

## Antiviral therapies for chronic hepatitis C virus infection with cirrhosis

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recognized as “difficult-to-treat” patients during an era when peginterferon and ribavirin combination therapy is the standard of care. Recent guidelines have clearly stated that treatment should be prioritized in this population to prevent complications such as decompensation and hepatocellular carcinoma. Recent advances in the treatment of chronic hepatitis C have been achieved through the development of direct-acting antiviral agents (DAAs). Boceprevir and telaprevir are first-generation DAAs that inhibit the HCV NS3/4A protease. Boceprevir or telaprevir, in combination with peginterferon and ribavirin, improved the sustained virological response rates compared with peginterferon and ribavirin alone and were tolerated in patients with HCV genotype 1 infection without cirrhosis or compensated cirrhosis. However, the efficacy is lower especially in prior non-responders with or without cirrhosis. Furthermore, a high incidence of adverse events was observed in patients with advanced liver disease, including cirrhosis, in real-life settings. Current guidelines in the United States and in some European countries no longer recommend these regimens for the treatment of HCV. Next-generation DAAs include second-generation HCV NS3/4A protease inhibitors, HCV NS5A inhibitors and HCV NS5B inhibitors, which have a high efficacy and a lower toxicity. These drugs are used in interferon-free or in interferon-based regimens with or without ribavirin in combination with different classes of DAAs. Interferon-based regimens, such as simeprevir in combination with peginterferon and ribavirin, are well tolerated and are highly effective especially in treatment-naïve patients and in patients who received treatment but who relapsed. The efficacy is less pronounced in null-responders and in patients with cirrhosis. Interferon-free regimens in combination with ribavirin and/or two or more DAAs could be used for treatment-naïve, treatment-experienced and even for interferon-ineligible or interferon-intolerant patients. Some clinical trials have demonstrated promising results, and have shown that the efficacy and safety were not different between patients with and without cirrhosis. There are also promising regimens for genotypes other than genotype 1. Interferon

### Abstract

Patients who are infected with hepatitis C virus (HCV) and also have advanced fibrosis or cirrhosis have been

is contraindicated in patients with decompensated cirrhosis, and further studies are needed to establish the optimal treatment regimen for this population. In the future, interferon-free and ribavirin-free regimens with high efficacy and improved safety are expected for HCV-infected patients with advanced liver diseases.

**Key words:** Hepatitis C virus; Hepatocellular carcinoma; Interferon-free regimen; Liver cirrhosis; Direct-acting antiviral agent

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**Core tip:** In general, patients with cirrhosis who are infected with hepatitis C virus (HCV) are at a higher risk for the development of hepatocellular carcinoma (HCC) compared with patients without cirrhosis. Antiviral treatments for patients with cirrhosis and HCV may reduce the occurrence of HCC and/or prevent the progression to hepatic failure. In this review, we discussed the sustained virological response (SVR) rates of interferon-containing and interferon-free regimens for these patients. Recent advances in the development of direct-acting antivirals against HCV have improved the SVR rates and have reduced the occurrence of adverse events during treatment. Interferon-free regimens might improve the prognosis of patients with cirrhosis and HCV.

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## INTRODUCTION

Patients with hepatitis C virus (HCV)-infection and cirrhosis have been recognized as “difficult-to-treat” patients in the era of peginterferon and ribavirin as the standard of care. Since 2011, new direct-acting antiviral agents (DAAs) have been approved for treatment against HCV infection. Interferon-based triple therapy including telaprevir or boceprevir has been more effective than peginterferon and ribavirin alone even in patients with cirrhosis, although some safety concerns also exist.

According to the current guidelines for the management and treatment of HCV infection in the United States and in the EU<sup>[1,2]</sup>, all patients with chronic HCV infection with compensated disease have an indication for treatment. Treatment should be prioritized for patients with advanced fibrosis and cirrhosis to prevent complications such as decompensation and hepatocellular carcinoma (HCC). In the HALT-C trial, patients with advanced chronic hepatitis C who achieved sustained virological response (SVR) demonstrated a marked

reduction in death/liver transplantation, and in liver-related morbidity/mortality<sup>[3]</sup>. Importantly, individuals with advanced liver disease also require long-term follow-up and surveillance for HCC, regardless of the treatment outcome, because HCV eradication reduces but does not abolish the risk of HCC<sup>[1,2]</sup>. However, the treatment response is generally low in patients with advanced fibrosis. In Japan, particular care should be taken in the management of side effects in such patients, who are usually older, have other comorbidities, and have worse tolerance. Currently, little data are available for the treatment of patients with decompensated cirrhosis. Interferon is contraindicated in this population because it may worsen hepatic function. Interferon-free regimens could benefit these patients, although the data are still sparse. In this review, recent data with regards to the efficacy and safety of newly developed DAAs in patients with advanced fibrosis and compensated cirrhosis were collected and analyzed.

## PEGINTERFERON/RIBAVIRIN TREATMENT IN PATIENTS WITH CIRRHOSIS

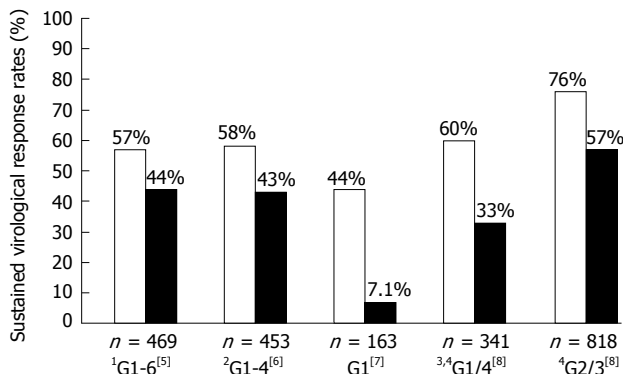
Peginterferon and ribavirin therapy had been the standard of care before the approval of protease inhibitors. The overall SVR rate is 40%-50% for individuals with genotype 1 HCV infection and is 70%-80% for individuals with genotype 2 and 3 infection in patients with chronic hepatitis. In patients with cirrhosis, the SVR rate is reported to be 22% for genotype 1 and 4 infections and 55% for genotype 2 and 3 infections in patients from 11 studies that were included in a systematic review<sup>[4]</sup>. In a sub-analysis of 2 randomized studies that compared peginterferon alpha-2a or -2b plus ribavirin with interferon alpha plus ribavirin<sup>[5,6]</sup>, the SVR of peginterferon plus ribavirin was lower in patients with cirrhosis and a mixed HCV genotype compared with patients with no cirrhosis (43%-44% vs 57%-58%, respectively) (Figure 1). Bruno *et al*<sup>[7]</sup> reported that the SVR of patients with genotype 1 infection who were treated with peginterferon and ribavirin therapy was negatively affected by the Ishak fibrosis score; the SVR of score 1 was 61% while that of score 6 was 7% (Figure 1)<sup>[7]</sup>. In the analysis of 3 randomized international studies<sup>[8]</sup>, the efficacy and safety of peginterferon alfa-2a and ribavirin were compared in patients with and without advanced fibrosis. In 341 patients who were infected with genotypes 1 and 4, the SVR was higher (60%) in patients without advanced fibrosis than in those with cirrhosis (33%), while in 818 patients who were infected with genotypes 2 and 3, the SVR was 76% and 57%, respectively (Figure 1). No significant differences were observed between patients with and without advanced fibrosis with respect to the incidence of serious adverse events. However, a statistically significant difference was noted in the incidence of platelet counts less than 50000/mm<sup>3</sup> during treatment between patients with and without advanced fibrosis or cirrhosis; this was attributed largely

**Table 1** Sustained virological response rates for cirrhotic patients who were treated with direct-acting antiviral agents against hepatitis C virus including peginterferon and ribavirin

Ref. (name of trial)	Regimen; genotype; No. of patients (n)	Tx history	SVR rates	
			Cirrhosis vs Non-cirrhosis	SVR rates for P + R
Jacobson <i>et al</i> <sup>[10]</sup> (ADVANCE)	TVR + P + R; G1; n = 363: P + R; n = 361	-	62% vs 78% <sup>1</sup>	33% vs 47%
Sherman <i>et al</i> <sup>[11]</sup> (ILLUMINATE)	TVR + P + R; G1; n = 540	-	63% vs 75% <sup>1</sup>	
Zeuzem <i>et al</i> <sup>[12]</sup> (REALIZE)	TVR + P + R; G1; n = 530: P + R; n = 132	+	Relapse; 84%-85% vs 83%-90% <sup>1</sup> PR; 40%-44% vs 70%-75% Null; 22%-28% vs 31%-50%	12% vs 38% 10% vs 18% 5% vs 6%
Poordad <i>et al</i> <sup>[13]</sup> (SPRINT-2)	BOC + P + R; G1; n = 734: P + R; n = 363	-	41%-52% vs 67% <sup>1</sup>	38% vs 38%
Bacon <i>et al</i> <sup>[14]</sup> (RESPOND-2)	BOC + P + R; G1; n = 299: P + R; n = 76	+, relapse or PR	35%-77% vs 64%-66%	0% vs 24%
Jacobson <i>et al</i> <sup>[17]</sup>	SMV + P + R; G1; n = 521: P + R; n = 264	-	60% vs 84% <sup>2,3</sup>	34% vs 55%
Manns <i>et al</i> <sup>[18]</sup> (QUEST1/2)				
Forns <i>et al</i> <sup>[19]</sup> (PROMISE)	SMV + P + R; G1; n = 260: P + R; n = 133	+, relapse	74% vs 82% <sup>2,3</sup>	26% vs 41%
Zeuzem <i>et al</i> <sup>[20]</sup> (ASPIRE)	SMV + P + R; G1; n = 199: P + R; n = 66	+	Relapse; 73% vs 95% PR; 82% vs 79% Null; 31% vs 66%	0% vs 56% <sup>2</sup> 0% vs 8% 0% vs 23%
Lawitz <i>et al</i> <sup>[25]</sup> (NEUTRINO)	SOF + P + R; G1, 4-6; n = 327	-	80% vs 92% <sup>3</sup>	

<sup>1</sup>Comparison between cirrhosis/bridging fibrosis vs others, or between F3, 4 vs F0-2 (METAVIR score); <sup>2</sup>Comparison between F4 vs F0-2 (METAVIR score);

<sup>3</sup>Data for SVR12. BOC: Boceprevir; G: Genotype; P: Peginterferon; PR: Partial response; R: Ribavirin; SMV: Simeprevir; SVR: Sustained virological response; TVR: Telaprevir; Tx: Treatment; SOF: Sofosbuvir.



**Figure 1** Sustained virological response rates for treatment-naïve patients with cirrhosis who were treated with peginterferon and ribavirin. <sup>1</sup>Comparison between cirrhosis/bridging fibrosis vs others; <sup>2</sup>Comparison between an Ishak fibrosis score of 6 vs scores of 0-5; <sup>3</sup>Data from 3 studies including the study by Fried *et al*<sup>[6]</sup> listed above; <sup>4</sup>Comparison between cirrhotic patients vs those without advanced fibrosis. White column: Non-cirrhosis (without advanced fibrosis); Black column: Cirrhosis (with advanced fibrosis). G: Genotype.

to a significantly higher incidence of thrombocytopenia in patients with cirrhosis.

## FIRST-GENERATION HCV PROTEASE INHIBITORS PLUS PEGINTERFERON/RIBAVIRIN FOR HCV GENOTYPE 1 INFECTION

In 2011, the HCV NS3/4A protease inhibitors telaprevir and boceprevir, in combination with peginterferon and ribavirin were approved for the treatment of HCV. The efficacy and safety of a regimen that comprises first-generation inhibitors for cirrhosis was reviewed in detail by Bourlière *et al*<sup>[9]</sup> In the ADVANCE study, 363 treatment-naïve patients were treated with triple therapy including telaprevir for 12 wk (Table 1). Of

these patients, 20% had bridging fibrosis or cirrhosis (METAVIR F3-4)<sup>[10]</sup>. The SVR rate in patients with cirrhosis/bridging fibrosis was lower than in the non-cirrhotic patients (62% vs 78%). This in turn was better than the SVR rate for patients who were treated with peginterferon and ribavirin alone - 33% in cirrhotic and 47% in non-cirrhotic patients. Similar results were observed in the ILLUMINATE study<sup>[11]</sup>. In the REALIZE study, 530 patients, including 25% of cirrhotic patients who experienced treatment failure after prior therapy, were treated with triple therapy with telaprevir<sup>[12]</sup>. The SVR rate was high (84%-90%) in patients who experienced a relapse regardless of the presence of F3/4 fibrosis (44% of patients), while the SVR rate in partial responders or non-responders with F3/4 fibrosis was lower than in patients with F0-2 fibrosis (partial responders: 40%-44% vs 70%-75% for F3/4 and F0-2 fibrosis, respectively; non-responders: 22%-28% vs 31%-50% for F3/4 and F0-2 fibrosis, respectively). In all groups, the SVR rates for triple therapy were higher than the SVR rates for peginterferon and ribavirin regardless of the fibrosis status. Similar differences with respect to the treatment efficacy between cirrhotic and non-cirrhotic patients are observed for regimens that contain boceprevir. In the SPRINT-2 study, the SVR rate in treatment-naïve patients with F3/4 fibrosis was lower than patients with F0-2 fibrosis (41%-52% vs 67% for F3/4 and F0-2, respectively)<sup>[13]</sup>. In patients with F3/4 fibrosis, the SVR rate of triple therapy did not differ from that of peginterferon and ribavirin. In patients who experienced a prior relapse and in partial responders (RESPOND-2 study)<sup>[14]</sup>, the SVR rates in non-cirrhotic patients were comparable or higher than those in cirrhotic patients (64%-66% vs 35%-77%, respectively); this was a better result than that of the cirrhotic patients who was treated with peginterferon and ribavirin alone (0%).

**Table 2** Safety data of antiviral treatments for cirrhotic patients infected with hepatitis C virus

Ref. (name of trial)	Regimen; genotypes; No. of patients ( <i>n</i> )	Patient characteristics	AE (serious AE) rate; cirrhosis vs non-cirrhosis
Kumada <i>et al</i> <sup>[27]</sup> (AI447026)	ASV + DCV; G1; <i>n</i> = 222	IFN-intolerant/IFN-ineligible or IFN-non-responders	(9% vs 6%)
Forns <i>et al</i> <sup>[19]</sup> (PROMISE)	SMV + P/RBV; G1; <i>n</i> = 260	Treatment experienced; relapse	100% vs 92%-93% (1% vs 1%) <sup>1</sup>
Jacobson <i>et al</i> <sup>[30]</sup> (POSITRON, FUSION)	SOF + RBV; G2-3; <i>n</i> = 408	IFN-ineligible/IFN-intolerant (POSITRON); IFN-failure (FUSION)	97% vs 88% (7% vs 5%)
		12-wk regimen	86% vs 91% (11% vs 2%)
		16-wk regimen	88% vs 88% (6% vs 2%)
Lawitz <i>et al</i> <sup>[35]</sup> (COSMOS)	SMV + SOF ± RBV for 12 or 24 wk; G1; <i>n</i> = 167	F0-2; non-responders	87% vs 88% (5% vs 0%)
		F3-4; non-responders or naïve	

<sup>1</sup>Comparison between F3-4 and F0-2 (METAVIR score) during the first 12 wk of therapy. AE: Adverse event; ASV: Asunaprevir; DCV: Daclatasvir; G: Genotype; IFN: Interferon; P: Peginterferon; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir.

With regards to safety problems, triple therapy with telaprevir or boceprevir is associated with an increased rate of adverse events such as anemia, dysgeusia or rash compared with peginterferon and ribavirin alone. In the HEP3002 study, 1782 patients with HCV genotype 1 and bridging fibrosis or compensated cirrhosis were treated with triple therapy with telaprevir<sup>[15]</sup>. Overall, 31% of the patients developed grade 3-4 anemia, 4% developed grade 3-4 rash, and 12% discontinued telaprevir due to adverse events. Seven patients (0.4%) died, including 6 patients with cirrhosis. The authors concluded that in patients with compensated cirrhosis and advanced liver fibrosis due to HCV genotype 1 who fulfilled the selection criteria of the registration trials, 16 wk of telaprevir triple therapy proved to be safe and well tolerated. However, the results in a real-life setting in France showed that triple therapy in treatment-experienced patients with cirrhosis was related to a high incidence (40%) of serious adverse events and of severe complications and death (6%), especially in patients with a low platelet count and a low serum albumin level<sup>[16]</sup>. The authors concluded that patients with cirrhosis require a careful follow-up during treatment due to the increase in side effects that are more common during treatment than in clinical studies<sup>[9]</sup>.

## SECOND-GENERATION HCV PROTEASE INHIBITOR PLUS PEGINTERFERON AND RIBAVIRIN

Simeprevir is a once-daily macrocyclic protease inhibitor that was initially approved in 2013 in the United States. In the QUEST-1/2 study<sup>[17,18]</sup>, 521 treatment-naïve patients infected with genotype 1 were treated with simeprevir plus peginterferon and ribavirin (Table 1). Of these patients, 9% had cirrhosis. Again, cirrhotic (F4) patients had a lower chance of a SVR than non-cirrhotic (F0-2) patients (60% vs 84%), which was still higher than the SVR rate for those who were treated with peginterferon and ribavirin (34% vs 55%, respectively). In the PROMISE and ASPIRE studies that included

treatment-experienced patients<sup>[19,20]</sup>, the SVR rate of the simeprevir-containing regimen in patients with cirrhosis was comparable to or lower than that in non-cirrhotic patients - 73%-74% vs 82%-95% for patients who experienced relapse, 82% vs 79% for partial responders, and 31% vs 66% for null responders. The SVR rate for patients with cirrhosis who were treated with triple therapy with simeprevir was greatly improved compared to that in patients with cirrhosis who were treated with peginterferon and ribavirin alone (0%). In the ATTAIN study, which compared simeprevir with telaprevir, each in combination with peginterferon and ribavirin, similar SVR rates were observed, although the incidence of adverse events was lower in the simeprevir group than in the telaprevir group<sup>[21]</sup>.

In clinical trials, adverse events that occur with simeprevir treatment were similar to those with peginterferon and ribavirin alone. In the PROMISE study<sup>[19]</sup>, adverse events were reported in most patients regardless of fibrosis stage (100% for F3-4 vs 92%-93% for F0-2; Table 2). The incidence of serious adverse events was low in both groups (1% vs 1%). Hepatic impairment is associated with substantial increases in exposure to simeprevir, which is also related to the increased frequency of adverse events; plasma exposure to simeprevir is 2- to 5-fold higher in HCV-uninfected subjects with Child-Pugh B or C cirrhosis than in those with normal hepatic function<sup>[22]</sup>. In the AASLD guideline, simeprevir-based treatment is not recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Pugh class B or C)<sup>[1]</sup>.

## HCV NS5B POLYMERASE INHIBITOR SOFOSBUVIR PLUS PEGINTERFERON AND RIBAVIRIN

Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor that was approved in 2013 in the United States<sup>[23]</sup>. A pharmacokinetic analysis in subjects who were treated with sofosbuvir for 7 d indicated that systemic exposure was approximately 2-fold higher in cirrhotic patients with moderate and severe hepatic



impairment (Child-Pugh B and C) than in non-cirrhotic patients, with minimal change in the primary systemic inactive metabolite GS331007<sup>[24]</sup>. The viral decline with sofosbuvir in subjects with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment was less profound than in non-cirrhotic patients.

In a phase 2 trial, the efficacy of sofosbuvir plus peginterferon alfa-2a and ribavirin were compared to peginterferon and ribavirin in non-cirrhotic, treatment-naïve patients infected with genotype 1 HCV<sup>[25]</sup>. The SVR rate at 12 wk (SVR12) in the sofosbuvir-containing arms were higher than in the peginterferon and ribavirin arm (90%-91% vs 58% for sofosbuvir and peginterferon and ribavirin, respectively). In phase 3, 327 treatment-naïve patients (mainly genotype 1, 89%) were treated with sofosbuvir plus peginterferon and ribavirin for 12 wk (NEUTRINO study)<sup>[26]</sup>. Of these patients, 17% had cirrhosis. The SVR12 rate in the non-cirrhotic patients was higher than in the cirrhotic patients (92% vs 80%, odds ratio 3). Adverse events were similar regardless of the presence of sofosbuvir. In patients with cirrhosis, only 1 of 54 discontinued the treatment with triple therapy that included sofosbuvir.

It was concluded by the manufacturer that cirrhosis had no clinically relevant effect on the exposure to sofosbuvir and that no dose adjustment was required for patients with mild, moderate or severe hepatic impairment (Child-Pugh A, B or C)<sup>[23]</sup>. However, efficacy seems somewhat worse in cirrhotic than in non-cirrhotic patients. Importantly, safety and efficacy have not been established in patients with decompensated cirrhosis. Decompensated cirrhosis has been considered a contraindication to interferon therapy.

## INTERFERON-FREE REGIMENS IN CIRRHOTIC PATIENTS

The second-generation HCV NS3/4A protease inhibitor asunaprevir in combination with the HCV NS5A inhibitor daclatasvir was approved in Japan in 2014 for patients infected with HCV genotype 1b including patients who were null-responders to prior treatment, and those who were ineligible or intolerant of interferon. In a phase 3 trial, a total of 222 patients with genotype 1b HCV were treated with this regimen for 24 wk (AI447026, Table 3)<sup>[27]</sup>. Of these patients, 10% had cirrhosis. A SVR was achieved by 87% of interferon-ineligible or interferon-intolerant patients and by 81% of previous non-responders. A subgroup analysis indicated that the SVR rates in patients with cirrhosis and in those without cirrhosis were comparable (91% vs 84%).

In the HALLMARK-DUAL study (Table 3), 203 treatment-naïve, 205 interferon-non-responder, and 235 interferon-ineligible or interferon-intolerant patients infected with HCV genotype 1b were treated with this regimen<sup>[28]</sup>. Of these patients, 16%, 31% and 47% of treatment-naïve patients, interferon non-responders and interferon-ineligible/interferon-intolerant patients

had cirrhosis, respectively. Overall, the SVR rate of the treatment-naïve group was slightly higher than that of the interferon-non-responder or interferon-ineligible/interferon-intolerant group (90% vs 82%). The SVR rates were similar in patients with (84%) and without cirrhosis (85%), irrespective of the patient group. The SVR rate in patients with baseline platelet counts between 50000/mm<sup>3</sup> and less than 90000/mm<sup>3</sup> was high (71%), but was slightly lower than that in patients without thrombocytopenia (86%). The most commonly observed adverse events were headache, fatigue, diarrhea, nausea, and asthenia. Serious adverse events that occurred during treatment were reported in 39 patients (6%), and similar incidences were reported across the different patient groups. Adverse events that led to the discontinuation of treatment occurred in 10 (2%) patients, and were mostly associated with higher transaminase levels (7 patients). Patients with and without cirrhosis had similar frequencies of alanine transaminase (1% vs 3%) and aspartate transaminase (1% vs 2%) that were increases greater than five times the upper limit of normal. In the AI447026 study, serious adverse events were observed in 9% of cirrhotic and 6% of non-cirrhotic patients (Table 3). Exposure to asunaprevir is 10- to 30-fold higher in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh B and C) compared with those with normal hepatic function. Asunaprevir-containing regimen is not recommended in patients with decompensated cirrhosis.

## SOFOSBUVIR-CONTAINING REGIMENS

### Sofosbuvir and ribavirin

In a phase 2 trial, Osinusi *et al.*<sup>[29]</sup> reported the efficacy of sofosbuvir plus ribavirin treatment for 24 wk in treatment-naïve patients who were infected with genotype 1 HCV<sup>[29]</sup> (Table 3). The SVR rate of the 37 patients with F0-2 fibrosis was 65%, while that of the 13 patients with F3-4 fibrosis was 38%. Advanced liver disease was associated with treatment relapse. In contrast, in patients who were infected with genotype 2 or 3 HCV, sofosbuvir and ribavirin therapy was shown to be highly effective. In the FISSION study, treatment-naïve patients who were infected with genotype 2 or 3 HCV were treated with this regimen for 12 wk. In 73 patients with genotype 2 infections who were treated with this regimen, the SVR rate was higher than in the patients who were treated with peginterferon plus ribavirin (95% vs 78%)<sup>[26]</sup>. Liver cirrhosis was present in 16% of the patients in the sofosbuvir arm, and 83% of them achieved a SVR.

In patients with genotype 3 HCV infections, the results of the 12-wk regimen was comparable to those after peginterferon and ribavirin treatment for 24 wk; however, the SVR rate was lower than in the patients with genotype 2 HCV infections. A total of 183 patients were treated with sofosbuvir and ribavirin. Of these patients, 16% had cirrhosis. The SVR rate in cirrhosis

**Table 3** Sustained virological response rates for cirrhotic patients who were treated with interferon-free regimens

Ref. (name of trial)	Regimen; genotypes; No. of patients (n)	Patient characteristics	SVR rates: cirrhosis vs non-cirrhosis
Kumada <i>et al</i> <sup>[27]</sup> (AI447026)	ASV + DCV; G1; n = 222	IFN-intolerant/IFN-ineligible	91% vs 87%
Manns <i>et al</i> <sup>[28]</sup> (HALLMARK-DUAL)	ASV + DCV; G1; n = 645	IFN-non-response <sup>1</sup>	91% vs 79%
		Treatment naïve	91% vs 89% <sup>3</sup>
		IFN-non-response <sup>1</sup>	87% vs 80%
Lawitz <i>et al</i> <sup>[32]</sup> (LONESTAR)	SOF + LDV ± RBV; G1; n = 40	IFN-intolerant/IFN-ineligible	79% vs 84%
		Treatment experienced <sup>2</sup>	91% vs 100% <sup>3,4</sup>
			100% vs 100% <sup>5</sup>
Osinusi <i>et al</i> <sup>[29]</sup>	SOF + RBV; G1; n = 50	Treatment naïve	38% vs 65% <sup>6</sup>
Lawitz <i>et al</i> <sup>[26]</sup> (FISSION)	SOF + RBV; G2-3; n = 256	Treatment naïve; 12-wk regimen	G2; 83% vs 97% <sup>3</sup>
			G3; 34% vs 61% <sup>3</sup>
Jacobson <i>et al</i> <sup>[30]</sup> (POSITRON, FUSION)	SOF + RBV; G2-3; n = 408	IFN-ineligible/IFN-intolerant (POSITRON); 12-wk regimen	G2; 94% vs 92% <sup>3</sup>
		IFN-failure <sup>7</sup> (FUSION)	G3; 21% vs 68% <sup>3</sup>
		12-wk regimen	G2; 60% vs 96% (90%)
			G3; 19% vs 37%
		16-wk regimen	G2; 78% vs 100% (92%)
			G3; 61% vs 63%
Zeuzem <i>et al</i> <sup>[31]</sup> (VALENCE)	SOF + RBV; G2-3; n = 323	Treatment-naïve	
		12-wk regimen	G2; 100% vs 97% <sup>3</sup>
		24-wk regimen	G3; 92% vs 93% <sup>3</sup>
		Treatment-experienced	
		12-wk regimen	G2; 88% vs 91%
		24-wk regimen	G3; 60% vs 85%
Lawitz <i>et al</i> <sup>[35]</sup> (COSMOS)	SMV + SOF ± RBV for 12 or 24 wk; G1; n = 167	F0-2; non-responders	F0-2; 90% <sup>3</sup>
		F3-4; non-responders or naïve	F3-4; 94%
Poordad <i>et al</i> <sup>[36]</sup> (TURQUOISE-II)	Paritaprevir, ritonavir, ombitasvir + dasabuvir + RBV 12 or 24 wk; G1; n = 380	Treatment-naïve	94% <sup>3,8</sup>
		Treatment-experienced	
		Relapse	98%
		Partial response	96%
		Null response	91%

<sup>1</sup>Null or partial response during previous treatment; <sup>2</sup>Patients experienced triple therapy including telaprevir or boceprevir; <sup>3</sup>Data for SVR12; <sup>4</sup>SVR rates for ribavirin-containing regimens; <sup>5</sup>SVR rates for regimens without ribavirin; <sup>6</sup>Comparison between F3-4 and F0-1 (Knodel score); <sup>7</sup>Relapse, null or partial response to previous treatment; <sup>8</sup>All patients included in the study had cirrhosis. ASV: Asunaprevir; DCV: Daclatasvir; G: Genotype; IFN: Interferon; LDV: Ledipasvir; RBV: Ribavirin; SOF: Sofosbuvir; SVR: Sustained virological response; SMV: Simeprevir.

was 34% while that in non-cirrhosis was 61%. For the peginterferon and ribavirin arm, the SVR rate in patients with cirrhosis was 30% and that in patients without cirrhosis was 71%.

In the POSITRON study, interferon-ineligible or interferon-intolerant patients were treated with sofosbuvir and ribavirin for 12 wk<sup>[30]</sup>. The result was similar to that of the FISSION study. In patients infected with genotype 2 HCV, the SVR rates were high in both the cirrhotic and non-cirrhotic patients (94% and 92%, respectively). In genotype 3 HCV-infected patients, only 21% of cirrhotic patients and 68% of non-cirrhotic patients achieved a SVR.

In the FUSION study, patients who did not achieve a SVR after prior therapy were treated with sofosbuvir and ribavirin for 12 or 16 wk<sup>[30]</sup>. In patients infected with genotype 2 HCV, the SVR rate was 82% for the 12-wk arm and 89% for the 16-wk arm. In an analysis of the small fraction of cirrhotic patients, 6 out of 10 (60%) patients in the 12-wk arm and 7 out of 9 (78%) patients in the 16-wk arm achieved a SVR. In patients infected with genotype 3 HCV, the SVR rate in the 12-wk arm was low in both cirrhotic and non-cirrhotic patients (19% and 37%, respectively), while that in the 16-wk arm was 61% and 63% in cirrhotic and non-

cirrhotic patients, respectively.

In the VALENCE study, patients infected with genotype 2 HCV were treated with sofosbuvir and ribavirin for 12 wk while patients infected with genotype 3 HCV were treated for 24 wk<sup>[31]</sup>. Of the treatment-naïve patients, more than 90% achieved a SVR among the 32 genotype 2- and 105 genotype 3-infected patients. Two of the 2 genotype 2-infected patients with cirrhosis and 12 of 13 genotype 3-infected patients with cirrhosis achieved a SVR. In treatment-experienced patients, 90% of 41 patients with genotype 2 infections and 77% of 145 patients with genotype 3 infections achieved a SVR. In genotype 2-infected patients, 7 of 8 (87%) cirrhotic patients achieved a SVR. In genotype 3-infected patients, 27 of 45 (60%) cirrhotic patients achieved a SVR.

The most common adverse events ( $\geq 20\%$ ) that were observed after sofosbuvir plus ribavirin combination therapy were fatigue and headache. The discontinuation of treatment due to adverse events was uncommon - one patient in the FUSION study and 2% in the POSITRON study<sup>[30]</sup>. In the POSITRON study, the incidences of adverse events and laboratory abnormalities among patients with cirrhosis who received sofosbuvir and ribavirin were similar to those among patients without

cirrhosis (Table 2). In the FUSION study, treatment-emergent serious adverse events were slightly higher in cirrhotic patients than in non-cirrhotic patients (11% vs 2% for 12-wk regimen and 6% vs 2% for 16-wk regimen, respectively).

#### ***Sofosbuvir plus ledipasvir with or without ribavirin***

In a phase 2 trial referred to as the "LONESTAR" study (Table 3), the efficacy of a fixed-dose combination of sofosbuvir (400 mg) and the HCV NS5A inhibitor ledipasvir (90 mg), with and without ribavirin, was examined in patients with genotype 1 infection who were treatment-naïve ( $n = 60$ ) or who were previously treated with a protease-inhibitor regimen ( $n = 40$ )<sup>[32]</sup>. Among them, 22 of the treatment-experienced patients had cirrhosis. The results showed that more than 90% of patients achieved a SVR irrespective of their treatment history or the presence of compensated cirrhosis. In the phase 3 ION-1 study<sup>[33]</sup>, 865 genotype 1-infected treatment-naïve patients including 16% of patients with cirrhosis, were treated with this regimen. More than 90% of the patients achieved a SVR regardless of the presence of cirrhosis, inclusion of ribavirin, or treatment duration (12 wk or 24 wk). The ION-2 study consisted of 440 treatment-experienced patients who were infected with genotype 1 HCV, 20% of whom had cirrhosis<sup>[34]</sup>. In non-cirrhotic patients, the SVR rate was higher than 90% irrespective of the treatment duration and the inclusion of ribavirin. In cirrhotic patients, the SVR rate for the 12-wk regimen was 82%-86%, which was lower than that for the 24-wk regimen (95%-100%). A multivariate logistic regression analysis identified cirrhosis as the only factor associated with treatment response. The most commonly observed adverse events included fatigue, headache, nausea, and insomnia. Serious adverse events were observed in 2%-3% of patients who were treated with a 12-wk regimen and in 3%-8% who were treated with a 24-wk regimen.

#### ***Sofosbuvir plus simeprevir with or without ribavirin***

In the COSMOS study<sup>[35]</sup>, the sofosbuvir and simeprevir combination therapy with or without ribavirin for 12 or 24 wk was tested in 81 previous non-responders with F0-2 fibrosis and in 87 treatment-naïve or previous non-responders with F3-4 fibrosis (Table 3). The SVR12 rate was high regardless of the fibrosis stage - 87% for patients with F0-1, 91% for patients with F2, 96% for patients with F3, and 93% for patients with F4 fibrosis. The most commonly observed adverse events were fatigue, headache, and nausea. Four patients (5%) in the 24-wk group discontinued treatment due to adverse events while no patients in the 12-wk group discontinued treatment. Serious adverse events that occurred during treatment were observed in 4 patients (5%) with F3-4 fibrosis and in 0 patients with F0-2 fibrosis. All 4 patients were treated with the 24-wk regimen, and 1 died. All serious adverse events and death were deemed unrelated to the treatment.

### **PARITAPREVR, RITONAVIR, OMBITASVIR AND DASABUVIR WITH RIBAVIRIN FOR CIRRHOTIC PATIENTS**

In the TURQUOISE-II trial (Table 3), the interferon-free combination of the following drugs was studied: the HCV protease inhibitor paritaprevir (ABT-450), the human immunodeficiency virus protease inhibitor ritonavir, which was used as pharmacologic booster, the HCV NS5A inhibitor ombitasvir (ABT-267), the non-nucleoside HCV polymerase inhibitor dasabuvir (ABT-333), and ribavirin. This combination therapy was studied in 160 previously untreated and 220 previously treated adults with HCV genotype 1 infection and compensated cirrhosis (Child A, METAVIR score  $> 3$  or Ishak score  $> 4$ )<sup>[36]</sup>. Overall, the SVR12 rate was 92% for the 12-wk regimen and 96% for the 24-wk regimen. The results were superior to the historical control rate of 47% (95%CI: 41%-54%), calculated from the telaprevir-based regimen and weighted to reflect the population. Among the patients who were infected with genotype 1a HCV and who were prior null responders, 80% of the patients in the 12-wk group achieved a SVR. A multivariate logistic-regression analysis showed that a prior null response and genotype 1a infection were independently associated with a lower likelihood of SVR. The most common adverse events were fatigue, headache and nausea. Serious adverse events occurred in 5%-6% of the patients. Seven to 10% of the patients had hemoglobin levels of less than 10 g/dL. Overall, 2% of patients discontinued the treatment due to adverse events. The pharmacokinetics of each drug in HCV-uninfected subjects with hepatic impairment are complex. Among them, paritaprevir exposure is 1.6- to 10-fold higher in patients with moderate to severe hepatic impairment (Child-Pugh B, C) compared with patients with normal hepatic function. Therefore, paritaprevir-containing combination therapy is not recommended in these patients<sup>[37]</sup>.

### **CONCLUSION**

The EASL guidelines recommend an interferon-free regimen over an interferon-containing regimen in patients with compensated cirrhosis, while the AASLD guidelines recommend that treatment-naïve patients with compensated cirrhosis should receive the same treatment as that given to patients without cirrhosis<sup>[1,2]</sup>. In patients with advanced liver fibrosis or cirrhosis, the treatment should be prioritized and should not be delayed to prevent disease progression. The initially approved DAAs telaprevir and boceprevir are currently not recommended for the treatment of HCV due to the higher rate of adverse events associated with these drugs<sup>[1,2,38]</sup>. Currently, second-stream DAAs including second-generation HCV protease inhibitors such as simeprevir and asunaprevir, the HCV NS5B inhibitor

sofosbuvir, and the HCV NS5A inhibitor daclatasvir have been approved; in addition, various combination regimens that include interferon and ribavirin have been developed. These DAAs-containing regimens improved the treatment efficacy in patients with both early and advanced liver disease. Furthermore, some regimens showed comparable efficacies and safety profiles between patients with and without cirrhosis. Interferon is contraindicated in patients with decompensated cirrhosis, and further studies are needed to establish optimal treatments for this population. In the future, interferon-free and ribavirin-free regimens with high efficacy and improved safety are expected for patients with advanced liver disease<sup>[39]</sup>.

## REFERENCES

- 1 **The American Association for the Study of Liver Diseases.** Recommendations for Testing, Managing, and Treating Hepatitis C. [Accessed on September, 2014]. Available from: URL: <http://www.hcvguidelines.org/>
- 2 **The European Association for the Study of the Liver.** EASL Recommendations on Treatment of Hepatitis C 2014. [Accessed on September, 2014]. Available from: URL: [http://www.easl.eu/\\_clinical-practice-guideline](http://www.easl.eu/_clinical-practice-guideline)
- 3 **Morgan TR,** Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, Lee WM, Di Bisceglie AM, Bonkovsky HL, Dienstag JL, Morishima C, Lindsay KL, Lok AS. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology* 2010; **52**: 833-844 [PMID: 20564351 DOI: 10.1002/hep.23744]
- 4 **Bota S,** Sporea I, Popescu A, Sirli R, Neghina AM, Danila M, Strain M. Response to standard of care antiviral treatment in patients with HCV liver cirrhosis - a systematic review. *J Gastrointest Liver Dis* 2011; **20**: 293-298 [PMID: 21961098]
- 5 **Manns MP,** McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958-965 [PMID: 11583749]
- 6 **Fried MW,** Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975-982 [PMID: 12324553]
- 7 **Bruno S,** Cammà C, Di Marco V, Rumi M, Vinci M, Camozzi M, Rebucci C, Di Bona D, Colombo M, Craxi A, Mondelli MU, Pinzello G. Peginterferon alfa-2b plus ribavirin for naïve patients with genotype 1 chronic hepatitis C: a randomized controlled trial. *J Hepatol* 2004; **41**: 474-481 [PMID: 15336451]
- 8 **Bruno S,** Shiffman ML, Roberts SK, Gane EJ, Messinger D, Hadziyannis SJ, Marcellin P. Efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in hepatitis C patients with advanced fibrosis and cirrhosis. *Hepatology* 2010; **51**: 388-397 [PMID: 19918980 DOI: 10.1002/hep.23340]
- 9 **Bourlière M,** Wendt A, Fontaine H, Hézode C, Pol S, Bronowicki JP. How to optimize HCV therapy in genotype 1 patients with cirrhosis. *Liver Int* 2013; **33** Suppl 1: 46-55 [PMID: 23286846 DOI: 10.1111/liv.12067]
- 10 **Jacobson IM,** McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405-2416 [PMID: 21696307 DOI: 10.1056/NEJMoa1012912]
- 11 **Sherman KE,** Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, Fried MW, Adler M, Reesink HW, Martin M, Sankoh AJ, Adda N, Kauffman RS, George S, Wright CI, Poordad F. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011; **365**: 1014-1024 [PMID: 21916639 DOI: 10.1056/NEJMoa1014463]
- 12 **Zeuzem S,** Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; **364**: 2417-2428 [PMID: 21696308 DOI: 10.1056/NEJMoa1013086]
- 13 **Poordad F,** McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195-1206 [PMID: 21449783 DOI: 10.1056/NEJMoa1010494]
- 14 **Bacon BR,** Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1207-1217 [PMID: 21449784 DOI: 10.1056/NEJMoa1009482]
- 15 **Colombo M,** Fernández I, Abdurakhmanov D, Ferreira PA, Strasser SI, Urbanek P, Moreno C, Streinu-Cercel A, Verheyen A, Iraqi W, DeMasi R, Hill A, Läufer JM, Lonjon-Domanec I, Wedemeyer H. Safety and on-treatment efficacy of telaprevir: the early access programme for patients with advanced hepatitis C. *Gut* 2014; **63**: 1150-1158 [PMID: 24201995 DOI: 10.1136/gutjnl-2013-305667]
- 16 **Hézode C,** Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, de Ledinghen V, Poynard T, Samuel D, Bourlière M, Zarski JP, Raabe JJ, Alric L, Marcellin P, Riachi G, Bernard PH, Loustaud-Ratti V, Métivier S, Tran A, Serfaty L, Abergel A, Causse X, Di Martino V, Guyader D, Lucidarme D, Grando-Lemaire V, Hillon P, Feray C, Dao T, Cacoub P, Rosa I, Attali P, Petrov-Sanchez V, Barthe Y, Pawlotsky JM, Pol S, Carrat F, Bronowicki JP. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J Hepatol* 2013; **59**: 434-441 [PMID: 23669289 DOI: 10.1016/j.jhep.2013.04.035]
- 17 **Jacobson IM,** Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, Moroz L, Craxi A, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, De La Rosa G, Kalmeijer R, Scott J, Sinha R, Beumont-Mauviel M. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014; **384**: 403-413 [PMID: 24907225 DOI: 10.1016/S0140-6736(14)60494-3]
- 18 **Manns M,** Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, Janczewska E, Villamil F, Scott J, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, De La Rosa G, Kalmeijer R, Sinha R, Beumont-Mauviel M. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2014; **384**: 414-426 [PMID: 24907224 DOI: 10.1016/S0140-6736(14)60538-9]
- 19 **Forns X,** Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, Horban A, Brown A, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, Scott J, De La Rosa G, Kalmeijer R, Sinha R, Beumont-Mauviel M. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. *Gastroenterology* 2014; **146**: 1669-79.e3 [PMID: 24602923 DOI: 10.1053/j.gastro.2014.02.051]
- 20 **Zeuzem S,** Berg T, Gane E, Ferenci P, Foster GR, Fried MW, Hezode C, Hirschfield GM, Jacobson I, Nikitin I, Pockros PJ, Poordad F, Scott J, Lenz O, Peeters M, Sekar V, De Smedt G, Sinha R, Beumont-Mauviel M. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology* 2014; **146**:



- 430-441.e6 [PMID: 24184810 DOI: 10.1053/j.gastro.2013.10.058]
- 21 **Reddy KR**, Zeuzem S, Zoulim F, Weiland O, Horban A, Stanciu C, Villamil F, Andreone P, George J, Dammers E, Fu M, Kurland D, Lenz O, Ouwerkerk-Mahadevan S, Verbinen T, Jessner W. A Phase III randomised, double-blind study to evaluate the efficacy, safety and tolerability of simeprevir vs telaprevir in combination with pegylated interferon and ribavirin in chronic hepatitis C virus genotype 1 treatment-experienced patients: the ATTAIN study. *Hepatol Int* 2014; **8**: S397
  - 22 Janssen Therapeutics, Division of Janssen Products, LP 2013. Olysio. Full prescribing information. [Accessed on September, 2014] Available from: URL: <http://www.olyzio.com/shared/product/olyzio/prescribing-information.pdf#search='Olysio'>
  - 23 Gilead Sciences 2013. Sovaldi. Full prescribing information. [Accessed on September, 2014]. Available from: URL: [http://www.gilead.com/~media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi\\_pi.pdf#search='Sovaldi'](http://www.gilead.com/~media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf#search='Sovaldi')
  - 24 **Lawitz E**, Rodriguez-Torres M, Cornpropst MT, Denning JM, Clemons D, McNair L, Fang L, Berrey M, Symonds WT. The effect of hepatic impairment on the pharmacokinetics and antiviral activity of PSI-7977 in hepatitis c infected subjects treated for seven days. *J Hepatol* 2012; **56**: S445-S446 [DOI: 10.1016/S0168-8278(12)61142-8]
  - 25 **Lawitz E**, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, Afdhal NH, Bernstein DE, DeJesus E, Freilich B, Nelson DR, Dieterich DT, Jacobson IM, Jensen D, Abrams GA, Darling JM, Rodriguez-Torres M, Reddy KR, Sulkowski MS, Bzowej NH, Hyland RH, Mo H, Lin M, Mader M, Hindes R, Albanis E, Symonds WT, Berrey MM, Muir A. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naïve patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis* 2013; **13**: 401-408 [PMID: 23499158 DOI: 10.1016/S1473-3099(13)70033-1]
  - 26 **Lawitz E**, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1878-1887 [PMID: 23607594 DOI: 10.1056/NEJMoa1214853]
  - 27 **Kumada H**, Suzuki Y, Ikeda K, Toyota J, Karino Y, Chayama K, Kawakami Y, Ido A, Yamamoto K, Takaguchi K, Izumi N, Koike K, Takehara T, Kawada N, Sata M, Miyagoshi H, Eley T, McPhee F, Damokosh A, Ishikawa H, Hughes E. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. *Hepatology* 2014; **59**: 2083-2091 [PMID: 24604476 DOI: 10.1002/hep.27113]
  - 28 **Manns M**, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY, Chang TT, Everson GT, Heo J, Gerken G, Yoffe B, Towner WJ, Bourliere M, Metivier S, Chu CJ, Sievert W, Bronowicki JP, Thabut D, Lee YJ, Kao JH, McPhee F, Kopit J, Mendez P, Linaberry M, Hughes E, Noviello S. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. *Lancet* 2014; **384**: 1597-1605 [PMID: 25078304 DOI: 10.1016/S0140-6736(14)61059-X]
  - 29 **Osinusi A**, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, Sneller M, Kohli A, Barrett L, Proschan M, Herrmann E, Shivakumar B, Gu W, Kwan R, Teferi G, Talwani R, Silk R, Kotb C, Wroblewski S, Fishbein D, Dewar R, Highbarger H, Zhang X, Kleiner D, Wood BJ, Chavez J, Symonds WT, Subramanian M, McHutchison J, Polis MA, Fauci AS, Masur H, Kottlilil S. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. *JAMA* 2013; **310**: 804-811 [PMID: 23982366 DOI: 10.1001/jama.2013.109309]
  - 30 **Jacobson IM**, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**: 1867-1877 [PMID: 23607593 DOI: 10.1056/NEJMoa1214854]
  - 31 **Zeuzem S**, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Weiland O, Reesink HW, Ferenci P, Hézode C, Esteban R. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; **370**: 1993-2001 [PMID: 24795201 DOI: 10.1056/NEJMoa1316145]
  - 32 **Lawitz E**, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet* 2014; **383**: 515-523 [PMID: 24209977 DOI: 10.1016/S0140-6736(13)62121-2]
  - 33 **Afdhal N**, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1889-1898 [PMID: 24725239 DOI: 10.1056/NEJMoa1402454]
  - 34 **Afdhal N**, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herring R, Lalezari J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1483-1493 [PMID: 24725238 DOI: 10.1056/NEJMoa1316366]
  - 35 **Lawitz E**, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, DeJesus E, Pearlman B, Rabinovitz M, Gitlin N, Lim JK, Pockros PJ, Scott JD, Fevery B, Lambrecht T, Ouwerkerk-Mahadevan S, Callewaert K, Symonds WT, Picchio G, Lindsay KL, Beumont M, Jacobson IM. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. *Lancet* 2014; **384**: 1756-1765 [PMID: 25078309 DOI: 10.1016/S0140-6736(14)61036-9]
  - 36 **Poordad F**, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, Shiffman ML, Wedemeyer H, Berg T, Yoshida EM, Forns X, Lovell SS, Da Silva-Tillmann B, Collins CA, Campbell AL, Podsadecki T, Bernstein B. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014; **370**: 1973-1982 [PMID: 24725237 DOI: 10.1056/NEJMoa1402869]
  - 37 **Viekira PAK**. Full prescribing information. [Accessed on December, 2014]. Available from: URL: [http://www.rxabbvie.com/pdf/viekirapak\\_pi.pdf](http://www.rxabbvie.com/pdf/viekirapak_pi.pdf)
  - 38 **Kanda T**, Imazeki F, Yokosuka O. New antiviral therapies for chronic hepatitis C. *Hepatol Int* 2010; **4**: 548-561 [PMID: 21063477 DOI: 10.1007/s12072-010-9193-3]
  - 39 **Kanda T**, Yokosuka O, Omata M. Treatment of hepatitis C virus infection in the future. *Clin Transl Med* 2013; **2**: 9 [PMID: 23577631 DOI: 10.1186/2001-1326-2-9]

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