A Review of the Treatment of Chronic Hepatitis C Virus Infection in Cirrhosis

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ABSTRACT

Background: Cirrhosis developing during chronic infection with the hepatitis C virus (HCV) poses a risk of anticipated liver-related death, therefore representing a dominant indication to anti-HCV therapy.

Objective: This review highlights the efficacy and safety of treatment of HCV infection in cirrhotic patients with respect to the clinical stage of the disease.

Methods: The PubMed, MEDLINE, EMBASE, and Cochrane databases, as well as the conference proceedings from the annual meetings of the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver, were searched for articles published in English from January 1990 through May 2010, fulfilling the following criteria: (1) randomized, prospective observational, retrospective, or meta-analysis; (2) involving adult patients with chronic HCV infection; and (3) data (fibrosis stage, treatment regimen, efficacy, safety) available for cirrhotics. Reviews were excluded. Search terms included *chronic hepatitis C, fibrosis, cirrhosis, interferon alfa, ribavirin, hepatocellular carcinoma,* and *liver decompensation*.

Results: Forty-five studies were identified. The rates of sustained virologic response to pegylated interferon in combination with ribavirin ranged from 10% to 44% for HCV genotypes 1/4 to 33% to 72% for genotypes 2/3 in compensated cirrhosis, while falling to 0% to 16% and 44% to 57%, respectively, in the decompensated stage, compared with 29% to 55% for genotypes 1/4 and 70% to 80% for genotypes 2/3 in noncirrhotic patients (compensated cirrhosis vs no cirrhosis: $P < 0.001$ for genotypes 1/4 and $P = 0.002$ for genotypes 2/3; decompensated cirrhosis vs no cirrhosis: $P < 0.001$ for all genotypes). HCV clearance was associated with a reduced risk of liver decompensation, hepatocellular carcinoma development, liver-related mortality, and hepatitis recurrence after liver transplantation. Treatment during compensated cirrhosis proved to be most cost-effective versus treatment after decompensation or a no-treatment strategy. Headache (54%), irritability (38%), fatigue (34%), and nausea (30%) were the most common adverse events in compensated patients, while anorexia (100%), fatigue (59%), neutropenia (53%), and thrombocytopenia (50%) were most common in decompensated patients.

Conclusions: Anti-HCV treatment in cirrhotic patients was less effective than in noncirrhotic patients. Viral eradication reduced the risk of liver complications and improved survival in noncirrhotics. Based on effectiveness and tolerability data, therapy has a significant effect in patients with compensated cirrhosis, while decompensated patients need to weigh the risks versus benefits of treatment. (*Clin Ther*. 2010;32:2117–2138)

Key words: hepatitis C, cirrhosis, interferon alfa, ribavirin, liver decompensation

INTRODUCTION

Chronic infection with the hepatitis C virus (HCV) is a major health problem affecting >180 million people worldwide.[1] In the United States, the rate of new cases declined from 5.2 per 100,000 population in 1995 to 0.5 per 100,000 population in 2007.[2] Nevertheless, the burden of HCV infection remains substantial with ~3.2 million persons being chronically infected.[3] The prognosis of HCV infection varies according to fibrosis progression, with the risk of cirrhosis development ranging from 5% to 25% over a 25- to 30-year period.[4,5] Persons with HCV-related cirrhosis develop hepatic

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decompensation at a rate of 30% over 10 years and hepatocellular carcinoma (HCC) at annual rates between 3% in North America, Europe, and Australia, and 8% in Asian and African countries.[6,7] HCV eradication is the only therapeutic intervention that may halt disease progression and improve the quality of life of infected patients. Among 235 patients (133 responders and 102 treatment failures) at an average of 3.7 years after the end of anti-HCV treatment, nonresponders had lower physical (42.5 vs 49.2) and mental (40.5 vs 46.1) component summary scores ($P < 0.01$). Additionally, treatment failures were more likely to have missed work, volunteer opportunities, or household activities (44% vs 9%; $P < 0.001$).[8] In Denmark, according to a nationwide cohort study[9] of 6292 patients, the 5-year survival rate was 86% (95% CI, 84%–87%) in the chronic HCV group compared with 92% (95% CI, 91%–94%) in the group with eradicated HCV infection. Persistent HCV infection was associated with higher overall mortality (relative risk [RR] = 1.55; 95% CI, 1.28–1.86) and liver-related death (RR = 2.42; 95% CI, 1.51–3.88).[9] The eradication of chronic HCV can be achieved by treatment with interferon (IFN)-based therapies coupled with ribavirin (Rbv), as reported in key trials and studies[10–12] that will be discussed further in the text. Patients most in need of treatment are those with advanced fibrosis or cirrhosis, in whom HCV eradication prevents liver-related complications such as decompensation and HCC, leading to improved survival.[13,14] However, antiviral treatment of these patients is challenging because of frequent comorbidities that affect patient adherence to the scheduled therapies, the risk of serious adverse events (AEs) related to therapy, and hyporesponsiveness to IFNα due to still poorly identified mechanisms.[15]

The objective of this article is to provide a review of the efficacy and safety of chronic HCV treatment in patients with cirrhosis according to clinical stage, based on the recently published literature.

METHODS

Studies that report at least one of the following aspects of antiviral treatment of HCV in patients with cirrhosis were sought: indications, safety, efficacy, and tolerability. Although preference was given to randomized controlled trials and prospective observational studies, retrospective studies and conference proceedings over the previous 5 years from the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver were also reviewed. For each of these topics, PubMed, MEDLINE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and EMBASE were searched for English-language articles published from January 1990 to May 2010. Search terms included *chronic hepatitis C, fibrosis, cirrhosis, interferon alfa, ribavirin*, and *hepatocellular carcinoma*. Articles were included in the review if the population consisted of adults aged ≥18 years with chronic HCV infection treated with IFN with or without Rbv, and if the reported data included baseline characteristics of the study population (age, sex, comorbidities, history of treatment), characteristics of the antiviral treatment (type of IFN, doses, duration of treatment), and data on efficacy (rates of viral eradication, recurrence of HCV infection after transplantation) and safety (adverse effects, need for dose reduction, dropouts). Studies involving cirrhotic and noncirrhotic patients were selected if data for cirrhotics were available. Review articles were not used except to identify other primary papers. To assess the safety and tolerability of antiviral treatment in cirrhotic patients, a database of studies was created. Based on available data, the median percentage and range of the reported AEs and discontinuation rates were then calculated.

WHY SHOULD PATIENTS WITH HCV-RELATED CIRRHOSIS BE TREATED?

The current standard of care therapy for chronic HCV is the combination of pegylated IFNα (PegIFNα) and the guanosine analogue Rbv, which provides a *sustained virologic response* (SVR), defined as the absence of detectable HCV RNA in serum 24 weeks after treatment discontinuation in 29% to 55% of patients with genotypes 1/4 and 70% to 80% in those with HCV genotypes 2/3.[10–12,16,17] Although the exact mechanisms of action of these 2 drugs are still elusive, IFN acts initially by inhibiting cell production of new virions, leading to a rapid first-phase decline in viremia, followed by a second, more lengthy phase of decline of viremia, which results from clearance of virus-producing infected liver cells.[18] Rbv has multiple effects, spanning from a direct antiviral effect to the enhancement of IFN signaling.[19] When administered as monotherapy, Rbv exhibits a weak antiviral action that conflicts with the ability to at least double the antiviral effect of IFNα once the 2 drugs are administered in combination.[20,21]

The AASLD recommends therapy for adults with chronic HCV who have detectable HCV RNA in serum,

elevations in aminotransferase levels, histologic evidence of progressive liver disease, and no other serious coexisting comorbidities or contraindications.[17] Identifying individuals at risk for developing progressive liver disease requires the assessment of the fibrosis stage by a liver biopsy, using a validated staging system such as Ishak (0–6)[22] or Metavir (0–4)[23] scores. Persons with no or minimal fibrosis (Metavir 0–1, Ishak 0–2) have a low risk for liver-related complications and liver-related death over 10 to 20 years of follow-up, whereas the presence of bridging fibrosis (Metavir 3, Ishak 4) predicts progression to cirrhosis (Metavir 4, Ishak 5–6), thus representing a priority for treatment.[24]

Currently, 2 forms of PegIFNα exist: PegIFNα-2a* and PegIFNα-2b,† which show differences in terms of pharmacokinetics and pharmacodynamics.[25,26] The recommended dose of PegIFNα-2a is 180 μg/wk given subcutaneously in combination with oral Rbv 1000 mg (actual body weight ≤75 kg) to 1200 mg (actual body weight ≥75 kg) daily for genotypes 1 or 4 and 800 mg daily, regardless of body weight, for genotypes 2 or 3. PegIFNα-2b is administered subcutaneously in a dose of 1.5 μg/kg of actual body weight per week together with slightly different daily doses of Rbv. The dose of PegIFNα-2b is 800 mg for patients <65 kg, 1000 mg for those 65 to 85 kg, 1200 mg for those 85 to 105 kg, and 1400 mg for patients weighing 105 to 125 kg. The duration of treatment is 48 weeks for patients infected with genotypes 1 or 4 and 24 weeks for those infected with genotypes 2 or 3. The absence of HCV RNA from serum at week 4 of treatment is defined as rapid virologic response (RVR); at week 12, complete early virologic response (cEVR); at the end of therapy, end of treatment response (ETR); and at 24 weeks following discontinuation of therapy, *SVR*, which is also defined as successful treatment or "virologic cure."[17]

The clinical utility of treating patients with established cirrhosis has been a matter of debate in the past. Studies on the treatment of HCV-related cirrhosis[27,28] failed to report the benefit of viral eradication in subjects with advanced liver disease. In the European Concerted Action on Viral Hepatitis multicenter, retrospective, longitudinal study[27] of 329 consecutive white cirrhotic patients (mean age, 55 years; 193 [59%] treated with IFN; median follow-up, 5 years), the annual incidence of HCC was 2.3% for untreated and 1.0% for treated patients ($P = 0.09$), whereas the incidence of hepatic decompensation was 1.5% and 5.7%, respectively ($P = 0.07$). A prospective, randomized controlled trial[28] compared 47 patients (median age, 57 years; male/female ratio, 2.36; median known duration of disease, 9.4 years) treated with IFNα-2b for 48 weeks with 52 untreated patients with similar demographic characteristics; both groups were followed for a median period of 160 weeks. The rates of liver decompensation (7/47 [15%] vs 5/52 [10%]), HCC development (5/47 [11%] vs 9/52 [17%]), and survival (37/47 [79%] vs 47/52 [90%]) did not differ between treated patients and the control group (P = NS for all comparisons).[28]

The aforementioned studies, however, were conducted with IFNα monotherapy given in a dose of 3 to 9 million units (MU) 3 times a week for a period of <48 weeks, a treatment strategy that is no longer recommended. This concept was overridden in recent years by studies[29–31] supporting the claim that eradication of HCV infection prevents progression to potentially fatal complications by ameliorating portal hypertension and eventually leading to fibrosis regression, effectively confronting the dogma of cirrhosis being a nonreversible condition. The analysis of 4 randomized trials, pooling data of 3010 naive patients (median age, 43 years; 65% males; median known duration of infection, 18 years) treated with 10 different regimens of standard IFNα or PegIFNα with or without Rbv, evaluated the severity of fibrosis via pre- and posttreatment liver biopsies.[29] The reversal of cirrhosis was observed in 75 (49%) of 153 patients with baseline cirrhosis. An open-label, randomized, parallel-dose trial[30] compared the effects of 48 weeks of treatment with 90 or 180 μg PegIFNα-2a once weekly and 3 MU of standard IFNα-2a 3 times weekly in 271 patients with bridging fibrosis or cirrhosis (mean age, 48 years; 72% males; 61% whites). Patients achieving SVR (n = 40) had the greatest improvements in fibrosis (–1.0; $P < 0.001$) and inflammation (–0.65; $P < 0.001$). Patients who achieved HCV RNA suppression under the level of detection during treatment, but relapsed after treatment discontinuation (n = 59), also experienced improvement in fibrosis (–0.04; $P < 0.001$) and inflammation (–0.14; $P = 0.077$). In nonresponders (n = 85), no significant improvement in inflammation or fibrosis was observed.[30]

The treatment-related improvement of liver histology has also been reported. In a retrospective analysis[31] of data from 8 trials with 1076 patients (median age, 44 years; 69% males; 77% white; 807 [75%] infected

*Trademark: Pegasys® (Hoffmann-La Roche Inc., Basel, Switzerland).

†Trademark: PegIntron® (Merck/Schering-Plough, Whitehouse Station, NJ).

with genotype 1; 269 [23%] with advanced fibrosis or cirrhosis) treated for 46 weeks with IFNα or PegIFNα with or without Rbv for 48 weeks, a positive correlation was found between the degree of virologic response and improvements in inflammation and fibrosis, as well as an inverse correlation with worsening activity and fibrosis (all comparisons, $P < 0.001$). Patients with SVR had the greatest histologic benefit. Relapsers and patients with breakthrough also demonstrated fibrosis regression compared with nonresponders ($P = 0.003$).[31]

Cirrhotic patients who have cleared HCV infection exhibited lower rates of liver decompensation, HCC development, and liver-related death (**Table I**).[14,32–37] This evidence initially was provided by Yoshida et al[38] in the retrospective Inhibition of Hepatocarcinogenesis by Interferon Therapy study, which included 2890 patients (337 [12%] cirrhotics) treated with IFNα 6 MU every other day, IFNβ 3.4 MU per day, or a combination of the 2 in a dosage of 4.2 MU per day. Cirrhotic patients achieving SVR were found to have reduced risk for HCC development (RR = 4.78; 95% CI, 1.13–20.18) versus those not achieving viral eradication (RR = 12.23; 95% CI, 6.81). Risk reduction was most prominent in patients aged <40 years (RR = 0.516; 95% CI, 0.358–0.742).[38] These results were confirmed by 3 prospective observational studies.[32,33,35] In Italy, a cohort of 920 patients with compensated cirrhosis[14] was treated with IFNα (3–6 MU 3 times a week for 1 year) and followed post-treatment for a median of 96 months. The incidence rates per 100 person-years of liver-related complications, HCC, and liver-related death were 0, 0.66, and 0.19, respectively, among patients with SVR and 1.88, 2.10, and 1.44 among those without SVR ($P < 0.001$). Failure to achieve SVR was associated with a higher risk of liver-related complications (RR not applicable), HCC (RR = 3.12; 95% CI, 1.42–6.86), and liver-related mortality (hazard ratio [HR] = 7.59; 95% CI, 1.84–31.29).[14] In another cohort of patients,[36] followed for up to 18 years (median, 11.4 years), achievement of SVR was found to prevent the development of esophageal varices (0% for SVR vs 31.9% for untreated and 39.1% for non-SVR patients; $P < 0.001$).

The favorable impact of an SVR in the context of HCV-related cirrhosis was confirmed in a study[34] that analyzed 479 patients with advanced fibrosis or cirrhosis (Ishak 4–6). SVR (29.6%) was associated with risk reduction of any event (HR = 0.20; 95% CI, 0.07–0.58; $P = 0.003$), including liver failure (HR = 0.03; 95% CI 0.00–0.91; P not applicable). Comparing clinical outcomes between patients with and without SVR, a numeric reduction in liver-related death (per 10,000 patient-years; incidence, 36 vs 283 patients, respectively) and HCC (107 vs 277) among patients with SVR was observed, although it did not reach a level of statistical significance (HR = 0.14; 95% CI, 0.02–1.03 and HR = 0.46; 95% CI, 0.14–1.52, respectively).[34]

In a study conducted by Cardoso et al,[37] which included 307 patients with bridging fibrosis or cirrhosis who were followed for 3.5 years and had a reported SVR rate of 33%, incidence rates per 100 person-years of liver-related complications, liver-related death, and HCC were significantly lower in SVR versus non-SVR patients (0.62 vs 4.16, 0.61 vs 3.76, and 1.24 vs 5.85, respectively; $P < 0.001$ for all comparisons). Non-SVR was an independent predictor of HCC (HR = 3.06; 95% CI, 1.12–8.39), liver-related complications (HR = 4.73; 95% CI, 1.09–20.57), and liver-related death (HR = 3.71; 95% CI, 1.05–13.05).[37]

The main results of the aforementioned studies are summarized in **Table I**.[14,32–37] Although these studies definitely outline the beneficial impact of successful antiviral treatment in terms of reduction and prevention of cirrhosis-related complications, they also report that viral eradication does not eliminate the risk of HCC, since liver cancer has been reported to occur years after a cure, especially in patients with cirrhosis at the time of achieving SVR, at a rate between 0.66 and 1.24 per 100 person-years[14,37] or between 0.6% and 2.5% annually.[32–34,39] Consequently, AASLD guidelines recommend that cirrhotic patients who achieve HCV eradication should remain on surveillance programs aimed at the early diagnosis of HCC.[40]

WHEN SHOULD PATIENTS WITH HCV-RELATED CIRRHOSIS BE TREATED?

To compare the cost-effectiveness of HCV therapy at different stages of cirrhosis, a Markov model was constructed in a 4000-patient entry cohort of patients aged 55 years, infected with genotype 1 that was followed for over 17 years.[41] Compared with a no-treatment strategy, the treatment of patients with compensated cirrhosis was found to save US $55,314 and to increase quality-adjusted life-years (QALYs) by 0.950. Treatment during decompensated cirrhosis saved $5511 and increased QALYs by 0.044, while treatment of recurrent HCV infection after liver transplantation saved $3223 and increased QALYs by 0.061. The treatment of patients with compensated cirrhosis resulted in 119 fewer deaths, 54 fewer cases of HCC, and 66 fewer liver transplantations

Table I. Overview of studies demonstrating the benefits of anti-HCV treatment in patients with advanced fibrosis and cirrhosis.

Study, Year	Study Design	Inclusion Criteria	No. of Patients	Regimen (n)	% SVR	Events and % Patients With and Without SVR	HR or RR (95% CI)	*P*
Shiratori et al, 2005[32]	Prospective observational	Cirrhosis (Metavir F4), Child-Pugh A, elevated ALT	345	IFNα-2a 6–9 MU tiw (157) Natural IFNα 6–9 MU tiw (114) No treatment (74)	23.6	Liver-related mortality: 0, 73 HCC: 17, 35	SVR vs non-SVR NA 0.31 (0.16–0.61)	 NA <0.001
Hung et al, 2006[33]	Prospective observational	Cirrhosis	132	IFNα-2b 3–5 MU tiw + Rbv 1000–1200 mg/d	55	HCC: 8, 28	Non-SVR vs SVR 3.5 (1.087–11.36)	0.036
Bruno et al, 2007[14]	Retrospective	Cirrhosis (Ishak 6 or Knodell 4), Child-Pugh A	920	IFNα-2b 3–6 MU tiw	13.5	Liver complications: 0, 14 HCC: 6, 16 Liver-related mortality: 2, 11	Non-SVR vs SVR NA NA 3.12 (1.42–6.86) 7.59 (1.84–31.29)	 <0.001 <0.001 <0.001
Veldt et al, 2007[34]	Retrospective	Advanced fibrosis/cirrhosis (Ishak 4–6)	479	IFNα (131) FNα + Rbv (130) PegIFNα (10) PegIFNα + Rbv (208) Dosage NA	29.6	Overall: 0.2, 17 Liver-related mortality: 0.2, 7 Liver failure: 0, 9 HCC: 0.6, 7	SVR vs non-SVR 0.21 (0.07–0.58) 0.19 (0.02–1.44) NA 0.46 (0.12–1.70)	 0.003 0.107 NA 0.25
Floreani et al, 2008[35]	Prospective observational	Chronic hepatitis C	87	PegIFNα-2b 0.8–1 μg/kg/wk + Rbv 1000–1200 mg/d	46	HCC: 0, 5	NA	NA
Bruno et al, 2010[36]	Prospective observational	Cirrhosis, Child-Pugh A, aged <70 years	218	IFNα 3 MU tiw (NA) IFNα 3 MU tiw + Rbv (NA) PegIFNα (NA) PegIFNα + Rbv (NA)†	22.8	Esophageal varices: 0, 31	NA	NA
Cardoso et al, 2010[37]	Retrospective	Bridging fibrosis/cirrhosis (Metavir 3–4)	307	IFNα ± Rbv (34) PegIFNα (21) PegIFNα + Rbv (252) Dosage NA	33	Liver complications: 1, 9 Liver-related mortality: 1, 9 HCC: 2, 13	Non-SVR vs SVR 4.73 (1.09–20.57) 3.71 (1.05–13.05) 3.06 (1.12–8.39)	 <0.001 <0.001 <0.001

HCV = hepatitis C virus; SVR = sustained virologic response; HR = hazard ratio; RR = relative risk; ALT = alanine transaminase; IFNα = interferon α; MU = million units; tiw = 3 times weekly; HCC = hepatocellular carcinoma; NA = not available; Rbv = ribavirin; PegIFNα = pegylated interferon α.

*Dosage of Rbv in studies is weight-based. See text for details.

† Exact dosages of PegIFNα and Rbv were not available in this study. According to the authors, drugs were administered in agreement with international guidelines.

compared with no treatment.[41] This analysis provides a rationale for offering therapy at the compensated stage, before progression to more advanced liver disease occurs.

TREATMENT OF COMPENSATED CIRRHOSIS

Compensated cirrhosis is defined by the presence of preserved liver function (Child-Pugh class A) and the absence of clinical complications such as ascites, variceal bleeding, and hepatic encephalopathy. Bridging fibrosis and cirrhosis have long been considered to be among the strongest negative predictors of treatment outcome, taking into consideration also that cirrhotic patients are often males, of older age, and commonly experience comorbidities such as obesity, diabetes mellitus, and alcohol consumption ≥50 g/d, negatively influencing adherence to and the safety and efficacy of antiviral treatment.[35,42] Indeed, the overall SVR rate among cirrhotic patients is lower compared with patients with a less advanced fibrosis stage (**Table II**).[33,35,43–52]

A landmark prospective randomized trial[43] comparing the efficacy of monotherapy with standard IFNα-2a and PegIFNα-2a among 271 patients with bridging fibrosis (33%) or cirrhosis (67%) reported that the SVR rate increased from 7% to 14% and 32% in those treated with standard IFNα 3 MU 3 times weekly, PegIFNα 90 μg/wk, and PegIFNα 180 μg/wk, respectively ($P = 0.001$), with no significant difference in tolerance of all regimens among cirrhotic patients. Helbling et al[44] were first to report an SVR rate of 32% for HCV genotypes 1/4 and 58% for genotypes 2/3 ($P = 0.004$) in patients with advanced fibrosis/cirrhosis receiving PegIFNα-2a 180 μg/wk and Rbv 600 to 1200 mg/d.

Further analysis focused on 102 patients with compensated cirrhosis and portal hypertension who were treated with PegIFNα-2b 1 μg/kg/wk with (n = 51) or without (n = 51) Rbv 800 mg/d.[46] SVR rates were 9.8% for PegIFNα-2b monotherapy and 21.6% for PegIFNα-2b plus Rbv ($P = 0.06$), and were poorer for genotypes 1/4 than genotypes 2/3 (11.3% vs 66.6%; $P = 0.001$). Liver decompensation (increase of Child-Pugh score ≥2, ascites, encephalopathy, HCC) was observed in 6.2% of patients with SVR and 38.3% of nonresponders ($P = 0.03$).[46] Similar results were obtained in a randomized controlled trial[47] of 93 purely cirrhotic patients who were treated with PegIFNα-2b 1 μg/kg/wk (n = 57) or standard IFNα-2b 3 MU 3 times weekly (n = 36); both groups also received Rbv 800 to 1200 mg/d for up to 48 weeks. Overall, SVR was achieved by 37 patients (40%) and more frequently in those with non-1 genotypes than in patients with genotype 1 (68% vs 25%; $P < 0.001$; odds ratio [OR] = 6.75; 95% CI, 2.56–17.76). The merit of this study lies in the correlation between the on-treatment viral kinetics and SVR rates. Indeed, according to logistic regression analysis, the most powerful predictor of SVR was cEVR, since 81% of patients with cEVR achieved SVR compared with only 6.7% of those without cEVR ($P < 0.005$; OR = 59.5; 95% CI, 35.0–248.6), attributing to cEVR a positive predictive value (PPV) of 81% and a negative predictive value (NPV) of 93% for SVR.[47] RVR was also found to be an important predictor of treatment outcome, since 82% of RVR patients achieved SVR compared with 23% of those without RVR ($P < 0.005$; OR = 15.44; 95% CI, 4.84–49.25); the PPV and NPV of RVR for SVR were 82% and 77%, respectively. This study failed to inform whether the rates of SVR differed between the 2 treatment regimens (44% vs 33%; P = NS), since it was underpowered to assess this issue. The study had other limitations, including the 48-week regimen administered regardless of HCV genotype, possibly explaining the high SVR rate in patients with genotypes 2 and 3 (69%), as well as the lower than recommended PegIFNα-2b dosage (1.0 μg/kg/wk), that could account for better tolerability.[47]

In 2004, Hadziyannis et al[53] found that a 24-week treatment schedule of PegIFNα-2a 180 μg/wk plus Rbv 800 to 1200 mg/d was comparable, in terms of SVR rates, to 48 weeks of the same regimen in patients infected with HCV genotypes 2 or 3 (81% and 80%, respectively; P = NS). Thus, the administration of PegIFNα and Rbv for 48 weeks in patients with genotypes 1 and 4, and for 24 weeks in those with genotypes 2 and 3, has been endorsed by the practice guidelines.[54] Further studies[33,45,48–51] based on these guidelines confirmed the higher SVR rates in HCV genotypes 2 or 3 (43%–72%) versus lower rates (13%–44%) for genotypes 1 or 4 in cirrhotic patients ($P < 0.001$) (**Table II**).[33,35,43–52]

TREATMENT OPTIMIZATION

Recently, great attention has been given to on-treatment HCV viral kinetics as a tool to predict the treatment outcome and eventually individualize the therapeutic schedule.[17,55–57] Indeed, for noncirrhotic patients, RVR has been found to be the strongest predictor of SVR.[55–57] The PPV of RVR was reported in a multicenter, randomized controlled trial[45] comparing the efficacy of PegIFNα-2b 1.5 μg/kg/wk (standard-dose group) versus

Table II. Overview of studies on efficacy of anti-HCV treatment in patients with compensated cirrhosis.

Study, Year	Study Design	Inclusion Criteria	Exclusion Criteria	No. of Cirrhotic Patients	Regimen, (n)*	% Discontinuation	% SVR	Predictors of Response†
Heathcote et al, 2000[43]	Prospective randomized open-label	Naive, bridging fibrosis or compensated cirrhosis	Concomitant or decompensated liver disease, HIV, alcohol abuse, comorbidities	212	IFNα-2a 3 MU tiw (67) PegIFNα-2a 90 μg/wk (76) PegIFNα-2a 180 μg/wk (69)	–	Genotype 1: 6 Other genotypes: 32	NA
Helbling et al, 2006[44]	Prospective randomized controlled	Naive, advanced fibrosis/ cirrhosis (Ishak 4–6), Child-Pugh ≤7	Concomitant liver disease, substance abuse, comorbidities	109	PegIFNα-2a 180 μg/wk + Rbv 1000–1200 mg/d (52) PegIFNα-2a 180 μg/wk + Rbv 600–800 mg/d (57)	33	PegIFNα-2a + Rbv 1000–1200 mg/d: 42 PegIFNα-2a + Rbv 600–800 mg/d: 41	Genotypes 2/3 PLT ≥150 × 10^9/L
Abergel et al, 2006[45]	Prospective randomized controlled	Naive, Metavir F3–4, ALT > ULN	Decompensation, HIV, HBV, HCC, substance abuse, hematologic abnormalities	104	PegIFNα-2b 1.5 μg/kg/wk + Rbv 800 mg/d (46) PegIFNα-2b 0.75 μg/kg/ wk + Rbv 800 mg/d (58)	Overall 44	PegIFNα-2b 1.5 μg/kg/ wk: 39 0.75 μg/kg/ wk: 35	Genotypes 2/3 GGT <1.6 × ULN
Hung et al, 2006[33]	Prospective observational	Compensated cirrhosis	Concomitant liver disease, decompensation comorbidities	132	IFNα-2b 3–5 MU + Rbv 1000–1200 mg/d	12	All genotypes: 55	Non-1 genotype, low viral load

(continued)

Table II (continued).

Study, Year	Study Design	Inclusion Criteria	Exclusion Criteria	No. of Cirrhotic Patients	Regimen, (n)*	% Discontinuation	% SVR	Predictors of Response†
Di Marco et al, 2007[46]	Prospective randomized controlled	Naive, compensated cirrhosis, portal hypertension	Child-Pugh ≥7, concomitant or decompensated liver diseases, comorbidities	102	PegIFNα-2b 1 μg/kg/wk (51) PegIFNα-2b 1 μg/kg/wk + Rbv 800 mg/d (51)	32	Genotypes 1/4: 12 Genotypes 2/3: 67	NA
Roffi et al, 2008[47]	Prospective randomized controlled	Naive, aged <65 years, compensated cirrhosis, ALT >1.5 × ULN	Child-Pugh B/C, medium/large varices, HIV, HBV, comorbidities	93	IFNα-2b 3 MU tiw + Rbv 800–1200 mg/d (36) PegIFNα-2b 1 μg/kg/wk + Rbv 800–1200 mg/d (57)	–	Genotype 1: 25 Genotype 2: 76 Genotype 3: 55	RVR, cEVR
Floreani et al, 2008[35]	Prospective controlled	Chronic hepatitis C, naive, ALT >1.5 × ULN	Concomitant or decompensated liver diseases, substance abuse	87	PegIFNα-2b 0.8–1 μg/kg/wk + Rbv 1000–1200 mg/d	31†	Genotypes 1: 21 Genotypes 2/3: 72	Of non-response: Genotype 1, viral load ≥1.5 × 10^6 IU/mL
Giannini et al, 2009[48]	Prospective observational	Compensated cirrhosis	Child-Pugh >9, concomitant or decompensated liver disease, comorbidities	85	PegIFNα-2a 180 μg/wk + Rbv 800–1200 mg/d (36) PegIFNα-2b 1.5 μg/kg/wk + Rbv 800–1200 mg/d (49)	16	Genotypes 1/4: 13 Genotypes 2/3: 43	Genotypes 2/3 HCV RNA <600,000 IU/mL, cEVR

(continued)

Table II (continued).

Study, Year	Study Design	Inclusion Criteria	Exclusion Criteria	No. of Cirrhotic Patients	Regimen, (n)*	% Discontinuation	% SVR	Predictors of Response†
Aghemo et al, 2009[49]	Retrospective	Chronic hepatitis C, naive, ALT > ULN	Concomitant or decompensated liver disease, HIV, alcohol abuse, drug dependence	106	PegIFNα-2b 1.5 μg/kg/wk + Rbv 800–1200 mg/d	5	Genotypes 1/4: 17 Genotype 2: 69 Genotype 3: 33	Of non-response: Cirrhosis genotypes 1/4
Rumi et al, 2010[50]	Prospective randomized	Chronic hepatitis C, naive, ALT > ULN	HIV, HBV, concomitant liver disease, normal ALT, hematologic abnormalities	82	PegIFNα-2a 180 μg/wk + Rbv 800–1000 mg/d (43) PegIFNα-2b 1.5 μg/kg/wk + Rbv 800–1200 mg/d (39)	NA	Genotypes 1/4: 22–44 Genotypes 2/3: 64–69	Aged <40 y, HCV RNA <600,000 IU/mL, genotypes 2/3, treatment with PegIFNα-2a
Cheng et al, 2010[51]	Randomized controlled	Chronic hepatitis C, genotype 1, naive, ALT > ULN	Concomitant or decompensated liver diseases (Child-Pugh ≥7), severe comorbidities	127 (F3/4)	PegIFNα-2a 360 μg/wk for 12 weeks → 180 μg/wk for 36 weeks + Rbv 1000–1200 mg/d (60) PegIFNα-2a 180 μg/wk for 48 weeks + Rbv 1000–1200 mg/d (67)	8–9	F3: 31 F4: 10	RVR, SVR

(continued)

Table II (continued).

Study, Year	Study Design	Inclusion Criteria	Exclusion Criteria	No. of Cirrhotic Patients	Regimen, (n)*	% Discontinuation	% SVR	Predictors of Response†
Bruno et al, 2010[52]	Analysis of 3 RCTs	Chronic hepatitis C	HIV, HBV, concomitant liver disease, Child-Pugh >7, contraindications for IFN	106	PegIFNα-2a 180 μg/wk + Rbv 800–1200 mg/d	16	Genotypes 1/4: 33 Genotypes 2/3: 57	Genotypes 1/4: RVR, cEVR, cumulative Rbv dose Genotypes 2/3: RVR, female sex, lower HCV RNA, higher ALT quotient, higher albumin, 24-wk treatment

HCV = hepatitis C virus; SVR = sustained virologic response; IFNα = interferon α; MU = million units; tiw = 3 times weekly; PegIFNα = pegylated interferon α; NA = not available; Rbv = ribavirin; PLT = platelet count; ALT = alanine transaminase; ULN = upper limit of normal; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; GGT = γ-glutamyltransferase; RVR = rapid virologic response; cEVR = complete early virologic response; IU = international units; RCTs = randomized controlled trials.

*Dosages of Rbv in studies are genotype and weight based. See text for details.

† According to multivariate analysis ($P < 0.05$).

PegIFNα-2b 0.75 μg/kg/wk (low-dose group), both in combination with Rbv 800 mg/d, in patients with severe fibrosis (Metavir F3) or cirrhosis (Metavir F4). Among cirrhotic patients (F4), SVR was attained by 39% in the standard-dose group and 35% in the low-dose group (P = NS). The essential observation of this study is the impact of on-treatment viral kinetics on treatment outcome. Ninety-two percent of patients with undetectable HCV RNA at week 4 of treatment achieved SVR (PPV, 92%), in contrast to only 26% of those with positive HCV RNA at week 4 (NPV, 79%). An HCV RNA decrease of <2 $\log_{10}$ was found to negatively predict SVR (NPV, 96%), whereas SVR was observed in 41% of patients when viremia decreased by >2 $\log_{10}$ or HCV RNA was negative at week 12 of treatment.[45]

The significance of on-treatment viral kinetics is also supported by the recent meta-analysis[52] of 3 randomized controlled studies, including 1888 patients (mean age, 47 years; 68% males; 88% white; 341 [18%] infected with genotypes 1 and 4; 871 [49%] without cirrhosis; 479 [25%] with bridging fibrosis or cirrhosis) assigned to PegIFNα-2a 180 μg plus Rbv 800 to 1200 mg/d.[52] The overall population was divided into 3 groups according to liver histology: patients without advanced fibrosis, those with bridging fibrosis, and those with cirrhosis. The efficacy of antiviral treatment was reported to be lower among patients with cirrhosis: 33% versus 60% among patients without advanced fibrosis in genotypes 1 or 4, respectively (P = 0.003), and 57% versus 76% in genotypes 2 or 3 (P < 0.001). The pattern of treatment failure was HCV genotype dependent. Namely, cirrhotic patients infected with HCV genotypes 1/4 showed lower rates of ETR than patients without cirrhosis (53% vs 74%, respectively; P = 0.02), in contrast to those with genotypes 2/3, whose rates of ETR were not statistically different from those without cirrhosis (86% vs 89%, respectively; P = 0.133). Relapse rates among this population, however, were higher (32% vs 15%; P < 0.001).[52] The main independent prognostic factor for achieving SVR in patients with cirrhosis was the viral clearance at week 4 of treatment (OR = 22.4; 95% CI, 6.87–73.03 for genotypes 1/4 and OR = 11.35; 95% CI, 6.56–19.61 for genotypes 2/3), which was achieved by a lower percentage of cirrhotic patients than by those without cirrhosis (53% vs 74% for genotypes 1/4, respectively; P = 0.004 and 84% and 89% for genotypes 2/3; P = 0.031). Importantly, in patients with genotypes 2/3 who achieved RVR, the SVR rate was not significantly different from that in noncirrhotic patients (79% vs 87%, respectively; P = 0.113). Another essential finding of the meta-analysis was that cirrhotic patients with genotypes 2/3 assigned to a full-duration (24-week) course of treatment achieved SVR in 57% compared with 48% of those who were treated for 16 weeks (OR, 2.52; 95% CI, 1.47–4.29).[52] This observation suggests that treatment abbreviation should not be considered in patients with cirrhosis, regardless of pretreatment characteristics and on-treatment viral kinetics.

Special attention should be given to the type of PegIFNα administered to cirrhotic patients. A recent randomized trial[58] assessed the effectiveness of PegIFNα-2a 180 μg/kg/wk versus PegIFNα-2b 1.5 μg/kg/wk, each combined with Rbv 800 to 1200 mg/d in 431 patients, 82 (19%) of whom had cirrhosis. SVR was achieved by 66% of patients treated with PegIFNα-2a versus 54% of those receiving PegIFNα-2b (OR = 1.71; 95% CI, 1.14–2.57; P = 0.02). Further subgroup analysis revealed that cirrhosis negatively influenced the response to PegIFNα-2b. Namely, in patients infected with genotypes 1/4 who were treated with PegIFNα-2a, SVR rates were independent from fibrosis (47% for no or mild fibrosis, 51% for moderate fibrosis, and 44% for cirrhosis; P = 0.84). Conversely, the corresponding SVR rates in those with genotypes 1/4 receiving PegIFNα-2b were 44%, 21%, and 24%, respectively (P = 0.04). In patients with HCV genotypes 2/3, SVR rates were not significantly influenced by fibrosis stage, and were 89%, 88%, and 69% in the PegIFNα-2a group (P = NS) and 83%, 76%, and 64% in the PegIFNα-2b group (P = NS). By logistic regression analysis, moderate fibrosis/cirrhosis emerged as an independent predictor of treatment failure in the PegIFNα-2b group only (OR = 2.4; 95% CI, 1.30–4.50).[58]

TREATMENT OF DECOMPENSATED CIRRHOSIS

Decompensated cirrhosis, defined as the appearance of jaundice, ascites, varices with risk of bleeding, and hepatic encephalopathy, refers to a special patient population that is almost invariably deferred from antiviral therapy due to the risk of infection and disease worsening conferred by PegIFNα and Rbv[59–61] (**Table III**).[10–12,16,35,43–49,51,52,59–66] The 5-year survival of patients with decompensated cirrhosis is 50% compared with 91% in those with compensated cirrhosis,[6] highlighting the greater need for therapy in decompensated patients. Liver transplantation represents the best therapeutic option for

Table III. Incidence of the most common adverse effects and treatment discontinuation in patients with chronic hepatitis C according to clinical stage of disease.*

Adverse Effect/Treatment Discontinuation	Noncirrhotic Patients, %[10–12,16,53]	Patients With Compensated Cirrhosis, %[35,43–49,51,52]	Patients With Decompensated Cirrhosis, %[59–66]
General disorders			
Fatigue	55 (42–66)	34 (15–53)	59 (17–100)
Fever	40 (23–56)	16 (2–29)	9 (1–17)
Irritability	27 (24–35)	38	NA
Anorexia	20 (14–22)	15	100
Injection-site inflammation	18 (9–25)	15	NA
Nervous system/psychiatric disorders			
Headache	50 (15–62)	54	45
Dizziness	21 (17–25)	20	NA
Impaired concentration	17 (16–21)	6	2
Depression	23 (15–34)	13 (6–21)	2
Insomnia	39 (16–42)	13 (6–19)	NA
Anxiety	27 (24–35)	11	12 (0–29)
Infections	NA	1	10 (5–33)
Severe infection	2 (1–3)	0	4 (0–17)
Hematologic abnormalities			
Anemia	15 (14–34)	35 (16–42)	50 (35–70)
Neutropenia	6 (2–32)	38 (12–33)	53 (6–100)
Thrombocytopenia	17 (6–24)	24 (14–33)	50 (22–53)
Gastrointestinal disorders			
Nausea	33 (13–43)	30	50 (22–53)
Vomiting	NA	21	NA
Diarrhea	22 (15–24)	21	NA
Abdominal pain	NA	19	7
Skin disorders			
Pruritis	26 (21–30)	7 (1–12)	NA
Alopecia	29 (21–36)	15	NA
Dermatitis/cutaneous rash	22 (19–28)	15 (11–22)	NA
Respiratory disorders			
Cough	15 (13–17)	10	7
Dyspnea	24 (23–26)	21 (15–25)	NA
Sinusitis	10	12	NA
Musculoskeletal disorders	43 (22–56)	12	NA
Myalgia	27 (24–34)	36	NA
Arthralgia	13 (10–33)	14 (9–22)	NA
Endocrinologic abnormalities			
Hypothyroidism	2 (1–9)	2 (1–9)	7
Clinical decompensation	NA	1.5 (0–3)	21 (9–60)
Bleeding	NA	3	6 (2–10)
Dose modification due to adverse effects	27 (19–43)	30 (13–68)	42 (15–67)
Treatment discontinuation due to adverse effects	13 (5–43)	12 (5–53)	20 (0–100)

NA = not available.

*Data were extracted by the authors from articles included in the review. Data are presented as median (range, when the adverse effect is reported in >1 study).

patients aged <60 years who lack contraindications.[67,68] As the successful outcome of liver transplantation is challenged by recurrent HCV, leading to a graft lost in ~30% of patients in the first year after transplantation, attempts have been made to suppress or eradicate HCV viremia in liver transplant candidates to reduce the risk of hepatitis recurrence after transplantation.[69,70]

A few uncontrolled, single-center studies[62,63,71] have investigated the role of standard IFN with or without Rbv (**Table IV**),[59–66,71] but unfortunately are hard to compare mainly due to significant differences in aims, study design, and treatment schedules. The merit of these studies, however, was to report that antiviral therapy in patients with decompensated cirrhosis is feasible and may prevent HCV recurrence after transplantation in a proportion of the cases, at the cost, however, of potentially fatal side effects.

In a prospective controlled trial[60] in patients with decompensated cirrhosis, PegIFNα-2b 1.0 μg/kg/wk and Rbv 800 to 1000 mg/d were administered for 24 weeks after patients achieved clinical recompensation (n = 66; mean age, 62 years; Child-Pugh value of 8; Model for End-Stage Liver Disease [MELD] score of 14); those who refused treatment served as controls (n = 63; mean age, 63 years; Child-Pugh 8; MELD 15; *P* = NS for all comparisons). The success rate among treated patients was comparable to that previously reported with standard IFN,[59,63] influenced by HCV genotype (44% for genotypes 2/3 and 7% for genotypes 1/4). Importantly, treatment with PegIFN was associated with a risk of infections (rate, 0.95/1000 patient-months; OR = 2.43; 95% CI, 1.02–5.77) and of death related to infections (rate, 0.20/1000 patient-months; OR = 1.97; 95% CI, 0.40–9.51) compared with controls (rates, 0.38 and 0.20/1000 patient-months, respectively).[60] Infections were more common in patients with advanced liver disease, namely in Child-Pugh class C, than in Child-Pugh A/B (50% vs 20%; *P* = 0.001), and in patients with MELD >18 than in those with MELD ≤18 (46% vs 17%; *P* = 0.001). In addition, infections were more common in patients with a low baseline absolute neutrophil count (≤900 mm^3; 82% vs 43% when >900 mm^3; *P* = 0.001). These AEs, however, were counterbalanced by a lower rate of decompensation during the 30-month follow-up period in responders (23%) compared with nonresponders (69%) or untreated patients (88%; OR = 0.04; 95% CI, 0.01–0.17 for SVR). Viral eradication was also associated with reduced mortality (0%, 19%, and 31% for SVR, nonresponse, and no treatment, respectively; OR = 0; 95% CI, 0–0.70 for SVR).[60]

A subsequent study[64] from the same research group of 94 patients treated with PegIFNα-2b 1.5 μg/kg/wk plus Rbv 800 to 1200 mg/d provided information on the ability of viral kinetics in predicting SVR. Overall, SVR rates were 35.1%, and 16% for genotypes 1/4 and 57% for genotypes 2/3 (*P* < 0.01). EVR, genotypes 2 and 3, and adherence to a full course and dosage of therapy emerged as independent predictors of SVR, with corresponding ORs of 25.5 (95% CI, 3.0–217.3), 4.2 (95% CI, 1.2–15.3), and 9.1 (95% CI, 2.2–38.0), respectively.[64] These findings are essential, as they provide the rationale for treatment cessation in patients with low probabilities of HCV eradication while reducing the risk of complications, which are not negligible.

Two further prospective observational studies[61,65] confirmed that therapy with PegIFNα and Rbv was beneficial in a subgroup of selected patients with decompensated cirrhosis awaiting liver transplantation, but was jeopardized, however, by the risk of AEs. In a study by Annicchiarico et al,[61] 15 HCV cirrhotic patients were treated with PegIFNα-2b (1.5 μg/kg/wk) and Rbv (≥10.6 mg/kg/d). SVR was achieved in 3 of 7 patients (43%) infected with genotype 2 and none of those with genotype 1. AEs occurred in all patients, leading to treatment withdrawal in 2 patients (40%).[61] Similar results were reported by Tekin et al[65] in a cohort of 20 patients receiving PegIFNα-2a 135 μg/wk and Rbv 1000 to 1200 mg/d. Again, only 12 patients (60%) were able to complete a 48-week treatment course, with viral eradication in 6 patients (30%). Reported AEs included cytopenia (65%) and bacterial infections (10%); hepatic encephalopathy and ascites were documented in 10% and 5% of patients, respectively.[65]

Another important issue in the anti-HCV treatment of patients with decompensated cirrhosis is the prevention of HCV recurrence in those eligible for liver transplantation. A retrospective study[66] from Barcelona compared the virologic outcome of 51 patients (median age, 59 years; 67% males; 80% infected with HCV genotype 1 and 59% with HCC) treated with PegIFNα-2a in combination with Rbv with that of 51 untreated subjects matched for baseline characteristics. At the time of transplantation, 15 treated patients (29%) were HCV RNA negative and 10 (20%) did not have HCV recurrence 6 months after transplantation. In this study, the positive predictors for viral clearance were RVR (*P* = 0.001), ≥2 $\log_{10}$ HCV RNA decrease at week 4 of treat-

Table IV. Overview of studies on efficacy of anti-HCV treatment in patients with decompensated cirrhosis.

Study, Year	Study Design	Inclusion Criteria	Exclusion Criteria	No. of Patients	Regimen (n)	% Discontinuation	% Viral Clearance	Predictors of Viral Clearance
Crippin et al, 2002[62]	Prospective randomized	Awaiting LT, expected time to LT <12 weeks	HBV, severe comorbidities, cytopenia, renal impairment	15	IFNα-2b 1 MU/d (3) IFNα-2b 1 MU 3 tiw (6) IFNα-2b 1 MU/d + Rbv 800 mg/d (6)	100	0	NA
Thomas et al, 2003[71]	Prospective observational	Awaiting LT	Thrombocytopenia (<50,000/mm^3)	20	IFNα-2b 5 MU/d	0	60*	NA
Forns et al, 2003[59]	Prospective observational	Awaiting LT, expected time to LT <4 months	HBV, HIV coinfections, cytopenia, participation in other trial, renal impairment, recurrent hepatic encephalopathy	30	IFNα-2b 3 MU/d + Rbv 800 mg/d	20	30*	NA
Everson et al, 2005[63]	Prospective observational	HCV-related cirrhosis	Refractory ascites, renal failure, unstable conditions, intolerance of or nonresponders to previous treatment	124	IFNα-2b + Rbv LADR† (119) PegIFNα-2b + Rbv LADR† (5)	13	Genotype 1: 13 Other genotypes: 46	Non-1 genotype, full dose and duration of therapy‡
Iacobellis et al, 2007[60]	Prospective controlled	Naive	Rapid deterioration of liver function, coinfections, substance abuse, comorbidities	66	PegIFNα-2b 1.0 μg/kg/wk + Rbv 800–1000 mg/d	20	Genotypes 1/4: 7 Genotypes 2/3: 44	Genotypes 2/3‡

(continued)

Table IV (continued).

Study, Year	Study Design	Inclusion Criteria	Exclusion Criteria	No. of Patients	Regimen (n)	% Discontinuation	% Viral Clearance	Predictors of Viral Clearance
Annicchiarico et al, 2008[61]	Prospective observational	Awaiting LT, aged <65 years	Comorbidities or conditions precluding antiviral treatment	15	PegIFNα-2b 1.5 μg/kg/wk + Rbv ≥10.6 mg/kg/d	40	Genotypes 1/3: 0 Genotype 2: 43	NA
Tekin et al, 2008[65]	Prospective observational	Child-Pugh A/B, genotype 1b	Severe comorbidities, coinfections, uncontrolled liver decompensation	20	PegIFNα-2a 135 μg/wk + Rbv 1000–1200 mg/d	40	30	NA
Iacobellis et al, 2009[64]	Prospective observational	Child-Pugh A/B, MELD ≤14	Severe comorbidities, coinfections, HCC, rapid deterioration of liver or renal function	94	PegIFNα-2b 1.5 μg/kg/wk + Rbv 800–1200 mg/d	19	Genotypes 1/4: 16 Genotypes 2/3: 57	Genotypes 2/3, EVR, full dosage and duration of treatment
Carrión et al, 2009[66]	Retrospective with matched control	HCV RNA positivity, awaiting LT (expected time to LT <4 months)	Nonresponse to previous treatment, organ transplantation, Child-Pugh >12, recurrent encephalopathy, thrombocytopenia, HIV, HBV, renal failure	51	PegIFNα-2a 180 μg/wk + Rbv 400–1200 mg/d	43	20	Non-1 genotype, low viral load, RVR, ≥2 $\log_{10}$ HCV RNA decrease at week 4 of treatment, EVR‡

HCV = hepatitis C virus; LT = liver transplantation; HBV = hepatitis B virus; IFNα = interferon α; MU = million units; tiw = 3 times weekly; Rbv = ribavirin; NA = not available; LADR = low accelerating dosage regimen; PegIFNα = pegylated interferon α; MELD = Model for End-Stage Liver Disease; HCC = hepatocellular carcinoma; EVR = early virologic response; RVR = rapid virologic response.

*Before liver transplantation.

†IFNα-2b 1.5 MU tiw or PegIFNα-2b 0.5 μg/kg/wk plus Rbv was used initially and in 2-week increments to reach maximum-tolerated or target-standard dose.

‡According to univariate analysis.

ment ($P < 0.001$), and EVR ($P = 0.001$), according to univariate analysis. Interestingly, although liver function was not associated with virologic response, no patients with Child-Pugh class C or MELD >18 achieved SVR. Once again, treatment efficacy was impaired by the high rates of dose reduction (49%) or discontinuation (43%) mainly due to hematologic abnormalities, which occurred in >20% of patients. In addition, bacterial infections occurred in 25% compared with 6% in the control group ($P = 0.01$), with septic shock occurring in 10% versus none of the controls ($P = 0.05$).[66]

TREATMENT OF RECURRENT HCV AFTER LIVER TRANSPLANTATION

Recurrence of HCV after orthotopic liver transplantation (OLT) is almost universal, with an expected median time after recurrence of HCV infection to cirrhosis of 10 years, and at least one episode of decompensation after a median 7.8 years following a diagnosis of cirrhosis.[72–75] In ~30% of patients, the liver graft is lost in the first 5 years after transplantation, owing to severe recurrence of HCV infection.[76] Given the many limitations of anti-HCV therapy with IFN, including an increased risk of allograft rejection and infections, indiscriminate treatment of all patients with recurrent HCV, particularly patients with surgical complications and those with cytopenia, is not advisable.[77,78] Observations suggest that treatment with PegIFNα and Rbv of patients with recurrent HCV should be carefully weighed against the risk of graft dysfunction such as cellular rejection and de novo hepatitis triggered by IFN therapy. Nevertheless, antiviral treatment did not prove to be a risk factor for the aforementioned adverse outcomes.[79–81] The most common strategy to treat recurrent HCV after OLT is to initiate antiviral therapy once hepatitis is histologically confirmed[82] or portal hypertension is present.[83] In these patients, in fact, the potential benefit of IFN therapy might outweigh the risks, provided that antiviral treatment is not delayed to the point of advanced graft fibrosis, limiting the applicability and likelihood of successful treatment.[84,85]

A standard treatment for recurrent HCV infection after OLT has yet to be established. Both standard IFN and PegIFNα with or without Rbv have been used. Two end points are currently presumed: viral eradication, which prevents disease progression to graft failure and is associated with improved survival,[86] and suppression of fibrosis progression.[84]

As supported by existing data, roughly half of the patients with recurrent HCV infection after OLT are eligible for antiviral treatment, and approximately one fourth may achieve SVR after PegIFNα and Rbv treatment (**Figure**),[81,82,84,86–93] but at a rather high price in terms of adverse effects and early withdrawal.[79–94] Only a few patients are able to maintain optimal Rbv dosing, as a consequence of baseline anemia, Rbv-induced hemolysis, impaired bone marrow regenerative capacity, and reduced glomerular filtration rate caused by calcineurin inhibitors.[82,84,94] As a consequence, blood transfusions, erythropoietin, and granulocyte colony–stimulating factor are needed in roughly 60% of patients to treat or prevent hematologic abnormalities and limit Rbv dosing reduction or premature discontinuation.[82,89] Altogether, restricted eligibility, AEs, and poor tolerability are important issues that require a high level of expertise in treating HCV infection recurring after liver transplantations.

SAFETY AND TOLERABILITY OF ANTI-HCV TREATMENT IN CIRRHOSIS

The combination of PegIFN and Rbv is associated with many adverse effects, including flu-like syndrome (28%; range, 17%–67%), depression (23%; range, 15%–34%), fatigue (55%; range, 42%–66%), and hematologic abnormalities (15%; range, 6%–17%). Nevertheless, the safety and tolerability of treatment among patients with compensated cirrhosis does not differ from those in noncirrhotic patients (**Table III**).[10–12,16,35,43–49,51,52,59–66] Discontinuation rates in compensated cirrhosis (12%; range, 5%–53%)[35,43,44,46,48] are not significantly different from those reported in patients with less advanced liver disease (13%; range, 5%–43%).[10–12,16,35,48,53] There are, however, differences between HCV-infected patients, since compensated cirrhotic patients with genotypes 2/3 are more often able (90%) to maintain full dosing and duration of treatment than cirrhotic patients with genotypes 1/4 (70%), a fact that is reasonably explained by the longer treatment duration required for those with genotypes 1/4 (48 vs 24 weeks).[52] Dose modification is more frequent in patients with compensated cirrhosis (30%; range, 13%–68%)[43,48,52] compared with patients with less severe liver disease (27%; range, 19%–43%),[10–12,16,53] mainly due to hematologic toxicity of antiviral therapy, since splenomegaly caused by portal hypertension increases the risk for cytopenia, especially anemia (35%),[46,47] neutropenia (38%),[46,47] and thrombocytopenia (24%).[46,47,53] This

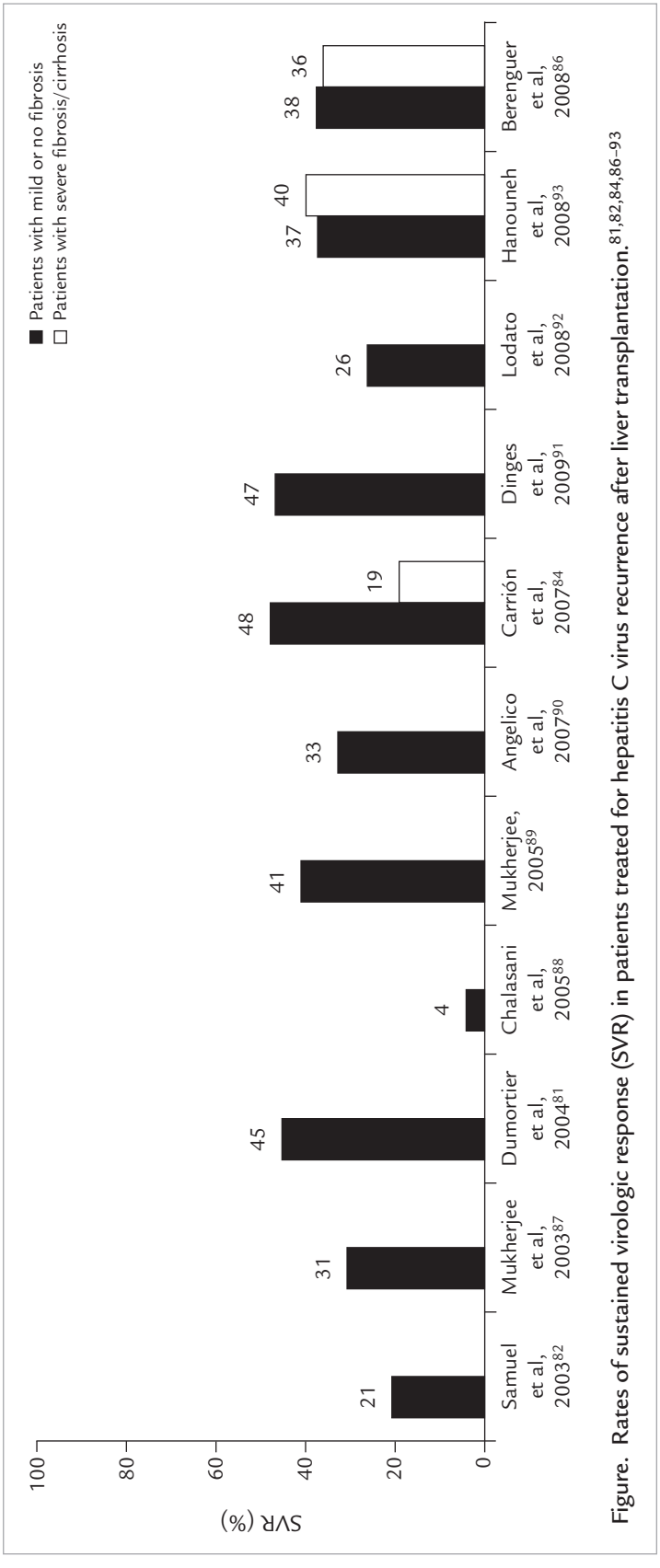

Figure. Rates of sustained virologic response (SVR) in patients treated for hepatitis C virus recurrence after liver transplantation.[81,82,84,86–93]

notwithstanding, the reported rate of clinical decompensation in compensated cirrhotic patients enrolled in randomized controlled trials is negligible (0%–3%; median, 1.5%),[46–48] likely reflecting a careful selection of patients with the exclusion of those with advanced liver disease who were at great risk of decompensation (rate, 14%).[43,47] These caveats suggest caution in transferring safety data obtained from highly selected patients to everyday clinical practice.[45–47]

The safety of IFN and Rbv is a major concern in decompensated cirrhosis, due to the high risk of thrombocytopenia, anemia, infections, or liver decompensation during therapy.[59–66] Patients with Child-Pugh class A remain the best candidates for treatment, whereas antiviral therapy is not indicated in class C patients.[63,95] The risk/benefit ratio of treating patients with Child-Pugh class B remains to be determined in prospective randomized trials.

DISCUSSION

Twenty years of experience in treating HCV patients with IFN-based regimens has clearly shown that HCV eradication is associated with improvements in survival and quality of life. This is even more apparent in patients with cirrhosis, in whom the achievement of SVR reduces the rate of disease progression toward liver decompensation and HCC development. However, while cirrhosis has the peculiarity of being a dominant indication for therapy, it is also one of the strongest negative predictors of treatment success. Indeed, the SVR rates are constantly lower in patients with histologically documented cirrhosis, independent of HCV genotype, compared with those attainable in noncirrhotic patients, yet they are far from being negligible and should never lead to treatment deferral.

Although treatment of decompensated or liver transplant patients can lead to SVR, the attainable rates of treatment success are considered suboptimal in these patients. High rates of AEs, mainly cytopenia, often lead to treatment failure in this patient population. The aggressive therapy of patients with compensated cirrhosis is strongly supported by modeling studies[41] that have reported that the treatment of these patients is most cost-effective and efficacious. The treatment of patients in the decompensated stage should be reserved for specialized centers.

LIMITATIONS OF REVIEW

Our review is limited by the inclusion of retrospective analysis, the heterogeneous patient population, and the variations in treatment regimens, duration, and patient monitoring. Five studies on effectiveness and tolerability of anti-HCV treatment combine patients with bridging fibrosis (Metavir 3 and Ishak 4) and with cirrhosis (Metavir 4 and Ishak 5–6). Further, the main body of evidence of beneficial effect of HCV eradication in cirrhotic patients comes from studies with standard IFNα with or without Rbv therapy, which is no longer recommended. In addition, the detailed rates of AEs and treatment discontinuation were difficult to estimate, since very few studies directly compared patients with compensated cirrhosis and noncirrhotic patients. Finally, the fact that roughly only half of the patients screened were available for randomization or treatment precludes the applicability of the results to a wide population of patients with decompensated HCV-related cirrhosis.

CONCLUSIONS

In this review, anti-HCV treatment in patients with cirrhosis was found to be less effective than in noncirrhotic patients. Viral eradication reduced the risk of liver complications and improved survival among noncirrhotics. Based on effectiveness and tolerability data, therapy has a significant effect in patients with compensated cirrhosis, but the individualized risks and benefits of treatment for patients in the decompensated stage need to be considered.

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