Research Article
Viral Hepatitis

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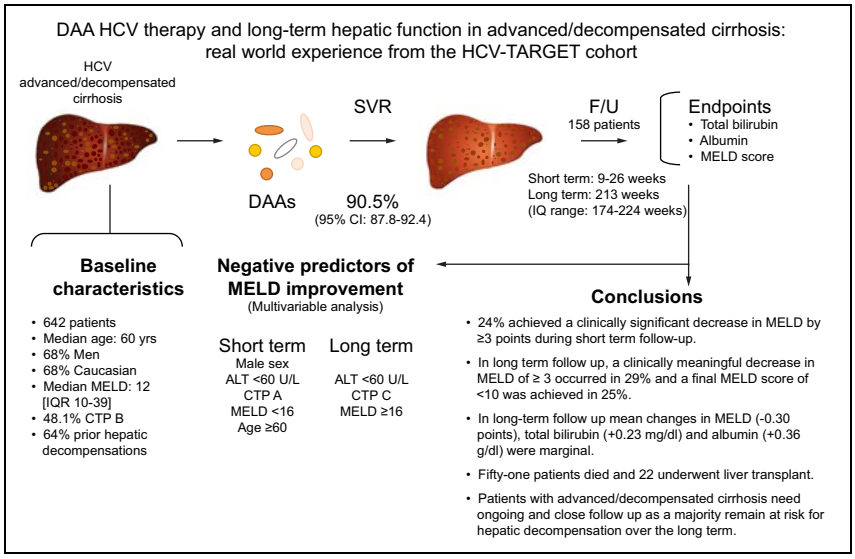
DAA therapy and long-term hepatic function in advanced/decompensated cirrhosis: Real-world experience from HCV-TARGET cohort

Graphical abstract



Highlights

- SVR was achieved in 90.5% of patients with advanced/decompensated cirrhosis treated with direct-acting antivirals.
- In long-term (>4 years) follow-up, overall mean changes in MELD, total bilirubin and albumin were marginal.
- A clinically meaningful decrease in MELD of ≥3 occurred in 29% and a final MELD score of <10 was achieved in 25%.
- Patients with advanced/decompensated liver disease should continue to be monitored following SVR.

Authors

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Lay summary

Hepatitis C virus infection can now be cured with medications, even in patients who have advanced scarring of the liver (cirrhosis). In this study, we evaluated whether liver function improves or deteriorates in the long-term, following successful treatment of hepatitis C in patients with cirrhosis. We found that overall liver function was relatively stable with only 29% of patients achieving a clinically meaningful improvement in liver function, and we therefore believe that these patients require ongoing monitoring.

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DAA therapy and long-term hepatic function in advanced/decompensated cirrhosis: Real-world experience from HCV-TARGET cohort

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Background & Aims: Direct-acting antiviral (DAA) therapy is used in patients with HCV-related decompensated cirrhosis with the expectation of improving hepatic function. However, little is known about the long-term hepatic benefit of successful antiviral treatment.

Methods: Patients with advanced/decompensated cirrhosis (model for end-stage liver disease [MELD] ≥10), in whom NS5A-containing DAA therapy was initiated prior to September 2018, were included (from the HCV-TARGET cohort). Treatment outcomes and the impact of treatment on short-term and long-term hepatic function were examined.

Results: A total of 642 patients were analyzed. The mean age was 60 years, 68% were male. The median baseline MELD was 12 (range 10–39) and 64% had prior decompensation. Among patients with available virologic outcomes, 90.5% achieved a sustained virologic response at 12 weeks (SVR12). Eighty (24%) patients achieved a clinically significant decrease in MELD by ≥3 points during short-term follow-up (9–26 weeks after the end of treatment). However, in long-term follow-up (median of 4 years after treatment), mean changes in MELD (−0.30 points), total bilirubin (+0.23 mg/dl) and albumin (+0.36 g/dl) were marginal. Fifty-one patients died and 22 underwent liver transplant. In long-term follow-up, a clinically meaningful decrease in MELD of ≥3 occurred in 29% and a final MELD score of <10 was achieved in 25%.

Conclusion: In a large real-world experience of patients with advanced/decompensated HCV-related cirrhosis treated with DAAs, there were only marginal improvements in MELD, total bilirubin, or albumin at long-term follow-up (after achieving SVR12). These patients may remain at high risk of decompensation and must continue to be closely monitored.

ClinicalTrials.gov: NCT01474811.

Lay summary: Hepatitis C virus infection can now be cured with medications, even in patients who have advanced scarring of the liver (cirrhosis). In this study, we evaluated whether liver function improves or deteriorates in the long-term, following successful treatment of hepatitis C in patients with cirrhosis. We found that overall liver function was relatively stable with only 29% of patients achieving a clinically meaningful improvement in liver function, and we therefore believe that these patients require ongoing monitoring.

Introduction

The high rates of sustained virologic response (SVR) in patients with HCV-compensated cirrhosis, in both clinical trials and real-world settings, has led to widespread recommendations for treatment in this setting[1] and concurrently there has been a decline in new listings for liver transplantation due to HCV-related liver disease.[2] However, some controversy exists regarding the treatment of patients with decompensated cirrhosis due to suboptimal SVR rates, and concerns over the impact of SVR on long-term outcomes among liver transplant candidates.[3,4]

While most studies have reported improvements in model for end-stage liver disease (MELD) score and/or Child-Pugh class in a significant proportion of patients,[3] the impact on the long-term trajectory of liver function, including resolution of portal

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hypertension, and transplant-free survival remains uncertain. Predictors of short-term resolution in liver dysfunction may include normal body mass index, lack of encephalopathy or ascites at treatment initiation, and normal serum levels of alanine aminotransferase and albumin.[5] However, those with complications of severe portal hypertension and MELD >20 may be less likely to achieve clinical improvement.[6–8] Concern remains that many patients with life-threatening complications of liver disease may be inadvertently disadvantaged in terms of transplant access by a moderate treatment-related decrease in MELD score, without resolution of cirrhosis complications.[3,6,7] Thus, we aimed to determine the effectiveness of DAA therapy in a large real-world cohort of patients with advanced/decompensated cirrhosis. In particular, we evaluated the impact of SVR on hepatic function at long-term follow-up (a median of 4 years after completion of treatment).

Patients and methods

Patients and study design

HCV-TARGET is an international consortium of academic (n = 46) and community (n = 16) medical centers in the US, Germany, Israel and Canada conducting a longitudinal, prospective observational cohort study of real-world administration of DAA therapy (NIH Clinical Trial NCT01474811). All patients were adults ≥18 years, who underwent HCV treatment administered according to local standard of care. Data from enrolled patients undergoing HCV therapy were captured from medical records within a common database utilizing centralized data abstraction.

Patients included in this analysis were those with advanced/decompensated cirrhosis who started HCV treatment between March, 2014 and September, 2018 with an all oral DAA regimen. Patients with prior liver transplantation were excluded.

The independent ethics committee at each participating study center or a central institutional review board approved the protocol. All patients provided written informed consent. All authors had complete access to the study data and reviewed and approved the final manuscript. Study data were collected and managed using REDCap electronic data capture tools[9] hosted at the University of North Carolina Chapel Hill. REDCap (Research Electronic Data Capture) is a secure, web-based application.

Advanced/decompensated cirrhosis assessment

Cirrhosis was defined at the time of enrollment by biopsy (METAVIR stage 4 fibrosis) or FibroScan (liver stiffness of ≥12.5 kPa) and/or a combination of clinical, laboratory, histologic, and imaging criteria. Patients with METAVIR stage 3 fibrosis by liver biopsy/FibroScan were considered to have cirrhosis if they had any of the following: platelet count <140,000/ml; presence of esophageal varices on esophagogastroduodenoscopy; nodular liver, portal hypertension, or ascites by radiologic imaging; or non-invasive serum panels such as FibroSURE (Laboratory Corporation of America, Burlington, NC) consistent with stage 4 fibrosis. In the absence of cirrhosis being confirmed by liver biopsy and/or FibroScan, cirrhosis was defined as meeting any 2 of the earlier described non-histologic criteria. Advanced/decompensated cirrhosis was defined as cases with both cirrhosis and MELD score ≥10. While there is no MELD cut-off that is known to define decompensated liver disease, this cut-off was chosen as it is associated with 3-month mortality of at least 6%, while also being low enough to capture patients with complications of portal hypertension that are out of proportion to MELD score elevation.[10,11]

History of hepatic decompensation was defined as evidence of prior or current diagnosis of ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, variceal hemorrhage, or baseline concomitant medications with a specific indication for ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or variceal hemorrhage. Baseline Child-Pugh score was estimated based on a validated algorithm,[12] including laboratory values within 90 days of HCV treatment initiation. Clinical records were reviewed up to 6 months prior to HCV treatment initiation for evidence of ascites and encephalopathy, and quantified for severity according to the operational definitions of the algorithm of Kaplan *et al.* in order to calculate Child-Pugh score.[12]

Outcomes

Efficacy

Treatment efficacy was measured as sustained virologic response (SVR12), defined as HCV RNA level below the limit of quantitation or undetected at least 9 weeks after treatment was discontinued (n = 577, Fig. 1 Efficacy population). Those who were lost to follow-up, died or had data missing at the time of this analysis were excluded.

Safety

All patients who started therapy during the study period and completed or discontinued therapy due to lack of efficacy, adverse event (AE), or death were included in the safety population (n = 642, Fig. 1). Safety events are reported for up to 30 days following treatment completion. Death, liver transplantation, and development of HCC were captured for all patients throughout the entire study period and were not restricted to 30 days post-treatment.

AEs included any new, untoward events or exacerbated baseline conditions noted in the medical record. Abnormal lab values were captured as AEs if the abnormality was treated with a prescription therapy or required adjustment/discontinuation of HCV therapy. Serious adverse events (SAEs) were any AEs that required hospitalization or met criteria for expedited reporting per Food and Drug Administration form MEDWATCH 35000.

Hepatic decompensation during therapy was defined as experiencing one or more of the following: hepatic decompensation listed as an AE by a healthcare professional, new onset or exacerbation of hepatic encephalopathy, spontaneous bacterial peritonitis, variceal hemorrhage, ascites or hepatic hydrothorax, hepatorenal syndrome, hepatopulmonary syndrome, liver failure, or a new prescription for a medication to treat one of the aforementioned indications.

Impact of treatment on hepatic function

Changes in measures of hepatic function from baseline to either the short-term or the long-term follow-up time point were calculated for all patients in the efficacy population who had sufficient follow-up time, as well as the laboratory data needed for MELD score calculation. Short-term follow-up was defined as the last available value recorded between 9–26 weeks after the end of treatment. Long-term follow-up was defined as the last available value recorded at least 36 weeks after the end of treatment. Hepatic function measures examined include total bilirubin, albumin, as well as the calculated MELD score. If a

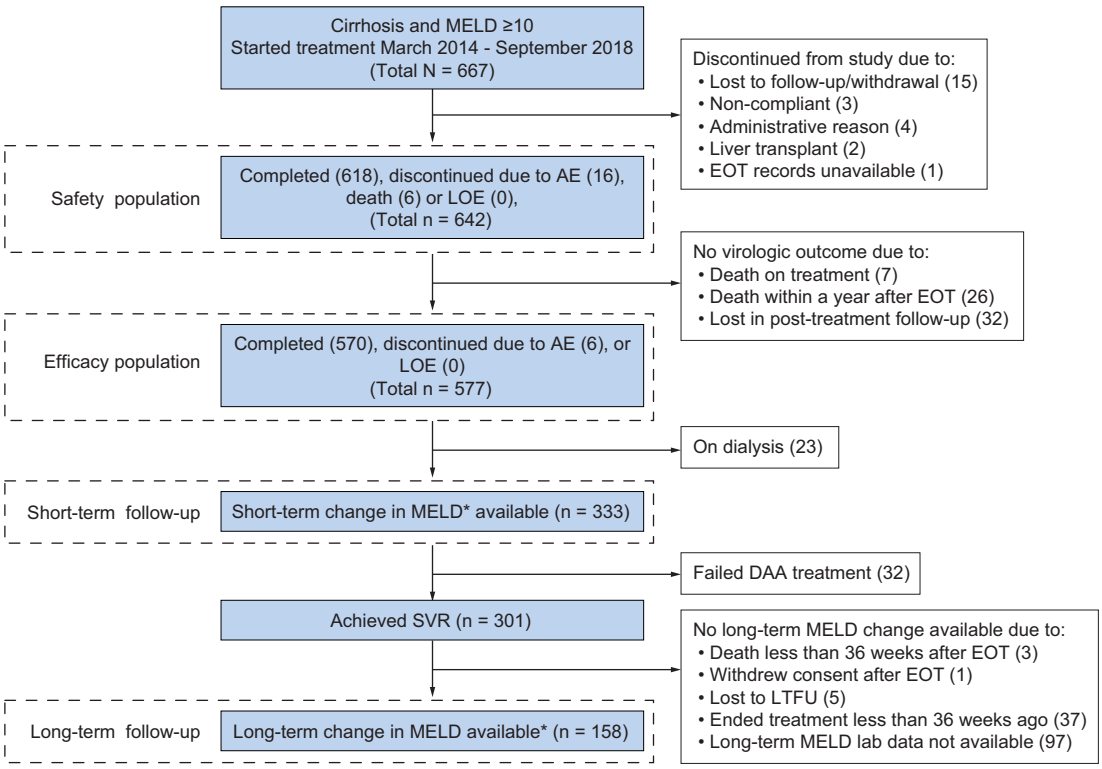

Fig. 1. Cohort description. AE, adverse event; DAA, direct-acting antiviral; EOT, end of treatment; LTFU, long-term follow-up; MELD, model for end-stage liver disease.

patient underwent liver transplant, all measures recorded at or after transplant were dismissed.

Statistical analysis

To assess treatment efficacy, unadjusted SVR12 rates with exact binomial confidence intervals were calculated for the overall efficacy population as well as by baseline MELD category (10–15, 16–20 and ≥21). To assess treatment effectiveness, SVR rates were also calculated for a subpopulation, which included the efficacy population and patients with no virologic outcomes because of death at or within 1 year after the end of treatment, with the latter considered 'failures'. Associations between SVR12 and each of the most well-established baseline characteristics were estimated with univariable logistic regression. In an attempt to better understand the relationship among risk factors and odds of achieving SVR, we also performed multivariable analysis.

MELD score, total bilirubin and albumin were compared between baseline, the short-term follow-up time point, and the long-term follow-up time point. Associations between short-term improvements in MELD of ≥3 points as well as achievement of final MELD <10, and baseline characteristics were also estimated. We selected at least a 3 MELD point improvement as clinically meaningful as it has been observed that intra-laboratory variability can have a significant impact on measured/calculated MELD, and most of this variability leads to a change in mean MELD of 3 points or less.[13] MELD analyses were performed excluding patients on dialysis at baseline to ensure that chronic kidney disease requiring dialysis did not have a significant impact on the trajectory of calculated MELD.

Time-to-event analysis was performed using the SAS PROC LIFETEST, for the events of death and liver transplant. Kaplan-Meier estimates of survivor functions were used for comparison of survival curves between groups of participants using a log-rank test. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patients

A total of 667 patients with advanced/decompensated cirrhosis in HCV-TARGET were treated with DAA therapy in the study period. Patients were not included in the cohort if they discontinued treatment early due to non-compliance (n = 3), or for administrative reasons (n = 4), were lost to follow-up/withdrew from the study (n = 15), underwent liver transplantation (n = 2) or had unavailable records at the time of analysis (n = 1) (Fig. 1). The remaining 642 patients comprised the safety population. The overall median age was 60 years, 68% of patients were men and 68% Caucasian (Table 1). Most patients had HCV genotype 1 (70%), and 45% were treatment experienced.

The median MELD score at the time of treatment initiation was 12 (range 10–39): 521 (81%) had a score of 10–15, 78 (12%) 16–20 and 43 (7%) ≥21. Overall, 309 patients (48.1%) had Child-Pugh class B cirrhosis, 64% had experienced prior clinical decompensation events, and 4% of patients were on dialysis at treatment initiation.

Table 1. Baseline characteristics of the safety population patients by MELD score.

	MELD 10–15 (n = 521)	MELD 16–20 (n = 78)	MELD ≥21 (n = 43)	Total (n = 642)
Male (%)	352 (67.6%)	52 (66.7%)	30 (69.8%)	434 (67.6%)
Age (years), median (range)	60 (25–89)	60 (37–83)	60 (31–80)	60 (25–89)
Race (%)				
White	357 (68.5%)	53 (67.9%)	27 (62.8%)	437 (68.1%)
Black	79 (15.2%)	14 (17.9%)	13 (30.2%)	106 (16.5%)
Other	85 (16.3%)	11 (14.1%)	3 (7.0%)	99 (15.4%)
Hispanic ethnicity (%)	67 (12.9%)	10 (12.8%)	5 (11.6%)	82 (12.8%)
Treatment experienced (%)	250 (48.0%)	23 (29.5%)	15 (34.9%)	288 (44.9%)
Prior 2nd generation DAA	114 (21.9%)	11 (14.1%)	5 (11.6%)	130 (20.2%)
HCV Genotype				
1	359 (68.9%)	60 (76.9%)	32 (74.4%)	451 (70.2%)
1a	255 (49.1%)	44 (56.4%)	23 (53.5%)	322 (50.3%)
1b	82 (15.8%)	14 (17.9%)	9 (20.9%)	105 (16.4%)
2	40 (7.7%)	5 (6.4%)	4 (9.3%)	49 (7.6%)
3	101 (19.4%)	11 (14.1%)	6 (14.0%)	118 (18.4%)
4	15 (2.9%)	2 (2.6%)	0 (0.0%)	17 (2.6%)
other/not reported	6 (1.2%)	0 (0.0%)	1 (2.3%)	7 (1.2%)
HCV RNA, median (range), (U/ml, log10)	5.8 (2–8)	5.9 (2–7)	5.6 (0–7)	5.8 (0–8)
HCC (%)	57 (10.9%)	9 (11.5%)	4 (9.3%)	70 (11.9%)
PPI use	238 (45.7%)	41 (52.6%)	30 (69.8%)	309 (48.1%)
Prior clinical decompensation (%)	325 (62.4%)	59 (75.6%)	28 (65.1%)	412 (64.2%)
Lab values, median (range)				
Albumin (n/dl)	3.2 (1.8–4.7)	2.9 (2.0–4.6)	3.6 (1.9–4.9)	3.2 (1.8–4.9)
Total bilirubin (mg/dl)	1.6 (0.0–9.3)	2.8 (0.2–11.3)	0.7 (0.3–16.1)	1.6 (0.0–16.1)
ALT	55.5 (9–398)	52.5 (9–166)	32.5 (9–163)	53 (9–398)
AST	79.5 (10–639)	77.5 (20–393)	41.5 (15–356)	76.5 (10–639)
Platelet count (×10^3/μl)	82 (15–647)	75 (28–545)	118 (23–258)	83 (15–647)
INR	1.3 (0.9–2.0)	1.5 (0.9–3.1)	1.2 (0.9–4.5)	1.3 (0.9–4.5)
Creatinine (mg/dl)	0.8 (0.4–2.4)	1.1 (0.4–10.3)	4.9 (0.6–12.8)	0.9 (0.4–12.8)
MELD	12 (10–15)	17 (16–20)	23 (21–39)	12 (10–39)
On dialysis (%)	0 (0.0%)	4 (5.1%)	22 (51.2%)	26 (4.0%)
Treatment Regimen (%)				
Sofosbuvir/ledipasvir	299 (57.4)	49 (62.8)	11 (25.6)	359 (55.9)
Sofosbuvir/daclatasvir	75 (14.4)	9 (11.5)	4 (9.3)	88 (13.7)
Sofosbuvir/velpatasvir	107 (20.5)	11 (14.1)	6 (14.0)	124 (19.3)
Elbasvir/grazoprevir	14 (2.7)	6 (7.7)	16 (37.2)	36 (5.6)
Glecaprevir/pibrentasvir	15 (2.9)	2 (2.6)	6 (14.0)	23 (3.6)
Sofosbuvir/velpatasvir/voxilaprevir	11 (2.1)	1 (1.3)	0 (0.0)	12 (1.9)
Ribavirin used (%)	169 (32.4)	24 (30.7)	4 (9.3)	197 (30.7)
Child-Pugh score				
A	145 (27.8)	10 (12.8)	23 (53.5)	178 (27.7)
B	276 (53.1)	26 (33.3)	7 (16.3)	309 (48.1)
C	39 (7.5)	35 (44.9)	10 (23.3)	84 (13.1)
Not available	61 (11.7)	7 (9.0)	3 (7.0)	71 (11.1)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease; PPI, proton pump inhibitor.

The efficacy population (n = 577) was restricted further by excluding patients who did not have a virologic outcome reported due to death (7 died during treatment and 26 died after treatment concluded but prior to evaluation of SVR, 21 of them within a year after treatment), and 32 who were lost to post-treatment follow-up.

Antiviral treatment regimen

The most common DAA regimen was sofosbuvir/ledipasvir (56%), followed by sofosbuvir/velpatasvir (19%), sofosbuvir/daclatasvir (14%), elbasvir/grazoprevir (6%), glecaprevir/pibrentasvir (4%), and sofosbuvir/velpatasvir/voxilaprevir (2%). The most common regimen in patients with MELD ≥21 was elbasvir/grazoprevir, all of whom had a baseline glomerular filtration rate (GFR) <30 ml/min. Ribavirin was used in 31% (197/642) of patients in the safety population with 32% (169/521) in the MELD 10–15 group, 31% (24/78) in the MELD 16–20 group, and 1% (4/43) in the MELD ≥21 group. Median (IQR) treatment duration for the entire cohort was 90 days (85–169), and 91.0 days (85–169) among patients who completed treatment.

Treatment response

Of the 577 patients in the efficacy population, 522 (90.5%) achieved SVR12. Rates of SVR12 by MELD categories were: 427/475 (89.9%; 95% CI 86.8–92.5) in MELD 10–15, 62/68 (91.2%; 95% CI 81.8–96.7) in MELD 16–20, and 33/34 (97.1%, 95% CI 84.7–99.9) in MELD ≥21 (Fig. 2).

However, the efficacy population (defined as those with available virologic SVR status) does not include patients with no virologic outcome due to death (7 on and 21 within 1 year after the DAA treatment; 16 of these patients had MELD 10–15, 4 with MELD 16–20 and 8 with MELD ≥21.) To assess treatment

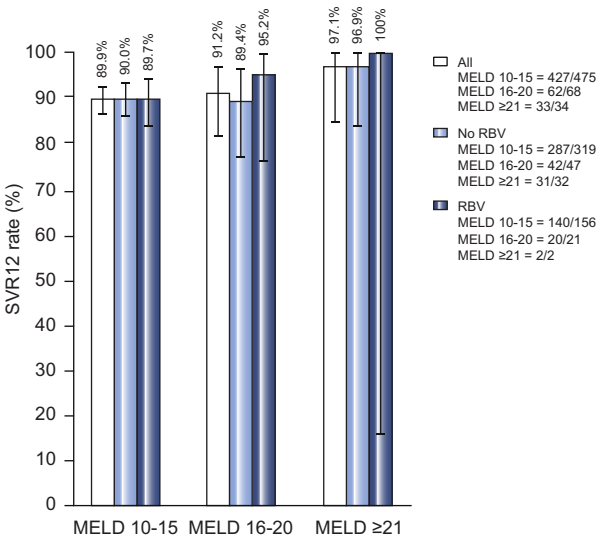

Fig. 2. SVR12 by MELD category and ribavirin use (efficacy population). MELD, model for end-stage liver disease; RBV, ribavirin; SVR12, sustained virologic response at least 9 weeks after treatment discontinuation.

effectiveness, we assigned virologic outcomes for these patients as 'failures' and calculated SVR rates by adding these 28 patients to the efficacy population defined above. SVR12 rates including these cases were statistically similar throughout all MELD categories: 427/491 (87.0%; 95% CI 83.7–89.8) in MELD 10–15, 62/72 (86.1%; 95% CI 75.9–93.1) in MELD 16–20 and 33/42 (78.6%; 95% CI 63.2–89.7) in MELD ≥21 (Fig. S1).

In univariable analysis, negative predictors of SVR included the presence of ascites (odds ratio [OR] 0.33; 95% CI 0.17–0.59; p <0.001), hepatocellular carcinoma (HCC)(OR 0.33; 95% CI 0.17–0.69; p = 0.002), albumin level <3.5 mg/dl (OR 0.31; 95% CI 0.14–0.61; p = 0.001) and proton pump inhibitor (PPI) use (OR 0.47; 95% CI 0.26–0.83; p = 0.010), while treatment experience, baseline MELD and ribavirin use did not show an association with treatment response. Positive predictors of SVR were total bilirubin ≤1.2 mg/dl (OR 1.94; 95% CI 1.05–3.80; p = 0.042) and Child-Pugh A (OR 4.33; 95% CI 1.90–12.04; p = 0.002)(not shown).

The multivariable model with least absolute shrinkage and selection operator (LASSO)-selected covariates for association with SVR included the presence of ascites (OR 0.58; 95% CI 0.26–1.21; p = 0.157), albumin level <3.5 mg/dl (OR 0.41; 95% CI 0.14–1.04; p = 0.070), history of HCC (OR 0.40; 95% CI 0.18–0.91; p = 0.024), PPI use (OR 0.59; 95% CI 0.31–1.10; p = 0.099), age <60 (OR 0.58; 95% CI 0.30–1.08; p = 0.085), male sex (OR 0.49; 95% CI 0.23–0.98; p = 0.049), MELD <16 (OR 0.36; 95% CI 0.11–0.93; p = 0.053), and Child-Pugh A (OR 1.84; 95% CI 0.53–7.28; p = 0.342) (Fig. S2).

Short-term changes in hepatic function

During short-term follow-up, MELD score decreased in 187 (56%), did not change in 54 (16%) and increased in 92 (28%) patients (Fig. 3A). A decline of at least 3 MELD points occurred in 80 (24%) patients and was more common among patients with a baseline MELD ≥16 (41%) (Fig. 3A). Short-term MELD changes were similar among patients who achieved SVR and those who failed DAA treatment (Fig. 3B).

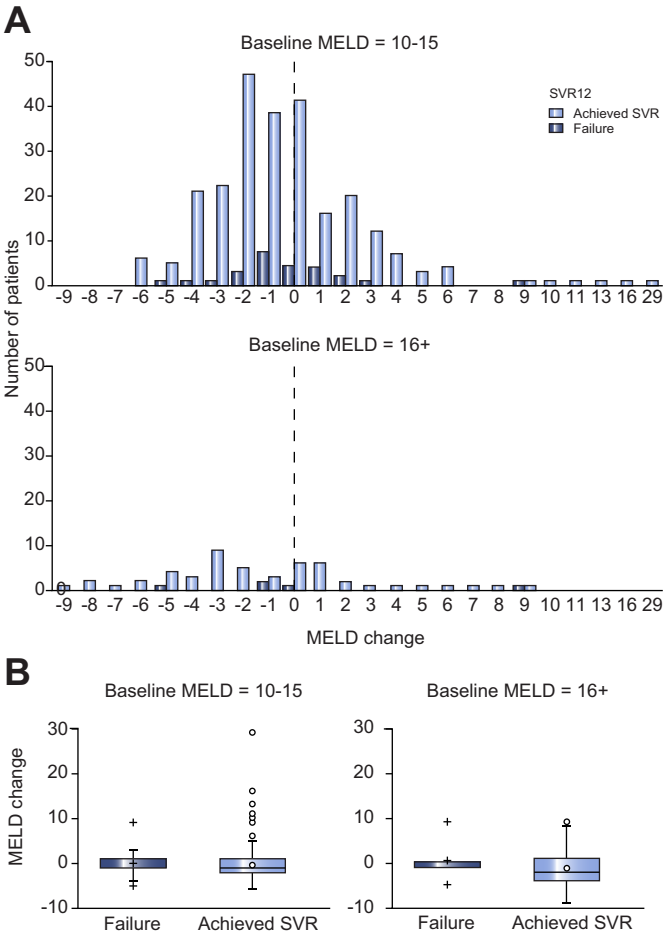

Fig. 3. Short-term change in MELD score from baseline to 9–26 weeks post-end of treatment (efficacy population patients who were not on dialysis at baseline). (A) Pre-treatment to post-treatment value change among individual patients. (B) Change from pre-treatment to post-treatment value by treatment outcome. MELD, model for end-stage liver disease.

In multivariable model with LASSO-selected covariates, male sex (OR 0.51; 95% CI 0.27–0.93; p = 0.029), baseline ALT <60 U/L (OR 0.41; 95% CI 0.22–0.75; p = 0.004), Child-Pugh A (OR 0.48; 95% CI 0.21–0.99; p = 0.058) and MELD <16 (OR 0.33; 95% CI 0.16–0.69; p = 0.003) were negatively associated with MELD improvement of at least 3 points, and age <60 (OR 2.15; 95% CI 1.20–3.93; p = 0.012) was predictive of this improvement (Fig. 4).

Long-term changes in hepatic function

A total of 218 patients in the efficacy population who achieved SVR and were not on dialysis at baseline were evaluable for long-term outcomes. Of these, 158 had MELD scores available at least 36 weeks after the end of treatment. The median (IQR) follow-up after the end of treatment was 213 (174–224) weeks. Baseline demographics were similar between patients with and without long-term follow-up, including age (mean 58.5 *vs.* 59.8, p = 0.168), HCC (8.2% *vs.* 11.9%, p = 0.290), baseline MELD (mean 13.2 *vs.* 12.9, p = 0.417), and baseline albumin (mean 3.2 *vs.* 3.3, p = 0.257) (Table 2). However, patients with long-term follow-up were more likely to have ascites at baseline (55.7% *vs.* 44.1%, p = 0.044) and prior hepatic decompensation events (71.5% *vs.* 60.8%, p = 0.050).

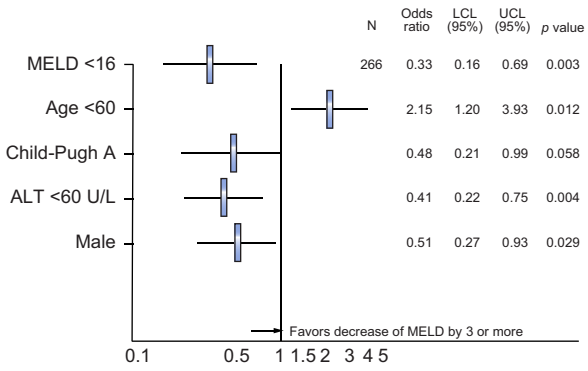

Fig. 4. Multivariable analysis to predict improvement in MELD (decrease by ≥3 points) from baseline to 9–26 weeks post-end of treatment. Least absolute shrinkage and selection operator regression was used to select variables that contributed to the outcome. MELD, model for end-stage liver disease.

The overall mean decrease in MELD score from the start of treatment until the end of long-term follow-up was 0.30 (95% CI −1.10 to 0.50) points. Patients with a baseline MELD ≥16 had a mean MELD improvement of 1.90 (95% CI −3.66 to −0.15) points, while those with a baseline MELD <16 had a mean increase of 0.09 (95% CI −0.80 to 0.99)(Fig. 5). A decline of at least 3 MELD points in long-term follow-up occurred in 45 (29%) patients and was more common among those with a baseline MELD ≥16 (45%). During long-term follow-up, 40 (25%) patients achieved a reduction in MELD score to <10, 38 of them with a baseline MELD of 10–15 and 2 with a baseline MELD of 16–20.

In univariable analysis, baseline MELD <16 (OR 5.08; 95% CI 1.57–25.81; p = 0.020) and baseline INR <1.5 (OR 2.67; 95% CI 1.00–8.82; p = 0.074) were predictive of achieving a final MELD score of <10 in long-term follow-up. The presence of ascites (OR 0.49; 95% CI 0.24–1.01; p = 0.057) and ALT <60 U/L (OR 0.40; 95% CI 0.19–0.83; p = 0.016) were negatively associated with this improvement, while age, gender, history of HCC and other baseline laboratory values did not show associations. We further evaluated the impact of Child-Pugh score on long-term MELD outcome of <10 and noted that Child-Pugh A did not show an association with long-term MELD <10 (OR 1.55; 95% CI 0.64–3.59; p = 0.324) while Child-Pugh C was negatively associated with long-term MELD <10 (OR 0.15; 95% CI 0.02–0.60; p = 0.029). In multivariable analysis, LASSO regression identified baseline ALT <60 U/L (OR 0.39; 95% CI 0.17–0.86; p = 0.022) and Child-Pugh C (OR 0.25; 95% CI 0.03–1.14; p = 0.127) as negative predictors and MELD <16 (OR 2.75; 95% 0.76–14.7; p = 0.165) as a positive predictor for this improvement.

In long-term follow-up, there was an overall increase in mean total bilirubin of 0.23 (95% CI −0.44 to 0.89) mg/dl (Fig. S3). Patients with a baseline MELD of ≥16 had a mean decrease of 0.67 (95% CI −1.31 to −0.03) mg/dl in total bilirubin, while those with a baseline MELD <16 experienced a mean increase in total bilirubin of 0.41 (95% CI −0.38 to 1.20) mg/dl. In long-term follow-up there was also an increase in mean albumin of 0.36 (95% CI 0.28–0.45) g/dl (Fig. S4). Patients with a baseline MELD of ≥16 had a mean improvement of 0.36 (0.14–0.58) g/dl in albumin, and those with a baseline MELD <16 experienced a mean improvement of 0.36 (0.27–0.46) g/dl.

Table 2. Comparison of patients with available long-term MELD change *vs.* patients with no available long-term MELD change[†].

	With long-term MELD (n = 158)	Without long-term MELD (n = 143)	*p* value
Male (%)	97 (61.4%)	100 (69.9%)	0.120
Age (years), mean (range)	58.5 (31–83)	59.8 (37–86)	0.168
Race (%)			
White	107 (71.3%)	98 (69.5%)	0.732
Non-white	43 (28.7%)	43 (30.5%)	
Hispanic ethnicity (%)			0.019
Hispanic	29 (18.6%)	13 (9.2%)	
Non-Hispanic	127 (81.4%)	129 (90.8%)	
HCV genotype			
1	123 (78.3%)	93 (65.5%)	0.013
2–6	34 (21.7%)	49 (34.5%)	
HCC (%)	13 (8.2%)	17 (11.9%)	0.290
Ascites (%)	88 (55.7%)	63 (44.1%)	0.044
Child-Pugh assessment			
A	32 (22.7%)	40 (31.2%)	0.103
B	84 (59.6%)	75 (58.6%)	
C	25 (17.7%)	13 (10.2%)	
PPI use	76 (48.1%)	60 (42.0%)	0.285
Prior clinical decompensation (%)	113 (71.5%)	87 (60.8%)	0.050
Lab values, mean (range)			
Albumin (n/dl)	3.2 (2.0–4.5)	3.3 (2.0–4.9)	0.257
Total bilirubin (mg/dl)	1.9 (0.0–10.3)	1.7 (0.2–8.7)	0.065
ALT	64.4 (9–283)	69.4 (9–326)	0.321
AST	91.4.0 (20–316)	95.3 (10–639)	0.596
Platelet count ($\times 10^3/\mu l$)	87.8 (26–237)	99.8 (20–329)	0.037
INR	1.35 (0.9–3.0)	1.34 (0.9–4.5)	0.799
Creatinine (mg/dl)	1.09 (0.4–7.6)	1.12 (0.5–6.7)	0.756
MELD	13.2 (10–28)	12.9 (10–27)	0.417

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease; PPI, proton pump inhibitor.
[†]Efficacy population who achieved sustained virologic response, were not on dialysis at baseline and with available short-term (9–23 weeks after treatment) change in MELD. *p* values represent Chi-square or 2 sample *t* test.

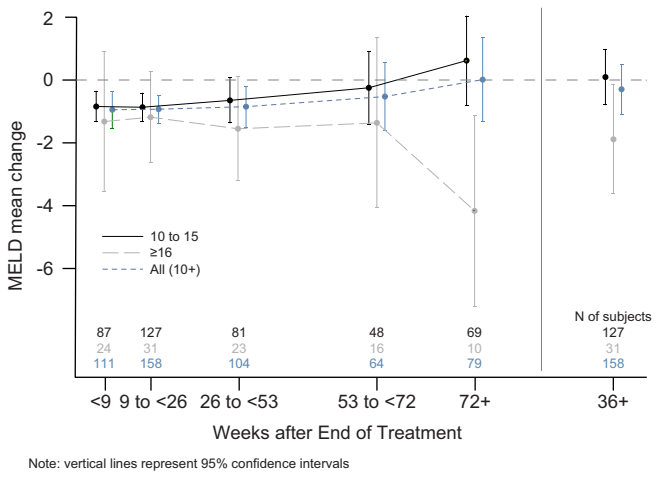

Fig. 5. Long-term change in MELD score from baseline to the end of long-term follow-up. At a median of 213 weeks post-treatment, the mean change in MELD was −0.30 points. MELD, model for end-stage liver disease.

Safety

Overall, 468 (73%) patients in the safety population experienced an AE, leading to treatment discontinuation in 3.6%. SAEs occurred in 20% of the entire safety population, including 17% in MELD 10–15, 39% in MELD 16–20 and 28% in MELD ≥21 patients (Table 3).

The most common liver-related SAEs of interest were the development of hepatic encephalopathy (4.4%), ascites (0.9%), and bacterial peritonitis (0.8%). Overall, 83 patients (12.9%) had new decompensating events either on treatment or up to 30 days after the end of treatment and 41 patients (6.4%) had decompensating events that were classified as SAEs. Of the 83 patients, only 7 patients (8%) had no reported history of decompensating events prior to DAA regimen. Of the 137 AEs, 94 (69%) were exacerbations of previously recorded conditions, experienced by 61 (73%) of these 83 patients. The fifteen remaining patients (18%) with a prior history of decompensating events had developed a different decompensating event than that recorded prior to the start of DAA treatment.

A total of 16 patients with baseline MELD ≥21 were treated with elbasvir/grazoprevir. All of these patients had eGFR of <30 mg/dl and 15 of them were on dialysis at baseline. There were no decompensating events characterized as SAEs recorded in this subpopulation.

Survival

Seven patients died on treatment (coronary artery disease, hepatic encephalopathy, hepatic failure, multi-organ failure, septic shock, and unknown cause in 2 patients), 4 of whom had a baseline MELD 10–15, 1 MELD 16–20 and 2 MELD ≥21. In addition, at least 44 patients died after the end of DAA treatment. Death was attributable to advanced liver disease in 12 patients, while the cause of death in the others was liver unrelated or unknown. Median duration (range) of time for survival follow-up was 15.5 (0–50.8) months. Baseline MELD <16 was predictive of overall survival (log-rank, p <0.0001). Survival rates at 1, 2, and 3 years were 96.0%-93.6%-89.7% and 85.9%-82.4%-71.7%, in participants with baseline MELD 10–15 and baseline MELD ≥16, respectively.

Five patients underwent liver transplantation while on treatment. Three achieved SVR, 1 failed treatment, and virologic data was unavailable in 1 patient. In addition, 17 patients underwent liver transplant after the end of treatment. Median (range) follow-up time for liver transplant events was 14.1 (0–50.8) months. The proportion of patients with baseline MELD 10–15, and baseline MELD ≥16, who underwent liver transplant 1, 2, and 3 years after treatment initiation was 2.6%-5.4%-9.0% and 1.2%-2.9%-2.9%, respectively. Median duration (range) of time for HCC diagnosis follow-up was 14.1 (0–50.8) months. A total of 13 patients with baseline MELD 10–15 and 3 patients with baseline MELD >16 developed HCC.

Discussion

Chronic hepatitis C therapy in those with advanced stage liver disease may improve hepatic function, as measured by MELD or Child-Pugh scores, although who will achieve this improvement and whether long-term transplant-free survival is a realistic goal of treatment remain uncertain.[5,6,14–19] This is a large real-life cohort of patients with advanced/decompensated liver disease

Table 3. Adverse events and serious adverse events by MELD score (safety population).

	MELD 10–15 (n = 521)	MELD 16–20 (n = 78)	MELD ≥21 (n = 43)	Total (n = 642)
Total number with AE*, n (%)	369 (70.8)	72 (92.3)	27 (62.8)	468 (72.9)
Total number with SAE*, n (%)	86 (16.5)	30 (38.5)	12 (27.9)	128 (19.9)
Hepatic decompensation*, n (%)	61(11.7)	17 (21.8)	5 (11.6)	83 (12.9)
SAEs, n (%)	31 (6.0)	8 (10.3)	2 (4.7)	41(6.4)
SAEs of interest, n (%)				
Ascites	5 (1.0)	0 (0.0)	1 (2.3)	6 (0.9)
Esophageal variceal hemorrhage	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Acute Hepatic failure	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.2)
Hepatorenal syndrome	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Bacterial peritonitis	5 (1.0)	0 (0.0)	0 (0.0)	5 (0.8)
Hepatic encephalopathy	18 (3.5)	8 (10.3)	2 (4.7)	28 (4.4)
Hepatic hydrothorax	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Death, n (%)				
During treatment	4 (0.8)	1 (1.3)	2 (4.7)	7 (1.1)
Liver transplantation, n (%)				
During treatment	4 (0.9)	1 (1.5)	0 (0.0)	5 (1.0)

AE, adverse event; MELD, model for end-stage liver disease; SAE, serious AE.
*AEs, SAEs and hepatic decompensation reported up to 30 days post-treatment.

who received HCV treatment, with the longest post-treatment follow-up available to date.

The overall SVR12 rate in the efficacy population (90.5%) is similar to those reported in clinical trials and previous real-world experiences.[3,4] Remarkably, 97% of the 34 patients with MELD over 21 who had available virologic outcome achieved viral eradication, though this SVR rate decreased to 78.6% when patient deaths on or after treatment but prior to the SVR12 time point were classified as failures. Elbasvir/grazoprevir, which is contraindicated in patients with advanced liver disease, was more commonly used in patients with MELD score of ≥21 because most patients in this high MELD group had advanced kidney disease. Despite high SVR rates, changes in MELD score and hepatic function tests in short- and long-term follow-up in this cohort were marginal. While 56% of patients experienced some improvement in MELD at the time of SVR12, the overall mean short-term change in MELD was less than a point and a clinically meaningful improvement of ≥3 MELD points occurred in only 24% of patients. Predictors of this improvement included female sex, age <60, high baseline ALT (≥60 U/ml), and baseline MELD ≥16. Our data are in line with clinical trials with a variety of regimens where median MELD improvement, over the short-term, was by 2 points in 60% of patients; and MELD score remained unchanged or worsened by a median MELD of 1 in the remaining 40%.[3]

Unique to this cohort is the long-term follow-up (median >4 years post-treatment). Patients with long-term follow-up were not dissimilar from those without, except that ascites and prior decompensating events were more common among patients included in the long-term follow-up, thus indicating that those in follow-up were as sick if not sicker than those lost to follow-up. At a median of 213 weeks of follow-up, there were only minimal overall mean changes in MELD score (decrease 0.30 points), total bilirubin (increase by 0.23 mg/dl) and albumin (increased by 0.36 g/dl). In addition, only 29% of patients experienced a clinically meaningful improvement in MELD by 3 or more points and 25% achieved a MELD score of <10; a threshold we used as a surrogate for reasonably good synthetic function and functional status.

Previous reports had noted improvements in hepatic function, to the degree of de-listing patients on a liver transplant list. Improvements in Child-Pugh scores have been noted and predictors of improvement have been described.[5–8] A prior study has evaluated changes in MELD in Child-Pugh B and C patients and noted that at 36 months after HCV treatment, a substantial number of patients with MELD ≥15 still remained in that category.[20] A few reports have suggested that some patients achieving SVR after DAA had an improvement in portal hypertension below the clinically significant portal hypertension threshold of 10 mmHg while MELD score may not reflect such benefit.[21,22] Unfortunately given the lack of widespread use and availability of hepatic venous pressure measurements in a real-life scenario, we were limited in generating such data.

While there has been a decrease in listings for liver transplantation with HCV as an etiology in national databases, it is unclear if this is because of preventing progression of liver disease and development of HCC in those with compensated cirrhosis or if it is due to improvements in hepatic function in those with decompensated cirrhosis.[2,23] Further, listing or de-listing criteria are arbitrary and center specific and thus difficult to compare across studies and liver centers. Our data would suggest that there is improvement in hepatic function in some patients but not necessarily to the degree where the risk of death and functional incapacity are mitigated if MELD changes were to be used as a surrogate for these events.

There are limitations to this study inherent to the real-world study design. In particular, the lack of data available to determine change in Child-Pugh class over time limits our ability to understand the impact of treatment on non-MELD based indications for liver transplant. We do not have quality of life and liver-specific symptom data, particularly pertaining to ascites and hepatic encephalopathy resolution, to verify ongoing symptoms of portal hypertension. It is possible that there are patients with elevated MELD scores due to factors other than decompensated liver disease, such as advanced chronic kidney disease. To mitigate this potential misclassification, patients on dialysis were excluded from MELD trajectory analysis.

In summary, in this real-world cohort of HCV treatment among patients with advanced/decompensated cirrhosis, while SVR rates were high, the improvement in MELD score, bilirubin or albumin after a median follow-up of 4 years were minimal. Thus, while an optimistic position would be that there was no worsening in the severity of liver disease in the majority of patients and few required liver transplant during follow-up, a state of MELD "purgatory" may evolve in some patients and most patients require ongoing close monitoring.

Abbreviations

ALT, alanine aminotransferase; AE, adverse event; AST, aspartate aminotransferase; DAA, direct-acting antiviral; EOT, end of treatment; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; INR, international normalized ratio; LASSO, least absolute shrinkage and selection operator; LTFU, long-term follow-up; MELD, model for end-stage liver disease; PPI, proton pump inhibitor; SAE, serious adverse event; SVR, sustained virologic response.

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Conflict of interest

RR: AbbVie, Gilead, BMS, Intercept, Conatus, Exact Sciences, HCC-TARGET, HCV-TARGET, NASH-TARGET, Mallinckrodt, Grifols, Merck, Spark Therapeutics, Dova, Shionogi. EV: Gilead. GM: Nothing to disclose. NAT: Gilead, Intercept, EXIGO Management Consultants LLC. ASL: BMS, Gilead. JKL: BMS, Genfit, Gilead, Hologic, Intercept, Prometheus. AMD: Gilead, Abbvie. SZ: AbbVie, Gilead, Intercept, Janssen, Merck. CSL: AbbVie, Gilead. PK: AbbVie, BMS, Gilead, Merck, Ribavirin pregnancy registry, Target Registries, Eiger, Aligos, Johnson and Johnson, Dova, Shionogi, Edigene, Durect, Ferring, Surrozen, Mallinckrodt, Allergan, PPD development, Conatus, Eisai, Quest. MH: Nothing to disclose. MPM: BMS, Gilead, Merck (MSD), AbbVie. MV: Nothing to disclose. LA: Nothing to disclose. DRN: AbbVie, Gilead, Merck, Target Pharma Solutions. MWF: AbbVie, Altavant, BMS, Gilead, Merck, Roche, Target Pharma Solutions.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: EV, RR. Acquisition of data: MV, LA. Analysis and interpretation of data: EV, RR, MV, LA. Drafting of manuscript: EV, RR. Critical revision of manuscript: GM, NAT, ASL, JKL, AMD, SZ, CSL, PK, MH, MPM, DRN, MWF, MV, LA.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.03.031.

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Author names in bold designate shared co-first authorship

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