Background

Introduction

Individuals with chronic hepatitis C virus (HCV) infection and cirrhosis have an increased risk of developing severe liver-related complications, including hepatic decompensation, hepatocellular cancer, and death. Accordingly, any person with chronic HCV infection who is diagnosed with compensated cirrhosis should be considered at a high priority for HCV treatment. For persons with chronic HCV infection and decompensated cirrhosis, the treatment plans and goals may need modifying if the patient is planning to undergo liver transplantation.

Distinguishing Compensated and Decompensated Cirrhosis

One important step in treating HCV in persons with cirrhosis is to determine whether the cirrhosis is compensated or decompensated.\(^1,2\) The treatment approach and goals are divergent based on the classification of compensated versus decompensated cirrhosis. In particular, HCV protease inhibitor-based regimens are not recommended for use in persons with decompensated cirrhosis, due to the risk of hepatotoxicity with some medications and lack of data with the others.\(^3\) In general, individuals with compensated cirrhosis have mild hepatic impairment (Child-Turcotte-Pugh class A) (Figure 1) and do not have jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy. In contrast, individuals should be considered to have decompensated cirrhosis if they have moderate or severe liver disease (Child-Turcotte-Pugh class B or C). Individuals are defined as having decompensated cirrhosis if they have experienced one or more of the following: ascites, jaundice, variceal hemorrhage, or hepatic encephalopathy.\(^1,4\) Patients who have significant clinical improvement after experiencing one feature of hepatic decompensation should be evaluated on a case-by-case basis to determine whether they could be considered for treatment similar to patients with compensated cirrhosis.
Impact of Treating HCV in Persons with Cirrhosis

Multiple studies, most from the interferon era, have shown that successful treatment of HCV in persons with compensated cirrhosis will decrease subsequent cirrhosis-related complications (Figure 2), including lowering the risk for hepatic failure, hepatocellular carcinoma (Figure 3), and liver-related deaths.[5,6,7] Concern was raised when several European studies reported treatment of HCV with direct-acting antiviral (DAA) medications appeared to increase the risk of hepatocellular carcinoma, particularly with recurrent hepatocellular carcinoma in persons who had received prior ablative therapy for their hepatocellular carcinoma.[8,9] A subsequent meta-analysis and national cohort study did not find this association, and the investigators underscored that post-treatment risk assessment of hepatocellular carcinoma is instead more closely tied to patient factors, such as age and liver disease severity; these variables need to be controlled when performing any post-treatment risk for hepatocellular carcinoma.[10,11] Multiple studies have shown that persons with chronic HCV and cirrhosis have significant improvement in inflammatory grade and have improvement in fibrosis following HCV therapy and achievement of a sustained virologic response (SVR).[5,12] The improvement in hepatic inflammation and fibrosis was initially shown with several studies involving interferon- or peginterferon-based treatment studies.[13,14,15] More recently, several investigators have shown substantial improvements in hepatic fibrosis following achievement of an SVR with DAA-based treatments.[16,17,18,19]
Treating HCV in Persons with Compensated Cirrhosis

HCV Treatment Goals in Persons with Compensated Cirrhosis

The most important immediate goal of treatment is to achieve an SVR, which is required before observing the subsequent benefit in liver-related and other outcomes. The next intermediate-term priority with therapy is to decrease the patient’s risk of developing hepatic decompensation. The long-term goals are to diminish the risk of developing HCV-related hepatocellular carcinoma and death.

Response to HCV Treatment

The impact of cirrhosis on the response to therapy has changed over time with evolving treatment regimens. The following summary illustrates a significant improvement in SVR rates among patients with cirrhosis with regimens that include new direct-acting agents.

- **Elbasvir-Grazoprevir**: In this study, investigators performed an integrated analysis of six elbasvir-grazoprevir phase 2/3 clinical trials to determine SVR12 treatment responses in 402 subjects with HCV genotype 1, 4, or 6 and compensated cirrhosis.[20] Participants received treatment with elbasvir-grazoprevir, with or without weight-based ribavirin; the treatment duration was 12 weeks for treatment-naïve participants (n=169) and 12, 16, or 18 weeks for treatment-experienced subjects (n=233).[20] Prior treatment regimens consisted of peginterferon and ribavirin, with or without a first-generation protease inhibitor (boceprevir, telaprevir or simeprevir). Notably, platelet counts less than 100,000 cells/mm$^3$ and serum albumin less than 3.5 g/dL were present in only 25% and 6% of participants respectively. Overall, using an intent-to-treatment analysis, SVR12 occurred in 96% of treatment-naïve participants and ranged from 89 to 100% among treatment-experienced subjects.[20] Genotype 1a patients were most likely to experience viral relapse with the strongest predictor for treatment failure being the presence of baseline NS5A resistance-associated substitutions. Asymptomatic grade 3-4 increases in hepatic aminotransferase levels were observed in 2.3%.

- **Glecaprevir-Pibrentasvir**: The efficacy of glecaprevir-pibrentasvir for 12 or 16 weeks was evaluated in a pooled analysis of 308 adults with HCV genotypes 1-6 and compensated cirrhosis.[21] Cirrhosis status was determined by FibroScan in 70% of the study subjects and 41% were treatment-experienced with prior peginterferon-based therapy. Child-Turcotte-Pugh score was 5 in 86% of those enrolled. Using an intent-to-treatment analysis, SVR12 was achieved in 96% (297/308) of the study participants.[21] The SVR12 rates by HCV genotype showed 94% with HCV genotype 1, 97% with genotype 3, and 100% with genotypes 2, 4, 5 or 6.[21] There were no DAA-associated serious adverse events and no grade 3-4 elevations in hepatic aminotransferase levels. Grade 3 hyperbilirubinemia developed in 3 study participants; this occurred without associated abnormalities in other liver parameters and it resolved without treatment discontinuation.

- **Ledipasvir-Sofosbuvir**: The ION-1 trial enrolled HCV treatment-naïve adults, with and without compensated cirrhosis, to receive 12 or 24 weeks of ledipasvir-sofosbuvir.[22] Among the subjects enrolled with compensated cirrhosis, 97% (63 of 65) achieved an SRV12; the results were similar with 12 or 24 weeks of therapy (Figure 4).[22] The ION-2 trial enrolled treatment-experienced adults, and those with cirrhosis had lower SVR12 rates if they received ledipasvir-sofosbuvir for 12 weeks (86%) versus 24 weeks (100%) (Figure 5).[23] In these studies, the addition of ribavirin did not significantly improve SVR12 rates. In the SIRIUS trial, 155 treatment-experienced adults with HCV genotype 1 and compensated cirrhosis received 12 weeks ledipasvir-sofosbuvir plus ribavirin or 24 weeks of ledipasvir-sofosbuvir; the SVR12 rates were 96% for participants in the 12-week group and 97% in the 24-week group (Figure 6).[24] In a post-hoc analysis of 7 clinical trials, investigators analyzed data from 513 adults with HCV genotype 1 and compensated cirrhosis who received ledipasvir-sofosbuvir, with or without ribavirin.[25] The treatment-naïve subjects did equally well with a 12- or 24-week treatment course, but treatment-experienced individuals had lower response rates with 12 versus 24 weeks; ribavirin did not significantly improve SVR rates.[25]
• **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir plus Ribavirin**: In the TURQUOISE II trial, 380 adults with chronic HCV genotype 1 infection and Child-Turcotte-Pugh class A cirrhosis were randomized to receive either 12 or 24 weeks of ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin.[26] The study included HCV treatment-naïve and treatment-experienced participants. In the 12-week group, 191 of 208 (92%) achieved an SVR12; for those in the 24-week group, SVR12 was achieved in 165 of 172 (96%) (Figure 7).[26] The treatment responses were similar in the treatment-naïve and treatment-experienced participants. Only 2% of the participants discontinued therapy due to adverse effects.

• **Sofosbuvir-Velpatasvir**: The main sofosbuvir-velpatasvir registration trials (ASTRAL 1, 2 and 3) included 14 to 30% of adults with compensated cirrhosis as part of the overall study population.[27,28] In the ASTRAL-1 trial of treatment-naïve and treatment-experienced adults with genotype 1, 2, 4, 5 or 6, the SVR12 rates with 12 weeks of sofosbuvir-velpatasvir treatment in participants with cirrhosis was 99% (120 of the 121).[27] Similarly, all 19 participants with cirrhosis and HCV genotype 2 in ASTRAL-2 achieved an SVR12.[28] In contrast, in the ASTRAL-3 study, which enrolled persons with HCV genotype 3, among the 80 patients with cirrhosis who received sofosbuvir-velpatasvir, the SVR12 rates were 93% for treatment-naïve and 89% for treatment-experienced participants.[28] Additional data suggest that persons with HCV genotype 3 and cirrhosis should undergo baseline NS5A resistance testing and those with pretreatment NS5A resistance-associated substitutions may benefit from the addition of ribavirin to reduce the risk of viral relapse.[29]

**Recommended HCV Treatment with Compensated Cirrhosis**

For individuals with compensated cirrhosis (Child-Turcotte-Pugh Class A), including those with hepatocellular carcinoma, the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA) HCV Guidance provides recommendations for initial treatment and retreatment (when prior therapy has failed).[30,31] Although the treatment recommendations for persons with and without cirrhosis have significant overlap, there are, in some instances, key differences in the recommended regimens, duration of therapy, or inclusion of ribavirin.[30,31] Thus, when treating HCV in persons with compensated cirrhosis, it should not be assumed the treatment is the same as those without cirrhosis and AASLD-IDSA treatment guidelines should be closely checked and followed.[30,31]
Treating HCV in Persons with Decompensated Cirrhosis

HCV Treatment Goals in Persons with Decompensated Cirrhosis

Individuals with cirrhosis are considered to have decompensated cirrhosis if they develop any of the following complications: ascites, jaundice, variceal hemorrhage, or hepatic encephalopathy.\[1,2,4\] The treatment of persons with decompensated cirrhosis (Child-Turcotte-Pugh class B or C) can be potentially challenging given the high rate of clinical events and complications that may occur in persons with decompensated cirrhosis. The immediate treatment goal for individuals with decompensated cirrhosis differs based on candidacy for liver transplantation. For those who are not a candidate for liver transplantation, the short-term goal of therapy is to achieve an SVR, with the hope that some degree of liver fibrosis will reverse as a result of therapy, which could then stabilize or improve their clinical condition. For persons with chronic HCV infection and decompensated cirrhosis who are candidates for liver transplantation, the short-term or intermediate goal of HCV therapy is to achieve virologic clearance of HCV prior to the liver transplantation. Individuals with detectable HCV at the time of liver transplantation will uniformly infect their new liver with HCV, which can reduce the life of the liver graft. The primary rationale for pretransplantation treatment of HCV is therefore to reduce the risk of HCV re-infection of the new liver and thus improve post-transplantation outcomes. In addition, for some pretransplantation individuals with decompensated cirrhosis, HCV treatment may prevent the need for a liver transplant. In a European study that enrolled 103 persons with chronic HCV who were on an active liver transplant list due to decompensated cirrhosis, treatment with DAA therapy resulted in delisting of 19% at 60 weeks after treatment.\[32\]

Response to HCV Treatment

Limited data exist for hepatitis C treatment in patients with decompensated cirrhosis, primarily because of concerns related to treatment-related toxicity.

- **Daclatasvir plus Sofosbuvir**: In the ALLY-1 trial, daclatasvir in combination with sofosbuvir and low-dose ribavirin was used to treat adults with HCV genotypes 1-6 and advanced cirrhosis or who had a post-transplantation HCV recurrence.\[33\] The advanced cirrhosis cohort included 48 participants with advanced cirrhosis (Child-Turcotte-Pugh class B or C).\[33\] An SVR12 was achieved in 22 of 24 (92%) participants with Child-Turcotte-Pugh class B and in 5 of 10 (50%) in those with Child-Turcotte-Pugh class C.\[33\]

- **Ledipasvir-Sofosbuvir plus Ribavirin**: In Cohort A of the phase 2, SOLAR-1 study, investigators prospectively enrolled 108 adults with hepatitis C genotype 1 or 4 infection and decompensated liver disease (Child-Turcotte-Pugh class B or C).\[34\] A total of 108 participants were randomized to receive either a 12-week or 24-week course of ledipasvir-sofosbuvir plus ribavirin; the ribavirin dose started at 600 mg per day and then was titrated up as tolerated.\[34\] Overall 65% of patients were HCV treatment experienced. Patients receiving the 12-week regimen had an SVR12 rate of 87%, which was similar to the SVR12 rate of 89% in the 24-week regimen; these data excluded 6 patients who underwent liver transplantation (Figure 8).\[34\] The results were similar in the Child-Turcotte-Pugh class B and C groups. Overall, the regimen of ledipasvir-sofosbuvir plus ribavirin was safe and well tolerated. In a similar phase 2 trial (SOLAR 2), investigators evaluated 12 or 24 weeks of ledipasvir-sofosbuvir plus ribavirin in adults with HCV genotype 1 or 4 and advanced liver disease.\[35\] The study cohort A included adults with Child-Turcotte Pugh class A, B, and C who had not undergone liver transplantation.\[35\] In participants with Child-Turcotte Pugh class B, the SVR12 rates were 87% with 12 weeks of treatment and 96% with 24 weeks. For those with Child-Turcotte-Pugh class C, the SVR12 rates were 85% with 12 weeks of treatment and 78% with 24 weeks (Figure 9).\[35\]

- **Sofosbuvir-Based Regimens**: In an open-label, nonrandomized, phase 2 trial, 50 adults with Child-Turcotte-Pugh cirrhosis and portal hypertension were randomized to receive immediate or deferred HCV treatment with sofosbuvir 400 mg once daily plus weight-based ribavirin 1000 to 1200 mg once daily.\[36\] The immediate group received treatment for 48 weeks; the deferred group was observed during the first 24 weeks after 24 weeks and then received 48 weeks of therapy.\[36\] Overall, 33 of 46
(72%) of the participants achieved an SVR. The results were better in those with Child-Turcotte-Pugh class A (78%) than in those with Child-Turcotte-Pugh class B (68%). For the 37 participants who had paired baseline and end-of-treatment hepatic venous gradient measurements, there was a mean decline of 1.0 mmHg. [36]

- **Sofosbuvir-Velpatasvir**: The ASTRAL-4 trial was a randomized, open-label phase 3 trial designed to examine the safety and efficacy of the fixed-dose combination of sofosbuvir-velpatasvir with or without ribavirin in adults with genotype 1, 2, 3, 4, or 6 chronic HCV infection and decompensated cirrhosis. [37] Treatment-naïve and treatment-experienced individuals with Child-Pugh-Turcotte (CTP) class B disease were randomized to one of three arms: (1) sofosbuvir-velpatasvir for 12 weeks (n=90), (2) sofosbuvir-velpatasvir plus ribavirin for 12 weeks (n=87), or (3) sofosbuvir-velpatasvir for 24 weeks (n=90). All three regimens were highly efficacious among genotype 1 patients (88%, 96%, and 92% respectively) and genotypes 2, 4 and 6 patients (100%, 100%, and 86% respectively) (Figure 10). [37] Notably among participants with HCV genotype 3, the treatment groups without ribavirin had lower SVR12 rates. The Model for End-Stage Liver Disease (MELD) scores improved over baseline in those with a baseline MELD score less than 15 (Figure 11) and in those with a baseline MELD score of 15 or greater (Figure 12). [37] A total of 22 study subjects experienced virologic failure; most (n=18) had NS5A variants at the time of failure with the Y93H/N occurring most frequently.

**Guidance for HCV Treatment with Decompensated Cirrhosis**

The AASLD-IDSA Hepatitis C guidance address this group of patients in the section Unique Patient Populations: Patients with Decompensated Cirrhosis. [3] The key recommendation from the AASLD/IDSA guidance is that general management and treatment of all patients with decompensated cirrhosis should be performed by a medical practitioner highly experienced in managing persons with chronic HCV infection and decompensated cirrhosis. Accordingly, referral of these patients to an expert, ideally at a transplant center, is strongly recommended. Patients with decompensated cirrhosis include patients who may or may not be a candidate for liver transplantation and may include patients with hepatocellular carcinoma.
Summary Points

- Treatment of HCV in persons with compensated cirrhosis (Child-Turcotte-Pugh class A) is a high priority because of the risk of developing severe liver-related complications.
- For persons with HCV-related cirrhosis, treatment of HCV is associated with significant reversal in hepatic fibrosis and reduced risk of developing hepatocellular carcinoma when an SVR occurs with therapy.
- For persons with HCV and compensated cirrhosis, the regimen choice and duration is generally generally similar to those without cirrhosis, except for longer duration and in select circumstances, the addition of ribavirin.
- With use of HCV DAA treatment, individuals with HCV and compensated cirrhosis can have comparable SVR12 rates as those without cirrhosis, especially with adjustments in therapy duration when indicated.
- Treatment of HCV is recommended in persons with decompensated cirrhosis who are eligible for liver transplantation, since the transplanted liver will become infected with HCV in all patients who have detectable HCV RNA levels at the time of liver transplantation. In addition, post-transplantation HCV infection is associated with an accelerated course of liver disease.
- Treatment of hepatitis C in patients with decompensated cirrhosis should be performed only by highly experienced hepatitis C medical providers.
Citations


3. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Unique populations: patients with decompensated cirrhosis. [AASLD-IDSA Hepatitis C Guidance] -


[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]


30. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection. [AASLD-IDSA Hepatitis C Guidance]

31. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy failed. [AASLD-IDSA Hepatitis C Guidance]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

[PubMed Abstract]

References


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- Gane EJ et al. Sofosbuvir/ledipasvir fixed dose combination is safe and effective in difficult-to-treat populations including genotype-3 patients, decompensated genotype-1 patients, and genotype-1 patients with prior sofosbuvir treatment experience. Presented at the 49th Annual Meeting of the European Association for the Study of the Liver, London; April 9-13, 2014. Abstract 06. [NATAP] -
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Figures

Figure 1 Child-Turcotte-Pugh Classification for Severity of Cirrhosis

The Child-Turcotte-Pugh (CTP) classification system utilizes two clinical parameters (encephalopathy and ascites) and three laboratory values (bilirubin, albumin, and prothrombin time). Patients are classified as class A, B, or C based on their total points.


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<th>Clinical and Lab Criteria</th>
<th>Points*</th>
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<td>1</td>
<td>2</td>
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<tr>
<td>Encephalopathy</td>
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<td>Mild to moderate (grade 1 or 2)</td>
<td>Severe (grade 3 or 4)</td>
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<td>Ascites</td>
<td>None</td>
<td>Mild to moderate (diuretic responsive)</td>
<td>Severe (diuretic refractory)</td>
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<td>Bilirubin (mg/dL)</td>
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<tr>
<td>Albumin (g/dL)</td>
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*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)

| Class A = 5 to 6 points (least severe liver disease) |
| Class B = 7 to 9 points (moderately severe liver disease) |
| Class C = 10 to 15 points (most severe liver disease) |
Figure 2 Clinical Events Related to HCV Treatment Response

Abbreviations: HCC = hepatocellular cancer
In this international, multicenter study, 530 adults with chronic hepatitis C and advanced fibrosis or cirrhosis were followed after receiving interferon-based therapy. Patients who achieved SVR had substantially lower hepatic-related complications and lower mortality.

Figure 3 Incidence of Hepatocellular Carcinoma Related to HCV Treatment in Adults with Cirrhosis

This study evaluated 345 individuals with chronic HCV and cirrhosis. Of the total 345 patients, 271 received treatment with an interferon-based regimen and 119 developed hepatocellular carcinoma over a median of 6.8 years’ follow-up. Treated patients had lower subsequent risk of developing HCC, particularly those who achieved an SVR.


*Note: hepatocellular cancer (HCC) rates based on median 6.8 years of follow-up*
In the ION-1 trial, treatment-naïve adults received 12 or 24 weeks of ledipasvir-sofosbuvir and all of these treatment arms had very high SVR rates, regardless of the duration of therapy or the presence of cirrhosis. The addition of ribavirin to the regimen did not improve SVR rates (data not shown).

In the ION-2 trial, treatment-experienced adults received 12 or 24 weeks of ledipasvir-sofosbuvir; individuals with cirrhosis had better SVR12 rates if they received 24 weeks of therapy. The addition of ribavirin to the regimen did not significantly improve SVR rates (data not shown).


**Figure 5 ION-2: Ledipasvir-Sofosbuvir in HCV Treatment-Experienced Adults with or without Cirrhosis**

Note: subgroup results do not include patients who withdrew consent or were lost to follow-up.
Figure 6 SIRIUS: Treatment of HCV Genotype 1 with Ledipasvir-Sofosbuvir in Adults with Cirrhosis

Treatment-experienced adults with genotype 1 HCV and compensated cirrhosis received either a 12-week course of ledipasvir-sofosbuvir and ribavirin or a 24-week course of ledipasvir-sofosbuvir. The SVR12 rates were similar in the two groups.

Figure 7 TURQUOISE II: Treatment of HCV Genotype 1 with Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir plus Ribavirin in Adults with Compensated Cirrhosis

This graph shows SVR12 rates with a 12- or 24-week course of ombitasvir-paritaprevir-ritonavir and dasabuvir plus ribavirin in adults with compensated cirrhosis. Results are shown based on prior treatment and prior treatment response.


3D = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; RBV = ribavirin
In Cohort A of this trial, adults with HCV genotype 1 or 4 and advanced liver disease (Child-Turcotte-Pugh B or C) received either a 12- or 24-week course of ledipasvir-sofosbuvir and ribavirin. This graph shows similar results with 12- or 24 weeks of therapy with ledipasvir-sofosbuvir and ribavirin.

In Cohort A of this trial, adults with advanced liver disease (Child-Turcotte-Pugh B or C) received either a 12- or 24-week course of ledipasvir-sofosbuvir and ribavirin.

Figure 10 ASTRAL 4: Sofosbuvir-Velpatasvir Treatment of HCV Genotypes 1-6 in Adults with Decompensated Cirrhosis

Figure 11 ASTRAL4: Change in MELD Score in Adults with Baseline MELD Score Less than 15

Figure 12 ASTRAL4: Change in MELD Score in Adults with Baseline MELD Score of 15 or Greater

Adults with chronic HCV infection and hepatocellular carcinoma received sofosbuvir plus ribavirin for up to 48 weeks prior to liver transplantation. Sofosbuvir plus ribavirin prevented hepatitis C recurrence in most of the treated patients, with the best success rates observed in those who had undetectable HCV RNA levels for at least 30 days prior to liver transplant.


**Figure 13 Treatment of HCV with Sofosbuvir and Ribavirin Prior to Liver Transplantation**

HCV RNA in Patient Receiving Transplant

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