificity ranging from 44 to 66 percent.[50,52] Serum ALT as a single marker of fibrosis showed areas under the curve of 0.75 or less by receiver operating characteristic (ROC) analysis.[40,52,53] Multivariate models of predictors of fibrosis did incorporate serum ALT in two studies.[40,45] In contrast, the ratio of aspartate aminotransferase (AST) to ALT was a specific but insensitive predictor of cirrhosis, with a sensitivity ranging from 31 to 56 percent and specificity of 90 percent to 100 percent.[55-58] One study calculated a negative predictive value of 88 percent and a positive predictive value of 74 percent for use of the AST/ALT ratio in predicting fibrosis.[57] Little information was reported on the role of AST/ALT ratio in predicting noncirrhotic stages of fibrosis.

Extracellular matrix tests Twenty-six studies investigated components of the extracellular matrix and/or markers of extracellular matrix degradation (Evidence Table 8). Markers of extracellular matrix included hyaluronic acid (HA), procollagen type III peptides (P-III-P), type IV collagen, 7s collagen, laminin, and fibronectin. Markers of matrix degradation included MMP-2, MMP-7, MMP-9, and TIMP-1-4. Though these markers showed broad overlap for any given fibrosis stage, they were still significantly associated with fibrosis in every study examined, except for one study in which P-III-P was not associated with fibrosis.[59] Hyaluronic acid correlated best with fibrosis stage overall, with correlation coefficients ranging from 0.42 to 0.79. Hyaluronic acid had sensitivities ranging from 47 to 88 percent and specificities ranging from 59 to 100 percent, and laminin had sensitivities of 52 to 80 percent with specificities of 80 to 85 percent. P-III-P correlation coefficients ranged from 0.30 to 0.51 and from 0.26 to 0.43 for type III collagen. P-III-P had a sensitivity ranging from 34 to 89 percent and specificity of 21 to 86 percent. Markers of extracellular matrix degradation such as TIMP were also associated significantly with fibrosis as single markers, but were generally less predictive than hyaluronic acid.

Other tests A number of cytokines and cytokine receptors were also investigated including tumor necrosis factors TNF-R55, TNF-R75, and TNF alpha,[60] as well as serum interleukin (IL)-2 receptors.[61] Except for TNF-alpha, the cytokine and cytokine receptors were significantly associated with fibrosis, but were less predictive than markers of extracellular matrix. In contrast, TNF-alpha was significantly associated with hepatic inflammation but not with fibrosis.

As shown in Evidence Table 8, a variety of other tests were investigated including glutathione,[46] alpha-fetoprotein,[42,62,63] prothrombin time,[38,39,51] PCHE,[38] Mn-SOD,[38] beta-NAG,[38] alpha-2-macroglobin,[38] beta-globulin,[38] albumin,[38,51] gamma glutamyl transpeptidase,[38,39,51] bilirubin,[39,40,51] LDH,[51] serum AST,[39,51] alkaline phosphatase,[51] white blood cell count,[51] creatinine,[39] total bile acids,[64] GGT,[64] and immunoglobulin G.[65] Similar to the cytokines, these tests frequently were statistically associated with fibrosis. However, these markers appeared less useful as a group than did the markers discussed above, and only limited data were available on these markers. The platelet count, an indicator of portal hypertension, was also a predictor of cirrhosis in three studies, both in isolation and in studies employing panels of markers.

Test panels Five of the studies,[38-40,50,51] used large panels of markers (greater than or equal to 5 markers) and achieved the greatest predictive values, with sensitivities ranging from 50 to 82 and specificities of 35 to 80 percent. Of these studies, a panel of MMP-2, IV-C7S, and hyaluronic acid optimally predicted no fibrosis/minimal fibrosis, with a sensitivity of 68.3 percent and specificity of 73 percent. However, up to 94 percent of cirrhotic patients could be correctly identified using multivariate models.[38] In another multivariate model using different markers, moderate to severe inflammation and/or bridging fibrosis to cirrhosis could be identified with a specificity of 95 percent and sensitivity of 52 percent.[39]

General observations All of the above studies used statistical tests to show correlations/associations between serum tests and histological evidence of liver fibrosis. Additionally, some studies reported the levels of their serological marker by fibrosis stage. They uniformly reported broad overlap between each fibrosis stage, with a general trend toward increased levels of the serological marker with increasing levels of fibrosis. Because of the broad overlap for any given histological stage of fibrosis, the tests were best at predicting the absence of fibrosis (or minimal fibrosis) or identifying those with advanced fibrosis/cirrhosis. Serologic tests were less effective in classifying intermediate stages of fibrosis.

Summary of Tests for Predicting Biopsy Findings

The published evidence was very heterogeneous regarding the utility of biochemical tests and serologic measures of fibrosis in predicting fibrosis in liver biopsy in chronic hepatitis C. The studies assessed numerous tests using a variety of methods for reporting results. Most of the studies had important limitations in one or more categories of study quality. Nonetheless, the studies were relatively consistent in showing that 1) serum liver enzymes have only modest value in predicting fibrosis on liver biopsy [Evidence Grade B], 2) the extracellular matrix tests, hyaluronic acid and laminin, may have value in predicting fibrosis on liver biopsy [Evidence Grade B], 3) cytokines have less value than the extracellular matrix tests in predicting fibrosis on liver biopsy [Evidence Grade B], and 4) panels of tests including MMP-2, IV-C7S, and hyaluronic acid may have the greatest value in predicting the absence of more than minimal

fibrosis on liver biopsy and in predicting the presence of cirrhosis on biopsy [Evidence Grade B]. None can consistently classify intermediate stages of fibrosis.

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, interferon plus ribavirin, and interferon plus amantadine?*

Results of Literature Search

We found 46 studies that met our eligibility criteria for key questions 2a or 2c, including studies that examined the efficacy and/or safety of treatment of chronic hepatitis C in the following patient populations:

1. treatment-naive patients (peginterferon alpha plus ribavirin in three studies; peginterferon alpha monotherapy in four studies; interferon alpha plus ribavirin in four studies; and interferon alpha plus amantadine in five studies);
2. patients who had not responded to previous interferon treatment (23 studies);
3. patients who had relapsed after previous interferon treatment (14 studies); and
4. clinically important subgroups of HCV-infected patients including patients with hemophilia (one study) or chronic renal insufficiency (one study), hepatitis B (one study), and subgroups defined by race/ethnicity (two studies).

In addition, data from previously published meta-analyses and/or systematic reviews met criteria for key questions 2a or 2c, including treatment-naive, relapsing and nonresponding patient populations.[66-68]

Studies on Peginterferon Alpha Plus Ribavirin for Chronic Hepatitis C in Treatment-naive Patients

Characteristics of the studies Three randomized controlled trials examined therapy with peginterferon and oral ribavirin.[12,18,69] Unfortunately, the results of the study by Fried et al,[69] have not yet been published, although the results have been presented at professional meetings.

Evidence Table 9 describes the aims of these trials and their eligibility criteria. The studies required a serum alanine aminotransferase greater than the upper limit of the normal range, quantifiable serum HCV RNA, and normal hematologic parameters. In addition, patients were excluded if they had HIV infection, previous interferon therapy, decompensated liver disease, other causes of liver disease, or significant medical or psychiatric co-morbidity.

These studies aimed to assess the safety and efficacy of peginterferon and ribavarin combination therapy. As shown in Evidence Table 10, Manns[18] compared peginterferon alpha-2b 1.5 µg/kg per week plus ribavirin 800 mg per day for 48 weeks to peginterferon 1.5 µg/kg for four weeks followed by 0.5 µg/kg for 44 weeks with ribavirin 1000-1200 mg per day for 48 weeks, and to standard interferon alpha-2b 3 million units (MU) three times per week plus ribavirin 1000-1200 mg per day for 48 weeks. In a dose finding study, Glue [12] compared six different treatment regimens for 24 weeks, three with three different doses of peginterferon plus

ribavirin, and three with varying doses of peginterferon alone. Although the results of the study by Fried et al[69] have not been published yet and thus are not included in the evidence tables, a published abstract reported that this study compared 180 µg of peginterferon alpha-2a once per week in combination with ribavirin 1000-1200 mg per day to standard interferon alpha-2b 3 million units (MU) three times per week plus ribavirin 1000-1200 mg to180 µg of peginterferon alpha-2a alone. The total treatment duration was 48 weeks.

Evidence Table 10 also summarizes the demographic and clinical characteristics of the patients enrolled in these studies. The study by Manns[18] was large. The mean age was 42 years; the percentage of males was 62 percent; and 64 percent had HCV genotype 1. Glue's study population was smaller (only 72 patients), had a lower mean age of 39.8 years, and a lower percentage of patients with genotype 1 (45 percent) than the other study.[12]

Quality of studies Evidence Table 11 summarizes the quality of these studies. The overall quality scores for the studies were 85 percent and 56 percent. The study by Manns et al, had a quality score greater than or equal to 75 percent for the five main study quality categories. The small study by Glue et al had a quality score greater than or equal to 75 percent for only two of the study quality categories. Neither study reported the type or degree of involvement of the funding source.

Results of studies Evidence Table 12 summarizes the results of these studies. Manns and colleagues treated the patients for 48 weeks and followed them for an additional 24 weeks.[18] The investigators did not report any statistically significant difference in biochemical ETR or sustained response among the three groups. However, 65 percent of patients in the high dose peginterferon
(1.5 µg/kg for 48 weeks) plus ribavirin group had a virological ETR compared with 54 percent in the standard interferon plus ribavirin group ($p<.001$) and 56 percent in the low dose peginterferon (1.5 µg/kg for 4 weeks then 0.5 µg/kg) plus ribavirin group. Moreover, 54 percent of the high dose peginterferon plus ribavirin group had a sustained virological response compared with 47 percent in the other two treatment groups ($p < 0.01$). Also, patients with genotype 1 had a significantly greater virological response to the high dose peginterferon plus ribavirin therapy compared with standard interferon plus ribavirin treatment ($p < 0.05$). Paired biopsies were performed in 68 percent of patients. All three treatment groups demonstrated improvement in histological evidence of inflammation and fibrosis, but there was no significant difference between the groups. Predictors of virological response included non-1 genotype, low baseline viral load, dose of peginterferon plus ribavirin treatment, younger age, and lack of bridging fibrosis. Dose discontinuation for adverse events occurred in 14 percent of patients in the high dose peginterferon plus ribavirin group versus 13 percent in the other two groups.

Glue compared six different treatment regimens in groups treated for 24 weeks and followed them for an average of 24 weeks (see Evidence Table 12). The investigators found that patients receiving 1.4 µg/kg of peginterferon 2b plus ribavirin had a 60 percent SVR rate compared to 53 percent in patients given 0.7 µg/kg of peginterferon plus ribavirin and 17 percent in patients receiving 0.35 µg/kg of peginterferon. Statistical significance was not reported. Five patients discontinued therapy: one secondary to neutopenia, two due to alcohol abuse, and two for personal reasons.

Summary Evidence on the efficacy of peginterferon and ribavirin, based on one large and one small dose finding study, is limited by our lack of access to the results of an additional large randomized trial. The two available studies are consistent in demonstrating the efficacy of peginterferon plus ribavirin in treatment-naive patients with chronic hepatitis C [Evidence Grade A].

Studies on Peginterferon Alone for Chronic Hepatitis C in Treatment-naive Patients

Characteristics of the studies Four studies assessed the safety and efficacy of peginterferon alone in treatment-naive patients with chronic hepatitis C.[13,22,37,70] See Evidence Table 9 for the study aims and eligibility criteria. Three of these studies examined the safety and efficacy of peginterferon-alpha-2a, and one study examined peginterferon-alpha-2b.[13] All four of these studies required an initial liver biopsy and an elevated ALT. All studies with the exception of Heathcote et al[37] required detectable HCV in the serum. In addition, all studies excluded patients previously treated with interferon as well as patients who had HIV infection, other causes of liver disease (including hepatitis B), abnormal hematologic parameters, and major medical and psychiatric co-morbidity. Furthermore, two studies excluded active intravenous drug users.[13,70] Finally, one study by Heathcote and colleagues included only patients with histologic evidence of advanced hepatic fibrosis (e.g., cirrhosis or bridging fibrosis) on biopsy.[37]

Evidence Table 10 describes the study groups and the baseline characteristics of the patients in these four randomized controlled trials. Zeuzem[22] compared patients receiving peginterferon alpha-2a 180 µg weekly for 48 weeks to standard interferon alpha-2a 6 MU three times per week for 12 weeks followed by 3 MU three times per week for 36 weeks in persons naive to HCV treatment. Reddy and colleagues[70] randomized patients to standard interferon alpha-2a, peginterferon alpha-2a 45 µg weekly, peginterferon alpha-2a 90 µg weekly, peginterferon alpha-2a 180 µg weekly, or peginterferon alpha-2a 240 µg weekly administered for 48 weeks in HCV treatment-naive subjects. The third study, by Heathcote[37] was an open-label randomized controlled trial of the safety and efficacy of standard interferon 3 MU three times per week for 48 weeks compared to peginterferon alpha-2a 90 µg and 180 µg weekly for 48 weeks in HCV treatment-naive patients with histological evidence of cirrhosis or fibrosis. Finally, Lindsay et al.[13] performed a randomized controlled trial evaluating the efficacy of standard interferon alpha-2b 3 MU three times per week for 48 weeks to three doses of peginterferon alpha-2b 0.5 µg per kilogram, 1.0 µg/kg and 1.5 µg/kg for 48 weeks in HCV-infected persons naive to HCV treatment.

The demographic characteristics were heterogeneous across studies. The mean age for the study performed by Zeuzem et al.[22] was 41 years old; 67 percent of the study group was male and 86 percent was white, 10 percent was black, and 10 percent was Asian; 61 to 63 percent had genotype 1. Only 4 percent in the peginterferon group and 10 percent in the standard interferon group were cirrhotic. There was no significant difference among the treatment groups. The mean age in Reddy's study[70] ranged from 41.6 to 43.1 years among the treatment groups. The percent of whites ranged from 78.7 percent in the standard interferon group to 90 percent in the peginterferon 45 µg group. The percentage of blacks ranged from 0 percent in the peginterferon 90 µg group to 12.5 percent in the standard interferon therapy group. The percent with genotype

1 ranged from 63 percent in the peginterferon 270 µg group to 81.8 percent in the standard interferon alone group. Heathcote and colleagues [37] had three treatment groups with an average age ranging from to 46.9 to 47.2 years. The percentage of males ranged from 70 to 74 percent and the percentage that were white ranged from 86 to 91 percent. Fifty to 55 percent of the patients had genotype 1. Twenty to 24 percent of the patients had bridging fibrosis and the remainder had cirrhosis. There were no significant differences across the treatment groups. The mean age in the study performed by Lindsay et al.[13] ranged between 42.6 and 43.7 years, 49.5 to 68.3 percent were male, and 74.4 to 90.9 percent were white. The proportion of patients who had genotype 1 ranged between 58 and 71.6 percent.

Quality of studies Evidence Table 11 summarizes the quality of these studies. The total quality score ranged from 68 to 91 percent with a median score of 77 percent. All four studies had a quality score of at least 50 percent in all five of the main study quality categories. Only one of the four studies reported the type or level of involvement of the funding source.

Results of the studies Evidence Table 12 summarizes the results for these studies. Zeuzem and colleagues [22] treated their patients for 48 weeks and followed them for an additional 24 weeks. They found that virological ETR and SVR was observed in a greater number of subjects receiving peginterferon alpha-2a 180 µg (ETR 69 percent and SVR 39 percent) than in those receiving standard interferon alpha-2a (ETR 28 percent and SVR 19 percent; $p < 0.01$ for both). Of those subjects with paired liver biopsies, histological improvement (defined as at least a 2-point improvement in HAI score from baseline) was observed as follows: standard interferon alpha-2a (92 subjects); and peginterferon alpha-2a 180 µg (116 subjects). Histological response was found in 44 percent and 47 percent of patients who failed to achieve an SVR. Seven percent of patients in the peginterferon group discontinued treatment compared to 10 percent of patients in the interferon-alone group.

Reddy et al,[70] comparing standard interferon to four different dosing regimens of peginterferon alpha-2a, observed a greater virological ETR and sustained response in subjects receiving peginterferon alpha-2a 180 µg (ETR 60 percent and SVR 36 percent) and peginterferon alpha-2a 240 µg (ETR 56 percent and SVR 29 percent) than in those receiving standard interferon alpha-2a (ETR 12 percent and SVR 3 percent), peginterferon alpha-2a 45 µg (ETR 30 percent and SVR 10 percent), or peginterferon alpha-2a 90 µg (ETR 45 percent and SVR 30 percent). For SVR, the *p* values observed compared with standard interferon alpha-2a were as follows: peginterferon alpha-2a 45 µg (> 0 .05), 90 µg (< 0.01), 180 µg (< 0.001), and 240 µg (< 0.01). Of those subjects with paired liver biopsies, histological improvement (defined as at least a 2-point improvement in HAI score from baseline) was observed as follows: standard interferon alpha-2a (57 percent); peginterferon alpha-2a 45 µg (47 percent), 90 µg (59 percent), 180 µg (63 percent) and 240 µg (66 percent) ($p > 0.05$ for all comparisons). There were more withdrawals secondary to adverse events in the peginterferon groups than in the standard interferon group (10 percent, 0 percent, 22 percent, 20 percent, and 9 percent, respectively).

Heathcote and colleagues,[37] studying patients with cirrhosis or bridging fibrosis, observed that the virological ETR rate and SVR rate for the peginterferon alpha-2a 180 µg group (ETR 44 percent and SVR 30 percent) were significantly greater compared to standard interferon therapy alpha-2a (ETR 14 percent and SVR 8 percent; $p < 0.001$). Patients who received peginterferon alpha-2a 90 µg were also found to have a significantly greater ETR rate, but this difference was

not sustained (ETR 42 percent and SVR 15 percent). Among the subset with paired liver biopsies, histological improvement (defined as at least a 2-point improvement in HAI score) was observed as follows: standard interferon alpha-2a (31 percent), peginterferon alpha-2a 90 µg (44 percent), and peginterferon alpha-2a 180 µg (54 percent) (p = 0.02 for comparison of peginterferon 180 µg and standard interferon alpha). Treatment discontinuation secondary to adverse events occurred in 14 percent of patients receiving standard interferon, 2 percent of patients in the 90 µg peginterferon group, and 13 percent of patients receiving 180 µg of peginterferon.

Lindsay and colleagues[13] studied the efficacy and safety of peginterferon alpha-2b in treatment-naive patients. They found that all of the peginterferon groups had significantly greater virological ETR and SVR rates compared to those receiving standard interferon therapy. The percentage of patients with virological ETR and SVR were as follows: peginterferon alpha-2b 1.5 µg (ETR 49 percent and SVR 23 percent), peginterferon alpha-2b 1.0 µg (ETR 41 percent and SVR 25 percent), peginterferon alpha-2b 0.5 µg (ETR 33 percent and SVR 18 percent), and standard interferon alpha-2a (ETR 24 percent and SVR 12 percent). Among the subset with paired liver biopsies, histological improvement (defined as at least a 2-point improvement in HAI score) was observed as follows: standard interferon alpha-2b (47 percent), peginterferon alpha-2b 0.5 µg (49 percent), peginterferon alpha-2b 1.0 µg (50 percent), and peginterferon alpha-2b 1.5 µg (48 percent). Treatment was discontinued because of adverse effects as follows: standard interferon alpha-2b (9 percent), peginterferon alpha-2b 0.5 µg (9 percent), peginterferon alpha-2b 1.0 µg (11 percent), and peginterferon alpha-2b 1.5 µg (9 percent).

Summary Evidence on the efficacy of peginterferon alone was heterogeneous and had important methodologic limitations. Among the studies, the racial and genotypic composition varied. In addition, there were differences in the proportion of cirrhotic patients across the studies. However, despite these differences, the studies were consistent in the finding that once weekly peginterferon is more effective than thrice weekly standard interferon alpha. In the three studies, the sustained virological response rate ranged from 30 to 39 percent among patients receiving peginterferon alpha-2a (180 µcg) compared to 3 to 19 percent among patients receiving standard interferon alpha [Evidence Grade A].

Studies on Standard Interferon Plus Ribavirin for Chronic Hepatitis C in Treatment-naive Patients

Characteristics of the studies In the fall of 2001, Kjaergard and colleagues[66] published a systematic review of the literature comparing the combination of standard interferon and ribavirin to standard interferon monotherapy. Their literature search, performed through August 2000, used MEDLINE, the Cochrane database, and manual searching. The systematic review[66] evaluated 15 randomized clinical trials of standard interferon alpha with or without ribavirin in treatment-naive patients. Among this patient group, the relative risk of not having a virological ETR with combination therapy compared to monotherapy was 0.74 (95 percent confidence interval (CI) 0.70 to 0.78) favoring combination therapy. The estimated number-needed-to-treat (NNT) to achieve an additional SVR was six among treatment-naive subjects. Patients receiving combination therapy had a higher risk of treatment discontinuation (relative risk 1.28; 95 percent

CI 1.07 to 1.52) and treatment dose reduction (relative risk 2.44; 95 percent CI 1.58 to 3.75) than did those receiving interferon monotherapy.

Four additional studies that examined the efficacy and safety of interferon alpha and ribavirin in treatment-naive patients were not included in the previously published systematic review. These studies represented a heterogeneous group with respect to treatment regimen, dose, and duration.[21,36,71,72] Evidence Table 9 summarizes the aims and eligibility criteria for these studies. El-Zayadi[71] assessed the efficacy of standard interferon alpha-2b alone and with ribavirin as initial therapy in Egyptian males with HCV genotype 4. Berg[36] examined whether 12-week combination therapy was more effective then standard interferon monotherapy in untreated patients. Ferenci[72] tested two different schedules of high-dose induction therapy with standard interferon in combination with ribavirin compared with standard interferon monotherapy. Finally, Mangia[21] compared the efficacy of high-dose interferon alpha-2b for 12 months either alone or in combination with ribavirin. The study performed by El-Zayadi included only patients with HCV genotype 4 who had HCV antibodies in the serum and an abnormal ALT. It excluded patients with decompensated liver disease, contraindications to interferon, and all other HCV genotypes. The other three studies were similar in their inclusion and exclusion criteria. They all included patients with detectable HCV in the serum and an elevated ALT. They all excluded intravenous drug users, patients with HIV infection, hepatitis B, alcohol use, decompensated liver disease, hematologic abnormalities, and major medical and psychiatric co-morbidity.

Evidence Table 10 describes the study groups and baseline characteristics of the patients in these studies. El-Zayadi compared standard interferon alpha-2b (3 MU three times per week plus ribavirin 1000 mg per day for 24 weeks) with the same dose and duration of interferon monotherapy. The percent with fibrosis or cirrhosis ranged from 27 to 30 percent. The mean age ranged from 36 to 42 years. No differences were found between the two groups. Berg compared two different induction treatments: interferon alpha-2a 6 MU three times per week for 12 weeks plus ribavirin 7 mg/kg in a divided dose twice daily for 12 weeks to interferon alpha-2a 6MU three times per week for 12 weeks. Those patients who showed a virological response to treatment were then given an additional 40 weeks of standard interferon. The average age of the patients in this study was 42 years, 55 to 57 percent were male, 11 to 13 percent had fibrosis or cirrhosis, and 73 percent in the combination group and 75 percent in the monotherapy group had genotype 1. There were no significant baseline differences in demography or clinical characteristics between the two groups. Ferenci compared three groups of patients: high dose induction, intermediate dose induction, and standard therapy. Most of the patients in the study were male, and most had HCV genotype 1. No significant differences were reported between the two groups. Finally, Mangia compared patients receiving interferon alpha-2b 5 MU three times per week for 12 months alone or with ribavirin. The mean age for the interferon alone group was 49 years, 72 were male, and 53 percent were genotype 1b. The combination therapy group had a mean age of 46 years, 61 percent were male, and 42 percent had HCV genotype 1b.

Quality of studies Evidence Table 11 summarizes our assessment of the quality of these studies. The median total quality score for the studies was 68 percent and scores ranged from 51 to 80 percent.

Results of the studies Evidence Table 12 summarizes the results of these studies. El-Zayadi found an increased biochemical SVR rate and increased virological ETR rate in Egyptian males with HCV genotype 4 who received combination therapy compared with interferon monotherapy ($p < 0.05$), but no difference in histological response. There were more adverse events reported in the combination therapy arm. Berg and colleagues found that patients receiving interferon and ribavirin induction treatment for 12 weeks compared to interferon monotherapy had a significantly greater virological ETR, but this was not sustained. Specifically, patients with genotype 1 receiving combination induction had a significantly greater response to induction than those receiving monotherapy, but at the end-of-treatment there was no difference among those with genotype 1. Ferenci and colleagues,[72] comparing different interferon induction doses, found no significant difference in biochemical or virological ETR and SR among the groups except when results were stratified by HCV genotype. They found that patients with HCV genotype 1 had a greater response to high dose induction than to intermediate dose induction or standard therapy ($p < 0.05$). Finally, Mangia, comparing interferon monotherapy to combination therapy, found that those receiving combination therapy had significantly higher virological ETR and SR.

Summary The systematic review published by Kjaergard[66] demonstrated an increased efficacy of interferon and ribavirin therapy compared to interferon alone in treatment-naive patients [Evidence Grade A]. The additional four studies were somewhat but not entirely consistent with respect to the conclusion that interferon and ribavarin is more effective than interferon alone [Evidence Grade B]. However, these studies were heterogeneous with respect to patient population and study design, which may limit the applicability of the derived data. This inconsistency may be related to the treatment protocols of these studies. The magnitude of the relative treatment effect may depend on the dose and duration of treatment.

Studies on Standard Interferon Plus Amantadine for Chronic Hepatitis C in Treatment-naive Patients

Characteristics of studies Five randomized controlled trials assessed the efficacy and safety of interferon with or without amantadine in treatment-naive patients.[25,34,73-75] Evidence Table 9 describes the aims and eligibility criteria of these trials. All of these studies included patients with detectable HCV in the serum and ALT elevation. In addition, they excluded patients with HIV (except Caronia et al),[75] hepatitis B coinfection, and major psychiatric and medical conditions,[25,34,73,74] chronic alcohol use, and active drug use. Tabon[74] specifically excluded cirrhotics.

Evidence Table 10 describes the study groups and their baseline characteristics. Helbling [73] used interferon alpha-2a 6 MU three times per week for 20 weeks, followed by 3 MU three times per week for 32 weeks, with or without amantadine 200 mg daily. Zeuzem[25] used interferon alpha-2a 6 MU three times per week for 24 weeks, followed by 3 MU three times per week for an additional 24 weeks, with or without amantadine for 48 weeks. Tabon[74] treated patients with interferon alpha-2a 6 MU three times per week for 6 months followed by 3 MU of interferon alpha-2a for six additional months with or without amantadine 200 mg daily for 12 months. Caronia[75] treated patients with interferon alpha-2a 4.5 MU three times per week for 48

weeks with or without daily amantadine 200 mg. Younossi[76] treated patients with 6 MU of interferon alpha-2a for 12 months with or without amantadine 200 mg daily.

The three studies with high dose interferon therapy followed by intermediate dose therapy [25,73,74] had similar patient ages ranging from 39 to 44 years. Helbling[73] had slightly more males than did the other two studies. In addition, the studies differed in their proportion of patients with genotype 1. Tabon[74] excluded cirrhotics. The mean age of the remaining two studies[34,75] ranged between 42[75] and 47 years.[34] In both studies, 60 to 70 percent of the patients were male. The proportions of patients with genotype 1 were 26 percent[75] and 52 to 61 percent.[34]

Quality of studies Evidence Table 11 summarizes our assessment of the quality of these studies. The total quality score for the studies ranged from 61 to 92 percent and the median score was 83 percent.

Results of studies Evidence Table 12 displays the results of these five studies. The follow-up period for these studies was 24 weeks. All three studies with high dose induction treated patients for 48 to 52 weeks. The SVR in patients receiving interferon and amantadine ranged from 10 to 29 percent. In those receiving monotherapy, the SVR ranged from 17 to 22 percent. There was no significant difference between patients treated with interferon and those receiving interferon and amantadine. Caronia[75] found no difference in sustained virological response between patients receiving interferon monotherapy versus combination therapy with amantadine. However, Mangia[34] did report a statistically significant difference between the two groups. Twenty-nine percent of those receiving combination therapy had an SVR compared with 17 percent in the monotherapy group ($p<.05$). Compared with those receiving monotherapy, patients with low baseline viral loads and genotype 1 receiving amantadine plus interferon had improved response rates.

Summary Evidence on the efficacy of interferon and amantadine was fairly homogeneous but had some methodologic limitations including varying treatment protocols. The studies were consistent in showing that interferon plus amantadine is not more effective than interferon monotherapy in treatment-naive patients [Evidence Grade A].

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?*

Previous Systematic Reviews

Three meta-analyses or systematic reviews[66-68] have examined randomized controlled trials of interferon alpha plus ribavirin compared to interferon alpha alone in persons who had failed to achieve a biochemical or virological response to prior interferon therapy or who had achieved a biochemical or virological response to interferon therapy followed by a relapse after treatment discontinuation.

In the systematic review discussed earlier, Kjaergard et al.[66] evaluated 15 trials including nonresponders, 10 with both relapsers and nonresponders, and one trial with relapsers and treatment-naive patients. They found that interferon nonresponders receiving interferon and ribavirin combination therapy had a 17 percent risk reduction in not achieving a virological ETR and a nine percent reduction in not achieving SVR compared with those receiving interferon monotherapy. In relapsers, combination therapy reduced the risk of not having a virological ETR or SVR by 47 percent and 38 percent, respectively, compared with interferon monotherapy.

Cummings[67] performed a meta-analysis assessing the efficacy and safety of standard interferon and ribavirin compared to interferon alone in previous interferon nonresponders. The literature was searched between January 1966 and December 1999 by means of MEDLINE and manual review of studies. Studies were included if they were randomized and compared combination therapy to monotherapy. The endpoints were ALT normalization, absence of HCV RNA, histology, and adverse events. 12 studies subsequently were included with a total of 941 patients. The pooled sustained virological response rate for combination therapy was 14 percent compared to 2 percent in patients receiving monotherapy with a risk difference of 7 percent ($p = 0.01$).

Cheng and colleagues[68] performed a literature search between January 1996 and June 2000 using MEDLINE. They included studies where treatment was at least 24 weeks, and the patients received a minimum of 800 mg of ribavirin daily and 9 MU of interferon per week. All patients had previously failed to respond to interferon. Outcomes measured were biochemical and virological ETR and SR. Seven randomized controlled trials with 766 patients demonstrated an overall weighted virological ETR of 23.1 percent with a common odds ratio of 4.9 (95 percent CI 2.9 to 8.1) in favor of combination therapy. The overall weighted SVR was 13.2 percent with

a common odds ratio of 4.9 (95 percent CI 2.1 to 11.2). The risk difference for all seven studies was 7 percent (95 percent CI 2 to13 percent).

These three systematic reviews reflected an increased SVR in previous nonresponders receiving a combination of standard interferon and ribavirin compared with those receiving standard interferon alone, although the overall response still remains low.

Twenty-three additional studies were identified that evaluated the efficacy of standard interferon and ribavirin in patients not achieving an SVR to interferon monotherapy.

Studies of Standard Interferon With and Without Ribavirin in Interferon Nonresponders

Characteristics and Quality of Recent Studies

Of the eight additional randomized controlled trials in interferon nonresponders, five studies compared combination therapy to interferon monotherapy.[32,77-80] The remainder compared different doses and/or durations of combination therapy.[19,33,81] Evidence Table 13 describes the aims and eligibility criteria. The five trials that compared the combination of standard interferon and ribavirin to standard interferon alone all required nonresponse to previous interferon therapy. Prior treatment regimens ranged from 3 MU to 6 MU of interferon for 3 to 6 months. One study [80] required nonresponse to two courses of interferon monotherapy. All of these studies excluded patients who were HIV positive, chronic alcoholics, or had hepatitis B or other causes of liver disease.

Evidence Table 14 describes the treatment groups and their demographic and clinical characteristics. The treatment regimens and study groups were heterogeneous.
Evidence Table 15 summarizes the assessment of the quality of these studies. The median total quality score was 70 percent with a range of 47 to 89 percent.

Results of Recent Studies

Evidence Table 16 summarizes the results of these studies. The study by Barbaro[77] found that the SVR in patients receiving short term beta-interferon was higher than in those receiving short term combination therapy (25 percent versus 13 percent; $p < 0.05$) at 24 weeks of follow-up. This difference was not sustained after 48 weeks of follow-up. Patients with genotype 1b receiving beta interferon had a greater SVR rate compared with the short term combination therapy group ($p = .012$). Histological improvement was also noted to be greater in patients receiving beta-interferon. The studies by Tripi[80] and Bresci[78] both reported a sustained virological and biochemical response in 6 to 7 percent of patients receiving standard interferon and ribavirin for six months. There was no difference between patients receiving interferon monotherapy and those receiving combination therapy. Combination therapy did lead to a 25 to 38 percent virological ETR, which was significantly greater than with monotherapy. Similarly, Ferenci found that 8 percent of nonresponding patients receiving high dose standard interferon and ribavirin therapy had an SVR compared to 1.5 percent of patients receiving high-dose interferon monotherapy. This difference was not statistically significant. Biochemical and virological ETR rates were significantly higher in the combination therapy group ($p < 0.05$). Finally, the study by Shiffman[32] reported that 12 to 14 percent of patients receiving combination

therapy had an SVR compared with 0 percent of patients receiving standard interferon monotherapy.

Summary

Evidence on the efficacy of standard interferon and ribavirin in nonresponders was heterogeneous and had methodologic limitations. In addition, there are differences in gender, genotype, and treatment protocols among the studies. The systematic reviews suggested a small but significant increase in sustained virological response in nonresponders receiving combination therapy. The additional studies are consistent in showing greater efficacy of combination therapy compared with interferon monotherapy in improving end of treatment response; however, this response is not consistently sustained through follow-up [Evidence Grade A].

Studies on Dose and Duration of Standard Interferon and Ribavirin for Previous Nonresponders

Characteristics and Quality of Recent Studies

The three trials[19,33,81] evaluating the optimal dose and/or duration of standard interferon and ribavirin therapy all required HCV in the serum and nonresponse to previous therapy (see Evidence Table 13). The studies by Saracco[19] and Puoti[81] excluded patients with HIV infection, chronic hepatitis B, major medical and psychiatric comorbidities, and illicit drug use. As shown in Evidence Table 14, these studies were quite heterogeneous in terms of the exact treatment regimens and characteristics of study subjects. Evidence Table 15 summarizes the assessment of the quality of these studies.

Results of Recent Studies

Evidence Table 16 describes the results of these studies. In the study by Di Bisceglie[33] 36 percent of patients with 48 weeks of therapy had SVR compared to 27 percent with 24 weeks of therapy. The statistical significance was not reported. The study by Saracco found that patients receiving 5 MU units of interferon three times per week plus ribavirin for 12 months had a significantly higher rate of SVR than those receiving 3 MU of standard interferon plus ribavirin for six months ($p < 0.05$). Finally, the study by Puoti[81] found that patients receiving daily standard interferon with ribavirin had higher rates of SVR than those receiving three times per week standard interferon ($p < 0.05$).

Summary

The studies reviewed were consistent in demonstrating increased efficacy of standard interferon and ribavirin therapy in interferon nonresponders when the dose or duration of treatment was increased [Evidence Grade B].

Studies on Standard Interferon Plus Ribavirin in Interferon Relapsers

Characteristics, Quality and Results of Recent Studies

Two studies evaluated standard interferon and ribavirin therapy for the retreatment of relapsers. The study aims varied. The study by Chapman [82] compared high-dose, long-term interferon therapy with a shorter-duration, and lower-dose of interferon and ribavirin combination therapy. The study by di Marco [83] evaluated sustained virological response in patients receiving either six or 12 months of combination therapy.

Evidence Tables 13 through 16 describe the studies' characteristics and results. Chapman's study[82] required for inclusion that patients received interferon alpha 2 MU three times per week for six months, with relapse during the 24-week follow-up period. An elevated ALT and detectable HCV in the serum were also required. The SVR after 24 weeks of follow-up was equivalent in both groups (50 percent).

In di Marco's study[83] patients were required to be positive for HCV antibodies and to have relapsed after interferon monotherapy. Patients with HIV, Hepatitis B, and major medical or psychiatric comorbid conditions were excluded. Seventy-two percent of patients receiving 12 months of therapy had an SVR, compared with 36 percent receiving six months of therapy ($p<.05$). The rate of response was higher in patients with non-1b genotype ($p<.05$).

Summary

The studies provide some evidence that longer duration of therapy with standard interferon and ribavirin but not interferon alone may have greater efficacy than shorter duration therapy in relapsers [Evidence Grade C].

Studies on Standard Interferon Plus Ribavirin in Nonresponders and Relapsers Combined

Characteristics, Quality and Results of Recent Studies

Four trials evaluated interferon and ribavirin therapy in mixed groups of relapsers and nonresponders.[84-87] These studies were heterogeneous in content. Evidence Tables 13 through 16 describe the aims, eligibility criteria, characteristics, quality, and results of these studies. In Cavalleto's study[84] patients received natural interferon 6 MU three times per week for two months followed by 3 MU three times per week for six months with or without ribavirin. Relapsing and nonresponding patients with HCV antibodies and detectable HCV in the serum were included. Patients with chronic hepatitis B, HIV, pregnancy, or decompensated liver disease were excluded. Sixty-six percent of previous relapsers had an ETR to combination therapy compared with 40 percent receiving monotherapy ($p = .02$). Sustained response (defined as both biochemical and virological) was found in 44 percent of patients receiving combination therapy compared with 16 percent in the monotherapy group ($p > .05$). In nonresponders, there was no difference in response by treatment regimen.

Enriquez' study[85] compared 24 versus 48 weeks of therapy with standard interferon alpha-2b plus ribavirin in previous nonresponders and relapsers. Patients were included if they

had HCV-RNA in their serum and an elevated ALT. Patients with cirrhosis, HIV, chronic hepatitis B, other causes of liver disease, and other major medical conditions were excluded. When results were stratified by genotype, relapsing patients with genotype 1b receiving 48 weeks of therapy had a significantly greater response than those receiving 24 weeks of treatment. This difference was not observed among nonresponders (37.1 percent of patients who completed 48 weeks of therapy compared with 15.5 percent of patients who received 24 weeks of therapy ($p = .013$)).

Min's study[86] compared high dose standard interferon plus ribavirin to a lower dose of standard interferon plus ribavirin. The study required a minimum of three months of previous interferon therapy without a sustained response. In addition, patients had to have detectable HCV-RNA in their serum and no evidence of other liver disease. The overall rate of SVR was 14 to 22 percent. The SVR rate did not differ between the two treatment groups. Relapsers, however, had a significantly greater response to therapy than did previous nonresponders ($p = .001$).

Bonkovsky's study[87] compared low-dose versus standard-dose ribavirin with standard interferon. The study required a minimum of three months of prior interferon therapy with nonresponse or relapse. The SVR in each group was 12 percent. There was no dose reduction of ribavirin in the lower-dose group.

Summary

Evidence on the efficacy of standard interferon and ribavirin in relapsers and nonresponders was heterogeneous and had methodologic limitations. The systematic review [66] suggested that combination therapy had a greater efficacy than interferon monotherapy [Evidence Grade A]. As indicated above, the additional studies were consistent in demonstrating that longer duration of interferon and ribavirin therapy has a greater efficacy than shorter duration in interferon relapsers and nonresponders. Furthermore, the evidence is consistent in showing that interferon relapsers have a better response to therapy than do previous nonresponders [Evidence Grade B].

Studies on Standard Interferon Plus Amantadine for Chronic Hepatitis C in Nonresponders

Characteristics, Quality and Results of Studies

Two trials compared interferon therapy with and without amantadine in previous interferon nonresponders.[88,89] Evidence Table 9 describes the aims and eligibility criteria. Both trials required nonresponse to previous interferon. Gaeta[88] required a minimum of four months of treatment, and Teuber[89] required a minimum of 3 months of treatment. Both excluded patients with chronic hepatitis B or HIV infection and those with decompensated liver disease. Gaeta and colleagues limited their study groups to patients with genotype 1b. Approximately 90 percent of Tueber's study population was genotype 1. Evidence Table 14 describes the baseline characteristics of the treatment groups. Evidence Table 15 summarizes the assessment of the quality of these studies.

Evidence Table 16 summarizes the results of these two trials. In neither trial was treatment with amantadine plus interferon superior to interferon alone. In fact, in Gaeta's study, the virological ETR was zero in both groups. Twenty-nine percent of the amantadine group compared with 15.8 percent of the interferon group had an end-of-treatment biochemical response, but no statistical significance was reported. Teuber and colleagues also found no significant difference in either SVR or ETR between the two treatment groups. ($p > .05$)

Summary

Evidence on the efficacy of interferon and amantadine had some methodologic limitations including differences in treatment protocols. The studies were consistent in showing that interferon plus amantadine is not more effective than interferon monotherapy in nonresponding patients [Evidence Grade B].

Studies on Standard Interferon, Amantadine and Ribavirin for Chronic Hepatitis C in Nonresponders

Characteristics, Quality and Results of Studies

Two studies evaluated standard interferon, amantadine, and ribavirin in previous interferon nonresponders.[76,90] Brillanti[90] assessed the safety and efficacy of standard interferon and ribavirin with or without amantadine. Younossi[76] compared retreatment with standard interferon and ribavirin to interferon and amantadine. Evidence Table 13 summarizes the aims and eligibility criteria of these two trials.

Brillanti and colleagues[90] included nonresponders with neither HCV-RNA clearance nor ALT normalization. Patients were required to have received standard interferon alpha 3 to 6 MU three times per week for a minimum of four months and a maximum of 12 months. Patients were excluded if they had HIV or HBV coinfection, significant medical or psychiatric comorbidities, alcoholic liver disease, or abnormal hematologic parameters.

Younossi and colleagues[76] included patients in the study if they were nonresponders to a minimum of 12 weeks of therapy. They were excluded if they were HIV positive, had decompensated liver disease, or had significant medical or psychiatric conditions.

Evidence Table 14 describes the study groups and their baseline characteristics. The assessment of the quality of these studies is summarized in Evidence Table 15.

Evidence Table 16 summarizes the results. In the small study by Brillanti et al, the SVR after six months was 48 percent in the triple therapy group, compared to 5 percent in the double therapy group ($p < .001$). Patients in the interferon/amantadine/ribavirin group also had an increase in sustained biochemical response compared to those receiving combination therapy ($p < .001$). There was no discontinuation of therapy secondary to adverse events.

Younossi found no increase in sustained virological or biochemical response in the standard interferon and amantadine group compared with the standard interferon and ribavirin group ($p > .05$).

Summary

One small study suggested that standard interferon in combination with ribavirin and amantadine may be more effective than interferon and ribavirin in nonresponders, but this conclusion is limited by the lack of genotye distribution in the countries where the studies were performed as well as lack of additional studies [Evidence Grade I].

Studies on Standard Interferon in Nonresponders and Relapsers

Characteristics, Quality and Results of Recent Studies

Eight randomized clinical trials were evaluated[23,91-97] that investigated various interferon regimens in persons who failed to achieve an SVR or SBR to a prior course of interferon therapy. These studies were heterogeneous in design and inclusion/exclusion criteria. Three studies evaluated only nonresponders to previous interferon and five studies evaluated both nonresponders and relapsers to prior interferon therapy. However, because the definition of nonresponse and relapsers varied considerably, there is a significant lack of homogeneity in the patient population studied (see Evidence Table 14). Of particular interest, one study [96] randomized persons who failed to achieve an on-treatment viral response after receiving 24 weeks of interferon alpha-2b, but who had evidence of a histological response by liver biopsy performed after six months of interferon, to receive continued interferon alpha (i.e., maintenance therapy) versus observation. Whereas the majority of studies sought to evaluate biochemical or viral response, the primary aim of this study was to evaluate progression of liver histology as determined by comparison of the first liver biopsy to a second biopsy performed after 24 months of continued therapy or observation. One study [23] evaluated the effect of longer duration of interferon therapy (6 versus 12 months) compared to higher dose of interferon (3 MU versus 10 MU) in relapsing patients.

There was also significant heterogeneity in the interferon regimens among studies (see Evidence Table 14). Several studies evaluated higher doses of interferon (e.g., > 3 MU) or greater frequency of administration (e.g., daily versus three times per week) or different types of interferon (e.g., interferon alpha-2a and-2b, alphacon1, lymphoblastoid interferon, and natural interferon). The clinical and demographic features of the study populations were also heterogeneous. One study [96] compared continued or maintenance interferon alpha-2b 5 MU three times per week to no treatment among histological responders to prior interferon. The study population was half male, white and had evidence of elevated serum ALT and hepatic fibrosis on liver biopsy.

Study quality was varied (Evidence Table 15). In general, among nonresponding patients, these studies demonstrated low rates of biochemical and/or virological response to retreatment with interferon-based regimens, whereas among relapsing patients, virological and biochemical responses were typically higher than those observed in nonresponders. Among interferon nonresponders, one study [96] demonstrated that continued interferon alpha-2b for 24 months was associated with the maintenance of histological benefit observed at study entry. Patients who received maintenance interferon had lower hepatic inflammation and fibrosis scores over time than did those who discontinued therapy despite persistent viremia, a finding that suggests long-term interferon therapy may be associated with histological benefit. Among interferon relapsers,

one study [23] demonstrated higher rates of SVR among patients who received longer duration (12 months) of low-dose interferon (3 MU) [SVR, 32 percent] compared to those who received shorter duration (6 months) of either low-dose (3 MU) [SVR, 14 percent] or higher-dose (10 MU) [SVR 17 percent] interferon. Consequently, among relapsers the duration of retreatment may be of greater importance than the dose delivered.

Summary

Evidence of the efficacy of interferon monotherapy was heterogeneous and had important methodologic limitations. The studies were consistent in showing that interferon monotherapy is relatively ineffective in the retreatment of nonresponders and relapsers [Evidence Grade B]. However, one study suggested histological benefits may be achieved in some nonresponding patients assigned to "maintenance" interferon, and a second study suggested duration of therapy in relapsing patients is an important predictor of sustained viral response.

Standard Interferon Therapy in Subgroups

Characteristics, Quality and Results of Recent Studies

Five studies met inclusion criteria for review in clinically important subgroups.[20,31,98-100] Two of these studies reported information on race,[20,98] one reported on patients with end stage renal disease requiring hemodialysis,[99] one studied hemophiliacs, and one studied hepatitis B and hepatitis C co-infected patients. Evidence Tables 13 through 16 summarize the characteristics and results of these studies.

The two studies reporting on race were subgroup analyses of large randomized controlled trials. The first[20] reported the results of two randomized controlled trials[101,102] and stratified outcomes by race. Reddy and colleagues[98] retrospectively analyzed data from the consensus interferon trial and stratified outcomes by race. McHutchinson[20] found that blacks had no response to interferon monotherapy compared with 13 percent of whites. In contrast, 20 percent and 23 percent of blacks responded to interferon plus ribavirin for 24 or 48 weeks, respectively. However, this response was lower than that of whites (32 percent and 42 percent respectively). When patients were analyzed by genotype, the researchers they found that Blacks and whites with genotype 1 had similar responses to combination therapy, whereas blacks with genotype 1 did not respond to interferon monotherapy.

Reddy and colleagues[98] found that blacks had significantly lower end-of-treatment biochemical and virological response than did whites. The rate of SVR was 12 percent in whites and 2 percent in blacks, but this did not reach statistical significance ($p = .07$). Multivariate analysis demonstrated that non-1 genotype predicted response to interferon.

Campistol and colleagues[99] performed a multicenter randomized controlled trial assessing the efficacy and tolerance of interferon alpha-2b in the treatment of chronic hepatitis C in patients undergoing hemodialysis. In the treatment group, 14 of the 19 patients had an ETR, and 42 percent (8/19) had a sustained response at two years. Treatment was discontinued in 10 out of 19 patients in the treatment group secondary to leucopenia in (three patients), anemia (1), diarrhea (1), and depression (1). Ten patients in the treatment group and five patients in the

control group underwent cadaveric renal transplant. Decreased ALT observed during treatment was also observed after transplant.

Rumi[100] reported on hemophiliacs randomized to either interferon alpha-2b 3 MU three times per week for six months or to the control group. Some 13 percent of patients treated with interferon had a complete biochemical and virological response at the end of 24 weeks of follow-up. This percentage was significantly greater than in the control group ($p < .01$). In conclusion, the response rate to interferon monotherapy in hemophiliacs is similar to that observed in persons without hemophilia.

Villa et al.[31] studied the effect of interferon in patients with hepatitis B and hepatitis C co-infection. They found that the virologic ETR of patients receiving 6 MU of interferon compared to that of those receiving 9 MU of interferon three times per week for six months was 86 percent and 75 percent, respectively. There were only 30 subjects in this study, thus limiting the generalizability of the results.

Relation Between HCV Genotype and Treatment Effect on SVR

Ten studies reported enough data to permit a multivariate logistic regression analysis of the relation of HCV genotype to the effect of treatment on the SVR rate (see Table 2 at end of chapter). The resulting analysis indicated that HCV genotype 1 generally was associated with a lower SVR rate than other genotypes. However, the analysis were relatively consistent in showing that were was no interaction between HCV genotype and the effect of different treatment regimens on the SVR rate. This suggests that the most efficacious treatment was the same for those with and without HCV genotype 1 despite having a lower SVR rate with genotype 1 than other genotypes.

Summary

Evidence on the efficacy of interferon in subgroups was heterogeneous and had important methodologic limitations [Evidence Grade I]. Evidence suggested that blacks respond differently to interferon monotherapy than do whites. One randomized controlled trial in renal patients presented evidence that patients on dialysis may respond to interferon therapy and that this response may be sustained post transplant. While encouraging, this one small study does not provide conclusive evidence of this phenomenon. One study suggested that standard interferon may have a small effect in hemophiliacs, and one study suggested that standard interferon may lead to virologic ETR in patients with both hepatitis B and C. There are important limitations to these findings. Because randomized controlled trials in these subgroups are few, generalizable conclusions are difficult to make. Despite the relatively high prevalence of HCV coinfection among HIV-infected persons, no randomized controlled trials were available to address the safety, efficacy and tolerability of standard interferon alpha or interferon alpha plus ribavarin in this population.

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

Results of the Literature Search

Forty studies ultimately met the criteria for question 2d. These studies were heterogeneous in study design, eligibility criteria, patient characteristics, and outcomes. Studies included were randomized controlled trials, prospective and retrospective cohorts and case series. Evidence Tables 17 through 20 summarize these features. Of the 40 studies, 17 assessed long-term outcomes of chronic hepatitis C in patients treated with interferon. The remaining 23 studies addressed the natural history of hepatitis C and either did not explicitly indicate whether treatment was received by any of the patients or stated that all patients were untreated. Twenty-five studies were performed at tertiary care centers. Seven were evaluated on community based cohorts and eight studies were unclear as to the source of patients.

Long-term Outcomes of Interferon-based Therapy

Characteristics of studies In the studies including interferon-treated patients in the assessment of long-term outcomes of chronic hepatitis C, progression of liver disease was measured in terms of the incidence of cirrhosis (three studies), HCC (15 studies), incidence of resectable HCC (two studies), hepatic decompensation (two studies), overall and liver-related mortality (two studies), liver transplantation (two studies), and SVR (two studies). Inclusion and exclusion criteria among these studies were fairly heterogeneous (Evidence Table 17). In most studies, patients had to have a liver biopsy and be HCV seropositive to be included. In addition, patients with chronic hepatitis B generally were excluded from these studies. The studies were inconsistent in their inclusion or exclusion of alcoholics, cirrhotics, and intravenous drug users. One study did not mention any eligibility criteria.[103]

As indicated in Evidence Table 18, the study designs were predominantly prospective and retrospective cohort studies, although there were a few randomized controlled trials.[104-106] The treatment protocols were highly variable ranging from daily standard interferon for two weeks[103] to every other day for six to 12 months. The majority of studies reported only partial details of the treatment regimens. Either interferon duration or frequency was not mentioned. A few studies mentioned only the numbers of patients receiving interferon in the cohort. In addition, members of individual cohorts may have received varying frequency, dose, or duration of therapy. The baseline characteristics of participants in these studies also varied. All of these studies included both men and women with a range of hepatitis C genotypes and histologic findings on liver biopsy. In many studies, racial and ethnic characteristics were not presented . The mean age ranged from 35 to 58 years old. The percentage of patients with cirrhosis in these studies ranged from 0 to 100 percent. The percentage of patients with alcohol consumption ranged from 0 to 49 percent, with alcohol consumption being defined differently across the studies.

Quality of studies Evidence Table 19 summarizes the assessment of the quality of these studies. The quality score for the cohort studies ranged from 35 to 90 percent. In general, these studies received higher scores in the representativeness and statistical analysis categories and lower scores in the bias and confounding category. Very few studies reported on the type or degree of involvement of the funding source. The quality score for the randomized controlled trials was 69 percent or greater. These randomized controlled trials had quality scores greater than or equal to 75 percent for the main study quality categories, except for the categories of bias and outcomes assessment in the study by Bernardinello [104]. The studies did not report the type or degree of involvement of the funding source.

Results of studies Four retrospective cohort studies stratified the reporting of outcomes by response to interferon therapy. Horiike [103] and colleagues compared patients who had a complete biochemical and virological response to standard interferon both to nonresponders and to those receiving no therapy. The authors found an annual incidence of HCC of 0 percent, 0.3 percent and 1.6 percent, respectively, ($p < 0.05$ comparing treatment versus no treatment) and an overall incidence of HCC of 0 percent, two percent, and 15 percent. When they further stratified their results by histology, they found that those untreated with F3 histology had a significantly greater incidence of HCC than did complete responders and nonresponders combined (36 percent versus 0 percent; $p < 0.05$). In contrast, Shindo [107] found the annual incidence of cirrhosis to be significantly higher in nonresponders than in relapsers or patients who had a biochemical response or complete response (15 percent versus 1 percent, 0 percent and 0 percent; $p < 0.001$). Moreover, they reported the annual incidence of HCC to be 6 percent in nonresponders, which was significantly higher than in all other study groups ($p = 0.0001$) except for the untreated controls. Tanaka[108] reported the risk of developing HCC seven years after standard interferon therapy and found the risk to be 17 percent in untreated controls versus 12 percent in those treated, regardless of response ($p = .076$). The annual incidence of HCC in patients having a biochemical sustained response was 0.35 percent and in relapsers it was 0.63 percent; by contrast it was 2.1 percent in nonresponders. The seven year cumulative risk of HCC was significantly greater in nonresponders than in relapsers and patients having a biochemical sustained response (22.4 percent versus 3.7 percent and 1.2 percent, respectively; $p < 0.01$). Multivariate analysis demonstrated that the risk ratio for developing HCC in sustained and transient responders versus controls was 0.16 ($p = 0.007$) and 0.27 ($p = 0.02$), respectively. Yabuuchi[109] reported the five year cumulative incidence of HCC to be 2.3 percent in complete responders, 2 percent in biochemical responders, and 14.3 percent in nonresponders ($p < 0.05$ for the comparisons to nonresponders).

Four studies, performed in tertiary care centers, stratified outcomes by treatment or control group. Inoue[110], in a retrospective study that excluded cirrhotics, reported the five year cumulative incidence of HCC as 2.2 percent in patients treated with standard interferon, compared with 9.5 percent in untreated patients with chronic hepatitis C ($p = 0.0015$). A Cox proportional hazard model adjusted for age, gender, ALT, platelet count, and AFP level found a 69 percent decrease in risk of HCC in patients receiving standard interferon ($p = 0.015$). Nishiguchi et al.[111] prospectively compared 90 cirrhotic patients randomized to standard interferon or symptomatic treatment. After nine years the incidence of HCC was 27 percent in interferon-treated patients versus 73 percent in untreated controls ($p < 0.001$). By multivariate

analysis the risk ratios of those treated were 0.26 for the development of HCC and 0.14 for death. Moreover, they found that as ALT increased, the risk of HCC increased. Bernadinello[104], in a randomized trial, compared three months of standard beta-interferon with no treatment and found no difference in SVR, the incidence of HCC, or the incidence of hepatic decompensation at five years among cirrhotic patients. Fattovich[5] compared treated and untreated cirrhotics with standard interferon and found a significant decrease in hepatic decompensation in those treated with interferon ($p < 0.01$) but no difference in HCC incidence over five years.
An additional two studies reported long-term outcomes by dose or duration of standard interferon treatment. In a randomized trial, Chemello et al[105] compared a daily dose of standard interferon for three months followed by three times a week dosing to six months of three times a week standard interferon and found no difference in viral or biochemical sustained response after 72 months. Toyoda[112] retrospectively looked at noncirrhotic relapsers and nonresponders who received more than 500 MU of standard interferon versus less than 500 MU of interferon. The overall incidence of HCC was 5.5 percent at a mean of 60 months. They found no difference in the rate of HCC by duration of therapy, but did find a significant difference in rate of HCC by dose of therapy. Those patients with higher doses of interferon had a lower incidence of HCC ($p < 0.05$). Moreover, total dose of interferon was an independent predictor of HCC. Ikeda[113] retrospectively compared untreated controls with patients receiving less than 12 months of standard interferon and greater than 12 months of standard interferon. He found the ten-year incidence of HCC to be significantly less in patients receiving longer courses of interferon therapy (21 percent) than in those receiving short-term therapy (65 percent) or those untreated (47 percent; $p < 0.05$). The ten year survival was 93 percent in the long-term interferon group compared with 68 percent in the short-term interferon group and 57.4 percent in the untreated group ($p < 0.01$ for the comparison to the untreated group).

The six remaining studies did not stratify outcomes by treatment received or treatment response but indicated that a portion of patients in the cohort underwent therapy. Yatsuhashi[114] followed 186 individuals prospectively and found the cumulative probability of developing HCC at 15 years to be 45 percent. They found fibrosis stage and age greater than 50 years to be risk factors for the development of HCC. Inflammatory activity and treatment status were not independent risk factors for HCC. Aizawa[115] retrospectively studied 153 men and women with chronic hepatitis C and found the cumulative incidence of HCC at 15 years to be 42 percent and the annual incidence to be 2.8 percent per year. Factors predictive of HCC included older age, habitual heavy drinking, and histological stage. Forty-five percent of patients with severe fibrosis at initial biopsy developed HCC at 13 years compared with 23 percent of patients with mild fibrosis at initial biopsy ($p <.01$). Kobayashi[116] retrospectively studied 61 patients consecutively treated with standard interferon for six months and found that patients with serum ALT less than 75 U/L had improved liver histology over five years compared to patients with an ALT greater than 75 U/L, who had worsened histology. Bruno[117] prospectively studied 163 Child's class A cirrhotics and found the incidence of HCC to be 13.5 percent at a median of 68 months of follow-up. In addition, 86 percent of these patients had genotype 1b. Only 18 percent of cases of HCC were resectable. The total mortality in this group was 13.5 percent, and 50 percent of these deaths were related to hepatitis C. The incidence of liver transplantation was 1.2 percent. Benvegnu[118] investigated the relation between HCV genotype and HCC in cirrhotic

patients and found the incidence of HCC over a mean time of 66.9 months to be about 21 percent. The incidence was not significantly different among HCV genotypes. Hepatitis C-specific mortality was 22 percent. Those with mixed HCV genotype had significantly more deaths than those with genotype 2 (66 percent versus 16 percent; $p < 0.05$). The incidence of liver transplantation was 1.25 percent. Shibata[119] compared untreated cirrhotics to treated noncirrhotics and found the incidence of HCC to be 52 percent versus 6.2 percent, respectively ($p < 0.01$).

Summary of studies on long-term outcomes of interferon-based therapy The evidence on the effect of standard interferon on long-term outcomes in chronic hepatitis C was heterogeneous and had important methodologic limitations. The studies were primarily retrospective and prospective cohorts. Retrospective studies are limited in their ability to determine the effect of interferon on outcomes secondary to selection bias. In these cohorts, interferon-treated patients were neither randomly selected nor selected by strict criteria. Thus, despite multivariate analysis with adjustment for confounders, there is residual bias toward a positive treatment effect. Consequently caution is necessary when interpreting retrospective cohorts. Long-term outcomes of randomized controlled trials would be ideal. Other limitations include variable lengths of follow-up within and among studies, variable numbers of patients with cirrhosis at baseline, different doses and durations of therapy (frequently missing details about dose and duration), 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 standard interferon-based therapy produces a moderate decrease in the risk of HCC and cirrhosis in complete responders [Evidence Grade B]. The evidence also suggested that patients having a biochemical response to standard interferon may have a decreased risk of HCC and progression of liver disease [Evidence Grade B]. However, the data were inconsistent regarding the impact of standard interferon therapy on long-term outcomes in nonresponders and relapsers compared to untreated patients. One long-term randomized controlled trial suggested that all patients treated with standard interferon, regardless of response, derived long-term benefits; other studies suggest that relapsers but not nonresponders may derive some long-term benefit from standard interferon therapy [Evidence Grade C].

Long-term Outcomes of Chronic Hepatitis C in Untreated Patients

Overview of characteristics of the studies Twenty-three studies addressed the long-term natural history of chronic hepatitis C. Table 17 summarizes their aims and eligibility criteria. Because of our selection criteria, all of these studies had a mean or median follow-up time of at least five years. Long-term outcomes mentioned in the objectives included histologic progression and hepatitis C-related morbidity and mortality. The patients followed were heterogeneous across studies as were the inclusion and exclusion criteria. Three studies described the natural history of hepatitis B and C in cirrhotics [120-122]; one study described the natural history of hepatitis B and C in noncirrhotics[123]; two studies prospectively looked at the progression of liver disease in patients with hepatitis C who had persistently normal serum ALT[124,125]; three studies assessed long-term outcomes in renal patients who had chronic hepatitis C[126-128]; three studies looked at patients with HIV and HCV co-infection[129,130,133]; two studies

focused only on patients with hepatitis C secondary to transfusion [131,132]; two studies looked primarily at intravenous drug users[133,134]; two studies looked at long-term progression of chronic hepatitis C by HCV genotype[135,136] and another by initial biopsy alone[137]; one study looked at patients with coagulation disorders and chronic hepatitis C[138]; one study looked at women with hepatitis C after receiving contaminated anti-d-immunoglobulin[139]; and finally, there were two miscellaneous cohort studies[140,141]

Characteristics and results of studies in patients with chronic hepatitis B and hepatitis C co-infection Chiaramonte[120], Gentilini[121], and Ikeda[122] looked at long-term outcomes in cirrhotics with hepatitis B or C. Although Chiaramonte and Ikeda included patients with hepatitis B and C co-infection, such patients were excluded from Gentilini's study. As shown in Evidence Table 17, exclusion criteria for Chiaramonte and Gentilini were otherwise similar in that those with alcoholic or decompensated liver disease were not included in the analysis. Ikeda excluded patients with portal hypertension, Budd-Chiari syndrome, subacute hepatitis or chronic aggressive hepatitis, but 65 patients had decompensated cirrhosis with ascites, history of encephalopathy, or both. The mean age of patients in these three studies ranged from 50 to 54 years. The percentage of men in the studies ranged from 57 percent to 78 percent.

The total study quality scores for the studies by Chiaramonte and Gentilini were 51.9 and 41 percent, respectively. They both received low scores for the description of therapy because they did not explicitly report whether patients received any primary or ancillary form of treatment.

Chiaramonte found the 10-year cumulative incidence of HCC to be 45 percent in patients with co-infection, and 28 percent in patients with hepatitis C alone. Factors predictive of HCC in Chiaramonte's study included hepatitis B and C co-infection, male gender, and age greater than 50 years. Gentilini reported the overall incidence of HCC to be 8.6 percent and the hepatitis C-related mortality to be 19.2 percent. Ikeda found the 10-year incidence of HCC in patients with hepatitis C to be 53.2 percent and 27.2 percent in patients with hepatitis B ($p = 0.003$). Risk factors for HCC in patients with HCV infection were age, AFP level, and previous alcohol intake. Risk factors for HCC in patients with HBV infection were age and findings on indocyanine green test. These three studies in cirrhotic patients suggested different rates of hepatocarcinogenesis between patients with HBV and those with HCV infection.

One study[123] retrospectively compared the incidence of HCC in non-cirrhotic patients with chronic hepatitis C versus hepatitis B. Patients were included if they had chronic persistent hepatitis or chronic active hepatitis on biopsy. Patients were excluded if they had co-infection with hepatitis B and C, an elevated AFP, or HCC. The mean age of patients with HBV infection was 33.2 years versus 49.6 years in patients with HCV. Eighty percent of the patients with HBV infection were male compared with 77 percent of the patients with HCV. The total study quality score was 65 percent. The incidence of HCC in patients with hepatitis C was 10.5 percent at a mean follow-up of 73 months compared to 3.9 percent in patients with hepatitis B at a mean follow-up of 73 months ($p < 0.05$). Moreover, for patients with chronic hepatitis C, the more histologically advanced the disease the shorter the time to HCC.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C by ALT level Two prospective cohort studies assessed the relation of serum ALT levels to long-term outcomes in untreated chronic hepatitis C. Persico[124] followed 37

asymptomatic patients with hepatitis C with persistently normal ALT. Hayashi[125] compared outcomes in patients with normal ALT, intermittently abnormal ALT, and always abnormal ALT. Both studies required positive HCV antibodies and excluded patients with hepatitis B. Persico additionally excluded intravenous drug users and patients with fibrosis. The two study populations also differed in location, as Persico's was conducted in Europe and Hayashi's in Japan. Finally, the two studies differed in the distribution of HCV genotype. Persico's study included primarily patients with genotypes 2a and 1b, while Hayashi's included patients with HCV genotype 1a. The total study quality scores of the studies were 71 and 80 percent as indicated in Evidence Table 19. The study by Hayashi received a low score for its reporting of outcomes. Persico found no significant change in histology in the patients with a sustained normal ALT. Hayashi reported no cases of HCC in patients with normal ALT levels. In contrast, patients with always abnormal ALT levels had a 31 percent five year incidence of HCC.

Characteristics and results of studies on long-term outcomes of untreated chronic Hepatitis C in patients with renal disease One study[126] prospectively followed three groups of patients: one group on hemodialysis with hepatitis C; one group on hemodialysis without HCV; and one group with HCV not on hemodialysis. The inclusion and exclusion criteria were not reported explicitly. The mean age was 58.9 years, 58 percent were male, and none used greater than 60 grams of alcohol per day or illicit drugs. Ultrasound imaging of the liver showed that HCV-positive patients on hemodialysis had a greater frequency of both coarse and nodular patterns than those without hepatitis C viremia (coarse in 51.3 percent versus 31.4 percent, $p < 0.05$; nodular in 21.3 percent versus 3.9 percent, $p = 0.0001$). In addition, most patients with HCV and on hemodialysis in this cohort had a normal ALT. The annual incidence of HCC was 0.53 percent and occurred only in HCV-positive patients.

Two retrospective cohort studies were performed looking at the effect of HCV after a renal transplant. The general aims were different for these two studies. Rostaing and colleagues [128] looked at the effect of immunosuppression on liver histology in renal transplant patients, while Kliem [127] assessed the impact of hepatitis C on morbidity and mortality post transplant. Renal transplantation and immunosuppressive therapy were inclusion criteria for both studies. As shown in Evidence Table 19, the study quality scores for the Rostaing study were lower than the scores for the Kliem study.

Rostaing found on biopsy that most of the transplant patients had chronic hepatitis and the mean Histology Activity Index was 6. They also found that the serum HCV RNA levels were high at the time of biopsy, an elevation they felt might be related to immunosuppression. Kliem concluded that there was a low morbidity related to hepatitis C in renal transplant patients, but hepatitis B co-infection and hemodialysis increased the risk of chronic liver disease in these patients.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C in patients with HIV infection Two studies followed patients with HIV infection and chronic hepatitis. These studies were heterogeneous in their study groups and aims (see Evidence Table 17). One study compared HCV negative and HIV positive hemophiliacs with HCV positive, HIV negative hemophiliacs[129]. The other study compared HIV and HCV co-infected patients treated with or without protease inhibitors[130].

Lesens[129] compared HIV and HCV co-infected hemophiliacs to those with HCV alone. The only stated inclusion criterion was detectable HCV in the serum. The total study quality score was 42.8 percent. All patients had hemophilia A or B. The mean age at infection was 19.7 years in the co-infected group compared to 22.2 years in the HCV-alone group. One patient in the co-infected group also had HBV infection. The rate of progressive liver disease was 27 percent in the co-infected group compared with 6 percent in the HCV-alone group. The mean time to progressive liver disease was 17 years. The hepatitis C-specific mortality rate was 8.6 percent in the co-infected group versus 0 percent in the HCV-alone group. This study provides some evidence that HCV and HIV co-infection leads to a more rapid progression of liver disease.

The second study[130] assessed the effect of protease inhibitors on liver fibrosis in patients co-infected with HIV and HCV. Patients were included in this study if they had HCV in their serum, HIV infection, and had used antiretroviral therapy. Patients were excluded if they had hepatitis B or received immunosuppression. The mean age was 37 years. All of the patients in the non-treatment group were males compared with 60 percent in the treatment group. Most of the patients were infected through intravenous drug use. The study's quality scores are shown in Evidence Table 19. The rate of progression of liver fibrosis was 1.36 percent per year in the treatment group compared with 2.1 percent per year in the no treatment group ($p < 0.05$). In addition, 29 percent of patients not receiving treatment progressed to cirrhosis compared to 6.3 percent of patients receiving protease inhibitors ($p < 0.01$). Cirrhosis was higher in patients drinking greater than 50 grams per day of alcohol, patients older than 20 years at the time of HCV infection, patients who had never received protease inhibitors, and patients with low CD4 counts ($p < 0.05$).

Characteristics and results of studies on long-term outcomes of chronic hepatitis C in patients with a history of blood transfusion Two studies reported long-term outcomes in transfusion recipients with HCV infection. Harris[131] performed a retrospective cohort study comparing transfusion recipients infected with HCV with those who were HCV negative. Patients were excluded if they were exposed to any other blood products, used intravenous drugs, or were transfused after being tested for HCV. The total study quality score was 70 percent. After the first decade of infection, the hepatitis C-specific mortality was 1 percent in those infected with HCV. Furthermore, they found that infected patients had an increased risk of death with high levels of alcohol consumption.

Murakami and colleagues[132] performed a prospective cohort study of patients with transfusion-related HCV. Patients were included in the analysis if they had detectable HCV in the serum, positive HCV antibodies, and no history of antiviral therapy. They were excluded if they had hepatitis B, intravenous drug use, greater than 80 grams of alcohol intake daily for the past three years, or other causes of liver disease. The incidence of cirrhosis was 23 percent. The mean time to cirrhosis was 6.5 years less for those transfused after 50 years of age compared to all other ages and was 19.8 years less for those transfused in their forties compared to all other ages. As age at time of transfusion increased, the cumulative incidence of HCC increased ($p < 0.001$).

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C in patients who use intravenous drugs Thomas[133] prospectively studied the natural history of hepatitis C in a cohort of intravenous drug users. Patients were included in the cohort

if they were older than 17 years, used intravenous drugs, and were positive for HCV antibodies. The population was primarily African American; 78 percent were male and 73 percent earned less than $5,000 per year. One third were HIV infected and two percent used alcohol. Sixty percent had HCV genotype 1a. Over a median follow-up of eight years, the incidence of cirrhosis in this population was 3.3 percent and the incidence of decompensation was 2.4 percent per year. In this study, 5.4 percent of patients spontaneously cleared their virus and the hepatitis C specific mortality was two percent.

Rodger[134] followed a cohort of intravenous drug users with 35 HCV positive individuals and 70 HCV negative controls available for follow-up. The study quality scores were low (see Evidence Table 19), and many of the cases of HCV infection were not reported from this cohort. However, there were no cases of HCC over this time, and only two cases of cirrhosis.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C by HCV genotype Two studies measured long-term outcomes of chronic hepatitis C by HCV genotype [135,136]. Kobayashi[135] retrospectively studied patients with either HCV genotype 1 or genotype 2 to assess if long-term outcomes differed by genotype. Inclusion criteria included an abnormal serum ALT and age between 18 and 60 years. Patients were excluded if they consumed more than 80 grams of alcohol per day, had received antiviral therapy, were HIV positive, or had evidence of hepatitis B. The two groups were equivalent in terms of gender, age, histology, and hepatic transaminases. The total study quality score was 92.7 percent. The incidence of HCC in patients with HCV genotype 1 was 29 percent, and in genotype 2 it was 5.5 percent ($p < 0.01$). In addition, patients with HCV genotype 1 had greater deterioration in grade and histology than those with genotype 2, and their mean HCV titer was significantly higher ($p < 0.001$).

Matsumura[136] studied the progression of chronic hepatitis C by HCV genotype. Patients were included if they had an abnormal serum ALT and positive serum HCV. The patients were excluded if they had hepatitis B or an autoimmune disease. The total study quality score was 75 percent. The mean age was 50 years, and 61 percent were male; 53 percent had received blood transfusions. The mean overall rate of progression per year of liver fibrosis was 0.12 percent for patients with F1, F2, F3, and F4 histology. There was no difference among patients with HCV genotypes 1b, 2a, or 2b. However, when rate of progression was broken down according to age of transfusion (greater than or less than 30 years old), the rate of progression of liver fibrosis for men and women with HCV genotype 1b was greater for patients transfused after the age of 30 years ($p = 0.001$). Multivariate analysis demonstrated that increased age and low platelet count were risk factors for HCC.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C by histology Yano[137] retrospectively assessed the pathologic evolution of HCV infection over time in 70 patients. Patients with a history of previous therapy, immune suppression, cirrhosis, hepatitis B infection, and habitual heavy drinking were excluded. An initial liver biopsy and HCV antibodies were required for inclusion. The population was predominantly male and Asian, and all patients had fibrosis. The total incidence of cirrhosis in this population was 50 percent. The initial presence of high grade or stage on biopsy predicted accelerated progression to cirrhosis.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C in patients with coagulation disorders Meijer[138] studied the natural history of hepatitis C in HIV-negative patients with coagulation disorders. The mean age of this cohort was 40 years old, 96 percent were male. The total study quality score was 68.5 percent. Thirty patients had hemophilia A, and 14 patients had hemophilia B. After a median of 19 years of infection, 16 percent had cirrhosis by ultrasound and only 4 percent of patients had symptomatic disease.

Characteristics and results of studies on long-term outcomes of untreated chronic hepatitis C in women who acquired HCV through contaminated anti-d-immunoglobulin Barrett[139] prospectively followed a cohort of Irish women infected with genotype 1 HCV during pregnancy as a result of contaminated anti-d-immunoglobulin. The study quality score was 56.2 percent. In 22 years of follow-up, there were no cases of HCC or cirrhosis. Ten women with hepatitis C did acquire mixed essential cryoglobulinemia.

Characteristics and results of miscellaneous other studies on long-term outcomes of untreated chronic hepatitis C Forns[141] followed a cohort of Spanish patients with chronic hepatitis C for more than 20 years. Patients were excluded if they had hepatitis B, cirrhosis, greater than 40 grams per day of alcohol intake, or autoimmune disease. This retrospective cohort study had a high total study quality score. Fifty-nine percent of patients were male, and the mean age was 43 years. Over this 20-year period, 39 percent of patients developed cirrhosis, 10.5 percent developed hepatic decompensation, and 7 percent developed HCC. The all-cause mortality rate was 22 percent, and the hepatitis C-specific mortality was 6 percent.

Punyagupta[140] assessed the long-term outcomes of Thai patients with hepatitis C. The study sample was 55 percent male and 9 percent had cirrhosis. The overall incidence of HCC in this population was 16 percent. Sixty percent of the patients with chronic hepatitis C were deceased at ten years, and 85 percent were deceased at 15 years.

Summary of Studies on Long-term Outcomes in Untreated Patients

The evidence on the natural history of chronic hepatitis C suggests that older age, cirrhosis, hepatitis B infection, HIV infection, alcohol use, male gender, and initial fibrosis all predict long-term outcomes in hepatitis C [Evidence Grade B]. This evidence is heterogeneous and does have methodologic limitations. Nevertheless, the studies are consistent in showing that these variables predict long-term outcomes.

The evidence of the effect of HCV genotype on the natural history of hepatitis C is based on two studies with relatively high study quality scores. The results of these studies are not consistent with each other. One study (with the highest quality score) suggested that HCV genotype 1 was associated with an increased risk of HCC and progressive liver disease, but the other study did not find a significant relationship between HCV genotype 1b and the risk of hepatocellular carcinoma or progressive liver disease [Evidence Grade I].

The evidence of the effect of hepatitis B infection on the natural history of hepatitis C is limited, but suggests that concurrent hepatitis B infection significantly increases the risk of HCC in patients with chronic hepatitis C [Evidence Grade C].

The evidence on the relation of serum ALT to long-term clinical outcomes in patients with untreated chronic hepatitis C is based on two studies, one of which is rather small. The two

studies agree that the risk of HCC is very low in patients with normal ALT levels [Evidence Grade B]. One of the studies also suggests that the risk of HCC increases significantly when the ALT is persistently elevated.

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

Incidence of HCC

Hepatocellular carcinoma is one of the most common cancers in the world. Incidence rates vary from continent to continent with the highest rates reported in Asia at 80 per 100,000.[142] Chronic hepatitis B and C have been linked as major factors increasing the risk of HCC. The incidence of HCC in patients with hepatitis B is as high as 0.46 percent per year[143-146] whereas the incidence in patients with hepatitis C may range between 0 percent and 1.6 percent per year.[103]

Several studies in our review of key question 2d demonstrated risk factors for HCC, including male gender, alcohol use, older age at which HCV was acquired, duration of infection, cirrhosis, alcohol abuse, and hepatitis B or HIV co-infection.

Screening for liver cancer is very controversial. There have been no randomized controlled trials of screening a cohort of hepatitis C patients for HCC. In addition, few studies have evaluated the cost, efficacy, and potential benefit.

Unlike hepatitis C, a number of screening and cohort studies have been reported for hepatitis B with varying results. For example, using AFP as a screening test, a study of 1,400 hepatitis B patients in Alaska detected 15 tumors, of which ten were resectable.[145] Another study prospectively screened 1,069 HBV carriers for 6 months to 6 years, and over this period detected 15 tumors, seven of which were resectable.[146]

Results of Literature Search on Outcome of Screening for HCC

Through the abstract review process we identified 40 articles that could have data on one of our key questions about screening for HCC in patients with chronic hepatitis C. After reviewing these 40 articles as well as all of the references for all articles pertaining to screening for HCC, we found one study that answered question 3a regarding outcomes with screening for HCC at entry into the study.[147]

Characteristics of the Study on Outcomes of Screening for HCC

Evidence Table 21 summarizes the aims and eligibility criteria of this study. The study population was remarkable for including patients with chronic liver disease, regardless of etiology, and included cirrhotics as well as noncirrhotics. The studied excluded patients with HCC at entry.

Quality of Study

As shown in Evidence Table 22, the overall quality score for this study was 70 percent with scores of 100 percent in representativeness and description. The low scores were 33 percent in statistics, 50 percent in bias and 65 percent in outcomes. This study did not report the source of funding or the type and degree of involvement of the funding agency.

Results of the Study on Outcomes of Screening for HCC

The one study[147] for question 3a was a prospective cohort analysis evaluating the efficacy of HCC screening in patients with cirrhosis or chronic hepatitis without cancer at one study center compared to patients with cirrhosis or chronic hepatitis followed in another hepatitis clinic.(Evidence Table 24) Three hundred sixty subjects with chronic liver disease were enrolled and received an ultrasound study of the liver as well as measurement of serum AFP and liver function parameters (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubins, coagulation studies, and albumin) every 6 months. This group was compared to a population of 2,170 patients with histologically documented cirrhosis or chronic hepatitis who did not undergo routine screening for HCC. These patients were followed outside the study protocol for various reasons. The etiology of underlying disease in the two groups was similar, as was the age and gender.

Outcomes analyzed were incidence of HCC and mean time to HCC. During the mean follow-up of 52 months, focal hepatic lesions that proved to be HCC were found in 24 (6.7 percent) of the patients in the screening group. Of the 24 cases, 18 (75 %) were unifocal and six were multifocal. All of the unifocal cases were less than 3 cm. At the time of diagnosis, serum AFP was normal (less than 20 ng/mL) in 11 patients, between 20 and 200 ng/mL in nine patients, and above 200 ng/mL in four patients. At these thresholds, sensitivities for detecting HCC were 46 percent, 38 percent, and 17 percent, respectively. In the control group, HCC was found in 129 (6 %) of the patients over the follow-up period. Only 20 (16 %) of these HCC's were unifocal and 16 percent had tumors that were less than 3 cm. Using serial ultrasonography and serum AFP on a population of patients at risk made it possible to detect small tumors in a high percentage of cases (75 percent versus 16 percent).[147] In this study serum AFP had poor sensitivity.

Summary

In this study of European patients with hepatitis C who were followed over time with ultrasound and AFP studies, HCC was detected earlier and was more often resectable when compared to patients who received standard care [Evidence Grade C].

Q3b *What are the sensitivity, specificity, and predictive values of tests that could be used to screen for HCC (especially resectable carcinoma)?*

Results of Literature Search on Performance Characteristics of Screening Tests for HCC

Through the abstract review process we identified 40 articles that could have data on one of our key questions about screening for HCC in patients with chronic hepatitis C. After reviewing these 40 articles, we found 23 studies provided information on the performance characteristics of screening tests.

Characteristics of Studies on Performance Characteristics of Screening Tests for HCC

Most of the studies were performed in cirrhotics, who are thought to be at highest risk of HCC. Evidence Table 25 summarizes the aims and eligibility criteria of this study. The studies are remarkable in that most were conducted in Europe or Asia with one study from Australia[148] and one from the United States.[149] Almost all studies excluded patients with other forms of liver disease such as hemachromatosis, autoimmune hepatitis, sclerosing cholangitis, and hepatitis delta infection. We evaluated studies of patients with hepatitis C infection only, as well as studies that included patients with hepatitis C or hepatitis B or both. We did not, however, include studies that evaluated screening methods only in patients with hepatitis B alone because the pathogenesis of hepatitis B and its association with HCC is believed to be different from that of hepatitis C.

Evidence Table 26 reveals the demographic and clinical characteristics of the study population. In all of the studies, the majority of participants were men, with the mean age ranging between 31 and 66 years. Most had advanced liver disease, the group thought to be at highest risk of HCC. Duration of infection, if reported, was generally over ten years. Genotypes were obtained routinely and varied according to the country in which the study was perfomed.

Quality of Studies on Performance Characteristics of Screening Tests for HCC

The quality of the study design varied widely for these studies and included cohort studies, case-control studies, and case-series. Table 27 shows the overall quality scores for articles pertaining to this question. The overall mean quality score for this group of studies was 63 percent. The median score for the studies was 65 percent with a range of 32 percent to 87 percent. The interquartile ranges were 57 percent and 70 percent. The mean scores for description and statistics were greater than 75 percent. A particular area of weakness of these

studies as a group was bias. Also, few studies reported both the funding source and the type and degree of involvement of the funding agency.

Results of Studies on Performance Characteristics of Screening Tests for HCC

Twenty-four studies met criteria for key question 3b (see Evidence Table 28). These studies were heterogeneous evaluating serologic, urinary, and radiologic studies. Numerous studies evaluated AFP. Two studies evaluated DCP and one study each evaluated Interleukin-2 receptor, tumor necrosis factor, interleukins 10 and 15, cytokeratin 19, MAGE-4, PIVKA-II, des gamma-carboxy prothrombin *les culinaris* AFP, and p53 antibody. One study evaluated urinary transforming growth factor beta. There were fewer studies evaluating radiologic tests than serologic tests, with six studies evaluating hepatic ultrasound and two studies evaluating computerized tomography or magnetic resonance imaging.

Screening with Alpha Fetoprotein in Patients with HCV Alone

As shown in Evidence Table 28, the studies evaluating use of serum AFP to detect HCC used different thresholds for sensitivity, specificity, and predictive values. Studies using AFP alone had variable sensitivities (Figure 2). The data on the following three studies are in patients with hepatitis C. One cohort study of 163 cirrhotics had a sensitivity of 27 percent with a threshold of 20 ng/mL and 4.5 percent with a threshold of 400 ng/mL.[117] By contrast, in another cohort study of Italian hemophiliacs with hepatitis C, the sensitivity of AFP was 100 percent for levels greater than 11 ng/mL and 17 percent if AFP was greater than 400 ng/mL.[150] A diagnostic test design study revealed decreasing sensitivities of 86 percent, 43 percent, and 14 percent as the AFP threshold increased from 20 to 100 to 400 ng/mL in German patients with hepatitis C.[151]

Screening with Alpha Fetoprotein in Patients with HCV or HBV

Seven cohort studies of patients with hepatitis B or C or both revealed varying sensitivities at different AFP thresholds and in different study populations.[106,148,149,153,154,158,163] Figure 2 displays different AFP thresholds versus sensitivity, and Figure 3 shows different AFP thresholds versus specificity. As expected, the sensitivity decreased as the threshold for AFP increased.

A cohort study using a threshold value for AFP of 81 ng/mL reported a sensitivity of 17 percent,[148] compared to sensitivities of 75 percent and 80 percent for a threshold of 10 ng/mL in two other cohort studies.[153,163] In another cohort study, which evaluated different thresholds of AFP, the highest accuracy was with an AFP threshold of 24 ng/mL, resulting in a sensitivity of 41 percent and specificity of 95 percent.[149] A final cohort study by Cottone[106] revealed a sensitivity of 36 percent for an AFP threshold of 50 ng/mL which decreased to zero percent as the AFP threshold increased to 400 ng/mL.

A prospective cohort study by Ishii and colleagues, which compared AFP and protein-induced vitamin K absence (PIVKA-II), demonstrated sensitivities of 61 percent for AFP greater than 20 ng/mL, 45 percent for AFP greater than 40 ng/mL, 41 percent for PIVKA-II greater than 60 mAU/ ml, and 66 percent for AFP greater than 40 ng/mL and PIVKA-II greater than 80

mAU/mL.[154] Specificities for these same cutoffs were 78 percent for AFP greater than 20 ng/mL, 91 percent for PIVKA greater than 60 mAu/mL and 85 percent for a combination of AFP greater then 40 ng/mL and PIVKA-II greater than 80 mAU/mL.[154]

A retrospective cohort study by Trevisani and colleagues determining the prevalence of etiologic factors and clinical manifestations of HCC in patients with and without cirrhosis demonstrated differing sensitivities for AFP levels as determined by the tumor presentation. Sensitivity for solitary and massive HCCs was approximately 50 percent for an AFP threshold of 20 ng/mL, but sensitivity increased to 70 percent for diffuse and multinodular HCC with the same AFP threshold. Increasing the threshold to 400 ng/mL resulted in sensitivities of 14 percent, 38 percent, 38 percent, and 27 percent, respectively, for the different HCC stages.[158]

Three case-control studies evaluated AFP and other serologic and urinary markers for detecting HCC,[152,161 155] and another evaluated the frequency of increased AFP level among Chinese patients with HCC.[159] Sassa et al.[155] showed greater sensitivity for detection of HCC less than 2 cm when using simultaneous measurement of high sensitivity des gamma carboxy prothrombin at greater than 40 mAU/mL and *lens culinaris* agglutinin A-reactive AFP of greater than 10 percent when using AFP alone with a threshold of 200 ng/mL, (54 percent versus 8 percent).[155] Using this combination of tests resulted in a specificity of 98 percent versus100 percent in those with AFP alone. A case control study by Tsai demonstrated increasing sensitivity of AFP from 64 to 77 percent as the threshold decreased from 400 ng/mL to 20 ng/mL.[161]

Another case-control study revealed that urinary transforming growth factor beta-1 levels increased in patients with cirrhosis and HCC compared to those with cirrhosis alone or healthy controls.[152] In addition, the sensitivity of AFP for detecting HCC increased from 48 percent to 55 percent as the threshold for AFP decreased from 400 ng/mL to 100 ng/mL. When urinary TGF-beta 1 was used in combination with AFP, the sensitivity for detecting HCC was 84 percent if the AFP threshold was 100 ng/mL and 80 percent if the AFP threshold was 400 ng/mL.

In the study of Chinese patients with hepatitis B or C, the sensitivity of AFP increased from 54 to 74 percent as the threshold of AFP decreased from 400 ng/mL to 20 ng/mL. The specificity for AFP greater than 20 ng/mL was 100 percent.[159]

In a cross sectional study by Cedrone, different levels of AFP were compared for diagnostic accuracy in detecting HCC in patients with cirrhosis and in all patients.[157] As the AFP threshold value decreased from 200 ng/mL to 10 ng/mL, the sensitivity for detecting HCC increased from 20 to 76 percent in patients with cirrhosis and all patients, while the specificity decreased from 99 to 60 percent in cirrhotics and from 99 to 78 percent in all patients. The threshold yielding the greatest overall accuracy was 83 percent for a threshold of 50 ng/mL in all patients and an accuracy of 71 percent for an AFP threshold of 13 ng/mL in cirrhotics. Positive predictive values varied from 48 to 88 percent in all patients and 65 to 94 percent in cirrhotics at the same thresholds.[157]

A case series of patients with HCC evaluated different thresholds for AFP and found sensitivities of 62, 55, and 43 percent for thresholds of greater than 20 ng/mL, greater than 50 ng/mL, and greater than 400 ng/mL.[156] Interestingly, AFP appeared to be a more sensitive marker of HCC in patients with hepatitis C than in those with other liver conditions.[156]

Other Serologic Markers

Des gamma carboxy prothrombin (DCP) and lens culinaris agglutinin A-reactive AFP In a case-control study of patients with chronic hepatitis, cirrhosis, or HCC, Sassa et al,[155] showed greater sensitivity for detection of HCC less than 2 cm when using simultaneous measurement of high sensitivity DCP at greater than 40 mAU/mL and *lens culinaris* agglutinin A-reactive AFP of greater than 10 percent than when using AFP alone at a threshold of 200 ng/mL (54 percent versus 8 percent).[155] Using high sensitivity DCP at greater than 40 mAU/mL and *lens culinaris* agglutinin A-reactive AFP of greater than 10 percent together resulted in a specificity of 98 versus 100 percent in those with AFP alone.[155] Another study by Nomura of patients with chronic hepatitis C revealed different sensitivities for DCP using conventional DCP (17 percent), overnight DCP (29 percent), and avidin biotin complex DCP (33 percent).[162]

Interleukin-2 receptor In a cohort study of those with hepatitis B or C or both, a soluble interleukin-2 (IL-2) receptor level greater than 850 U/mL was significantly more sensitive than an AFP level greater than 10 ng/mL (sensitivity 99 percent versus 80 percent).[163] The specificity of soluble IL-2 receptor level and AFP at these thresholds were both 95 percent.

Tumor necrosing factor (TNF) alpha receptor, interleukin-10 (IL-10), and interleukin-15 (IL-15) As shown in Evidence Table 28, a prospective cohort study by Kakumu evaluating the use of TNF-alpha receptor and interleukins 10 and 15 to detect HCC found that IL-10 was significantly higher in HCC patients than in asymptomatic carriers and patients with chronic hepatitis. TNF-alpha receptor also was significantly elevated in HCC cases compared with patients with chronic hepatitis.[164] The sensitivity of IL-10 greater than 5 pg/mL was 63 percent, sensitivity of IL-15 greater than 70 pg/mL was 45 percent, and sensitivity of TNF-alpha receptor could not be calculated.as the data was not presented in an abstractable format.[164]

Cytokeratin 19 (CK-19) In a case-control study in Japan, cytokeratin 19 (CK-19) fragments in the serum of patients with HCC were significantly elevated compared with patients with chronic hepatitis C and those with liver cirrhosis.[165] CK-19 was elevated in 12.3 percent of HCC patients with normal AFP. The sensitivity of CK-19 fragment levels greater than 2.6 ng/mL for the detection of HCC was 47 percent with a specificity of 95 percent.[165]

MAGE-4 A cross sectional analysis by Tsuzurahra and colleagues study that evaluated use of serum MAGE-4 to detect HCC in patients with hepatitis C reported a sensitivity of 47 percent and specificity of 95 percent for a threshold of 1.04 ng/mL[166] and a sensitivity of 45 percent for a threshold of 2.5 ng/mL.

PIVKA-II Another prospective cohort study by Ishii and colleague in patients with hepatitis B or C or both that compared AFP and PIVKA-II found a sensitivity of 61 percent for AFP greater than 20 ng/mL, 45 percent for AFP greater than 40 ng/mL, 41 percent for PIVKA-II greater than 60 mAU/mL, and 66 percent for AFP greater than 40 ng/mL and PIVKA-II greater than 80 mAU/mL.[154] Specificities for these same cutoffs were 78 percent for AFP greater than 20 ng/mL, 91 percent for PIVKA greater than 60 mAU/mL, and 85 percent for a combination of AFP greater then 40 ng/mL and PIVKA-II greater than 80 mAU/mL.[154]

P53 autoantibodies In a cross-sectional study by Raedle and colleague of patients with hepatitis C, positive p53 autoantibodies had a sensitivity of 43 percent and a specificity of 100 percent.[151] Combination of p53 antibody with AFP greater than 100 ng/mL resulted in a sensitivity of 71 percent and specificity of 99 percent. Decreasing the threshold of AFP to 20

ng/mL with positive p53 antibodies increased sensitivity to 86 percent with a specificity of 86 percent.[151]

Circulating immune complexes In a case control study by Tsai and colleagues,[161] evaluating 3 percent pegcirculating immune complexes (CIC), they reported a sensitivity of 65 percent and a specificity of 100 percent in cirrhotics with hepatitis B or C. When combined with AFP at a threshold of 120 ng/mL, the sensitivity increased to 84 percent and the specificity remained 100 percent. When the AFP threshold was increased to 400 ng/mL, the sensitivity remained relatively unchanged at 83 percent, and the specificity remained 100 percent.

Urinary Transforming Growth Factor (TGF)-Beta 1

In a case-control study in Taiwan, the sensitivity of urinary TGF-beta 1 for detecting HCC was 53 percent using a threshold of greater than 50 micrograms per gram of creatinine. When urinary TGF-beta 1 was used in combination with AFP, the sensitivity for detecting HCC was 84 percent if the AFP threshold was 100 ng/mL and 80 percent if the AFP threshold was 400 ng/mL.[152]

Ultrasound

A study evaluating use of computerized tomography (CT) or ultrasonography[167] to detect HCC provided limited data on the utility of screening tests as the study was designed primarily to evaluate the incidence of HCC in patients with hepatitis C.[167] However, the study data indicated a specificity of 96 percent for the combination of the tests.

Studies of ultrasonography with patients having hepatitis B or C or both revealed heterogeneous results. An Australian study by Larcos et al[148] evaluated the utility of sonographic screening for HCC by reviewing 647 ultrasounds in patients with chronic hepatitis or cirrhosis. According to the study, liver masses were detected by sonography in 25 patients (11 percent); however, only six ultimately had HCC. In an Italian study by Izzo et al.[153], evaluating the outcomes of patients with chronic hepatitis screened for HCC with ultrasound, the sensitivity of ultrasonography was 87 percent at detecting tumors at baseline or in follow-up. A prospective cohort study of cirrhotic patients with HCV or HBV revealed a sensitivity of 49 percent for ultrasound.[168] Two other cohort studies evaluating ultrasonography of the liver demonstrated varying sensitivities of 66 percent[163] and 100 percent with 98 percent specificity.[149]

Finally, a study of 154 consecutive patients with HCC in Belgium demonstrated that ultrasonography had a sensitivity of 51 percent.[156] In this study, the most common cause for error on interpretation of ultrasound was between regenerative nodules and HCC.[156]

Computerized Tomography and Magnetic Resonance Imaging

The study evaluating use of CT or ultrasonography[167] in patients with hepatitis C to detect HCC provided limited data on the utility of screening tests as the study was designed primarily to evaluate the incidence of HCC in patients with hepatitis C. However, the study data indicated a specificity of 96 percent for the combination of the tests. A study by Colombo reported a sensitivity of 93 percent for the combination of ultrasound and CT in cirrhosis patients.[168] Another study in patients with either hepatitis B or C or both reported a sensitivity of 100 percent for computerized tomography or magnetic resonance imaging of the liver.[163]

AFP and Ultrasound

Several studies compared the sensitivities of ultrasound and AFP,[149,156,163,169] but did not use the tests in combination. One study, however, evaluated the sensitivity of AFP greater than 10 ng/mL with ultrasound and demonstrated a sensitivity of 100 percent. There was an increase in sensitivity compared to either test alone: AFP greater than 10 ng/mL, (75 percent) and ultrasound, (87 percent).[153]

Summary of Studies on Performance Characteristics of Screening Tests for HCC

The evidence on the value of AFP in screening for HCC in patients with hepatitis C was based on a moderate number of very heterogeneous studies that have important methodologic limitations. These studies were relatively consistent in demonstrating that the sensitivity of AFP for detecting HCC in patients with hepatitis C increases from about 10 percent to 100 percent as the threshold value decreases from 400 ng/mL to 10 ng/mL, with the corresponding specificity decreasing from about 100 percent to 90 percent [Evidence Grade B].

The evidence on the value of IL-2 receptor, TNF, Interleukins 10 and 15, CK-19, MAGE-4, PIVKA, DCP, *lens culinaris agglitutinin A-reactive AFP* and p53 autoantibody in screening for HCC in patients with hepatitis C were based on one or two studies each, and had important methodologic limitations [Evidence Grade I]. These studies demonstrated that of all the tests, the sensitivity of IL-2 receptor for detecting HCC in patients with hepatitis C was the best at 99 percent; however, future research on other possible tests and combinations with AFP may be useful in determining the ideal screening regimen for HCC.

The evidence on the value of urinary transforming growth factor beta in screening for HCC in patients with hepatitis C was based on one study that had important methodologic limitations. This study indicated that the sensitivity of urinary transforming growth factor beta for detecting HCC in patients with hepatitis C was 84 percent [Evidence Grade I].

The evidence on the value of ultrasound in screening for HCC in patients with hepatitis C was based on a moderate number of very heterogeneous studies that had methodologic limitations. These studies demonstrated the inconsistency of ultrasound for detecting HCC in patients with hepatitis C, as sensitivity varied from about 24 percent to 100 percent depending on the study design and study population, with a generally high specificity of 96 percent [Evidence Grade C].

The evidence on the value of CT or magnetic resonance imaging in screening for HCC in patients with hepatitis B or C was based on two studies that had methodologic limitations. These studies were relatively consistent in demonstrating a high sensitivity and specificity of CT or magnetic resonance imaging for detecting HCC in patients with hepatitis C [Evidence Grade C].

The evidence on the value of AFP and ultrasound in screening for HCC was based on one study that had limitations. This study demonstrated an increase in sensitivity from 87 percent to 100 percent when the tests were used in combination for detecting HCC in patients with hepatitis B or C [Evidence Grade C].