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Antiviral Treatment for Chronic Hepatitis C

Description of Treatment

Hepatitis C is an infection of the liver caused by the hepatitis C virus (HCV). Acute infection from HCV is usually asymptomatic and evolves into chronic HCV infection in up to 85% of cases. In the United States about 4 million people (1.8%) are infected with HCV. Data suggest that there are about 10,000 to 12,000 deaths annually in the United States due to HCV or its sequelae. HCV transmission is mainly through exposure to infected blood. In the United States, transmission of HCV occurs primarily through injection drug use, resulting in 60% of new cases. Less common modes of transmission include needle-stick accidents, sexual contact, mother-to-infant transmission (either in utero or by breast feeding) and blood transfusions prior to 1990. Many cases of chronic hepatitis C are asymptomatic, and symptoms may not occur until the disease is advanced (up to 20 or more years since primary infection). Hepatitis C may eventually result in severe fibrosis and cirrhosis, ultimately with decompensation or liver failure. The purpose of treatment is to stop the progression of the disease and avoid cirrhosis and possible progression to hepatocellular carcinoma. The major antiviral drugs used for treatment include combination therapy with peginterferon-alfa2a/2b (PEG-IFN) and ribavirin, with treatment courses varying with the genotype of the virus. Genotypes 1, 2, 3 are the most common genotypes in the United States, with genotype 1 predominating.

A sustained virologic response (SVR) is the primary endpoint in many studies, and pertains to undetectable HCV levels 24 to 26 weeks after treatment completion. Patients achieving an SVR are generally considered at low risk for disease progression.

Committee Conclusions

With regard to antiviral therapy for chronic hepatitis C, the ICSI Technology Assessment Committee finds that:

1. PEG-IFN and the combination of PEG-IFN and ribavirin are relatively safe when closely monitored by an experienced center. Serious side effects that may lead to discontinuation of treatment occur in 10% to 15% of patients and include neuropsychiatric effects (especially depression), influenza-like symptoms, and hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia.

2. HCV treatment with PEG-IFN plus ribavirin is presently the most efficacious treatment available for chronic HCV. (Conclusion Grade I)

3. For optimal treatment of HCV in genotype 1 patients, standard weekly dose PEG-IFN along with 1000 – 1200 mg/day ribavirin (depending on weight) given for a 48-week period leads to SVR in about 40% to 50% of patients.

4. For optimal treatment of HCV in genotypes 2 and 3, standard weekly dose PEG-IFN along with 800 mg/day ribavirin for 24 weeks is adequate for 73% to 78% conversion to SVR status. Longer courses of treatment have not further improved outcomes in this subgroup.

5. Long-term follow-up of HCV cases with an SVR shows regression of fibrosis, a significantly decreased rate of cirrhosis development, and lower HCC rates. However, the precise amount of risk reduction is unknown. (Conclusion Grade II)

6. Treatment non-responders (those who underwent previous treatment and did not achieve an SVR) show a low response rate on retreatment (15% to 20% SVR rate). Optimal selection criteria for treating non-responders are not known.

7. Predictors for a lower (worse) SVR rate include HCV genotype of 1, the presence of severe fibrosis or cirrhosis, advanced age, heavy alcohol use, obesity, and high viral load.

Please see full report for potential uses, contraindications, efficacy, safety, alternatives, and comparative costs.

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Technology Assessment Report:
Antiviral Therapy for Chronic Hepatitis C

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ICSI Technology Assessment Report Process:
• A topic is selected by the Technology Assessment Committee (TAC) based on its relevance to the ICSI Health Care Guidelines and/or interest in the topic by ICSI member or sponsor organizations.
• A work group of 4 to 6 physicians and other health care professionals is identified. The work group includes a leader who does not perform the procedure/treatment/test that is the focus of the report, a critical reading expert, content expert(s), and, preferably, a primary care physician. Prospective work group members are asked to disclose any potential conflicts of interest relevant to the topic of the report; disclosures are reviewed for unacceptable conflicts.
• The literature search is completed using MEDLINE; in addition, bibliographies of articles obtained from the literature search are examined to identify articles that may have been missed and work group members are asked to provide key references.
• The ICSI staff person gets direction on the scope of the report from the work group and prepares a draft report based on the available literature. The evidence is graded according to the system described in the References section of the report.
• The work group meets to review the draft report and direct the ICSI staff person in revising the report.
• After approval of the draft report by the work group, the work group leader presents the report to the TAC. Committee members review the report and provide feedback to the work group. The draft report is concurrently distributed to ICSI member organizations and content experts nationwide for their review.
• All comments received are shared with the work group leader and revisions to the report are made, if necessary.
• With work group approval of the revisions, the TAC makes the final decision regarding approval of the report for distribution. Reports are approved or not approved based on whether a) the conclusions are supported by the evidence, and b) whether the reviewers’ comments were reasonably addressed. Newly approved reports are posted at www.icsi.org.
• Reports are reviewed and revised, if warranted.

*See Potential Conflict of Interest Disclosure at the end of the report
Introduction

Epidemiology of Hepatitis C

Hepatitis C is an infection of the liver caused by the hepatitis C virus (HCV). Acute infection from HCV is usually asymptomatic and evolves into chronic HCV infection in up to 85% of cases (Heathcote and Main, 2005; Somsouk et al., 2003; Teo and Hayes, 2004). Chronic hepatitis C is defined as persistence of the virus for at least 6 months. In the United States about 4 million people (1.8%) are infected with HCV, which was formerly classified as “non-A, non-B hepatitis”, although the incidence of new infections is decreasing (Dove, 2004; NIH Consensus Statement, 2002). In addition, hepatitis C is the most common cause of cirrhosis and hepatocellular carcinoma as well as the most common reason for liver transplant (Davis et al., 1994; NIH Consensus Statement, 2002). Data suggest that there are about 10,000 to 12,000 deaths annually in the United States due to HCV and/or its sequelae (NIH Consensus Statement, 2002).

Once chronic infection develops, the virus is rarely cleared spontaneously (Somsouk et al., 2003; Heathcote and Main, 2005). HCV transmission is mainly through exposure to infected blood. In the United States, transmission of HCV occurs primarily through injection drug use, resulting in 60% of new cases (Dove, 2004). Less common modes of transmission include needle-stick accidents, sexual contact, mother-to-infant transmission (either in utero or by breast feeding) and blood transfusions prior to 1990 (Dove, 2004). Since 1990, HCV from transplanted organs or through blood transfusions is rarely transmitted due to the development of a sensitive blood product screening test for antibodies to HCV.

HCV is characterized by a high degree of genetic heterogeneity which may explain the variation observed in clinical course, the difficulty in developing a vaccine, and the variable response to therapy. There are 6 HCV genotypes and over 50 subtypes. Genotype 1 is the most common in the United States, followed by 2 and 3 (NIH Consensus Statement, 2002). Chronic hepatitis C is characterized by persistent but sometimes intermittent viremia, intermittently or persistently abnormal serum alanine aminotransferase (ALT) concentrations, and the presence of anti-HCV antibodies. Although common symptoms of chronic HCV infection are nonspecific and include fatigue, arthralgia, myalgia, pruritus, and depression (Teo and Hayes, 2004), symptoms often do not appear until the development of advanced liver disease (up to two decades after infection) (Koff, 1997). Inflammation and necrosis may lead to fibrosis which can progress to cirrhosis. Based on retrospective and prospective-retrospective studies, it is estimated that 15% to 20% of infected patients will develop cirrhosis after 20 years of persistent HCV infection. After the development of cirrhosis, hepatocellular carcinoma (HCC) may occur at a rate of 1% to 4% per year as HCC rarely occurs without the presence of cirrhosis or advanced fibrosis in these patients (NIH Consensus Statement, 2002). Much remains unknown about the natural history of the disease including reasons for the highly variable rate of progression, especially after 20 years of infection. Factors associated with more rapid disease progression to cirrhosis include male gender, age > 40 years at primary infection, high alcohol intake, and coinfection with HIV and/or hepatitis B virus. (Teo and Hayes, 2004). Immunocompetence of the infected person, degree of hepatic inflammation, stage of hepatic fibrosis, and other viral factors (Tillman & Manns, 1996; Koff, 1997) may also play a role in the speed of progression to cirrhosis.

Description of Treatment

Testing

There are several different tests that are used to diagnose and monitor patients with hepatitis C. Third generation enzyme-linked immunosorbsent assay (ELISA or EIA) techniques are used to detect the presence of anti-HCV antibodies. Once seroconversion occurs (7 to 8 weeks after primary infection), these tests have a sensitivity and specificity of 99% and thus are accurate methods for diagnosing infection (Teo and Hayes, 2004), although the test can remain positive for some time after an infection is cleared.

A test to further confirm active infection is the direct testing of HCV RNA with polymerase chain reaction (PCR) assays. These tests are quite sensitive and can detect a viral load as low as 50 IU/ml (100 viral
particles/ml) in the qualitative HCV RNA test. HCV RNA tests can detect HCV infection as early as 1 to 2 weeks after primary infection. Patients with a positive HCV antibody test and 2 subsequent negative HCV RNA tests can be reassured that the previous infection has been cleared (Teo and Hayes, 2004). Quantitative HCV RNA can be used to determine viral loads, which may provide prognostic information. Loss of HCV RNA as a result of treatment has been found to be a strong predictor of sustained beneficial response (NIH Consensus Statement, 2002). However, virological investigation of HCV has been difficult due to the low number of circulating viral particles in most patients and the heterogeneity of the HCV genome (Esteban, 1996). Although not diagnostic of HCV in itself, liver biopsy is the “gold standard” for evaluating histological stage or response to treatment, although liver biopsies are invasive procedures and do have significant risks (NIH Consensus Statement, 2002). Uncomplicated patients with the relatively treatment-responsive HCV genotypes 2 or 3 in general can start treatment without a liver biopsy. Patients with the more treatment-resistant genotype 1 (or less commonly genotype 4, which is also considered relatively treatment-resistant) will need staging through ultrasound and liver biopsy (McGinn et al., 2005).

Treatment

As an antiviral treatment for chronic hepatitis C, interferon alpha-2b (IFN-a2b) was FDA approved in 1993. It is typically administered by subcutaneous injection three times per week for 6 months or longer. Recombinant IFN-a2b is thought to act by direct inhibition of replication of the hepatocytopathic HCV (Davis et al., 1994). Several other forms of interferon have also been tested including leukocyte derived IFN, lymphoblastoid IFN, consensus IFN (FDA approved in 1997), and IFN-beta (IFN-ß) (Villa et al., 1996). A combination of a variety of interferons has been proposed (Davis et al., 1994). Different doses and durations of treatment have also been evaluated. In 1998, the FDA approved a combination of ribavirin and IFN for patients with chronic hepatitis C who have relapsed following IFN therapy. Ribavirin is an antiviral agent that is also used for treatment of infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus. In 2002, the FDA approved the combination of Pegysys® (peginterferon alfa-2a) plus Copegus® (ribavirin) for use in hepatitis C treatment. The statement reads “Peginterferon alfa-2a alone or in combination with Copegus®, is indicated for the treatment of adults with chronic hepatitis C virus infection who have compensated liver disease and have not been previously treated with interferon alpha”. This report focuses on the safety and efficacy of these two treatments (peginterferon and ribavirin). Peginterferon alfa-2b was FDA approved in 2001 and has similar labeling.

Endpoints of Treatment

A course of treatment usually lasts from 24 weeks to 48 weeks depending on a number of factors (discussed elsewhere in the document). Normalization of serum ALT levels with treatment is referred to as a biochemical response (BR). Clearance of circulating HCV RNA levels is referred to as a virological response. Biochemical and virological responses can be assessed at the end of treatment (End-of-Treatment Response or ETR, also known as a “complete response” or CR). Some studies have evaluated the prognostic value of an early virologic response (EVR), referring to a 2-log (100 times) or greater decrease in HCV RNA from baseline at 12 weeks of treatment. Viral RNA is also measured at the end of post-treatment follow-up (usually 24 to 26 weeks after cessation of treatment). If viral RNA is still undetectable, the patient is known to have a sustained virologic response (SVR), which is correlated with a better outcome than those who do not achieve SVR. Non-responders fail to show a normalization of ALT levels or clearance of HCV RNA. Relapsers are those that had an initial response to treatment but subsequently had a return to HCV RNA positive status.

Patient Monitoring and Follow-up

The standard workup for hepatitis C prior to treatment consists of 2 or 3 office visits, multiple blood tests (liver enzymes, confirmation of chronic hepatitis C infection, viral RNA load, viral genotype, and other tests), ultrasound, and liver biopsy especially for HCV genotype 1. Consults with other providers such as mental health and substance abuse may also be required. EKGs and ophthalmic exams are often given pre-treatment to rule out cardiac or eye disorders that may be exacerbated by treatment. The interferons are injected subcutaneously and thus the patient may need training for proper self-injection. Furthermore, a collaborative relationship between primary care providers and hepatologists is critical.
although usually treatment can be received in the primary care setting (McGinn et al., 2005). Adherence to therapy is critical where possible. Patients receiving at least 80% of the recommended doses of both drugs for at least 80% of the expected time course of treatment have the best response rates.

Treatment is on an outpatient basis and includes visits at least every 4 weeks depending on patient preference and adverse events/side effects. Complete blood counts and liver function tests may be performed at these visits. Blood counts are considered in making dosage adjustments, especially with ribavirin. Side effects are ascertained and treated. A quantitative HCV RNA level (viral load) is checked at week 12 of treatment for genotype 1 to monitor progress. Qualitative viral load is checked at the end of treatment and 6 months later to test for sustained virologic response (SVR) (Teo and Hayes, 2004).

Significant comorbidities exist that may increase the risk associated with hepatitis C therapy, such as depression, anemia, substance abuse, and/or diabetes. If these comorbidities are severe enough to preclude treatment, patients should still be followed by a primary care provider, subspecialists, and other providers (e.g., mental health professionals) based on presenting comorbid conditions until specific parameters are met and the patient becomes eligible for hepatitis C therapy (McGinn et al., 2005).

**Literature search strategy**

PubMed was searched using the term *Hepatitis C* in combination with *(treatment or antiviral)*. Randomized controlled trials, meta-analyses, and systematic reviews were explicitly searched for in PubMed. Review articles were also captured for background information and additional references as necessary. Trials with less than 80 subjects were excluded from the analysis.

**Described Uses**

Treatment is recommended for patients with chronic hepatitis C who are at greatest risk for progression to cirrhosis (NIH Consensus Statement, 2002). However, to date, there are no predictors of disease progression that allow definite identification of patients most suitable for, or most likely to benefit from, antiviral therapy. Liver biopsy results provide the best prediction of disease progression. Treatment may be considered for patients with persistently (at least 6 months) elevated serum ALT concentrations, positive HCV RNA, evidence of hepatitis on liver biopsy, and presence of anti-HCV antibodies. Other factors that may affect the decision for treatment include the HCV genotype, the presence or absence of cirrhosis, and the level of viremia (Terrault & Wright, 1995; Esteban, 1996). The need for a liver biopsy prior to treatment has been questioned, especially for genotypes 2 and 3 (McGinn et al., 2005). Esteban (1996) concluded that, in the absence of contraindications to biopsy (e.g., hemophilia or chronic renal failure), a biopsy was necessary because there is no correlation between the degree of histologic lesion and virological data. In addition, the biopsy would enable other disorders to be excluded.

Given the general asymptomatic nature of hepatitis C in its early and intermediate stages, screening for HCV may be indicated for certain populations so that treatment can be initiated. Examples of candidates include patients receiving blood products prior to 1992, patients with a history of injection drug use, patients on chronic dialysis, patients with HIV disease, immigrants from areas with a high prevalence of hepatitis C, and any patient with liver disease found on laboratory analysis and/or patient symptomatology (Dove, 2004).

There is debate over whether to treat patients with mild disease given the slowly progressive nature of hepatitis C. Those who support use of antiviral therapy for early treatment note the higher complete and sustained response rates compared to patients with advanced disease. Those against early treatment argue that those with mild disease generally have minimal symptoms, the disease progresses slowly, not all patients will respond, the treatment may result in some side effects, relapse is likely, and the treatment is expensive (Bennett et al., 1996).
Efficacy of Treatment

**PEG-IFN Treatment for Previously Untreated Patients**

Interferon has a short half-life that can lead to fluctuations in plasma concentrations of interferon during treatment periods. PEG-IFN has shown sustained absorption, slower rate of clearance, and a longer half life than IFN (Zeuzem et al., 2000).

In a randomized controlled trial (RCT) of patients with chronic hepatitis C who had not previously taken interferon, one group of 267 patients were given 180 ug of peginterferon alfa-2a once per week for 48 weeks and another group of 264 patients were given interferon 3 times per week (6 MU for 12 weeks then 3 MU for 36 weeks). In the PEG-IFN group 84% (223 of 267) completed follow-up compared to 61% (161 of 264) completing treatment and 58% (154 of 264) completing follow-up in the IFN group. Reasons for patient withdrawal included insufficient therapeutic response (13 PEG-IFN and 53 IFN patients), refusal of treatment (5 and 13), failure to return for treatment (4 and 8), laboratory abnormalities or adverse events (19 and 27), and other factors (3 and 2). Patients who missed exams at the end of treatment or follow-up were included in the analysis as not having a response to treatment at that point (intention-to-treat analysis). The rate of virological response was significantly higher in the PEG-IFN group at 48 weeks (end-of-treatment-response [ETR] 69% vs 28%, p=0.001) and 72 weeks (SVR 39% vs 19%, p=0.001) as compared to the IFN group. The number of patients discontinuing medication due to adverse events was similar in both groups (7% vs 10%, respectively) as were the frequency and severity of adverse events (Zeuzem et al., 2000).

A dose finding RCT by Reddy et al. (2001) compared PEG-IFN doses with IFN. Patients with untreated chronic hepatitis C (CHC) were randomized to five groups receiving 45 ug (20 patients), 90 ug (20 patients), 180 ug (45 patients), or 270 ug (41 patients) of PEG-IFN alfa 2a once per week or 3 MU of IFN (33 patients) 3 times per week for 48 weeks. ETR virological response rates were 30% (45 ug; p=NS), 45% (90ug; p=0.01), 60% (180ug; p=0.0002), and 56% (270ug; p=0.00009) compared to 12% in the IFN group at 48 weeks. SVR rates were 10% (45 ug; p=NS), 30% (90 ug; p=0.009), 36% (180 ug; p=0.0006), and 29% (270 ug; p=0.004) compared to 3% in the IFN group at 72 weeks. Patients with HCV genotype 1 had lower proportions of SVRs as compared to HCV genotype non-1 in each of the PEG-IFN groups. Severe adverse events were similar among all groups (7%, 2%, 10%, 7%, PEG-IFN groups, respectively, and 10% for the IFN group).

Another dose finding study by Lindsay, et al. (2001) compared IFN alfa-2b (303 randomized patients) to three different doses of PEG-IFN alpha-2b: 0.5ug/kg (315 randomized patients), 1.0 ug/kg (297 patients) and 1.5 ug/kg (297 patients) given once per week for 48 weeks in patients with previously untreated CHC. All 3 PEG-IFN doses showed significantly higher rates of virological response at end-of treatment (ETR 33%, 41%, and 49%) and end of follow-up (SVR 18%, 25%, and 23%) as compared to IFN (ETR 24% and SVR 12%; p<0.042 for all). Many of the patients in the 1.5 ug/kg PEG-IFN group who relapsed were HCV genotype 1. The rates of discontinuation of treatment were 9 - 11% in the PEG-IFN groups as compared to 6% in the IFN group.

In a RCT of patients with HCV-related cirrhosis or bridging fibrosis, one group of 87 (79% cirrhotic) patients were given 180 ug of PEG-IFN alfa-2a once per week for 48 weeks (peg180 group), another group of 96 (79% cirrhotic) patients were given 90 ug of PEG-IFN alfa-2a once per week for 48 weeks (peg90 group), and a third group of 88 (76% cirrhotic) patients were given 3 MU interferon 3 times per week for 48 weeks (IFN group). Treatment was completed by 67 (77%), 78 (81%), and 64 (73%) patients in each group, respectively. Reasons for withdrawal were adverse events, failure to return for treatment, insufficient therapeutic effects, or laboratory abnormalities. The rates of virological responses (number of patients with undetectable HCV RNA levels) were 44%, 42%, and 14% at 48 weeks and 30%, 15%, and 8% at 72 weeks in the peg180, peg90, and IFN groups, respectively (p=0.001 for peg180 vs interferon at 48 [ETR] and 72 weeks [SVR]). The rates of histological responses in a subgroup of 184 patients with paired liver biopsy specimens were 54%, 44%, and 31% at 72 weeks (p=0.02 for peg180 vs interferon). Among patients with HCV genotype 1, sustained virologic responses were 13%, 5%, and 2%, and peg180 had a higher sustained response among genotype 1b than genotype 1a (20% vs 9%). Tolerance of all treatments was similar (Heathcote et al., 2000).
PEG-IFN Plus Ribavirin Treatment for Previously Untreated Patients

An RCT compared the efficacy of PEG-IFN plus ribavirin to IFN and ribavirin in 1530 patients with chronic hepatitis C. Patients were randomized to receive one of three treatments for 48 weeks: IFN alfa-2b (3 MU 3 times /week) plus ribavirin (1000-1200 mg/day orally), PEG-IFN alfa-2b (1.5 ug/kg each week) plus ribavirin (800 mg/day), or PEG-IFN alfa-2b (1.5 ug/kg each week for 4 weeks then 0.5 ug/kg each week) plus ribavirin (1000-1200 mg/day). At 24-weeks follow-up, the virological sustained response rate was significantly higher in the higher dose PEG-IFN group (54%, 274 of 511 patients) as compared to the low-dose PEG-IFN (47%, 244 of 514) and the IFN groups (47%, 235 of 505; |p = 0.01 for both comparisons|). Among HCV genotype 1 patients, the virological sustained response rates were 42% (145 of 348 patients), 34% (118 of 349), and 33% (114 of 343), respectively. Virological sustained response rates for genotypes 2 and 3 were 80% for all three treatment groups. Secondary analysis showed that important predictors of higher SVR rates on multivariate analysis included HCV genotype (other than 1), baseline viral load (lower), body weight (lighter), and age (younger). The absence of bridging fibrosis/cirrhosis showed a significant association (p=0.001) with higher SVR rates, although the absence of cirrhosis alone was not significantly correlated (p = 0.07) which may be due to the low number of cirrhotics in the sample overall. Sex was no longer a significant predictor of SVR when weight was taken into account. Side effects were similar in all groups (Manns, et al., 2001).

In a large multicenter randomized controlled trial (Fried et al., 2002), 1121 hepatitis C patients were randomized to three groups consisting of peginterferon alfa-2a (PEG-IFN) plus ribavirin (180 ug of peginterferon alfa-2a once weekly and ribavirin 1000 or 1200 mg depending on body weight; n = 453), interferon alfa-2b (3 million units three times per week) plus ribavirin (IFN + ribavirin, n = 444) and weekly peginterferon alfa-2a plus placebo (PEG-IFN only, n = 224). Eligible subjects have not received any previous interferon treatment, have elevated alanine aminotransferase, no neutropenia, thrombocytopenia, anemia, HIV infection, decompensated liver disease, high serum creatinine, poorly controlled psychiatric disease, recent alcohol/drug dependence, or other significant medical conditions. Participants had an average age of about 42 to 43 years and 67% to 73% were male. A significantly higher proportion of patients who received PEG-IFN plus ribavirin had an EVR than did patients in the IFN plus ribavirin group and those in PEG-IFN only group (69%, 52%, and 59% of patients achieved SVR from each group, respectively). A significantly higher proportion of patients who received PEG-IFN plus ribavirin had an SVR than did patients in the IFN plus ribavirin group and those in the PEG-IFN only group (56%, 44%, and 29% of patients achieved SVR from each group, respectively, p < 0.001 for all comparisons between the PEG-IFN plus ribavirin group and the other two groups). Stratification by viral genotype showed that for genotype 1 the proportion of patients achieving an SVR were 46%, 36%, and 21% for the three treatment groups respectively (p = 0.01 for comparison between the PEG-IFN plus ribavirin group and IFN plus ribavirin group; p = 0.001 for comparison between the PEG-IFN plus ribavirin group and PEG-IFN only group. For patients with genotype 1 and high base-line HCV RNA levels (> 2 million copies per ml) the SVR rates were 41%, 33%, and 13% for the three treatment groups respectively (statistically significant between PEG-IFN plus ribavirin and IFN plus ribavirin). As for genotypes 2 and 3, significant differences were noted between the PEG-IFN plus ribavirin and the IFN plus ribavirin group (76% vs. 61%, p = 0.005). Among patients in the PEG-IFN plus ribavirin group that had EVR (86% of these patients) 68% of these patients went on to have an SVR. Among the 63 patients who did not have an EVR at week 12, only 2 patients went on to have an SVR. Multivariate analysis showed that an HCV genotype other than 1 (odds ratio (OR) = 3.25, p < 0.001), an age of 41 years or less (OR = 2.60, p < 0.001), and a body weight of 75 kg or less (OR = 1.91, p = 0.002) were significantly associated with a higher response rate (SVR). The three treatments also had a similar safety profile. However, the incidence of flu-like symptoms and depression was lower in the two peginterferon alfa-2a groups as compared to the group treated with interferon alfa-2b plus ribavirin. Withdrawal rates (i.e., discontinuation of treatment before the end of the 48-week course) for side effects or other reasons was 22%, 32%, and 32% in the PEG-IFN plus ribavirin, IFN plus ribavirin, and PEG-IFN alone groups. Adverse effects lead to about an 8% discontinuation rate. No treatment-related deaths occurred. The authors concluded that PEG-IFN plus ribavirin achieved a significantly greater response rate than did IFN plus ribavirin or PEG-IFN alone, including some apparently difficult to treat patients (e.g., genotype 1 with high viral load). They suggest further research is needed concerning the possibility of discontinuing treatment for patients without an EVR at week 12, since these results suggest that those without an EVR respond with an SVR at only about a 3% rate. Overall, this was a well-designed study.
although the inclusion and exclusion criteria for this population may limit generalizability to clinical practice through eliminating those in otherwise fair to poor health who will be much more frequently encountered in actual practice.

Bruno et al. (2004) randomized 311 naïve patients (without history of interferon treatment) infected with genotype 1 HCV in a multicenter study. The study groups consisted of a PEG-IFN (peginterferon alfa-2b) induction group (80 – 100 ug depending on body weight for 8 weeks, then 50 ug for the next 40 weeks (48 weeks total, n=163)) or standard nonpegylated interferon alfa-2b (IFN) 6 million units on alternate days (n=148). Both groups also received ribavirin 1000-1200 mg/day, depending on weight. Inclusion criteria were age between 18 and 65 years (mean age of about 50 years), aminotransferase (ALT) values >1.5 of the upper normal limit, liver biopsy performed within 6 months prior to enrollment, and diagnosis of chronic hepatitis. Patients with advanced cirrhosis, hepatocellular carcinoma, anti-HIV or HbsAg positivity, alcohol or parenteral drug abuse, and general contraindications to interferon or ribavirin were excluded. PEG-IFN plus ribavirin (“PEG-IFN group”) significantly increased SVR compared with nonpegylated IFN plus ribavirin (“IFN group”) (41.1% vs. 29.3%, respectively, p=0.030). Fewer patients discontinued the PEG-IFN group than the IFN group (19% vs. 31%, p=0.010). Logistic regression showed that SVR in the PEG-IFN group was independently associated with age less than 50 years and mild fibrosis on liver biopsy. Combining data for both groups, patients over 50 years old achieved a 24.0% SVR response and patients with fibrosis stage >= 3 only achieved a 17.2% rate of SVR. Body weight was not an independent predictor of SVR. In the PEG-IFN group, 64.1% of patients were HCV-RNA negative by 12 weeks of treatment, and nearly 70% of these patients achieved SVR. Of the 12-week nonresponders, only about 2% achieved SVR. Results were similar in the standard IFN group. In terms of safety, 24.8% of patients discontinued treatment, usually in the first 24 weeks. The rate of discontinuation was less in the PEG-IFN group than the standard IFN group (19% vs. 31%). Also, 42.7% of patients required dose reduction in one or more drugs, most commonly due to anemia. In the PEG-IFN group, dermatological, neuropsychiatric, and gastrointestinal symptoms were also major causes of dose reduction. Lowering of the ribavirin dose did not affect SVR rates in the PEG-IFN group, whereas reductions in PEG-IFN did affect the viral clearance rates (p=0.002). The authors state that the findings point to the importance of hepatitis C patients receiving treatment early while they are still at a relatively young age and fibrosis is not advanced. The patients in the study did not tolerate the treatment well, and showed discontinuation and dose reduction rates that were higher than reports from other studies. The authors could find no baseline differences between those discontinuing the treatment and those continuing treatment.

However, compliance may be difficult to evaluate in the context of a randomized trial since it introduces a non-randomized factor, although the limitation of the study to genotype 1 patients may predispose some to have more severe adverse effects than in studies enrolling types 1 with types 2 and 3 which have a better prognosis. Since the PEG-IFN arm also had an induction dose, it is unclear from this study whether the differences in dosing patterns or the pegylation of IFN was more of a factor in improving SVR rates in the PEG-IFN arm.

Hadziyannis et al. (2004) evaluated peginterferon-alfa2a and ribavirin combination therapy with varying doses of ribavirin and duration of treatment. A total of 1311 chronic hepatitis C patients were randomized into the following four groups (all patients received peginterferon-alfa2a 180 ug/week for at least 24 weeks):

- Peginterferon-alfa2a with ribavirin 800 mg/day for 24 weeks (low dose group or 24-LD, n=214)
- Peginterferon-alfa2a with standard dose ribavirin 1000 mg/day if wt < 75 kg or 1200 mg/day if weight >= 75 kg (standard dose group or 24-SD, n=288) for 24 weeks
- Peginterferon-alfa2a with ribavirin 800 mg/day for 48 weeks (48-LD, n=365)
- Peginterferon-alfa2a with ribavirin 1000 or 1200 mg/day depending on weight (48-SD, n=444) for 48 weeks

Patients needed to be treatment-naïve, have an elevated ALT value, and diagnosis confirmed by liver biopsy. Exclusions included existence of neutropenia, thrombocytopenia, anemia, high serum creatinine, coinfection with Hep B or HIV, decompensated liver disease, significant psychiatric disease, alcohol/drug dependence, and clinically significant comorbid medical conditions. As for the primary end point, patients treated for 48 weeks were significantly more likely to have an SVR than patients treated for 24 weeks, regardless of the ribavirin dose (OR=1.53, 95% confidence interval (CI), 1.17 to 2.01, p=0.002). The likelihood of achieving an SVR was higher in patients receiving a daily dose of 1000 mg/day or 1200 mg/day ribavirin than for patients receiving the low dose of 800 mg/day (OR=1.41, CI,
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1.10 to 1.81, p=0.01). The response rate for patients receiving peginterferon and standard ribavirin doses for 48 weeks was 63%. Response varied significantly based on genotype, which was the prominent predictor of response using multiple regression techniques (OR=5.4, CI 4.1 to 7.1, p=0.001). Interaction between treatment duration and genotype was also significant (OR=0.42, CI 0.24 to 0.75, p=0.003). For patients with HCV genotype 1, treatment for 48 weeks was significantly more effective than treatment for 24 weeks in terms of producing an SVR (OR=2.19, CI 1.52 to 3.16, p<0.001), and standard dose ribavirin was more effective than low-dose ribavirin for these patients (OR=1.55, CI 1.14 to 2.10, p=0.005). Group 48-SD had the highest SVR rate for genotype 1 patients and was statistically significant compared to other treatment groups. For patients with genotypes 2 and 3, the response rate did not vary between the four groups, and viral load did not appear to influence response rates in these patients. Most adverse events were mild to moderate in severity, with adverse events occurring least frequently in the 24-SD group. There were 2 deaths considered to be related to study medications (1 suicide and 1 from septicemia).

Patients treated for 48 weeks had a higher rate of premature withdrawal from treatment with a completion rate of 68% to 73% for 48 weeks and 92% and 93% for a 24-week course, depending on ribavirin subgroup. Overall, the investigators state that treatment response was primarily driven by genotype even in the presence of other prognostic factors that are less favorable. Genotype 1 achieved the highest SVR with the group (48-SD) with the most intensive treatment, while genotypes 2 and 3 may be treated for a shorter duration and a lower ribavirin dose. In general, this was a well-done study with a large sample size, and had a large enough sample size to additionally stratify by genotype (2 categories; genotype 1 vs. genotype 2/3) and obtain significant findings.

The effect of a further decrease in treatment duration was evaluated by Mangia et al. (2005) for HCV genotypes 2 and 3 in a randomized controlled trial. A total of 283 patients were randomized into a standard 24-week regimen of peginterferon alfa-2b (1.0 ug/kg body weight weekly) plus standard dose ribavirin based on body weight (“standard duration group”, n=70) and a variable duration group of 213 patients who were assigned to a regimen of 12 or 24 weeks depending on the outcome of HCV RNA tests on week 4 (positive HCV RNA test will be treated for a total of 24 weeks, with a negative test leading to cessation of treatment after 12 weeks). Eligibility criteria included an age of 18-70 years, confirmed infection with HCV genotype 2 or 3, elevated ALT levels, and had not previously received therapy. Exclusions included low WBC, RBC, and platelet counts, coinfection with HIV, heavy alcohol intake, drug abuse, psychiatric disease, chronic disease, or pregnancy/lactation. In the variable treatment group, 133 patients (62%) had an early response at week 4 (HCV RNA not detectable) and thus stopped treatment at week 12, while 80 patients (38%) had detectable HCV RNA at week 4 and thus were treated for 24 weeks. For comparison, the standard treatment group had a 64% 4-week early response. Overall, an SVR was noted in 76% of the standard treatment group patients and 77% in the variable duration treatment group. Of patients with a negative HCV RNA test at 4 weeks (in both the standard duration and the variable duration groups), 91% in the standard duration group (treated for 24 weeks) were later shown to have an SVR, while 85% of the variable-duration group (treatment for 12 weeks) had an SVR (difference NS). For the variable duration group without a response at week 4 (thus treated for 24 weeks), 64% later had an SVR. Overall, 80% of genotype 2 patients and 66% of genotype 3 patients had an SVR (p < 0.001). Adverse events (such as depression and thyroid dysfunction) occurred in 6% of patients treated for 12 weeks and in 13% of patients treated for 24 weeks. In addition, there were fewer adverse-event related withdrawals in those treated for 12 weeks (p = 0.045). Multivariate analysis did not find any other significant predictors of SVR. As for relapse rates (in those with undetectable HCV RNA at end of treatment), 3.6% of patients in the standard duration group and 8.9% of patients in the variable-duration group had detectable HCV RNA titers 24 weeks after the end of treatment (p = 0.16). Relapse rates among patients in the variable duration group treated for 12 weeks were not significantly different from relapse rates in 4-week treatment responders in the standard 24-week treatment group (p=0.19). All relapsed patients treated for 12 weeks in the variable duration group were offered an additional 24-weeks of treatment. Of the 10 out of 13 that agreed to retreatment, 9 achieved an SVR, suggesting that in these patients 12-weeks of treatment may have been too short. The authors stated that a response at week 4 suggests that treatment is needed for 12 weeks rather than the standard 24 weeks as responses in patients treated for 12 weeks (having a response at week 4) had equally as good outcomes as patients in a 24-week regimen. Treatment adherence rates were higher and fewer adverse effects occurred in the 12-week treatment course. There was also a non-significant trend toward higher relapse in the variable-treatment group, although the overall small numbers of relapsed patients lead to sparse data for analyzing relapse rates between groups. The study shows that for many patients with HCV genotype 2 and 3 with early (4-week) clearing of the HCV virus a 12-week regimen of standard antiviral therapy may be adequate.
However, the relapse rates suggest that there may be subgroups of this population that may not benefit despite early clearing of the virus, and thus further research is needed prior to routinely applying the study results to practice.

In a systematic review Chander et al. (2002) addresses the efficacy and safety of HCV therapy in treatment-naïve patients as well as in selected subgroups of patients. Long-term outcomes of treatment were also addressed. For the review, articles from 1996 through early 2002 were selected. Virological, histological, and clinical outcome measures were collected from human study data. The review found that treatment with combined high-dose peginterferon and ribavirin was significantly more efficacious than nonpegylated interferon plus ribavirin in treating HCV genotype 1, with an SVR rate of 42% and 33% respectively. For genotypes 2 and 3, the SVR rates were similar for patients receiving peginterferon plus ribavirin or standard interferon plus ribavirin, ranging from 79% to 82%. As for a comparison of monotherapy using peginterferon versus interferon, SVR ranges were 10% to 39% (for peginterferon) and 3% to 19% (for nonpegylated interferon) in treatment naïve patients (statistical significance not reported). Similar dose reduction and discontinuation rates were noted for both drugs. Studies were consistent in their reporting that interferon plus ribavirin was more efficacious than interferon monotherapy in treatment naïve patients (relative risk of virologic failure (RR), 0.74; CI, 0.70 to 0.78). However, the risk of requiring medication dose reduction was higher with the combination therapy (RR, 2.44; CI 1.58 to 3.75) as was discontinuation of treatment (RR, 1.28; CI, 1.07 to 1.52). In terms of combined treatment using interferon and ribavirin, the inclusion of an induction phase which uses higher doses of interferon at the beginning of treatment showed no increase in SVR rate for treatment naïve patients. Also, interferon plus ribavirin treatment was more efficacious that interferon monotherapy in non-responders and relapsers, although overall response rates were low, with only 13% to 14% of nonresponders achieving SVR. Treatment was more efficacious in relapsers as compared to non-responders. Studies were also moderately consistent in depicting that treatment decreases the risk of HCC. There is a lack of randomized controlled trials pertaining to treatment in selected subgroups, including ethnicity, coinfection with hepatitis B and/or HIV, end-stage renal disease, and those with hemophilia. As for long-term outcomes (5 years or greater) the evidence was consistent in showing a decreased incidence of HCC in treated vs. untreated patients. Responders (biochemical or virological) had lower HCC risk than nonresponders and relapsers, although there was not a clear decrease in HCC risk for nonresponders compared to untreated patients. Of note is that most trials enrolled predominantly white males between 30 and 50 years old. The prevalence of cirrhosis varied widely between trials, and consistent exclusion of higher risk patients from the studies may lead to more difficult generalizability of results. The major conclusion of the review was that combination therapy with peginterferon and ribavirin was the most efficacious treatment for treatment-naïve patients with HCV genotype 1.

Zaman et al. (2003) systematically reviewed studies comparing peginterferon (with and without ribavirin) versus standard interferon (with and without ribavirin) for treating chronic hepatitis C. Five citations pertaining to randomized controlled trials that compared at least 2 different interferon regimens and used the SVR as the primary endpoint were included. Three studies compared peginterferon with standard interferon used as monotherapy. All three demonstrated that peginterferon monotherapy lead to higher SVRs than standard interferon, including for those with advanced fibrosis. Two articles compared peginterferon plus ribavirin with standard interferon plus ribavirin. Both studies were consistent in showing that peginterferon plus ribavirin also lead to higher SVRs than did interferon plus ribavirin. However, subgroup analysis and determination of which peginterferon formulation is superior was difficult due to the heterogeneity between the two trials. Peginterferon tolerability was comparable to that of standard interferon. Overall, the authors state in their recommendations that in treatment-naïve patients, peginterferon as monotherapy was superior to standard interferon monotherapy. Also, peginterferon plus ribavirin is statistically more efficacious than standard interferon plus ribavirin in treatment of hepatitis C, including patients with genotype 1 or high levels of serum HCV RNA. In addition, peginterferon monotherapy was less efficacious than any of the combination regimens, including standard interferon plus ribavirin. The authors suggest that peginterferon monotherapy should be reserved for patients with contraindications to ribavirin.
Long-term follow-up and Progression of Hepatitis C

In a retrospective cohort study, 593 patients with chronic hepatitis C who had repeated liver biopsies 1-10 years apart were analyzed. Patients had received 2-6 months of IFN therapy within 6 months after initial biopsy (487 patients) or were untreated (106 patients). Of the treated patients, 38% had a sustained response. Activity grade was improved in 89% of sustained responders and unchanged in 50-60% of untreated patients. Sustained response was associated with a 0.88 mean reduction in fibrosis score at more than 3-year follow-up (as compared to 0.59 mean increase in untreated patients). Rates of fibrosis progression were -0.28 units/year in sustained responders, 0.02 units/year in nonsustained responders, and 0.10 unit/year in untreated patients (Shiratori et al., 2000).

A meta-analysis performed by Veldt et al (2004) assessed outcomes from long-term follow-up after HCV treatment in European patients from 8 studies (cohort or randomized controlled trials). Although the treatment analyzed was nonpegylated interferon monotherapy (average duration 39 weeks, with genotype 1 patients being assigned to an average of 41 weeks of treatment with higher interferon doses), analysis of SVR cases and biochemical responders (defined as detectable HCV but normal ALT levels) cases may be similar to those achieving responses on pegylated interferon and ribavirin. Follow-up period was 59 months for 286 SVR cases and 50 biochemical responders. Cirrhosis was present prior to treatment in 5.2% of sustained virological responders, and 39% of the overall population had genotype 1. Regression of hepatic fibrosis was noted in 29% of SVR patients. Multivariate analysis showed that older age, lower pretreatment fibrosis score, and biochemical response without SVR were statistically significant risk factors for fibrosis progression. Late virological relapses occurred in 4.7% of patients over 5 years of follow-up (CI, 2.0 to 7.4) for SVR cases, all occurring within 4 years post-treatment. Decompensated liver disease in SVR cases was found in 1.0% (CI, 0.0 to 2.3) and none developed hepatocellular carcinoma (HCC). Survival was similar to the age-sex matched general population, with the standard mortality being 1.4 (CI, 0.3-2.5). Clinical outcomes for cirrhotic patients with an SVR were similar to other SVR cases. Biochemical responders without SVR showed a prognosis that was not as good, with liver-related decompensation and HCC developing in 9.1% (CI, 0.5 to 17.7) and 7.1% (CI, 0 to 15.0) respectively. The authors concluded that 5-year survival of European patients exhibiting SVR is as good as the general population matched for age and sex. Although the study does not use peginterferon and ribavirin, the mainstays of treatment in other recent studies, these treatments were not generally available at the time these patients were treated. Although there may be generalizability questions in terms of comparisons to modern treatments, SVR is a common denominator for outcome measurement in most studies and, in fact, standard treatment is considered to have a higher efficacy rate than interferon monotherapy and thus if present-day analysis would vary from this meta-analysis, it will likely vary in the direction of more positive outcomes.

Pertaining to HCC, Azzaroli et al. (2004) studied the differential effect of treatment using interferon plus ribavirin compared to interferon in preventing HCC. A total of 101 patients with proven HCV-related cirrhosis were enrolled. Follow-up lasted 5 years. Forty-one patients who were ending a 1-year IFN-alpha2b course were subsequently followed-up without undergoing further treatment (old treatment control group, OTCG). Sixty naïve patients were stratified according to sex and AgNOR-PI (silver-stained nucleolar organizer region – proliferative index, used as a marker for hepatocyte regeneration), and then randomized such that 30 patients were treated with IFN-alpha2b and ribavirin (treatment group, TG) and 30 patients were placed into an untreated (no drugs) control group (CG). Nonresponders and relapers in the TG received further treatment (IFN/ribavirin) after a withdrawal period of 6 months. Results show that AgNOR-PI was significantly decreased by IFN (p < 0.001) given that the incidence of HCC was higher in patients with AgNOR-PI > 2.5 (p < 0.01). As for development of HCC, 2 nonresponders in the OTCG, 9 in the CG, and none in the TG developed HCC during the follow-up period. Statistically significant differences in HCC incidence were found between the OTCG and CG (p < 0.004) as well as between the TG and CG (p < 0.003) using Kaplan-Meier survival curves. The authors concluded that IFN can prevent HCC development in cirrhotic patients both alone and with ribavirin. However, given the relative rarity of new onset HCC occurring over a 5-year period, even in cirrhotics, small numbers in some cells make interpretation difficult. Larger studies are needed to prevent sparse matrices, possibly done as an observational study given its potential usefulness for analyzing large numbers of patients, which is needed to study rarer conditions over longer follow-up periods.
An additional systematic review was performed by Almasio et al. (2003) using articles that reported data on long-term follow-up of patients with virological response in terms of the course of HCV infection, including development of cirrhosis and HCC in responders as compared to non-responders. Data were pooled using random effects modeling to report on relative risk (RR). Of patients who achieved an SVR, the estimates of late virological relapse was about 13%, with a range from 0% to 86% and a follow-up period ranging from 0.1 to 13 years, showing high heterogeneity in the data. Factors explaining the wide differences between studies include differences in overall dosages and duration of IFN treatment, heterogenous patient characteristics (virological and clinical), and possibly different sensitivities of HCV RNA assays. The report also states that the stage of fibrosis and histological activity from liver biopsies performed within 2 years after treatment cessation remains the most reliable parameter to assess short-term benefit of viral clearance. The calculated risk reduction of liver cirrhosis between SVR patients and those who did not respond to treatment is –0.22 (CI, –0.36 to –0.08). Heterogeneity of timing of diagnosis and criteria for definition of cirrhosis, heterogeneity of criteria for defining cirrhosis during follow-up, including underestimates due to lack of repeated biopsies at appropriate intervals, and patient differences may hamper the interpretation of results. As for risk of developing HCC, the risk is lower in patients with SVR than in non-responders and relapers. Overall risk reduction was –0.097 (CI, –0.13 to –0.07), although such prognostic studies were few in number. There was also no stratification by genotype, although less was known about the effect of genotype on treatment responses at the time of this review.

Poynard et al. (2002) studied the impact of treatment using pegylated interferon alfa-2b plus ribavirin on liver fibrosis. Individual data on 3010 treatment-naive patients from 4 randomized trials were utilized. All patients had at least one pretreatment and posttreatment liver biopsy. Ten different regimens were compared using standard interferon, peginterferon, and ribavirin. The METAVIR fibrosis score consisted of a scale from 0 (no fibrosis) to 4 (cirrhosis). METAVIR also has a necrosis and inflammation score ranging from A0 (no histological activity) to A3 (severe activity). Based on the METAVIR scores, measures were made of the percentages of patients improving by at least 1 stage, worsening by at least one stage, and fibrosis progression per year. The mean number of months between liver biopsies (pretreatment and post-treatment) was 18 to 21 months depending on the group. The range of improvement in terms of necrosis and inflammation was 39% of patients (standard interferon given for 24 weeks) to 73% (peginterferon 1.5 plus high-dose ribavirin; p < 0.001 for comparison). Patients with worsening fibrosis ranged from 23% (interferon for 24 weeks) to 8% (PEG IFN plus high-dose ribavirin; p = 0.001 for comparison).

As for fibrosis rates, all regimens significantly reduced fibrosis progression rates as compared to corresponding rates prior to treatment, including both responders and non-responders (p < 0.001). However, there was a significant difference in progression between responders and non-responders (p < 0.001). Reversal of cirrhosis occurred in 49% of 153 patients with cirrhosis, with one-third of patients with reversal of cirrhosis having a sustained response. Factors associated with the absence of significant fibrosis after treatment include fibrosis stage of F0 or F1 at baseline (odds ratio (OR) = 0.12; p < 0.0001), SVR (OR = 0.36; p < 0.0001); age less than 40 years (OR = 0.51; p < 0.001), BMI < 27 (OR = 0.65; p < 0.001), undetectable or minimal baseline activity (OR = 0.70; p = 0.02), and viral load less than 3.5 million copies of viral RNA per milliliter (OR = 0.79; p = 0.03). In this pooled study, treatment of hepatitis C appears to have a positive effect in reversal of fibrosis in treatment-naive patients, especially those treated with a combination regimen of peginterferon and ribavirin.

**Treatment of Patients Who Did Not Respond or Who Relapsed after Initial Treatment**

As for the efficacy of peginterferon and ribavirin in patients with chronic hepatitis C who have failed prior treatment, Shiffman et al. (2004) evaluated 604 patients enrolled in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C), a randomized controlled trial who failed to respond (did not achieve an SVR) to previous interferon-based therapy (with or without ribavirin). The mean age of the patients was 50, with an average duration of HCV infection of 26.5 years. A sizable proportion of patients had cirrhosis (39%). In addition, 89% of patients were infected with genotype 1 HCV. There was a 5.6% withdrawal rate during the first 20 weeks, mainly due to adverse events. Peginterferon alfa-2a 180 ug/week plus ribavirin 1000 – 1200 mg/day was administered. Patients without detectable HCV mRNA at week 20 (35% of patients) continued treatment for an additional 28 weeks for a total of 48 weeks. Follow-up lasted for 24 weeks after treatment cessation, with 18% achieving SVR. Variables associated with an SVR on multivariate analysis included prior treatment with interferon monotherapy, serum HCV RNA levels less than 1.5 million IU/ml, viral genotypes 2 or 3, an AST/ALT ratio of less than 1.0, and
absence of cirrhosis. Reducing the ribavirin dose to 60% of the starting dose or less was associated with a significant decline in SVR (11% of patients, p <= 0.05). Reducing the dose of peginterferon or reducing the dose of ribavirin after week 20 did not significantly affect SVR. Overall, the results showed a low response to retreatment therapy, especially for those with cirrhosis, high viral load, and genotype 1 infection. Of note is that infection with genotype 1 HCV was disproportionately represented in this population (nearly 90% were infected with genotype 1), underscoring the difficult to treat nature and high non-response rate of this genotype.

Patients who have relapsed after anti-HCV therapy are also an important population to consider. In a randomized controlled pilot trial by Herrine et al. (2005) various drug combinations for relapsers and patients who had a viral breakthrough were evaluated. A sample of patients who relapsed or had viral breakthrough (n=124) were randomized to 48 weeks of peginterferon alfa-2a (180 ug once per week) plus ribavirin (800 - 1000mg/day), mycophenolate mofetil (2g/day), amantadine (200 mg/day), or ribavirin and amantadine. Patients were followed for 24 weeks after treatment cessation. Main exclusion criteria consisted of those undergoing any systemic antiviral therapy during the last 24 weeks, HIV infection, decompensated liver disease, anemia, neutropenia, thrombocytopenia, high serum creatinine, history of alcohol or drug abuse within the last year, history of severe psychiatric disease, or substantial coexisting medical conditions. Average age was 46 – 48 years and mostly male (61% to 75% depending on study group). The sustained virologic response rate was as follows:

<table>
<thead>
<tr>
<th>Treatment provided</th>
<th>SVR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon alpha-2a plus ribavirin</td>
<td>38%</td>
</tr>
<tr>
<td>Peginterferon alpha-2a plus ribavirin plus amantadine</td>
<td>45%</td>
</tr>
<tr>
<td>Peginterferon alpha-2a plus mycophenolate mofetil</td>
<td>17%</td>
</tr>
<tr>
<td>Peginterferon alpha-2a plus amantadine</td>
<td>10%</td>
</tr>
</tbody>
</table>

The only comparison to reach statistical significance was the comparison of peginterferon alpha-2a plus ribavirin plus amantadine to peginterferon alpha-2a plus amantadine (p = 0.0216). Twelve percent of patients withdrew due to adverse events. The purpose of the study was to compare the above 4 treatment regimens as there is no standard therapy for relapsing patients. The authors state that the regimens with ribavirin were more effective than those without the drug. Given the small sample size in this trial, statistical significance was difficult to reach. Further study is needed with larger sample sizes prior to drawing conclusions concerning the efficacy of the above therapies in relapsing patients. However, regimens with ribavirin seemed to perform at an overall better rate in terms of SVR than those without ribavirin.

Predictors and Prognostic Factors for SVR

Lee et al. (2002) investigated the prognostic factors and predictive variables for SVR in chronic hepatitis C patients treated with peginterferon alfa-2a. A pooled analysis of data from 3 randomized controlled trials with a total of 814 patients was utilized (HCV RNA of less than 2 million copies per ml). Independent prognostic factors for SVR included a viral genotype other than 1, lower pretreatment viral load (less than 2 million copies/ml), age less than 40 years, body weight less than 85 kg, no cirrhosis or bridging fibrosis, alanine aminotransferase quotient greater than 3, and histological activity score greater than 10 (both of the latter factors are considered markers for necroinflammation). Detectable or less than a 2-log decline in viral RNA at the 12 week point in treatment was a strong predictor of a lack of SVR, with a negative predictive value of 98%. The authors state that in patients treated with peginterferon alfa-2a, the decision to stop or continue treatment may be made as early as the 12th week of treatment. However, these results do not include patients treated with peginterferon plus ribavirin and thus these results are not necessarily generalizable to that population, although studies using combination therapy have suggested similar predictive factor profiles.

HCV Treatment in Special Populations

Human immunodeficiency virus (HIV) infection is known to accelerate the natural history of hepatitis C toward complications such as severe fibrosis and cirrhosis. In one study of 868 patients infected with HIV and HCV, a 40% SVR was obtained with a combination of peginterferon alfa-2a and ribavirin. Patients infected with genotype 1 had the smallest percentage of SVRs (29%), which is less than the
corresponding SVR results in non-HIV patients (Torriani et al., 2004; Michielsen and Bottieau, 2005). Overall, recent data indicate a HCV treatment regimen similar to non-HIV infected hepatitis C patients. However, HCV coinfection increases the liver toxicity of Highly Active Antiretroviral Therapy (HAART) and thus dose adjustments of the antiretroviral therapy may be indicated (Michielsen and Bottieau, 2005).

Zeuzem et al. (2004) studied treatment of hepatitis C in patients with normal aminotransferase (ALT) levels. Approximately 30% of patients with chronic hepatitis C infection have normal ALT levels. This subgroup has often been excluded from treatment trials. In this study, patients were randomized into a peginterferon plus ribavirin group (n = 212) for 24 weeks, the same treatment for 48 weeks (n = 210), or a no treatment control group (n = 69). Total monitoring time was 72 weeks to allow measurement of SVR. No patients cleared the virus in the control group. The 24-week group noted a 30% SVR rate while the 48-week group noted a rate of 52%. The authors state that the rate of SVR was similar to that of studies enrolling only patients with elevated ALT activity. They recommend that the decision to treat should rest on factors other than ALT activity (e.g., presence of comorbidities, age, histology, symptomatology, etc.).

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Jacobson et al. (2002) reviewed studies concerning treatment of HCV in children. Nineteen trials were included in the evaluation, having a total of 366 treated and 105 untreated children in 5 countries. Average SVR was 36% (0% to 73%) using interferon monotherapy, which is comparable to adults. At this time there are no large-scale randomized controlled trials evaluating the safety and efficacy of treatment with a combination of peginterferon and ribavirin in children.

Safety of Treatment

Morbidty Rate

Adverse events (AEs) may lead to treatment discontinuation in about 10 – 15% of patients. Additional patients, up to 18-20%, may receive dose reduction as a result of AEs. The most frequent side effects include flu-like symptoms, myalgia, headache, alopecia, dermatitis, fatigue, psychiatric disorders, and gastrointestinal disturbances. Hematological abnormalities may result from the drug combination, which includes anemia (12-22% of patients), in particular hemolytic anemia, neutropenia (17-20%) and thrombocytopenia (3-6%) (Aspinall and Pockros, 2004). Ophthalmic effects and arrhythmias have also been described. Depression is a significant side effect in 21-34% of patients and needs close monitoring and treatment if indicated (Aspinall and Pockros, 2004; Teo and Hayes, 2004). There are also potential teratogenic risks of ribavirin for both male and female germ cells.

Mortality Rate

With appropriate follow-up and management of side effects, mortality due to treatment should be rare, well below 1%.

Training and Experience Required to Administer the Treatment

Appropriate infrastructures are needed to ensure proper follow-up, drug dosages and duration of treatment. The patient should be followed by a multidisciplinary team which may include hepatologists or gastroenterologists, infectious disease specialists, and primary care practitioners (McGinn et al., 2005). Psychologists and psychiatrists may be needed to manage neuropsychiatric adverse effects, and hematologists (for hematologic side effects) need to be available for consultation.
Conditions and Setting of Treatment

Infrastructures are required to assure patient safety and appropriate clinical and laboratory monitoring. However, teaching home administration of injections is safe and done routinely, and treatment can normally be performed in the outpatient setting with close monitoring by the primary care provider. Subspecialists such as hepatologists also need to be a part of the team for collaboration and consultation (McGinn et al., 2005).

Contraindications and Comorbidities that Increase the Risk Associated with Treatment

Clinical experience shows that if patients are actively using drugs of abuse or patients are on chronic oral narcotics for pain, they are less likely to be able to complete a course of treatment. Potential hematologic effects (such as leukopenia and thrombocytopenia) require periodic evaluation. Mental illness or mild to moderate depression may increase risks associated with treatment.

Absolute contraindications to therapy with peginterferon or ribavirin include hepatic decompensation, autoimmune disease, cardiac arrhythmias, uncorrected anemia, ischemic vascular disease, and pregnancy. Relative contraindications include pancytopenia, psychiatric disorders, and seizure disorders (Heathcote and Main, 2005).

The treatment should be used with caution in patients with a history of significant or unstable cardiac disease (which may be worsened by drug induced anemia), patients with evidence of pulmonary infiltrates or pulmonary function impairment, patients with creatinine clearance < 50 mL/min, patients with potential for ophthalmologic disorders, and patients with serious hypersensitivity reactions. Treatment is discontinued indefinitely in patients who experience doubling of the ALT levels during therapy.

Potential for Inappropriate Use of the Technology

Due to the long course of treatment and propensity for significant side effects, it is unlikely that the treatment will be abused or overused. Underuse of the treatment is likely more common, as chronic hepatitis C infection may be asymptomatic in some individuals for up to 20 years and thus left untreated.

Alternative Treatments

There are essentially no treatments other than interferon/peginterferon and ribavirin that have been shown efficacious in achieving a sustained virologic response. A systematic review of trials using glucocorticoids in hepatitis C patients found that the evidence is not sufficient to allow conclusions regarding benefits and harms of the drug class in this patient population (Brok et al., 2004). Complementary treatments have also been tried. A systematic review (Coon and Ernst, 2004) was published on the efficacy of complementary therapy (herbal products and supplements) as an adjunct or replacement for standard treatment (peginterferon and ribavirin). Of 27 studies reviewed, only 11 were of good methodological quality. Sample sizes tended to be small, with most individual studies enrolling fewer than 100 patients. Compared with the control groups (consisting of a wide range of drug combinations including IFN, ribavirin, and/or placebo) significant improvements in virological and/or biochemical response were seen in investigations of vitamin E, thymic extract, zinc, traditional Chinese medicine, oxymatrine, and Glycyrrhiza glabra. However, few studies measured the SVR 6 months post-treatment. Thus, lack of completeness of outcome measures and difficulties in generalizing the results due to methodological problems limits the conclusions that can be drawn based on these studies. Further research is needed in terms of larger studies with a comprehensive evaluation of outcome measures.

Additional therapies have been tried as an adjunct to peginterferon and ribavirin treatment. Amantadine has been given with interferons (double therapy) or with interferons and ribavirin (triple therapy). In a meta-analysis of the use of amantadine in chronic hepatitis C, thirty-one studies with 4831 patients were
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Committee Conclusions

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included (Deltenre et al., 2004). Overall, triple therapy was best for improving the sustained response (mean difference 8.4%, p = 0.002). On subgroup analysis, the authors concluded that combination therapy that included amantadine had no effect upon treatment-naive patients and relapers. However, triple therapy with amantadine improved the sustained response for nonresponders. Number needed to treat analysis showed that 13 non-responders would need to be treated with amantadine combination therapy to obtain one additional SVR over the expected comparison group rate (the SVR rate was 22.9% in patients treated with amantadine combination therapy and 14.9% in other non-responders). When only triple combination therapy was used, a mean difference in response rate of 12.7% (p = 0.005) was obtained, with a number needed to treat of 8. The authors concluded that new randomized trials are required to confirm these findings.

Other adjunctive therapies include cyclosporin A combined with interferon (Inoue et al., 2003), which in a small trial (120 patients) did achieve statistical significance (SVR) when compared with interferon monotherapy. This was particularly true in patients with genotype 1 and high viral loads. However, the study only compared combination therapy with interferon monotherapy and thus the control group may have been inadequate in terms of recent treatment standards.

Epoetin alfa is another proposed therapy intended to counteract the anemia that is a relatively frequent sequela of treatment. One randomized study (n = 185) of patients who developed anemia during treatment (8 week double-blind phase, 8-week open label phase) depicted that ribavirin doses were maintained in 88% of patients in the epoetin alfa group as compared to 60% of patients receiving placebo (p < 0.001). Quality of life scores also improved significantly. Similar results were shown in patients crossing over to epoetin alfa treatment in the open label phase. However, additional trials with a larger sample size are needed to confirm the ability of epoetin alfa to maintain ribavirin dosages as well as patient characteristics that would result in the highest likelihood of benefit (Afdhal et al., 2004).

Economic Implications of Treatment

For drug costs alone, monotherapy with peginterferon ranges from about $153 per week to $167 per week. For combination treatment with peginterferon plus ribavirin (i.e., Pegasys® plus Copegus®), the cost ranges from $327 to $380 per week (Tortorice, 2002). Using a midpoint value of about $354, the calculated drug cost for a 48-week course of treatment is $16,992. By way of comparison, treatment of decompensated cirrhosis was reported to cost over $20,000 per year and liver transplantation was estimated at $200,000 the first year and $20,000 in subsequent years (Kim et al., 1997).

Costs of treatment in an inmate population were described by Sterling et al. (2005). The cost to evaluate and treat 100 inmates from the Virginia department of corrections with chronic hepatitis C was calculated to be $1,775,900 or $17,759 per inmate. Given the genotype distribution (80% of patients were genotype 1) and the assumption that 42% with genotype 1 will achieve an SVR and 82% of genotypes 2 and 3 will achieve an SVR, the cost per patient that obtains an SVR was calculated to be $35,517.

Committee Conclusions

With regard to antiviral therapy for chronic hepatitis C, the ICSI Technology Assessment Committee finds that:

1. PEG-IFN and the combination of PEG-IFN and ribavirin are relatively safe when closely monitored by an experienced center. Serious side effects that may lead to discontinuation of treatment occur in 10% to 15% of patients and include neuropsychiatric effects (especially depression), influenza-like symptoms, and hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia.
2. HCV treatment with PEG-IFN plus ribavirin is presently the most efficacious treatment available for chronic HCV. (Conclusion Grade I based on class A, M evidence. See Appendix A.)
3. For optimal treatment of HCV in genotype 1 patients, standard weekly dose PEG-IFN along with 1000 – 1200 mg/day ribavirin (depending on weight) given for a 48-week period leads to SVR in about 40% to 50% of patients.
4. For optimal treatment of HCV in genotypes 2 and 3, standard weekly dose PEG-IFN along with 800 mg/day ribavirin for 24 weeks is adequate for 73% to 78% conversion to SVR status. Longer courses of treatment have not further improved outcomes in this subgroup.

5. Long-term follow-up of HCV cases with an SVR shows regression of fibrosis, a significantly decreased rate of cirrhosis development, and lower HCC rates. However, the precise amount of risk reduction is unknown. (Conclusion Grade II based on class A, M evidence. See Appendix B)

6. Treatment non-responders (those who underwent previous treatment and did not achieve an SVR) show a low response rate on retreatment (15% to 20% SVR rate). Optimal selection criteria for treating non-responders are not known.

7. Predictors for a lower (worse) SVR rate includes HCV genotype of 1, the presence of severe fibrosis or cirrhosis, advanced age, heavy alcohol use, obesity, and high viral load.

**Potential Conflict of Interest Disclosure**

In the interest of full disclosure, ICSI has adopted the policy of revealing relationships work group members have with companies that sell products or services that are relevant to this technology assessment report topic. The reader should not assume that these financial interests will have an adverse impact on the content of the technology assessment report, but they are noted here to fully inform readers. Readers of the technology assessment report may assume that only work group members listed below have potential conflicts of interest to disclose.

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**Evidence Grading System**

Evidence is classed and graded as described below.

I. **CLASSES OF RESEARCH REPORTS**

A. **Primary Reports of New Data Collection:**

- **Class A:** Randomized, controlled trial
- **Class B:** Cohort study
- **Class C:** Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

- **Class D:** Cross-sectional study
- Case series
- Case report

B. **Reports that Synthesize or Reflect upon Collections of Primary Reports:**

- **Class M:** Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

- **Class R:** Consensus statement
- Consensus report
- Narrative review

- **Class X:** Medical opinion
II. CONCLUSION GRADES

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system defined in Section I, above, and are assigned a designator of +, -, or ø to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

**Grade I:** The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

**Grade II:** The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

**Grade III:** The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

**Grade Not Assignable:** There is no evidence available that directly supports or refutes the conclusion.

The symbols +, –, ø, and N/A found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

+ indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;

– indicates that these issues have not been adequately addressed;

ø indicates that the report or review is neither exceptionally strong or exceptionally weak;

N/A indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

References


Aspinall RJ, Pockros PJ. The management of side-effects during therapy for hepatitis C. *Aliment Pharmacol Ther* 2004;20:917-929. (Class R)


Bruno S, Camma C, Di Marco V, et al. Peginterferon alfa-2b plus ribavirin for naive patients with genotype 1 chronic hepatitis C: a randomized controlled trial. *J Hepatol* 2004;41:474-481. (Class A)


Shiffman ML, Di Bisceglie AM, Lindsay KL, et al. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology* 2004;126:1015-1023. (Class A)


Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology* 2004;127:1724-1732. (Class A)

**Conclusion Grading Worksheet**

See next pages
## Appendix A: Conclusion Grading Worksheet

**Work Group’s Conclusion:** HCV treatment with PEG-IFN plus ribavirin is presently the most efficacious treatment available for chronic HCV.

**Conclusion Grade:** I

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Design Type</th>
<th>Class Quality</th>
<th>Population Studied/Sample Size</th>
<th>Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)</th>
<th>Authors’ Conclusions/Work Group’s Comments (italicized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fried et al., 2002</td>
<td>RCT</td>
<td>A</td>
<td>1121 hepatitis C patients randomized to PEG-IFN plus ribavirin (n=453, group 1), IFN plus ribavirin (n=444, group 2), and peg-IFN plus placebo (n=224, group 3) -- Subjects had not received any previous interferon treatment and had no other significant medical conditions -- Average age 42-43 years, about 67% to 73% were male</td>
<td>-- A significantly higher proportion of patients had an EVR (early viral response at week 12 of treatment) in group 1 than did other groups (69%, 22%, and 59% for groups 1, 2, and 3 respectively) -- Patients in groups 1, 2, and 3 achieved a SVR of 56%, 44%, and 29% for groups 1, 2, and 3 respectively (p &lt; 0.001 favoring group 1) -- Genotype 1 patients had SVR responses of 46%, 36%, and 21% for groups 1, 2, and 3 respectively (p &lt; 0.01 in favor of group 1) Significant differences in favor of group 1 were also noted for genotype 1 patients with high baseline RNA levels (41%, 33%, and 13% for groups 1, 2, and 3 respectively), and genotypes 2 and 3 (76% vs. 61% for groups 1 and 2 respectively). -- Multivariance analysis showed that genotype other than 1, age of 41 years or less, and a body weight less than or equal to 75 kg were favorable traits for an SVR -- Complications: flu-like symptoms and depression (lower in the two PEG-IFN groups than the INF group) -- Withdrawal rates due to adverse effects: 8%</td>
<td>-- The authors concluded that PEG-IFN plus ribavirin resulted in a significantly greater response rate than did IFN plus ribavirin or PEG-IFN alone, including for some patients with clinical characteristics associated with lower response rates (e.g. genotype 1 with high viral load) -- Further research was suggested in terms of the possibility of discontinuing treatment early for those without an EVR at week 12.</td>
</tr>
</tbody>
</table>
### Appendix A: Conclusion Grading Worksheet (cont)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Design Type</th>
<th>Class</th>
<th>Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)</th>
<th>Authors’ Conclusions/Work Group’s Comments (italicized)</th>
</tr>
</thead>
</table>
| Chander et al., 2002 | Systematic review | M     | -- Selected articles from 1996 through early 2002  
-- Collected clinical, histological, and virological outcome data from human studies | Main conclusion is that the combination of PEG-IFN and ribavirin was the most efficacious treatment for treatment-naive patients infected with HCV genotype 1.  
-- Most trials enrolled mainly white males 30 – 50 years old; prevalence of cirrhosis varied widely between studies  
-- Exclusion of higher risk groups may decrease generalizability of the findings |
|             |                   |       | -- PEG-IFN plus ribavirin was significantly more efficacious than non-peg IFN plus ribavirin for genotype 1 (SVR rate of 42% and 33% respectively)  
-- Genotypes 2 and 3 patients were not shown to have a greater probably of an SVR with PEG-IFN plus ribavirin as compared to standard IFN plus ribavirin (SVR percentages ranging from 79% to 82%)  
-- Treatment with IFN plus ribavirin was consistently reported to be more effective than treatment with IFN alone (RR 0.74), although the probability of requiring dose reductions (RR = 2.44) and discontinuations (RR=1.28) was significantly higher with the combination therapy  
-- Inclusion of induction phases (i.e. with higher initial doses of interferon) did not increase SVR in treatment-naive patients  
-- Combination treatment was more effective than IFN alone in non-responders and relapers, although only 13% to 14% of this population achieves SVR  
-- Studies consistent in showing that treatment decreases the risk of HCC (amount of risk reduction not known) |
Appendix B: Conclusion Grading Worksheet

**Work Group's Conclusion:** Long-term follow-up of HCV cases with an SVR shows regression of fibrosis, a significantly decreased rate of cirrhosis development, and lower HCC rates. However, the precise amount of risk reduction is unknown.

**Conclusion Grade:** II

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Design Type</th>
<th>Class</th>
<th>Quality</th>
<th>Population Studied/Sample Size</th>
<th>Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)</th>
<th>Authors' Conclusions/Work Group's Comments (italicized)</th>
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<tr>
<td>Veldt et al., 2004</td>
<td>Systematic review</td>
<td>M</td>
<td>o</td>
<td>- Assessed 8 European trials (cohort or RCT) with long-term follow-up &lt;br&gt; -- Treatment analyzed was non-pegylated IFN monotherapy &lt;br&gt; -- Follow-up was about 5 years &lt;br&gt; -- Cirrhosis was present in 5.2% of virological responders &lt;br&gt; -- 39% of the overall population had genotype 1 &lt;br&gt; -- 29% of SVR patients showed regression of hepatic fibrosis</td>
<td>-- For SVR cases, late virological relapses occurred in 4.7% of patients over the 5-year follow-up period &lt;br&gt; -- Decompensated liver disease in patients with SVR was present in 1.0% of patients, without the development of hepatocellular carcinoma (HCC) &lt;br&gt; -- Clinical outcomes for cirrhotic patients with an SVR were similar to other patients with an SVR &lt;br&gt; -- Biochemical responders without SVR showed a liver-related decompensation rate of 9.1% and development of HCC at 7.0%</td>
<td>-- The authors concluded that the 5-year survival of European patients with SVR is as good as the age-gender matched general population &lt;br&gt; -- Note: peginterferon and ribavirin treatment was not generally available at the time of the studies</td>
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<tr>
<td>Author/Year</td>
<td>Design Type</td>
<td>Class</td>
<td>Quality</td>
<td>Population Studied/Sample Size</td>
<td>Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)</td>
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<td>Azzaroli et al. (2004)</td>
<td>RCT</td>
<td>A</td>
<td>0</td>
<td>- Enrolled 101 patients with proven cirrhosis related to HCV -- 5-year follow-up period -- 41 patients who were ending a 1-year IFN treatment course were followed up without undergoing further treatment (old treatment control group or OTCG) -- An additional 60 treatment-naïve patients were stratified according to sex and AgNOR-PI (a marker for hepatocyte regeneration); these patients were randomized to an IFN and ribavirin group (treatment group, TG, n=30) and an untreated control group (CG) -- Nonresponders and relapsers in the TG received further IFN/ribavirin after a 6-month withdrawal period</td>
<td>-- AgNOR-PI was significantly decreased in the IFN group (p &lt; 0.001) -- HCC incidence was higher in patients with AgNOR-PI &gt; 2.5 (p &lt; 0.01) -- 2 nonresponders in the OTCG, 9 in the TG, and none in the CG developed HCC during the follow-up period; the differences were significant between the OTCG and CG (p = 0.004) and between the TC and CG (p &lt; 0.003)</td>
<td>-- IFN either alone or with ribavirin can prevent HCC in cirrhotic patients -- Given the relatively small rates of incidence of HCC during a 5-year period, small numbers in some cells may make interpretation and generalizability difficult; studies with larger sample sizes and at least a similar follow-up period are needed</td>
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<tr>
<td>Poynard et al., 2002</td>
<td>Meta-analysis</td>
<td>M</td>
<td>+</td>
<td>-- Impact of treatment using PEG-IFN/IFN plus ribavirin on liver fibrosis in 2010 patients in 4 RCTs (pooled data) -- All pts had pre-treatment and post-treatment liver biopsies -- 10 different regimens were compared using the above medications -- Used METAVIR fibrosis (0-4) score (0 = no fibrosis, 4 = cirrhosis) and necrosis and inflammation (A0-A3) score (A0 = no histological activity, A3 = severe activity) Mean interval between pre-and post-treatment liver biopsies was 18-21 months</td>
<td>Range of improvement in terms of necrosis and inflammation was 39% of patients (standard IFN given for 24 weeks) to 73% (PEG-IFN plus high-dose ribavirin, p &lt; 0.001 for comparison) -- Patients with worsening fibrosis: 23% (IFN for 24 weeks) to 8% (PEG-IFN plus high-dose ribavirin, p &lt; 0.001 for comparison) -- All regimens significantly reduced fibrosis progression rates as compared to corresponding rates prior to treatment -- Cirrhosis was reversed in 49% of 153 cirrhotic patients -- Factors that are significantly associated with absence of significant fibrosis post treatment include baseline fibrosis stage (OR = 0.12), SVR (OR = 0.36), age &lt; 40 yrs (OR = 0.51), BMI &lt; 27 (OR = 0.65), minimal or undetectable baseline activity (OR = 0.70), and low viral load (OR = 0.79)</td>
<td>-- Treatment of hepatitis C appears to have a positive effect in terms of reversal of fibrosis in treatment-naïve patients; this is especially true in patients treated with combined peginterferon and ribavirin</td>
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