

Response to Standard of Care Antiviral Treatment in Patients with HCV Liver Cirrhosis – a Systematic Review

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Abstract

Background: Patients with HCV liver cirrhosis are a category difficult to treat. The **aim** of this study was to establish the sustained virological response (SVR) rates in HCV patients with liver cirrhosis treated with standard of care therapy (Pegylated Interferon and Ribavirin for 48 weeks in genotypes 1 and 4 and 24 weeks in genotypes 2 and 3). **Methods:** Searching the PubMed, Medline, Lilacs, Scopus, Ovid and Medscape databases we identified all the articles published until February 2011 that included only HCV cirrhotic patients. These studies evaluated the SVR after standard of care treatment: Pegylated Interferon alpha 2a (doses ranging between 135-180 µg/week) or Pegylated Interferon alpha 2b (1 or 1.5 µg/kg/week) and Ribavirin (doses ranging between 800-1200 mg/day). We used the following key words: HCV, liver cirrhosis, sustained virological response (SVR). **Results:** The overall SVR rate was 33.3% (95%CI-confidence interval=30.6-36.2%). SVR was significantly higher in patients with genotypes 2 and 3 (422 patients) as compared to those with genotypes 1 and 4 (692 patients): 55.4% (95%CI=50.7-60.1) versus 21.7% (95%CI=18.7-25), $p < 0.0001$. **Conclusion:** The overall SVR rate in cirrhotic patients treated with standard of care therapy is 33.3%, but lower in cases affected by genotypes 1 and 4 (21.6%) which makes them a priority regarding the development of more potent drugs for effective treatment.

Key words

Hepatitis C – HCV – liver cirrhosis – sustained virological response – systematic review – pegylated interferon – ribavirin.

Introduction

Chronic HCV infection is an important public health concern worldwide. The World Health Organization has estimated the prevalence of HCV infection at about 3%, with approximately 170 million affected people [1]. In Europe, the estimated prevalence of 1% varies largely among different countries [2]. HCV is responsible for 25-30% of global cases of cirrhosis associated with an annual risk of hepatic decompensation and hepatocellular carcinoma in up to 5% and 1-4% cases, respectively [3-4]. In patients with compensated liver cirrhosis, the 5-year risk of decompensation is estimated at 15-28%, and the risk of hepatocellular carcinoma is 1.4-6.7% annually [5-6]. HCV liver cirrhosis is the most common indication for liver transplantation. In patients with detectable viral HCV load before transplantation, recurrence of HCV is universal and immediate after transplantation [7]. Some studies show that both the graft and the patients' survival rates in HCV-infected cases are shorter as compared to non-HCV-infected ones following liver transplantation [8].

Pegylated Interferon and Ribavirin represent the standard of care (SOC) treatment in chronic HCV infection. In randomized controlled trials, the SVR rates were reported as follows: 42-46% in patients with genotype 1 infection, and 76-82% in patients with genotype 2 or 3 infection [9-10].

Patients with HCV-related cirrhosis usually have a poor therapeutic response as well as reduced tolerance to therapy [11-12], but the risk of complications is reduced in patients with SVR [13].

This systematic review aims at identifying and analyzing the pooled SVR rates in HCV patients with liver cirrhosis treated with SOC therapy.

Methods

Eligibility criteria

This review included all studies published in English until February 2011 which evaluated the SVR rates in cirrhotic patients with HCV infection treated with SOC therapy: Pegylated Interferon alpha 2a (dosage range: 135-180 µg/

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week) or Pegylated Interferon alpha 2b (dosage: 1 or 1.5 µg/kg/week) and Ribavirin (dosage range: 800-1200 mg/day). Patients with genotypes 1 and 4 underwent treatment for 48 weeks, whereas those with genotypes 2 and 3 were treated for 24 weeks. The diagnosis of cirrhosis was established either by liver biopsy or by clinical, ultrasonographic, endoscopic, laparoscopic signs of cirrhosis. Studies that included liver-transplanted patients were excluded from the analysis.

Outcomes

The preestablished primary outcome was SVR rate in HCV liver cirrhosis. SVR was defined as undetectable hepatitis C virus RNA in serum by real-time polymerase chain reaction (PCR) 6 months after discontinuation of therapy. The secondary outcomes were the possible relationships between the SVR rate in cirrhotic patients and the following factors: genotype of hepatitis C virus, patient status (naïve or formerly treated with standard Interferon-IFN standard and Ribavirin), type of Pegylated Inteferon used in SOC therapy, portal hypertension (presence of esophageal varices) or decompensation of the disease (class Child-Pugh B or C).

Data sources and searches

Relevant studies published until February 2011 were searched in Medline, Lilacs, Scopus, Ovid and Medscape databases using the following keywords: HCV, hepatitis C, liver cirrhosis, sustained virological response, SVR.

Study selection and data collection

Two authors independently screened titles and abstracts for potential eligibility and the full texts for final eligibility. We extracted the data using a standardized data collection form to record study design and methodological characteristics, patient characteristics, interventions, outcomes, and missing outcome data.

Data synthesis and analysis

Statistical analyses were carried out with the software package SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistics (percentage, 95% confidence interval - 95%CI) were calculated for each variable as appropriate. Standard binomial tests for differences in proportions were used to compare patient subgroups („n” designates the total number of patients included in a particular subgroup). A p-value of less than 0.05 was regarded as statistically significant.

Results

Of 7,326 titles identified at the initial search, 7,315 were excluded based on either of the following reasons: data published only in an abstract, duplicated titles, not only cirrhotics included in the study, treatment other than SOC therapy (Fig.1). Finally, 11 papers including 1,149 patients (764 men - 66.4% and 385 women - 33.6%) with HCV liver cirrhosis were retrieved for the analysis [14-24] (Table I). Nine studies were from Europe [14, 15-20, 22-24] and two studies were from Asia [16, 21].

The SVR rate for each study included in this analysis is presented in Table II.

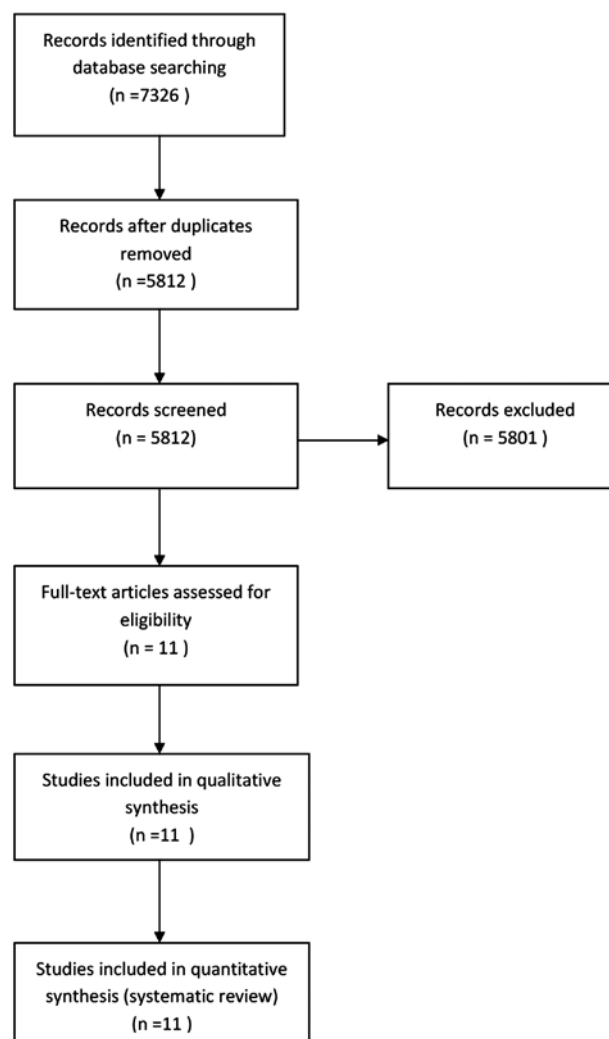


Fig 1. Study screening flow chart

The overall SVR rate was 33.3% (95%CI=30.6-36.2). SVR was significantly higher in patients with genotypes 2 and 3 (n=442) as compared to those with genotypes 1 and 4 (n=692): 55.4% (95%CI=50.7-60.1) versus 21.7% (95%CI=18.7-25), $p < 0.0001$.

Nine articles [14, 16-21, 24] reported on SVR rates in naïve HCV cirrhotic patients, whereas four studies [14, 16, 17, 24] reported on SVR rates in patients previously treated with standard IFN and Ribavirin. SVR was higher in naïve patients (n=419) as compared to those previously treated (n=131): 41% (95%CI=36.3-45.9) versus 25.9% (95%CI=18.9-34.5), $p = 0.003$.

Pegylated Interferon alpha 2a was used in 4 studies [15, 16, 18, 22] and Pegylated Interferon alpha 2b was administered in 7 studies [15, 16, 19-21, 24]. The SVR rate was similar for Pegylated Interferon alpha 2a (n=432) and Pegylated Interferon alpha 2b (n=516): 35.6% (95%CI=31.2-40.4) versus 34.9% (95%CI=30.8-39.2), $p = 0.9$.

Two studies [15, 21] reported on SVR rates in cirrhotic patients with or without esophageal varices. The rate values were similar in cirrhotic cases regardless of the presence (n=157) or absence (n=434) of the esophageal varices: 26.8%

Table I. Characteristics of the studies included in the systematic analysis

Study	Study design	Number of patients	Age (years)	Weight	HCV genotype	Baseline treatment history	Child-Pugh class	Treatment
Syed 2008 [14]	retrospective cohort study	104	52 ± 7.6	82 ± 15 kg (mean weight)	1, 2, 3	Naïve and previously treated	A	PegIFN alpha 2a (180 µg/week) or alpha 2b (1-1.5 µg/kg/week) Ribavirin (800-1200 mg/day)
Fernandez-Rodriguez 2010 [15]	retrospective cohort study	568	51 ± 0.5	26.4 ± 3.78 kg/m ² (mean body mass index -BMI)	1, 2, 3	Naïve and previously treated	A	PegIFN alpha 2a (180 µg/week) or alpha 2b (1.5 µg/kg/week) Ribavirin (800-1200 mg/day)
Butt 2009 [16]	prospective cohort study	66	46.2 ± 10.1	22.3 ± 3.1 kg/m ² (mean BMI)	3	Naïve and previously treated	A, B	PegIFN alpha 2a (180 µg/week) or alpha 2b (1 µg/kg/week) Ribavirin (10-12 mg/kg/day)
Giannini 2009 [17]	retrospective cohort study	85	56 ± 9	Not specified	1, 2, 3, 4	Naïve and previously treated	A, B	PegIFN alpha 2a (180 µg/week) or alpha 2b (1.5 µg/kg/week) Ribavirin (800-1200 mg/kg/day)
Helbling 2006 [18]	randomized controlled trial (standard doses vs. low doses)	64	47 (median age)	74 kg (median weight)	1, 2, 3, 4	Naïve	A	PegIFN alpha 2a (180 µg/week) Ribavirin (1000-1200 mg/kg/day)
Iacobellis 2009 [19]	prospective cohort study	94	Not specified	Not specified	1, 2, 3, 4	Naïve	B	Pegylated Inteferon alpha 2b (1.5 µg/kg/week) Ribavirin (800-1200 mg/day)
Roffi 2008 [20]	randomized controlled trial (PegIFN vs. IFN standard)	57	56 (median age)	75 kg (median weight)	1, 2, 3	Naïve	A	PegIFN alpha 2b (1 µg/kg/week) Ribavirin (800-1200 mg/day)
Sood 2006 [21]	retrospective cohort study	28	48.3 ± 7	73.9±11.2 kg (mean weight)	3 (25/28 patients) and not specified for the other patients	Naïve	A, B	PegIFN alpha 2b (1 µg/kg/week) Ribavirin (10-12 mg/kg/day)
Tekin 2008 [22]	cohort study	20	54.2 ± 5.9	Not specified	1	Not specified	A, B	PegIFN alpha 2a (135 µg/week) Ribavirin (1000-1200 mg/kg/day)
Morreno-Planas 2005 [23]	cohort study	12	52 ± 8	Not specified	1, 3	Naïve and previously treated	A, B	PegIFN alpha 2b (1.5 µg/kg/week) Ribavirin (10.6 mg/kg/day)
Di Marco 2007 [24]	randomized controlled trial (PegIFN alpha 2B + Ribavirin vs. PegIFN alpha 2b)	52	57 ± 6.6	71±10.1 kg (mean weight)	1, 2, 3, 4	Naïve and previously treated	A, B	PegIFN alpha 2b (1 µg/kg/week) Ribavirin (800 mg/kg/day)

(95%CI=20.2-34.5) versus 27.2% (95%CI=23.1-31.7), p=1.

The Child-Pugh class (that shows the decompensation of liver cirrhosis) was reported in 7 studies, of which 5

included patients with class A cirrhosis [14-16, 18, 20] and the other 2 included class B cirrhotic patients [16, 19]. The SVR rates were similar for class A (n=854) and class

Table II. The SVR in the studies included in analysis

Study	Nr. patients included	Nr. patients with SVR	% of patients with SVR
Syed 2008 [14]	104	24	23
Fernandez-Rodriguez 2010 [15]	568	174	30.6
Butt 2009 [16]	66	38	57.5
Giannini 2009 [17]	85	22	25.8
Helbling 2006 [18]	64	32	50
Iacobellis 2009 [19]	94	33	35.1
Roffi 2008 [20]	57	25	43.8
Sood 2006 [21]	28	15	53.5
Tekin 2008 [22]	20	6	30
Morreno-Planas 2005 [23]	12	3	25
Di Marco 2007 [24]	51	11	21.5

B (n=99) HCV liver cirrhosis treated with SOC therapy: 34.2% (95%CI=30.2-39.6) versus 34.3% (95%CI=30.4-39.9), $p=0.9$.

Discussion

This systematic review summarizes and analyzes the available data on SVR in HCV liver cirrhosis managed with SOC therapy and finally shows an overall value of 33.3%, with better results in genotypes 2 and 3 as compared to genotypes 1 and 4 ($p<0.0001$).

A recent meta-analysis [25], that included 5,008 cases from 12 randomized controlled clinical trials, compared the SVR rates in patients treated with Pegylated Interferon alpha 2a plus Ribavirin versus Pegylated Interferon alpha 2b plus Ribavirin. Overall, Pegylated Interferon alpha 2a significantly increased the number of patients who achieved SVR versus Pegylated Interferon alpha 2b (47% versus 41%; risk ratio=1.11, 95%CI=1.04-1.19; $p=0.004$). Pegylated Interferon alpha 2a was associated with higher SVR than Pegylated Interferon alpha 2b in those affected by genotype 1 (risk ratio=1.25, 95%CI=1.03-1.42) as well as genotypes 2 and 3 (risk ratio=1.11, 95%CI=1.02-1.22).

Our systematic analysis in cirrhotic patients shows similar SVR rates regardless of the type of Pegylated Interferon used in SOC therapy (Pegylated Interferon alpha 2a -35.6% vs. Pegylated Interferon alpha 2b - 34.8%, $p=0.9$).

Also the SVR rates did not differ significantly in patients with or without esophageal varices ($p=1$), and in patients with Child-Pugh class A or Child-Pugh class B cirrhosis ($p=0.9$). The results of the latter subgroup may have been biased by the low number of patients with Child-Pugh class B as compared to those with Child-Pugh class A cirrhosis (99 patients vs. 854 patients).

As expected, the SVR rate was significantly lower in patients treated with standard IFN as compared to naïve patients ($p=0.003$).

The limitations of this systematic review are that not all the studies were randomized, and that the SVR rate according to the treatment status, the Child-Pugh class or the presence of esophageal varices were not analyzed in all the studies.

Regarding the antiviral treatment in cirrhotic patients, Saab et al [26] published a study that tried to determine the most cost-effective timing for Pegylated Interferon plus Ribavirin treatment (48 weeks) in patients with advanced liver disease related to genotype 1 HCV infection. The study included about 4,000 participants followed over 17 years. A Markov model was constructed to compare treatment strategies: no treatment, antiviral therapy in patients with compensated cirrhosis, antiviral therapy in patients with decompensated cirrhosis, and antiviral therapy in patients with progressive fibrosis due to recurrent HCV post-transplantation. Outcomes of interest included the total cost per patient, number of quality-adjusted life years (QALYs) saved, cost per QALY saved, number of deaths and hepatocellular carcinomas and number of transplants required. Compared to the no-antiviral treatment strategy, treatment during compensated cirrhosis increased QALYs by 0.950 and saved 55,314 dollars, treatment during decompensated cirrhosis increased QALYs by 0.044 and saved 5,511 dollars and treatment during posttransplant advanced recurrence increased QALYs by 0.061 and saved 3,223 dollars. Treatment of patients with compensated cirrhosis resulted in 119 fewer deaths, 54 fewer hepatocellular carcinomas and 66 fewer transplantations with respect to the no-treatment strategy.

So, even if the SVR rate in HCV cirrhotic patients with genotype 1+4 is very low (21.6% in our current review), with lots of adverse events (especially hematological: anemia, neutropenia, thrombocytopenia) which determined the discontinuation of therapy, according to the previous presented study [26], it is cost-effective to treat cirrhotic patients with antiviral therapy.

The low SVR rate in genotypes 1 and 4 urges also the need for new therapies and new predictors of SVR even in cirrhotic patients treated previously with IFN standard.

In recent years, several studies reported that genetic polymorphism in the IL28B gene, encoding interferon-lambda-3, is associated with an approximately twofold change in response to treatment [27-30].

IL28B genotypes are significantly related to the SVR rates following SOC treatment (Pegylated Interferon plus

Ribavirin). In patients of European ancestry, CC genotype is associated with a twofold (95%CI=1.8-2.3) higher rate of SVR than the TT genotype [27]. It has been also shown that SVR rate was 69% in CC genotype as compared to 33% in TC genotype and 27% in TT genotype ($p<0.0001$) [31].

No studies that analyzed the relationship between IL28B genotype and SVR matched the inclusion criteria used in this systematic review.

In the latter years, several studies have used triple therapy (SOC therapy + direct antiviral agents) in patients with HCV genotype 1 infection [32-34]. The most studied direct antiviral agents were Boceprevir (SPRINT 2 trial) and Telaprevir (ADVANCE and ILLUMINATE trials) [34, 35]. These trials included naïve patients and the proportion of patients with bridging fibrosis/cirrhosis was 20-23% in the ADVANCE trial, and 7-11% in the SPRINT 2 trial.

In the trial with Telaprevir, the SVR rate in patients with F0-F2 ($n=290$) was higher than in patients with F3-F4 ($n=73$) (78% vs. 62%, $p=0.007$) [36, 37]. Also, in the trial that used Boceprevir [35], the SVR rate was significantly higher in non-cirrhotic versus cirrhotic patients (odds ratio=2.5, 95%CI=1.4-4.6, $p=0.003$).

The REALIZE trial used Telaprevir and Pegylated Interferon alpha 2a plus Ribavirin in patients with HCV genotype 1 infection who had no response or a partial response to previous therapy or who had a relapse after an initial response. A total of 663 patients were assigned to one of three groups: two which included Telaprevir and the control group with SOC therapy [38]. In cirrhotics, the SVR rates with SOC therapy as well as for the pooled 12 weeks Telaprevir + 48 weeks Pegylated Interferon and Ribavirin therapy were as follows: prior relapsers - 13% and 84%, respectively; prior partial responders - 20% and 34%, respectively; null-responders - 10% and 14%, respectively [38, 39].

The RESPOND-2 trial, that used Boceprevir in patients previously treated, included prior relapsers and prior partial responders, but excluded the null responders. There were also three arms in this study: SOC therapy and two arms with Boceprevir (for 32 weeks and 44 weeks, respectively, in association with SOC therapy). The SVR rates for the three arms in patients with F3-F4 were 13%, 44% and 68%, respectively [40].

A recent study [41] used both Pegylated Interferon alpha 2a and Pegylated Interferon alpha 2b in combination with Ribavirin and Telaprevir with similar rates of SVR.

IL28B genotyping in the ADVANCE trial showed a higher SVR rate in CC genotype (90%) as compared to CT and TT genotypes (71% and 73%, respectively) [42]. Similarly, in the trial that used Boceprevir, the SVR rate was significantly higher in the CC genotype as compared with the CT and TT genotypes [43].

This data shows that triple therapy had good results for the treatment of naïve patients affected by genotype 1 HCV with advanced fibrosis and cirrhosis – F3-F4 (62%) as compared to SOC therapy (SVR rate of 21.6% reported by this review in cirrhotic patients with genotype 1 and 4).

Both SOC therapy and triple therapy are influenced by the IL28B genotype.

In cirrhotic patients formerly treated with standard IFN, the SVR rate with SOC therapy in this review was 25.9%. Therefore, patients with genotype 1 HCV who do not achieve SVR need to be treated with triple therapy. The results of the studies presented above are very encouraging for prior relapsers patients (84% in REALIZE trial) and satisfying for the partial responder patients (34% in REALIZE trial), but of important concern remain the non-responder patients (14% in REALIZE trial). The SVR rate obtained with triple therapy in cirrhotic non-responder patients is comparable with the value reported in those who underwent SOC therapy (10%). Thus, new drugs should be developed and made available to the former as soon as possible.

Conclusion

The overall SVR rate in cirrhotic patients treated with standard of care therapy is 33.3%, but lower in cases affected by genotypes 1 and 4 which makes them a priority with regard to the development of more potent drugs for effective treatment.

Conflicts of interest

None to declare.

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