# Unique Populations: Patients with Decompensated Cirrhosis

| Recommended for All Patients with HCV Infection Who Have Decompensated Cirrhosis | |
|---|---|
| RECOMMENDED | RATING |
| Patients with HCV infection who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center). | I, C |

In the decompensated population, most subjects receiving DAA therapy experienced improvement in clinical and biochemical indicators of liver disease between baseline and post-treatment week 12 including patients with CTP class C cirrhosis (Fontana, 2015a). However, death and the need for liver transplantation were observed in treatment studies in the decompensated population, highlighting that not everyone benefits from therapy. Most deaths were related to the severity of underlying liver disease. The predictors of improvement or decline have not been clearly identified.

## Decompensated Cirrhosis: HCV Genotype 1, 4, 5, or 6 Infection

**Recommended Regimens by evidence level and alphabetically for:**

### Patients with Genotype 1, 4, 5, or 6, Who Have Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; CTP Class B or C), Who May or May Not Be Candidates for Liver Transplantation, Including Those with Hepatocellular Carcinoma

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated); for patients with genotype 1, 4, 5, or 6 | 12 weeks | I, A• |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin;‖ for patients with genotype 1, 4, 5, or 6 | 12 weeks | I, A♦ |
| Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated); for patients with genotype 1 or 4 | 12 weeks | I, B |

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
‖ Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small numbers of patients with compensated cirrhosis.

**Recommended Regimens by evidence level and alphabetically for:**

## Patients with Genotype 1, 4, 5, or 6, Who Have Decompensated Cirrhosis, and Are Ribavirin Ineligible

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg); for patients with genotype 1, 4, 5, or 6 | 24 weeks | I, A♦ |
| Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg); for patients with genotype 1 or 4 | 24 weeks | II, C |
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg); for patients with genotype 1, 4, 5, or 6 | 24 weeks | II, C• |

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small numbers of patients with compensated cirrhosis.

**Recommended Regimens by evidence level and alphabetically for:**

## Patients with Genotype 1, 4, 5, or 6, Who Have Decompensated Cirrhosis, and in Whom Prior Sofosbuvir-based or NS5A-based Treatment Has Failed

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated); for patients with genotype 1, 4, 5, or 6 | 24 weeks | II, C• |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin;‖ for patients with genotype 1, 4, 5, or 6 | 24 weeks | II, C♦ |

‖ Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.
• Only available data for genotype 6 are in patients with compensated cirrhosis.
♦ Only available data for genotype 5 and 6 are in small numbers of patients with compensated cirrhosis.

## Ledipasvir/sofosbuvir

The SOLAR-1 study was a multicenter, randomized controlled trial of 108 patients with HCV genotype 1 and 4 who had decompensated cirrhosis, of whom 59 were classified as CTP class B (score 7 to 9) and 49 classified as CTP class C (score 10 to 12) cirrhosis. Subjects were randomly assigned to receive daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and ribavirin (initial dose of 600 mg, increased as tolerated) for 12 or 24 weeks (Charlton, 2015b ). After excluding the 7 subjects who underwent transplantation during the study, the SVR rate was 87% in CTP class B patients who received 12 weeks of treatment and 89% in subjects who received 24 weeks of treatment. Post-therapy virologic relapse occurred in 8% and 5% of the 12- and 24-week groups, respectively. Similarly, the rates of SVR were 86% and 87%, respectively, with 12 and 24 weeks of antiviral therapy in the CTP class C subjects. In the majority of subjects with CTP class B and C disease, the Model for End-Stage Liver Disease (MELD) and CTP scores decreased between baseline and post-treatment week 4. Of the 7 transplanted patients, 6 achieved a posttransplant virologic response and 1 died of multiorgan failure at posttransplant week 2. During the study, only 1 patient with CTP class C cirrhosis died. As expected, the frequency of serious adverse events increased with treatment duration in the CTP class B group (34% vs 10% in week 24 vs 12) as well as the CTP class C group (42% vs 26% in week 24 vs 12). Most serious adverse events were related to ribavirin. The mean daily dose of ribavirin in the decompensated patients was 600 mg/day and therapy was discontinued in 7% of the CTP class B patients and 8% of the CTP class C patients treated with 24 weeks.

The SOLAR-2 study was a multicenter randomized controlled trial of 108 patients with HCV genotypes 1 and 4 who had decompensated cirrhosis. Study participants who were treatment-naive or -experienced, with CTP class B cirrhosis or CTP class C cirrhosis, were randomly assigned to receive daily fixed-dose combination ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) and ribavirin (initial dose of 600 mg, increased as tolerated) for 12 weeks or 24 weeks. All participants had a hemoglobin level greater than 10 g/dL and an estimated glomerular filtration rate (eGFR) greater than 40 mL/min (Manns, 2016).

Excluding 6 patients who had received a transplant, sustained virologic response (SVR) was achieved in 87% of those given the 12-week treatment course and 89% of those given the 24-week treatment course. Post-therapy virologic relapse occurred in 8% and 4% of the 12- and 24-week groups, respectively. Total bilirubin and serum albumin levels improved substantially at week 4 post-therapy compared with baseline in both treatment groups. Baseline CTP and MELD scores improved in more than 50% of the treated patients, but some patients did have worsening hepatic function. During the course of the study, 5 (5%) patients died from various causes but none of the deaths were attributed to antiviral therapy. Grade 3 or 4 adverse events were more common in the 24-week arm (34%) than in the 12-week arm (15%). These results indicate that a 12-week course of ledipasvir/sofosbuvir and ribavirin (initial dose of 600 mg, increased as tolerated) is an appropriate regimen for patients with decompensated cirrhosis who are infected with HCV genotype 1 or 4. Such therapy may lead to objective improvements in hepatic function and reduce the likelihood of recurrent HCV infection after subsequent transplantation. Most patients who started ribavirin at 600 mg per day did not receive higher doses.

A pilot study of 14 patients with compensated cirrhosis and HCV genotype 1 infection in whom prior sofosbuvir-based therapy had failed demonstrated that ledipasvir/sofosbuvir for 12 weeks was associated with a 100% SVR rate (Osinusi, 2014). In addition, results of a study of 51 HCV genotype 1-infected patients in whom prior sofosbuvir-based therapy had failed demonstrated that a 12-week course of ledipasvir/sofosbuvir and weight-based ribavirin (1000 to 1200 mg per day) led to a 98% rate of SVR at 12 weeks and the SVR rate in the 14 patients with compensated cirrhosis was 100% (SVR12) (Wyles, 2015b).

A multicenter, double-blind study from France reported on the use of daily ledipasvir/sofosbuvir for 24 weeks compared with daily ledipasvir/sofosbuvir and ribavirin for 12 weeks, with a 12-week placebo phase, in 154 patients with compensated cirrhosis and HCV genotype 1 infection in whom prior PEG-IFN/ribavirin treatment had failed (for most, treatment with PEG-IFN, ribavirin, and a protease inhibitor had also failed) (Bourliere, 2015). The mean MELD score was 7 (range, 6 to 16), 26% of patients had varices, and 13% had low serum albumin levels. The SVR12 rates were 96% with the 12-week regimen and 97% with the 24-week regimen. The most common adverse events were asthenia, headache,

and pruritus, but the frequency of severe adverse events and the need for early drug discontinuation were low in both treatment groups. In light of these results, it is reasonable to consider daily ledipasvir/sofosbuvir and ribavirin for 12 weeks in patients with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed.

Ledipasvir/sofosbuvir for 24 weeks also appears to be effective for patients with a 71% SVR in 41 HCV genotype 1-infected patients with compensated liver disease who failed a prior course of sofosbuvir-based therapy for 8 or 12 weeks (Lawitz, 2015b). As of February 2017, there are no data of this regimen given for 24 weeks in decompensated cirrhosis. However, a pilot study of 20 patients with CTP class B cirrhosis treated with ledipasvir/sofosbuvir for 12 weeks demonstrated an SVR of 65% (Gane, 2014a).

Data on the use of ledipasvir/sofosbuvir in patients with HCV genotypes 5 and 6 are very limited. Gane et al reported an SVR12 of 96% in 25 patients with HCV genotype 6 treated with ledipasvir/sofosbuvir in phase II clinical trials (Gane, 2015 ). Wong et al also reported an SVR12 of 95.3% with ledipasvir/sofosbuvir for 8 to 24 weeks without ribavirin in 65 adult Asian Americans with compensated cirrhosis and genotype 6 infection. The overall SVR was 92.3% in patients with cirrhosis and 97.4% in patients without cirrhosis (Wong, 2017). In an open-label study in France, ledipasvir/sofosbuvir was administered for 12 weeks to 41 treatment-naive or previously-treated subjects with genotype 5 HCV infection, with or without cirrhosis. The overall SVR12 was 93% (38/41) (Abergel, 2016).

## Sofosbuvir/velpatasvir

The ASTRAL-4 study was a multicenter, randomized, controlled trial of 267 patients with multiple HCV genotypes and decompensated cirrhosis who were treatment-naive (45%) or -experienced (55%) with CTP class A (10%), B, or C cirrhosis. Patients were randomly assigned to receive daily fixed-dose combination sofosbuvir (400 mg) and velpatasvir (100 mg) (hereafter sofosbuvir/velpatasvir) with or without weight-based ribavirin (initial dose of 1000 mg/day if weight <75 kg and 1200 mg/day if weight ≥75 kg) for 12 weeks or sofosbuvir/velpatasvir for 24 weeks in a 1:1:1 ratio. All participants had a hemoglobin level greater than 10 g/dL and an eGFR greater than 40 mL/min and randomization was stratified by HCV genotype (Curry, 2015b). Overall, 60% of patients had HCV genotype 1a, 18% genotype 1b, 4% genotype 2, 15% genotype 3, 3% genotype 4, and <1% genotype 6. 95% of the patients had a baseline MELD <15.

SVR was achieved in 83% in those who received sofosbuvir/velpatasvir for 12 weeks, 94% in those who received sofosbuvir/velpatasvir with ribavirin for 12 weeks, and 86% in those who received sofosbuvir/velpatasvir for 24 weeks. Among patients with genotype 1, the SVR was 88%, 96%, and 92%, respectively. A total of 22 patients had virological failure including 20 patients with a post-therapy relapse and 2 patients with HCV genotype 3 who had an on-treatment virological breakthrough. The presence of baseline NS5A resistant substitutions was not associated with virological relapse. At post-treatment week 12, 47% had an improvement in CTP score while 42% had no change and 11% had worsening CTP scores. During the course of the study, 9 (3%) patients died from various causes, none of which were felt to be related to antiviral therapy. Serious adverse events were reported in 16% to 19% of the treated patients. Anemia defined as a hemoglobin <10 g/dL was reported in 23% of the group receiving ribavirin and 8% and 9% in those who received 12 and 24 weeks of therapy without ribavirin, respectively.

Sofosbuvir/velpatasvir with weight-based ribavirin for 24 weeks was also given to 65 patients with compensated cirrhosis who had failed a prior NS5A-containing regimen (Gane, 2016). The overall SVR was 95% and was 97% in subjects with HCV genotype 1a and 1b, 91% in genotype 2, and 76% in HCV genotype 3. As of May 2016, there are no data for this regimen given for 24 weeks in patients with decompensated cirrhosis.

In ASTRAL-1, sofosbuvir/velpatasvir without ribavirin was given for 12 weeks to 35 patients with compensated cirrhosis and genotype 5, and 41 patients with compensated cirrhosis and genotype 6 (Feld, 2015). The overall SVR12 was 97% in the genotype 5 patients and 100% in the genotype 6 patients. Of note, a 100% SVR was achieved in the small number of genotype 5 patients (n=5) and genotype 6 patients (n=6) with compensated cirrhosis enrolled in ASTRAL-1.

## Daclatasvir + sofosbuvir

In the phase III ALLY-1 study (Poordad, 2016) daily daclatasvir (60 mg) was administered in combination with daily sofosbuvir (400 mg) and low initial dose of ribavirin (600 mg) for 12 weeks to treatment-naive and -experienced patients

who predominantly had HCV genotype 1 infection, in 2 specific populations: those with advanced cirrhosis (CTP class B and C; n=60) and those with recurrent HCV infection posttransplant (n=53). The SVR12 rate was 83% among those with advanced cirrhosis and 94% among those with recurrent HCV infection posttransplant. In the population with advanced cirrhosis, SVR12 rate was 76% among patients with HCV genotype 1a and 100% among patients with HCV genotype 1b. Response rates differed based on severity of disease among those with advanced cirrhosis, SVR12 rate was 94% among patients with CTP class B cirrhosis but only 56% among patients with CTP class C cirrhosis. Among subjects with HCV genotype 3, SVR12 rates were 83% and 91%, respectively, in those with advanced cirrhosis and recurrent HCV infection posttransplant.

## Real-world studies

Observational cohort studies have evaluated other combinations of DAA agents in patients with decompensated cirrhosis. Foster and colleagues reported on the use of ledipasvir (90 mg)/sofosbuvir (400 mg) or daclatasvir (60 mg) plus sofosbuvir (400 mg) with or without ribavirin for 12 weeks in 235 genotype-1 patients from the United Kingdom (Foster, 2016). The SVR rates were similar in the 235 genotype-1 subjects receiving ledipasvir/sofosbuvir plus ribavirin or ledipasvir/sofosbuvir (86% to 81%, respectively) and those receiving daclatasvir plus sofosbuvir with ribavirin or daclatasvir plus sofosbuvir therapy (82% to 60%). In this real-world study, 91% of the patients received ribavirin and only 6% discontinued ribavirin while 20% required a ribavirin dose reduction. MELD scores improved in 42% of treated patients and worsened in 11%. In addition, there were 14 deaths and 26% of the patients had an SAE but none were treatment related.

A multicenter study from Spain also described the safety and efficacy of sofosbuvir-based therapy in 739 HCV patients with decompensated cirrhosis (Fernandez-Carillo, 2016). In this study, the majority of patients had HCV genotype 1a or 1b infection, 76% had CTP class A, and 24% had CTP class B/C cirrhosis. Patients were treated with a variety of regimens including simeprevir plus sofosbuvir (45%), daclatasvir plus sofosbuvir (22%), and ledipasvir/sofosbuvir (16%). Overall SVR was 94% in CTP class A patients compared to 78% in CTP class B/C patients and rates of virological relapse were 4% and 14%, respectively. Sixteen patients died. Both deaths and SAEs were significantly more common in those with CTP class B/C. These data highlight the lower efficacy and increased safety concerns when treating patients with more advanced liver failure.

## Protease-inhibitor containing regimens

To date, the fixed-dose combination of elbasvir (50 mg) and grazoprevir (100 mg) (hereafter, elbasvir/grazoprevir) has not been studied in decompensated cirrhosis. A phase II, non-randomized, open-label study of elbasvir (50 mg) and grazoprevir (50 mg) for 12 weeks was completed in 30 HCV genotype 1 patients with CTP class B cirrhosis (Jacobson, 2015). The SVR12 rate was 90% and 1 patient died of liver failure at post-treatment week 4. MELD scores improved in 15 treated patients, were unchanged in 9, and increased in 6. However, there are no safety or efficacy data regarding the approved FDC elbasvir/grazoprevir doses in patients with decompensated cirrhosis. Therefore, until further data are available, treatment of patients with decompensated cirrhosis with elbasvir/grazoprevir is not recommended.

Recent data reported by the US FDA have demonstrated that some patients with compensated cirrhosis and HCV genotype 1 treated with paritaprevir, ombitasvir, and dasabuvir may develop rapid onset of direct hyperbilirubinemia within 1 to 4 weeks of starting treatment without ALT elevations that can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received PrOD and also developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died (Zuckerman, 2016). Therefore, this antiviral treatment regimen is CONTRAINDICATED in all patients with decompensated cirrhosis due to concerns of hepatotoxicity. In addition, all patients with cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks on therapy.

## Decompensated Cirrhosis: Genotype 2 and 3 HCV Infection

**Recommended Regimens by evidence level and alphabetically for:**

### Patients with Genotype 2 or 3, Who Have Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; CTP Class B or C), and Who May or May Not Be Candidates for Liver Transplantation, Including Those with Hepatocellular Carcinoma

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin | 12 weeks | I, A |
| Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) | 12 weeks | II, B |

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

## Sofosbuvir/velpatasvir

In the ASTRAL-4 study, the SVR in 12 patients CTP class B cirrhosis with genotype 2 was 100% with sofosbuvir/velpatasvir for 12 weeks with and without ribavirin and 75% with sofosbuvir/velpatasvir for 24 weeks. Similarly, among 39 patients with CTP class B cirrhosis with HCV genotype 3, the SVR was 50% and 85% with sofosbuvir/velpatasvir for 12 weeks without and with ribavirin and 50% with sofosbuvir/velpatasvir without ribavirin for 24 weeks. Therefore, genotype 3 patients in particular appear to benefit from the addition of ribavirin to the regimen (Curry, 2015b). For decompensated HCV patients who are ribavirin ineligible, daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) for 24 weeks is currently recommended but further studies in larger numbers of patients are needed to define the optimal duration of therapy. Sofosbuvir/velpatasvir has not been studied in CTP class C patients.

## Daclatasvir + sofosbuvir

Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients without and with cirrhosis. Although daclatasvir with sofosbuvir was not approved for the treatment of HCV genotype 2 infection, daclatasvir maintains adequate activity against HCV genotype 2 despite a 50% effective concentration ($EC_{50}$) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir with sofosbuvir was associated with high rates of SVR in treatment-naive patients with HCV genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014). It is unclear if there is a subgroup of HCV genotype 2-infected patients who would benefit from extending treatment to 24 weeks. For patients who require treatment but cannot tolerate ribavirin, an alternative regimen of daclatasvir with sofosbuvir for 12 weeks is recommended with consideration of extending treatment to 24 weeks for patients with poor baseline characteristics (ie, decompensated cirrhosis). Relevant data supporting daclatasvir, sofosbuvir, and ribavirin from the ALLY-1 trial are described here. In

addition, use of daclatasvir plus sofosbuvir with or without ribavirin from an ongoing observational cohort study in 121 patients with decompensated cirrhosis and genotype 3 infection from the UK demonstrated an SVR of 70% and 71%, respectively (Foster, 2016). In comparison, the SVR in 68 patients with decompensated genotype 3 treated with ledipasvir/sofosbuvir with or without ribavirin were 43% and 59%, respectively.

A multicenter, compassionate use study of daclatasvir (60 mg), sofosbuvir (400 mg) ± ribavirin for 24 weeks in 101 genotype 3 European patients was reported (Welzel, 2015). 81% of the patients had CTP class B cirrhosis, the MELD score was >15 in 16%, and 7% were LT recipients. To date, SVR 12 data has demonstrated an SVR of 85% to 100%. Twenty-two patients had an SAE and therapy was discontinued in 5, while 2 patients died.

## Mixed genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration is unclear, expert consultation should be sought.

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