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</thead>
<tbody>
<tr>
<td>Date of Review:</td>
<td>March 22, 2015</td>
</tr>
<tr>
<td>Reviewer(s):</td>
<td>Christine Hu</td>
</tr>
</tbody>
</table>

**Part A**

**Category:**
- Basic Science □
- Clinical Science □
- Public Health/Epidemiology □
- Social Science □
- Programmatic Review ☑

**Best Practice/Intervention:**
- Focus: Hepatitis C ☑
- Hepatitis C/HIV ☑
- Other: liver disease
- Level: Group ☑
- Individual □
- Other: □

**Target Population:** chronic HCV patients

**Setting:** Health care setting/Clinic ☑
- Home □
- Other: □

**Country of Origin:** United States

**Language:** English ☑
- French □
- Other: □

**Part B**

**Is the best practice/intervention a meta-analysis or primary research?**
- YES □
- NO ☑
- N/A □

Systematic review to determine the impact of sustained virological response on liver-related mortality, development of hepatocellular carcinoma, and liver disease progression

**Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?**
- YES □
- NO ☑
- N/A □

Findings were not used for decision making. Authors concluded that given the long-term benefits of SVR shown in HCV patients to reduce liver disease progression, development of hepatocellular carcinoma, and liver-related mortality, SVR should continue to be the goal when treating patients with HCV. Future studies should aim to
maximize the potential of achieving SVR.

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<tr>
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<th>Comments</th>
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<td>Are the best practices/methodology/results described applicable in developed countries?</td>
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<td>Findings can be extended to patients worldwide.</td>
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<tr>
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<td>The research study/tool/data dictionary is easily accessed/available electronically</td>
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<td>Open access for view at <a href="http://www.cghjournal.org/">http://www.cghjournal.org/</a></td>
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</table>

Other relevant criteria:

- Patients with normal serum ALT levels have reduced rate of disease progression to cirrhosis compared with patients with higher ALT levels
- Achievement of SVR before liver transplantation can improve outcome after transplantation in patients with cirrhosis and advanced liver disease

WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW
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<td>Search of literature from January 1991 through March 2011</td>
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<td>Are these data regularly collected at and/or below a national level?</td>
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<td>Electronic search of MEDLINE</td>
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<td>Are these data collected manually or electronically?</td>
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<td>Manually searched references cited in identified articles for additional studies</td>
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**RESEARCH REPORTS**

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<th>Details</th>
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<td><em>Clinical Gastroenterology &amp; Hepatology</em></td>
</tr>
<tr>
<td>Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?</td>
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<td><em>Existing data</em></td>
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</table>
For patients with chronic hepatitis C virus infection, the goal of antiviral therapy is to achieve a sustained virologic response (SVR). We review the durability of the SVR and its effects on liver-related mortality, hepatic decompensation, and the development of hepatocellular carcinoma. We performed a systematic review of the effects of the SVR on liver-related hepatic outcomes and found the SVR to be durable (range, 98.4%–100%). An SVR reduced liver-related mortality among patients with chronic hepatitis C (3.3- to 25-fold), the incidence of hepatocellular carcinoma (1.7- to 4.2-fold), and hepatic decompensation (2.7- to 17.4-fold). An SVR can lead to regression of fibrosis and cirrhosis, and has been associated with a reduced rate of hepatic decompensation, a reduced risk for hepatocellular carcinoma, and reduced liver-related mortality.

Keywords: HCV; Sustained Viral Response; Liver-Related Mortality; Hepatocellular Carcinoma; Hepatic Decompensation.
transferase (ALT) levels. We also searched article reference lists for relevant articles or abstracts. We excluded data with follow-up evaluation of less than 2 years, and also studies with ongoing maintenance therapy, defined as therapy beyond standard acceptable courses (Figure 1).

**Data Extraction and Quality Assessment**

Reviewers abstracted data from the identified studies, and extracted characteristics of each study and its participants. A formal scoring system to rate the study quality of each individual study was not used. Based on inclusion criteria, only studies with a long follow-up period (at least 2 years) were included. Of the studies included, most had cohorts of more than 100 patients, and only 3 cohort studies had fewer than 100 patients studied. Reviewers noted the following as outcomes of interest: rate of SVR, liver-related mortality, development of HCC, and hepatic decompensation. In addition, reviewers noted the degree of fibrosis of the patient population when stratified in the studies.

**Data Synthesis**

The investigators qualitatively synthesized the included studies and summarized the pertinent results into tables, stratifying the discussion of evidence by similar groups such as across all stages of fibrosis, and for those patients with advanced fibrosis.

**Results**

**Durability of Sustained Viral Response**

Sustained viral response is considered to be extremely durable. Yu et al\(^1\) described a cohort of patients and evaluated different doses of IFN, they showed no statistical dose-dependent difference in durability. A combined 63 of 64 patients maintained SVR, with a mean follow-up period of 6.81 years. Formann et al\(^2\) examined 187 patients who had achieved SVR via IFN, IFN and ribavirin, and pegylated (PEG)-IFN and ribavirin. None of the patients had a relapse with a median follow-up period of 29 months.\(^3\) In a long-term follow-up study of patients previously enrolled in clinical trials,\(^3,5,17-22\) with patients receiving either IFN or IFN and ribavirin, it was found that only 12 of 1343 patients (0.9%) who initially achieved SVR were found to have re-infection during a mean follow-up period of 4.1 years.\(^23\) This large cohort of patients included different patient subsets such as those with normal ALT levels, and those with HIV and HCV co-infection. Desmond et al\(^24\) also showed this high durability, with 146 of 147 patients maintaining negative HCV RNA levels over a mean follow-up period of 2.3 years. Giannini et al\(^25\) studied a cohort of 231 chronic hepatitis C patients with at least 48 weeks of follow-up evaluation after therapy with PEG-IFN and ribavirin, and saw that SVR was maintained in 99% of their cohort (Table 1).

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Patients, n</th>
<th>Genotype</th>
<th>Antiviral agent used</th>
<th>Mean follow-up period, y</th>
<th>% SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al(^1)</td>
<td>2005</td>
<td>Taiwan</td>
<td>64</td>
<td>17 genotype 1b, 47 genotype non-1b</td>
<td>IFN</td>
<td>6.81</td>
<td>63/64 (98.4%)</td>
</tr>
<tr>
<td>Formann et al(^2)</td>
<td>2006</td>
<td>Austria</td>
<td>187</td>
<td>91 genotype 1, 92 genotype non-1</td>
<td>12 Standard IFN 73 Standard IFN/RBV 102 PEG-IFN/RBV PEG-IFN/RBV</td>
<td>2.4</td>
<td>187/187 (100%)</td>
</tr>
<tr>
<td>Giannini et al(^25)</td>
<td>2009</td>
<td>Italy</td>
<td>231</td>
<td>77 genotype 1, 80 genotype 2, 70 genotype 3, 4 genotype 4</td>
<td>PEG-IFN/RBV</td>
<td>3.2</td>
<td>229/231 (99.1%)</td>
</tr>
<tr>
<td>Swain et al(^23)</td>
<td>2010</td>
<td>19 countries</td>
<td>1343</td>
<td>Not reported</td>
<td>166 PEG-IFN 1077 PEG-IFN/RBV 100 PEG/IFN ± RBV</td>
<td>4.1</td>
<td>1331/1343 (99.1%)</td>
</tr>
<tr>
<td>Marcellin et al(^13)</td>
<td>1997</td>
<td>France</td>
<td>80</td>
<td>23 genotype 1, 11 genotype 2, 33 genotype 3, 2 other genotypes</td>
<td>IFN</td>
<td>4.0</td>
<td>96%</td>
</tr>
<tr>
<td>Desmond et al(^24)</td>
<td>2006</td>
<td>Australia</td>
<td>147</td>
<td>51 genotype 1, 96 genotype 2/3</td>
<td>34 IFN 76 IFN/RBV 37 PEG-IFN/RBV</td>
<td>2.3</td>
<td>146/147 (99.9%)</td>
</tr>
</tbody>
</table>

RBV, ribavirin.
Patients With Normal Serum Aminotransferase Levels

It is estimated that approximately 30% of patients with chronic hepatitis C have normal ALT levels, and it is believed that their rate of disease progression to cirrhosis is reduced compared with patients with higher ALT levels.26,27 Gordon et al28 studied 1744 patients with HCV treated with IFN therapy, and 105 patients (6%) had normal serum ALT levels. There was no difference in the SVR rate between patients with normal ALT levels (24.8%) compared with those with increased ALT levels (26.8%). Although most patients with normal ALT levels often have no fibrosis on liver histology, there are some patients with normal ALT levels with advanced fibrosis and cirrhosis on liver biopsy, placing them at increased risk for disease progression, and developing HCC.29 Therefore, the decision to treat with IFN should not be based solely on aminotransferase levels.

Impact of Pretransplant Sustained Virologic Response After Liver Transplantation

In patients with cirrhosis and advanced liver disease, achievement of SVR before liver transplantation can improve outcomes after transplantation. There have been observations that treatment with IFN therapy for HCV before transplantation can be beneficial in preventing HCV recurrence, particularly if SVR is achieved.30 However, duration and dose adherence is limited because these patients have difficulty tolerating IFN-based therapy.31 Everson et al32 followed up 124 patients with advanced cirrhosis who were treated with IFN therapy. Of the 124 patients, 47 patients (37.9%) underwent liver transplantation, and of these 47 patients SVR was achieved in 12 (26%). Of the 4 patients who had achieved SVR before transplantation, none of these patients had recurrence of hepatitis in the long-term follow-up evaluation after liver transplantation. In a separate study by Nudo et al,33 patients who achieved an SVR, defined using a sensitive viral assay, and no evidence of viral recurrence after liver transplantation. The patients who had undetectable viral levels prior to liver transplantation (without achieving an SVR) were seen to have a significantly decreased risk of recurrent infection after liver transplantation when compared to patients with a measurable viral load at time of liver transplantation.

Human Immunodeficiency Virus/Hepatitis C Virus Co-infection

Patients who are co-infected with HIV and HCV often have a higher rate of liver disease progression, cirrhosis, and HCC development.34,35 Successful control of HIV infection with highly active antiretroviral therapy can reduce the rate of liver disease progression.36 In a review by Singal et al,37 the SVR rate in HIV/HCV co-infected patients was found to range between 17% and 53%. The pooled SVR rate from 7 randomized controlled trials or prospective cohort studies involving 784 HIV/HCV co-infected patients was 33.3% (range, 27.3%–44.2%) when treated with IFN and ribavirin.38 When measures are taken to increase treatment monitoring and compliance, SVR rates increased significantly and were equivalent to patients with HCV mono-infection. In a retrospective study conducted in a methadone maintenance treatment program of 73 patients with HCV infection, of whom 32% were co-infected with HIV, it was found that HIV/HCV co-infected patients achieved an SVR rate of 43%, and HCV mono-infected patients had an SVR rate of 46%.39

Liver-Related Mortality: All Stages of Fibrosis

Multiple studies have shown a positive effect of SVR on liver-related mortality, regardless of the stage of liver fibrosis (Table 2). Arase et al40 studied a cohort of 500 patients who received IFN therapy for hepatitis C in which 140 patients (28%) reached SVR and looked at long-term outcomes over a follow-up period of 7.4 years. The number of liver-related deaths was decreased significantly in the group that reached SVR, with 2 liver-related deaths of 9 total deaths in the SVR group (22% of

Table 2. Liver-Related Mortality in Sustained Viral Responders and Nonresponders: Outcomes Reported by Each Primary Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Patients, n</th>
<th>Antiviral agent used</th>
<th>Mean follow-up period, y</th>
<th>% SVR</th>
<th>Liver-related deaths, SVR group</th>
<th>Liver-related deaths, non-SVR group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stages of fibrosis</td>
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<td></td>
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<td></td>
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<tr>
<td>Arase et al40</td>
<td>2007</td>
<td>Japan</td>
<td>500</td>
<td>469 IFN, 31 IFN/RBV</td>
<td>7.4</td>
<td>140/500 (28%)</td>
<td>2/140 (1.4%)</td>
<td>32/360 (8.9%)</td>
</tr>
<tr>
<td>Coverdale et al41</td>
<td>2004</td>
<td>Australia</td>
<td>343</td>
<td>IFNalfa</td>
<td>6.81</td>
<td>50/343 (14.6%)</td>
<td>1/50 (2%)</td>
<td>24/293 (8.2%)</td>
</tr>
<tr>
<td>Kasahara et al12</td>
<td>2004</td>
<td>Japan</td>
<td>2668</td>
<td>IFN</td>
<td>6</td>
<td>738/2668 (27.7%)</td>
<td>1/738 (0.14%)</td>
<td>68/1930 (3.5%)</td>
</tr>
<tr>
<td>Yoshida et al12</td>
<td>2002</td>
<td>Japan</td>
<td>2430</td>
<td>IFN</td>
<td>5.4</td>
<td>817/2430 (33.6%)</td>
<td>2/817 (0.24%)</td>
<td>33/1613 (2%)</td>
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<td>Advanced fibrosis</td>
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<tr>
<td>Morgan et al43</td>
<td>2010</td>
<td>United States</td>
<td>526</td>
<td>PEG-IFN/RBV</td>
<td>7.5</td>
<td>140/526 (26.6%)</td>
<td>1/140 (0.7%)</td>
<td>23/386 (6%)</td>
</tr>
<tr>
<td>Bruno et al41</td>
<td>2007</td>
<td>Italy</td>
<td>920</td>
<td>IFN</td>
<td>8</td>
<td>124/920 (13.5%)</td>
<td>2/120 (1.7%)</td>
<td>83/728 (11.4%)</td>
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<td>Braks also</td>
<td>2007</td>
<td>France</td>
<td>113</td>
<td>35 IFN, 40 IFN/RBV, 38 PEG-IFN/RBV</td>
<td>7.7</td>
<td>57/113 (32.7%)</td>
<td>0/37 (0%)</td>
<td>17/113 (15%)</td>
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<td>Mallet et al67</td>
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<td>France</td>
<td>96</td>
<td>61 IFN, 34 IFN/RBV, 1 PEG-IFN/RBV</td>
<td>9.8</td>
<td>39/96 (40.6%)</td>
<td>3/39 (8.6%)</td>
<td>19/57 (31.1%)</td>
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<td>Veldt et al64</td>
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<td>479</td>
<td>131 IFN, 130 IFN/RBV, 10 PEG-IFN/RBV</td>
<td>2.1</td>
<td>142/479 (29.6%)</td>
<td>1/142 (0.7%)</td>
<td>34/479 (7.1%)</td>
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</table>

RBV, ribavirin.

*Number of patients derived from the number of patients with chronic hepatitis C who were treated with IFN therapy, and includes nonresponders and patients who attained SVR. This does not include patients who were recruited into the respective studies but not treated with IFN therapy.
genotype 3 hazard ratio, 0.51; rate of liver-related morbidity/mortality in the SVR group (14.0% related mortality over a course of 7.5 years. They found an adjusted ratio, 0.04; 95% CI, 0.005–0.301; lower for those with SVR than those who were untreated (risk ratio, 0.04; 95% CI, 0.005–0.301; P < .002).12 Yoshida et al12 performed a retrospective study of 2430 patients treated with IFN and 459 untreated patients, and found that liver-related mortality was reduced for those with SVR compared with untreated patients (risk ratio, 0.050; 95% CI, 0.012–0.216). A meta-analysis by Singal et al13 quantitatively assessed the reduction in compensated cirrhosis, development of HCC, and liver-related mortality in patients who achieve SVR compared with those who were nonresponders to therapy. Two investigators independently reviewed 26 studies and pooled rates of compensated cirrhosis, development of HCC, and liver-related mortality in patients with SVR and nonresponders.32–40 In a study by the US Department of Veterans Affairs, followed up a large cohort of 16,864 patients with HCV treated with PEG-IFN and ribavirin, and looked at effects of SVR on all-cause mortality. They followed up 12,166 patients with HCV genotype 1, 2904 patients with HCV genotype 2, and 1794 patients with HCV genotype 3, with SVR rates observed to be 35% in the HCV genotype 1 group, 72% in the HCV genotype 2 group, and 62% in the HCV genotype 3 group. By using genotype-specific multivariate survival models, the study concluded that SVR was associated with a substantially reduced mortality risk for each genotype (hazard ratio, 0.70; P < .0001; genotype 2 hazard ratio, 0.64; P = .006; genotype 3 hazard ratio, 0.51; P = .0002).65

Liver-Related Mortality: Advanced Fibrosis

Patients with advanced fibrosis and hepatitis C also benefit from IFN therapy, and achieving SVR also leads to a lower incidence of liver-related mortality. A recent study including patients with histologically advanced chronic hepatitis C (Ishak fibrosis score, ≥3) who achieved SVR had a lower rate of liver-related mortality over a course of 7.5 years. They found an adjusted rate of liver-related morbidity/mortality in the SVR group (140 patients) of 2.7% compared with 27.2% in the nonresponder group (309 patients) (P < .001).66 Bruno et al66 studied the effect of SVR after IFN therapy on patients with histologically proven cirrhosis (Ishak score, 6; or Knodell score, 4), and found that liver-related mortality was reduced among those who attained SVR (124 patients), compared with those who were nonresponders (759 patients) over 96.1 months of follow-up evaluation. The incidence rate per 100 person-years of liver-related death was 0.19 among those with SVR and 1.44 among those with nonresponse (P < .001).61 Another study looking at the clinical benefit of SVR in patients with hepatitis C and biopsy-proven cirrhosis found that during follow-up evaluation of 7.7 years, none of the 37 patients with SVR had any deaths, whereas 20 of the 76 patients who were nonresponders had liver-related deaths (risk ratio, 0.06; 95% CI, 0.00–0.97; P = .002).66 A study in France followed up 96 patients with chronic hepatitis C and biopsy-proven cirrhosis treated with IFN for 118 months and found that of the 39 patients with SVR, there were 3 liver-related deaths (8.6%), compared with 19 deaths in the 57 patients who were nonresponders (31.1%) (P = .012).67 A 2007 study following up 479 patients with chronic hepatitis C and biopsy-proven advanced fibrosis or cirrhosis who received IFN therapy found that the 29.6% of patients with SVR, attaining SVR was associated with a statistically significant reduction in liver-related death. There was a reduction in the hazard of liver-related death between patients with SVR when compared with nonresponders (adjusted hazard ratio, 0.19; 95% CI, 0.02–1.44; P = .107).64

Hepatocellular Carcinoma Occurrence: All Stages of Fibrosis

Another important outcome of HCV treatment is the development of HCC, and multiple studies have looked at the effect of HCV therapy and SVR on the incidence of developing HCC (Table 3). Arase et al68 studied 500 Japanese patients with chronic hepatitis C in which 140 (28%) had SVR, and a total of 71 patients (14.2%) developed HCC during the follow-up period. A significant difference was seen in the incidence of HCC among those who were nonresponders compared with those with SVR (risk ratio, 1/0.22; 95% CI, 0.096–0.52; P < .0001). In the study by Coverdale et al69 among the 384 patients treated with IFN therapy, 50 patients (15%) reached SVR, whereas 136 patients (40%) relapsed, and 157 patients (46%) were nonresponders. One patient (2%) in the SVR group developed HCC, whereas 5 patients (4%) in the relapse group and 18 patients (11%) in the nonresponse group developed HCC over a 9-year follow-up period. By using a univariate model, the chance of developing HCC was calculated as increased by a factor of 3.3 across each treatment response category (95% CI, 1.4–7.6; P = .004).61 Another study in Japan studied 594 patients who received IFN therapy, with a follow-up period of (mean ± standard deviation) 57.2 ± 13.9 months to assess for HCC development. Of the 594 treated patients, 175 patients (29.5%) had SVR, and it was seen that IFN therapy significantly decreased the incidence of HCC among patients with SVR (hazard rate ratio, 0.16; 95% CI, 0.09–0.79; P < .001) compared with nonresponders.66 A retrospective cohort study in 2007 of 1124 patients who received IFN therapy showed a 3.5% rate of HCC development in the 373 patients with SVR, compared with an 8.1% rate in the patients who did not have SVR.64 Hung et al61 also showed a similar difference in HCC incidence rates. Of 132 patients treated with IFN, 73 patients (55%) achieved SVR, and during a median follow-up period of 37 months, HCC developed in 5 patients with SVR (6.8%), and in 11 patients who did not have SVR (18.6%) (P = .0178). Bruno et al61 enrolled 920 patients, of whom 124 patients (13.5%) achieved SVR, and during a mean follow-up period of 96.1 months, the rate of HCC per 100 person-years of follow-up evaluation was 0.66 (95% CI, 0.27–1.37) for those with SVR and 2.10 (95% CI, 1.75–2.51) for those without SVR (P < .001). Therefore, patients who did not achieve SVR had a 2.59-fold increased rate of HCC development than those with SVR.61
Table 3. HCC Occurrence in Sustained Viral Responders and Nonresponders: Outcomes Reported by Each Primary Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Patients, n</th>
<th>Antiviral agent used</th>
<th>Mean follow-up period, y</th>
<th>% SVR</th>
<th>HCC occurrence, SVR group</th>
<th>HCC occurrence, non-SVR group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stages of fibrosis</td>
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</tr>
<tr>
<td>Arase et al&lt;sup&gt;60&lt;/sup&gt;</td>
<td>2007</td>
<td>Japan</td>
<td>500</td>
<td>469 IFN, 31 IFN/RBV</td>
<td>7.4</td>
<td>140/500 (28%)</td>
<td>13/140 (9.3%)</td>
<td>58/360 (16.1%)</td>
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<td>Coverdale et al&lt;sup&gt;41&lt;/sup&gt;</td>
<td>2004</td>
<td>Australia</td>
<td>343</td>
<td>IFN</td>
<td>6.81</td>
<td>50/343 (14.6%)</td>
<td>1/50 (2%)</td>
<td>23/293 (7.8%)</td>
</tr>
<tr>
<td>Tanaka et al&lt;sup&gt;68&lt;/sup&gt;</td>
<td>2000</td>
<td>Japan</td>
<td>594</td>
<td>IFN</td>
<td>4.8</td>
<td>175/594 (29.5%)</td>
<td>3/175 (1.7%)</td>
<td>30/419 (7.2%)</td>
</tr>
<tr>
<td>Kobayashi et al&lt;sup&gt;69&lt;/sup&gt;</td>
<td>2007</td>
<td>Japan</td>
<td>1124</td>
<td>1039 IFN, 85 IFN/RBV</td>
<td>5.5</td>
<td>373/1124 (33.2%)</td>
<td>13/373 (3.5%)</td>
<td>61/751 (8.1%)</td>
</tr>
<tr>
<td>Hung et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2006</td>
<td>Taiwan</td>
<td>132</td>
<td>IFN/RBV</td>
<td>3.1</td>
<td>73/132 (55%)</td>
<td>5/73 (6.8%)</td>
<td>11/59 (18.6%)</td>
</tr>
<tr>
<td>Bruno et al&lt;sup&gt;61&lt;/sup&gt;</td>
<td>2007</td>
<td>Italy</td>
<td>920</td>
<td>IFN</td>
<td>8</td>
<td>124/920 (13.5%)</td>
<td>7/124 (5.6%)</td>
<td>122/759 (16.1%)</td>
</tr>
<tr>
<td>Advanced fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirakawa et al&lt;sup&gt;60&lt;/sup&gt;</td>
<td>2008</td>
<td>Japan</td>
<td>1193</td>
<td>1032 IFN, 161 IFN/RBV</td>
<td>8.3</td>
<td>1193/1193 (100%)</td>
<td>9/1193 (0.75%)</td>
<td></td>
</tr>
<tr>
<td>Mallet et al&lt;sup&gt;67&lt;/sup&gt;</td>
<td>2008</td>
<td>France</td>
<td>96</td>
<td>IFN, 34 IFN/RBV, 1 PEG-IFN/RBV</td>
<td>9.8</td>
<td>39/96 (40.6%)</td>
<td>3/39 (8.6%)</td>
<td>14/57 (24.6%)</td>
</tr>
<tr>
<td>Cardoso et al&lt;sup&gt;72&lt;/sup&gt;</td>
<td>2010</td>
<td>France</td>
<td>307</td>
<td>33 IFN ± RBV, 22 PEG-IFN, 252 PEG-IFN/RBV</td>
<td>3.5</td>
<td>103/307 (33%)</td>
<td>6/103 (5.8%)</td>
<td>40/204 (19.6%)</td>
</tr>
</tbody>
</table>

RBV, ribavirin.

<sup>a</sup>Number of patients derived from the number of patients with chronic hepatitis C who were treated with IFN therapy, and includes nonresponders and patients who attained SVR. This does not include patients who were recruited into the respective studies but not treated with IFN therapy.

<sup>b</sup>Inclusion criteria of this study was to have SVR, therefore the percentage of SVR is 100%.

**Hepatocellular Carcinoma Occurrence: Advanced Fibrosis**

There are few studies that have examined the incidence of HCC development in patients with advanced fibrosis treated with IFN therapy and have achieved SVR. This may be owing to the small subset of patients with advanced fibrosis who typically are treated with IFN therapy. A 2008 study of 1193 patients who achieved SVR after IFN therapy showed the rate of developing HCC was significantly higher in the 41 patients with cirrhosis (liver fibrosis stage, F4), than in the 1106 patients with liver fibrosis stages F0 to F3 (hazard ratio, 12.9; 95% CI, 5.5–30.6; P < .001). The cumulative HCC development rate in patients with cirrhosis after attaining SVR was 15.5%, 24.2%, and 39.4%, at 5, 10, and 15 years after SVR, respectively, and the rates for those with liver fibrosis stages F0 to F3 were 1.00%, 1.68%, and 1.68% at 5, 10, and 15 years after SVR, respectively.<sup>70</sup> In a study by Mallet et al<sup>67</sup> 96 patients with biopsy-proven cirrhosis (liver fibrosis stage, F4) treated with IFN therapy for hepatitis C were followed up for a median period of 118 months. Of this group, 39 patients (40.6%) achieved SVR, and 3 patients (8.6%) with SVR developed HCC during the follow-up period, compared with 14 patients (23.3%) in the nonresponder group (P = .097). Cardoso et al<sup>71</sup> evaluated 307 patients with chronic hepatitis C, of whom 127 patients (41.4%) had bridging fibrosis and 180 patients (58.6%) had cirrhosis. Cox regression analysis was used to assess the impact of IFN therapy on the incidence of HCC. SVR was seen in 37% of patients with bridging fibrosis and 30% of patients with cirrhosis (P = .186), and over a median follow-up period of 3.5 years, the incidence rates per 100 person-years of HCC was 1.24 for those with SVR and 5.85 among non-SVR patients (log-rank test, P < .001). The data from these studies show that achieving SVR in advanced fibrosis decreases the risk of HCC occurrence.

**Liver Disease Progression and Hepatic Decompensation: All Stages of Fibrosis**

Treatment for HCV is associated with a reduced risk of liver disease progression<sup>7–9</sup> (Table 4). Bruno et al<sup>72</sup> followed up 47 patients who attained SVR over 102 months, and observed that liver histology progressively improved in the patients with SVR. In all 47 patients, there were no decompensated events, and no deterioration in the histologic scores over time, and an improvement was noted in 88% of the patients (P < .0001). A retrospective study by Shiratori et al<sup>73</sup> assessing changes in hepatic fibrosis after IFN therapy saw that of the 183 patients who attained SVR, activity grade on histology was improved in 89% of those patients, whereas untreated patients had an unchanged activity grade (95% CI, 83%–93%). Those with SVR had an associated mean reduction in fibrosis score at more than 3 years of follow-up evaluation. Only 2 of the 183 patients who attained SVR had increased disease activity on biopsy (1.1%) compared with 58 of the 304 patients without SVR who had increased disease activity on repeat biopsy (19.1%). They also found that among patients without pre-existing cirrhosis, 10.9% of the 274 treated patients without SVR progressed to cirrhosis over 38 months, whereas none of the 159 patients with SVR developed cirrhosis. George et al<sup>74</sup> conducted a study of 150 patients with SVR followed up for 5 years after therapy for chronic HCV and monitored liver-related outcomes and evidence of biochemical or virologic relapse. Of the 150 patients, virologic relapse was not seen, and in a blind rescoring of 49 paired biopsies (taken pretreatment and at long-term follow-up evaluation), 40 patients (82%) had a decrease in fibrosis score. Only 1 patient had an increase in inflammation seen on histology and developed HCC. None of the patients in the study had decompensated liver disease. Huang et al<sup>75</sup> studied biopsy-proven, noncirrhotic, chronic hepatitis C patients who received IFN-based ther-
Advanced fibrosis and chronic hepatitis C, attaining SVR with IFN therapy, has shown promising data on preventing progression or even leading to regression of disease. In the study by Bruno et al.\(^2\), of the 47 patients who attained SVR with IFN therapy, 10 of the patients had biopsy-proven liver cirrhosis at the time of initial evaluation, and at follow-up evaluation 5 patients had a reduction of their fibrosis score, and 4 patients did not show any change. None of these patients showed progression of their liver disease. A study conducted in Spain followed up a group of 153 patients with SVR after IFN therapy over a mean follow-up period of 76 ± 13 months (SD), in which no evidence of virologic relapse was seen after the therapy period. Five patients (3.26%) had biopsy-proven cirrhosis before treatment and none of the patients showed evidence of hepatic decompensation during the follow-up period.\(^3\) Another study by Iacobellis et al.\(^4\) studied patients with decompensated cirrhosis as a result of hepatitis C, in which 129 patients were enrolled and 66 patients received IFN therapy. After a follow-up period of 30 months, it was found that decompensated events occurred in 52, 33, and 3 of controls, nonresponders, and SVR patients, respectively. The annualized incidence of death was 2.34, 1.91, and 0 per 1000 patient-years, respectively, in controls, nonresponders, and SVR patients. Because patients with decompensated cirrhosis have a high risk of adverse events on IFN therapy, liver transplantation is still recommended, but these limited data do provide a promising alternative for those who are not transplantation candidates and warrants further investigation.

### Conclusions

The significance of SVR has been shown in the individual studies detailed in this review article. Long-term benefits of SVR have been shown in patients with chronic hepatitis C because SVR has been associated with reducing liver disease progression, development of HCC, and liver-related mortality. These benefits are seen in those with all degrees of liver fibrosis, and the effects are significant even in those with advanced fibrosis. SVR should continue to be the goal in treating patients with chronic hepatitis C because it is the best marker of successful therapy. Future studies of treatment regimens and outcomes should be conducted with aims to maximize the potential of achieving SVR.

### References


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### Table 4. Liver Disease Progression and Hepatic Decompensation in Sustained Viral Responders and Nonresponders: Outcomes Reported by Each Primary Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Patients, n(^a)</th>
<th>Antiviral agent used</th>
<th>Mean follow-up period, y</th>
<th>% SVR</th>
<th>Disease progression/hepatic decompensation, SVR group</th>
<th>Disease progression/hepatic decompensation, non-SVR group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruno et al(^2),(^b)</td>
<td>2001</td>
<td>Italy</td>
<td>47(^c)</td>
<td>IFN</td>
<td>8.5</td>
<td>47/47 (100%)</td>
<td>0/47(^d) (0%)</td>
<td></td>
</tr>
<tr>
<td>Shiratori et al(^3),(^b)</td>
<td>2000</td>
<td>Japan</td>
<td>487</td>
<td>IFN</td>
<td>3.7</td>
<td>183/487 (37.6%)</td>
<td>2/183 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Huang et al(^4),(^b)</td>
<td>2007</td>
<td>Taiwan</td>
<td>892</td>
<td>IFN/RBV, 264</td>
<td>5</td>
<td>630/892 (70.6%)</td>
<td>24/630 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>George et al(^5),(^b)</td>
<td>2008</td>
<td>United States</td>
<td>150(^d)</td>
<td>146 IFN/RBV, 4 PEG-IFN/RBV</td>
<td>5</td>
<td>150/150 (100%)</td>
<td>1/150 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>Bruno et al(^2),(^b)</td>
<td>2001</td>
<td>Italy</td>
<td>47(^d)</td>
<td>IFN</td>
<td>8.5</td>
<td>47/47 (100%)</td>
<td>0/47(^d) (0%)</td>
<td></td>
</tr>
<tr>
<td>Trapero-Marugan et al(^6)</td>
<td>2011</td>
<td>Spain</td>
<td>5(^d)</td>
<td>PEG-IFN/RBV</td>
<td>6.3</td>
<td>5/5 (100%)</td>
<td>0/5 (0%)</td>
<td></td>
</tr>
<tr>
<td>Iacobellis et al(^7),(^e)</td>
<td>2007</td>
<td>Italy</td>
<td>61</td>
<td>PEG-IFN/RBV</td>
<td>2.5</td>
<td>13/61 (21.3%)</td>
<td>3/13 (23.1%)</td>
<td></td>
</tr>
</tbody>
</table>

RBV, ribavirin.

\(^a\) Number of patients derived from the number of patients with chronic hepatitis C who were treated with IFN therapy, and includes nonresponders and patients who attained SVR. This does not include patients who were recruited into the respective studies but not treated with IFN therapy.

\(^b\) Study of liver disease progression by liver histology.

\(^c\) Number of patients derived from the number of patients with chronic hepatitis C who were treated with IFN therapy, and includes nonresponders and patients who attained SVR. This does not include patients who were recruited into the respective studies but not treated with IFN therapy.

\(^d\) Study of liver disease progression by events.

\(^e\) Inclusion criteria of this study was to have SVR, therefore the percentage of SVR is 100%.

\(^f\) Study of hepatic decompensation by events.
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carcinoma in patients with hepatitis C virus-related cirrhosis. J
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long-term follow-up of chronic hepatitis C patients. Aliment
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78. This author discloses the following: Sammy Saab is on the advisory board and on the speaker bureau for Genentech, Merck, and Vertex. The remaining author discloses no conflicts.