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SOFOSBUVIR AND DACLATASVIR THERAPY IN PATIENTS WITH HEPATITIS C RELATED ADVANCED DECOMPENSATED LIVER DISEASE (MELD ≥ 15)

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SOFOSBUVIR AND DACLATASVIR THERAPY IN PATIENTS WITH HEPATITIS C RELATED ADVANCED DECOMPENSATED LIVER DISEASE (MELD ≥ 15)

Introduction:

Antiviral therapy for hepatitis c has the potential to improve liver function in patients with decompensated cirrhosis. Data on treatment outcomes in this population are limited.

Methods:

We prospectively collected data on patients who satisfied the minimum criteria for transplantation in decompensated cirrhosis who commenced sofosbuvir/daclatasvir for 24-weeks under the Australian Patient Supply Program (TOSCAR) and analysed outcomes including SVR12, death and transplant.

Results:

The study included 108 patients (M/F,79/29; median age 56years; Child-Pugh 10; MELD 16; genotype 1/3,55/47). All patients received sofosbuvir/daclatasvir and two also received ribavirin. On intention-to-treat, the SVR12 rate was 70% (76/108). Seventy-eight patients completed 24-weeks therapy. SVR12 was achieved in 56 of these patients on per-protocol-analysis (76%). SVR12 was 80% in genotype 1 compared to 69% in genotype 3 (p=0.41). Thirty patients failed to complete therapy. In patients achieving SVR12, median MELD and Child-Pugh fell from 16(IQR15-17) to 14(12-17) and 10(9-11) to 8(7-9), respectively (p<0.001). In those who died, MELD increased from 16 to 23 at death (p=0.036). Patients who required transplantation had a significantly higher baseline MELD (20) compared to those patients completing treatment (16)(p=0.0010), which was not significantly different at transplant (20; p=0.85). The odds ratio for transplant in patients with baseline MELD ≥20 was 13.8(95%CI 2.78-69.04).

Conclusion:

SVR12 with sofosbuvir/daclatasvir in advanced liver disease are lower than reported in compensated disease. Although treatment improves MELD and Child-Pugh in most patients, a significant proportion will die or require transplantation. In those with MELD≥20 it may be better to delay treatment until post-transplant.

Introduction

Interferon-based therapy for hepatitis C (HCV) is contraindicated in patients with advanced cirrhosis because of poor tolerability and safety concerns. Until recently, the lack of a safe antiviral therapy to prevent disease progression in patients with severe HCV-induced liver injury meant that most eventually developed liver failure for which the only effective treatment was liver transplantation. Indeed decompensated cirrhosis due to chronic hepatitis C viral infection has become the commonest indication for liver transplantation [1]. However, recurrent HCV infection post-transplant is almost universal, often following an accelerated course with rapid progression to cirrhosis in the absence of treatment[2,3].

Direct acting antivirals have greatly improved the results of HCV treatment[4]. Furthermore, a very low incidence of side effects has enabled the use of some classes of these drugs in patients with advanced liver disease who are poor candidates for interferon. There is emerging evidence that treatment of patients with advanced HCV cirrhosis with regimens, which include the nucleoside inhibitor, sofosbuvir, in combination with an NS5A inhibitor is well tolerated and effective across multiple genotypes, although the reported SVR12 rates appear to be lower than in non-cirrhotic populations [5-7]. Recent findings suggest that successful antiviral therapy can improve liver function in patients with decompensated HCV cirrhosis [5,8-10]. However, these studies have several limitations. Firstly the majority of patients included were Child-Pugh B with relatively low Model for End-stage Liver Disease (MELD) scores [6-9]. Secondly, patients with genotype 3 infection were not well represented. Thirdly, in several studies the direct acting antiviral regimen was not uniform and of varying treatment duration and, finally, there is limited data regarding on-treatment mortality and need for rescue liver transplantation.

In Australia, access to the direct acting antivirals outside of clinical trials was very limited until March 1, 2016 when access was given to most patients following funding of treatment under the Pharmaceutical Benefits Scheme. In the preceding 18 months, the only access to any form of direct acting antiviral therapy was through randomised controlled trials or compassionate use programs.

In the second quarter of 2014 an investigator-initiated, prospective, open-label study was commenced which provided access to sofosbuvir and daclatasvir therapy for patients with decompensated HCV cirrhosis with all genotypes including genotype 3. Treatment was provided only to patients who had MELD scores of 15 or greater and were therefore at significant risk of dying or requiring liver transplantation before government-funded drug

therapy became available. The decision to treat all patients in the study with sofosbuvir and daclatasvir for six months was based on limited data at that time suggesting that these drugs have pan-genotypic efficacy and that three months combination therapy may not be sufficient in advanced cirrhosis [11]. Although clinicians were given the option of using ribavirin, this occurred in a minimal number of patients (n = 2) because of concern regarding its potential toxicity in advanced liver failure patients.

This paper reports the outcomes in all patients satisfying the minimum MELD score criteria for liver transplantation in decompensated cirrhosis in Australia (MELD ≥ 15) who were treated under this protocol between October 2014 and June 2015. Forty-three percent of these patients had difficult-to-cure genotype 3 infection.

Patients and Methods

All hepatitis c viraemic patients with MELD ≥ 15 HCV-related cirrhosis (thus meeting the minimum eligibility criteria for liver transplantation in Australia) and who were commenced on direct acting antiviral therapy under the compassionate access program, TOSCAR (**T**ransplant **O**utcomes of **S**ofosbuvir plus da**C**l**A**tasvir with or without **R**ibavirin), were included in this multi-centre study. Patients could be either treatment naive or treatment experienced. Key exclusion criteria included MELD score <15; HIV or Hepatitis B co-infection; history of allergy to nucleoside/nucleotides; pregnancy or breastfeeding; and calculated glomerular filtration rate of less than 30mL/min/1.73m^2. Patients received once daily sofosbuvir (400mg) and daclatasvir (60mg) with or without ribavirin (weight based dose, as tolerated) for 24 weeks. The two patients treated with ribavirin were both prescribed a total of 1000mg daily. Sofosbuvir and daclatasvir were provided on a compassionate basis by Gilead Sciences and Bristol-Myers Squibb, respectively.

Patient baseline characteristics were collected including demographics, hepatitis c genotype, prior antiviral therapy and history of hepatocellular carcinoma. Patients were reviewed at their respective treatment centres at minimum, at baseline/start of treatment, week 12 of treatment, end of treatment (week 24) and at 12 weeks post-treatment (sustained virologic response 12 (SVR12) visit). Assessments of clinical state were performed. Routine tests performed at each visit included full blood count, measurement of renal function, INR, liver biochemistry and hepatitis c viral load. MELD and Child-Pugh scores were calculated.

Endpoints

The primary outcomes included a) treatment completion; b) SVR12 defined as sustained virologic response 12 weeks after completion of treatment; and c) liver related outcomes including death, transplantation and changes in MELD and Child-Pugh scores.

The study was approved by the institution review board and ethics committees at each clinical site prior to study commencement. All patients provided written, informed consent prior to commencing the treatment.

Statistical analysis

Data were collected and stored on a central database. Analysis was performed using Stata© version 10 software (StataCorp LP College Station, Texas USA). The analysis approached possible predictors of outcome in the per-protocol group and differences between those who achieved completion of treatment and those who failed. Distribution of data was assessed and univariate testing of statistical significance was undertaken using the Student's t-test, Wilcoxon rank-sum test, Chi-square or Fisher's exact test, where appropriate. Logistic regression was utilized to create a multivariable model, reporting odds-ratios (OR). The paired t-test, Wilcoxon matched-pairs signed rank test, McNemar's test and Friedman's test were used to test the statistical significance of changes. A p-value of 0.05 is considered significant.

Results

Patients

A total of 108 patients with HCV-related cirrhosis (MELD ≥15) were enrolled between October 2014 and July 2015 at 13 sites in Australia. Outcome data up to 12 weeks post treatment was available for all patients except one who was lost to follow up after treatment completion (Figure 1). Baseline characteristics are shown in Table 1. Patients were mostly male (73%) and Caucasian (90%) with a median age of 56 years. The median (interquartile range, IQR) Child-Pugh and median (IQR) MELD scores were 10 (9-11) and 16 (15-18) at baseline, respectively. Consistent with the known genotype distribution in Australia [12], genotype 1 (predominantly 1a) (50%) and genotype 3 (43%) were most common, with the remaining 6% consisting of genotypes 2 and 4. Over one third of patients had failed previous HCV therapy (40%) and 23% of patients had a history of hepatocellular carcinoma (n = 25).

All 108 patients were treated with sofosbuvir and daclatasvir of whom two also received ribavirin. Seventy-eight of the 108 patients (72%) completed 24 weeks of treatment. The median (IQR) treatment duration in these patients was 168 (167-175) days. For all patients, the study outcomes are reported as at the three-month follow up post end of treatment.

Safety

Thirty patients were unable to complete treatment and are discussed in more detail below. Of these, 27 underwent liver transplantation (n = 16) or died (n = 11) on treatment. The remaining three stopped treatment at physician discretion due to "failure to improve" with documented increase in ascites or bilirubin and deterioration in MELD score (after 29, 34 and 60 days of treatment). Eleven patients experienced adverse events, which were not treatment limiting, including infection (cellulitis, aspergillus infection, pneumonia), variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma and choledocholithiasis. Neither of the two patients on ribavirin experienced adverse events (haemoglobin baseline 116g/dL and 106 g / dL, unchanged) and no dose reduction was required. No dose adjustments of sofosbuvir or daclatasvir were required.

Efficacy of treatment

Figure 1 shows treatment outcomes in all 108 patients. The SVR12 for the whole 108 patients based on intention-to-treat (ITT) was 70% (76 out of 108 patients). In the 78 patients who completed treatment, 73 (94%) were hepatitis c PCR negative at the end of treatment and five remained HCV PCR positive (6%). Twelve patients (16%) who were PCR negative at end of treatment relapsed during the following 12 weeks post-treatment and one patient was lost to follow-up. SVR12 was achieved in 60 patients. SVR12 according to those completing treatment was 77% (60 out of 78) on intention-to-treat analysis. Four of these patients received liver transplantation in the 12 weeks after completing treatment (for the indication of liver failure, not hepatocellular carcinoma) and all achieved sustained virologic response. The SVR12 rate was thus 56 out of 74 (75.7%) on a per protocol analysis when these four patients were excluded.

In those who failed to complete treatment, 16 of 30 achieved SVR12. The median duration of treatment in this group of 30 patients was 141 days (IQR 60 – 171). Sixteen of the 30 patients underwent liver transplantation on treatment, of which ten were transplanted for liver failure (the others were transplanted for hepatocellular carcinoma). The median duration of treatment

for those 10, including treatment continuing after transplantation, was 176 days (IQR 140 – 204). Interestingly, two of the patients who ceased treatment early achieved SVR12 (genotype 1 and 1a; treated for 29 and 34 days). The patient who ceased treatment at 60 days failed to clear the virus (genotype 1a).

Factors predicting SVR12 in those completing treatment

Tables 2 and 3 shows the factors analysed with respect to end of treatment response and SVR12. Given that the intervention of liver transplantation can affect SVR12 rates, the four patients who were transplanted post-treatment but within the 12 week follow-up period were removed from the subsequent analysis of baseline factors associated with SVR12.

There was no statistically significant difference in SVR12 rates between genotypes (Fisher's exact test, $p = 0.368$). Per protocol, SVR12 in genotype 1 was achieved in 27 of 34 patients (79.1%), 24 of 35 genotype 3 patients (68.6 %) and 100% of genotype 2 and genotype 4 (n= 2 and 3, respectively).

Whilst serum alanine aminotransferase (ALT) at baseline was significantly associated with hepatitis c PCR negativity at the end of treatment, it was not associated with SVR12 or failure to complete treatment due to death or transplantation (Figure 2) (Tables 2 and 3). There were no other statistically significant predictors of SVR12 identified using baseline characteristics (including MELD and Child-Pugh score).

Change in liver disease parameters

Figure 2 is a waterfall plot showing the overall changes in MELD score in the 108 patients from baseline to end of treatment. Table 4 shows the changes in Child-Pugh score, MELD score and ALT. In the 73 patients who were hepatitis c PCR negative at end of treatment, there was a significant change noted in median (IQR) MELD score (-2 (-4 -, -1), $p = 0.000$), median Child-Pugh score (-2 (-3 -, -1) $p=0.000$) and median ALT (-28 (-60 -, -12), $p = 0.000$). The five patients whom failed to clear the hepatitis c at end of treatment had significant improvement in median Child-Pugh score -1 (-2 -, -1) only ($p = 0.04$).

In the 56 patients who achieved SVR12, the improvements in liver parameters observed at end of treatment persisted at 12 weeks post-treatment (Table 5). Relapse was not associated with significant deterioration in liver function. In those who relapsed, ALT increased from

median 27.5 U/L to 57.5 U/L, while the median MELD decreased from 14 to 12.5 and median Child-Pugh score changed insignificantly from 8 to 9 (p=0.88) between end of treatment and 12 weeks post-treatment, respectively.

Improvement in completed treatment group

The effect of DAA therapy on ascites and encephalopathy were evaluated (Table 6). Eighty-two percent of patients (89 of 108) had ascites at baseline. Of the 68 patients who achieved negative hepatitis c PCR at end of treatment, 55 patients had ascites at baseline (80.9%). At 12-weeks post-treatment, four patients (6%) were noted to have worsening of ascites, whilst 29 patients had improvement in the severity of ascites. There was no change documented in the remaining 34 patients and data was missing in one patient. Overall, there was an improvement in severity of ascites in both groups (SVR12 and hepatitis c relapse) regardless of hepatitis c clearance (Friedman test, p = 0.014). There was no difference in the degree of improvement between the groups (SVR12 versus relapse) (Fisher's exact test, = 1.000).

Encephalopathy was present in 69% (n = 74) of patients at baseline (Table 1). In the 68 patients who were hepatitis c PCR negative at end of treatment and followed to 12 weeks post treatment (and not transplanted), encephalopathy had been recorded in 44 patients at baseline, of whom 30 patients were noted to have improved at the week 12 post-treatment assessment. However, this improvement did not reach statistical significance overall (Friedman test, p = 0.069) (Table 6). In the SVR12 group, improvement in encephalopathy trended towards significance (p = 0.051). Thirty-three patients had no change in encephalopathy severity documented, while five were noted to have worsening encephalopathy. There was no difference in the improvement between groups (SVR12 versus relapse) (Fisher's exact test, p = 0.238).

Deaths and transplantation

Thirty patients did not complete treatment due to death, transplantation or cessation due to adverse events. A further four patients underwent liver transplantation prior to SVR12 (i.e within 12 weeks post-treatment). Eleven patients died on treatment (one stroke and 10 due to liver failure) and 16 were transplanted (10 for the indication of liver failure and six for hepatocellular carcinoma). The median duration of treatment in these patients was 141 days (including those patients who continued therapy post-transplant). The median (IQR) number

of days after commencing therapy at which death or liver transplantation occurred was 87 (56 – 122) days.

As might be expected, the most common reason for failing to complete treatment (13 of 21) was death or liver transplantation for liver failure (see figure 2). Of the four patients who were transplanted following completion of the 24-week sofosbuvir and daclatasvir treatment, only one patient was noted to have an increase in MELD score (MELD 20 at baseline and 27 immediately pre-transplantation).

In those who died (M/F = 8/3; genotype 1 (n=8) and genotype 3 (n=3); treatment naïve (n = 9)), baseline MELD score was no different to the baseline MELD score of those patients who completed treatment. However, the MELD score significantly increased from baseline to prior to death (16 to 23; p=0.037). There was no significant change in Child-Pugh score or ALT (Table 7).

In contrast to those who died on treatment, in the 14 patients who underwent transplantation for the indication of liver failure during the study period (10 during treatment and 4 post treatment), the median MELD prior to starting therapy was significantly higher than those who were not transplanted (Figure 3). Unexpectedly, the MELD score did not change from baseline (20) to immediately pre-transplantation (20) (p=0.85). The median duration of treatment until time of transplant for the group was 118 days, which was significantly less than the duration of treatment in the treatment completion group (Wilcoxon rank-sum test test; $p < 0.001$). Most patients continued treatment post-transplantation (n=10), the median duration of treatment in total, being 176 days. Hepatitis c PCR negativity was achieved in 85.7% overall with 12 of 14 patients achieving an undetectable hepatitis c viral load at 12 week post completion of treatment/transplantation.

Baseline platelet count, Child-Pugh score and MELD were found to significantly predict transplantation compared to those completing treatment and whom were not transplanted (Table 8). The only variable that remained significant on multivariable analysis was the MELD score. A MELD of 20 or more was highly predictive of transplantation, the odds ratio for MELD $\geq$ 20 being 13.8 (95 % CI 2.78-69.04). The baseline MELD score as a continuous variable was 1.33 (95% CI 1.09-1.63), which remained significant on multivariable analysis. A satisfactory multivariable model could not be produced.

Discussion

This paper reports the outcome of direct acting antiviral-based rescue therapy in a cohort of patients with severely decompensated hepatitis c-related cirrhosis. In the current study, all patients had MELD scores greater than 15, the majority of whom (64%) were patients with Child-Pugh C at baseline, with 82% percent having ascites and 69% with hepatic encephalopathy. Other studies investigating the outcomes of direct acting antiviral therapy in decompensated disease have included patients with relatively low MELD and Child-Pugh scores compared to our cohort. In the SOLAR 1 and SOLAR 2 studies of sofosbuvir and ledipasvir with and without ribavirin, over 50% of patients were Child-Pugh B and in the Ally-1 study only 26% were Child-Pugh C, whilst 53% were Child-Pugh B [6-8]. In the UK-EAP study, 68% were Child-Pugh B and less than 10% were Child-Pugh C with a median MELD of 11 [9]. Likewise, the patients in Astral-4 had a median Child-Pugh score of B8 and MELD of 10 with 95% having MELD scores less than 15 [10]. Thus this is the largest report of treatment outcomes in such a uniformly advanced group of patients, all of whom met criteria for liver transplantation. This may explain the low SVR12 in our study of 70% compared to these other studies in decompensated patients, which report SVR12 rates of around 90% and is in keeping with the recent findings of Guarino et al., reporting overall mean SVR12 rates of 74.9% in their systematic review of Child-Pugh C patients [6-10,13,14].

The genotype 3 patients in our study are of particular interest (n = 47; 43.5%). In the group of 78 patients who completed treatment, that is, did not die and were not transplanted on treatment, 49% had genotype 3 infection. There is limited data on treatment outcomes for genotype 3 patients with decompensated liver disease. In the SOLAR 1 and 2 studies, all patients had genotype 1 infection and Astral-4 consisted of only 15% genotype 3. The UK–EAP study had 41% genotype 3 patients enrolled but less severe liver disease, as did the French cohort (100% genotype 3; only 15% Child-Pugh B/C classes) and ALLY-3 study patients (compensated cirrhosis with median albumin 43 g/L and platelet count of 161 x 10^9/L) [14,15]. Thus this is the first report of outcomes in genotype 3 infected patients with such severe liver disease. Previous studies have suggested that cirrhotic genotype 3 patients treated with direct acting antivirals have significantly lower SVR12 rates compared to genotype 1 infected patients [9,16]. In the current study, although the rates were lower in the genotype 3 patients (68% on per protocol analysis) compared to those with genotype 1 (78%), this was not statistically significant. These results suggest that the low SVR12 rates in our study related to the presence of decompensated disease per se rather than any major difference in the response of different genotypes in advanced cirrhosis. Interestingly, the majority of

treatment failures (66%) in those who completed treatment were related to relapse, suggesting that the failure to achieve SVR12 in these patients was not due to a primary failure to achieve suppression of viral replication in the advanced cirrhotic liver.

In the evaluation of factors predicting treatment failure, baseline ALT was noted to be significantly higher in those patients who were hepatitis c PCR positive at the end of treatment compared to those who were hepatitis c PCR negative. In the study by Reddy et al., a positive predictor of SVR12 was albumin level, whilst negative predictors were found to be elevated bilirubin and genotype 1a[17]. Other studies have suggested that low platelet count and hypoalbuminaemia are associated with reduced SVR rates. In our cohort of very advanced cirrhotic patients, measures of diseases severity including platelet count, albumin, MELD and Child-Pugh score did *not* have predictive value (Table 3). This is probably because, in contrast to other studies, at baseline almost all patients had hypoalbuminaemia and thrombocytopaenia and all had MELD scores greater than or equal to 15.

It should be noted that all patients received a uniform and standardised treatment regimen of sofosbuvir and daclatasvir for six months and only two patients received the additional ribavirin. This compares to the SOLAR studies, in which sofosbuvir and ledipasvir was prescribed for 12 weeks all with ribavirin for genotype 1 patients [6]. In other studies including the French study, 21% of patients received sofosbuvir, daclatasvir and ribavirin for mostly 24 weeks (while 20% of the patients received sofosbuvir and daclatasvir without ribavirin for 12 weeks and 59% received 24 weeks)[15]. The overall SVR12 rate was 89% (including non-cirrhotics)[15]. We chose the pan-genotypic sofosbuvir and daclatasvir regimen primarily because of the prevalence of genotype 3 infection in the Australian community [12]. In addition, sofosbuvir and ledipasvir was not available to treat genotype 1 patients at that time. We chose a six-month course of therapy because of the severity of the disease in the cohort and anticipated ribavirin would have been poorly tolerated in these patients. Whether SVR12 rates are altered by the addition of ribavirin to the various direct acting antiviral regimens in patients with advanced decompensated liver disease remains unknown. The results of the Ally 3+ study suggest that the addition of ribavirin improves SVR rates in compensated cirrhotic genotype 3 patients treated with sofosbuvir and daclatasvir for 12 weeks [14]. There did not appear to be a significant change in SVR12 with extension of this treatment to 16 weeks. In our cohort of decompensated patients, it is therefore possible that the addition of ribavirin to the 24-week sofosbuvir and daclatasvir regimen may have improved results in our patients.

In the patients who completed therapy, achievement of SVR12 was associated with significant improvement in MELD score, Child-Pugh score and ALT as well as clinic parameters of liver disease including ascites severity. Overall, improvement in MELD occurred in two thirds of the total patient group and this was consistent with other studies of direct acting antiviral treatment outcomes in hepatitis c patients with decompensated disease, although as a group the patients in our study had more severe disease. Approximately a quarter of the 108 patients had no change or worsening of MELD scores.

There is limited data regarding the factors that predict mortality and transplant rates in patients with advanced decompensated disease who receive direct acting antiviral therapy. Not surprisingly, it was in the group of patients who did not improve on treatment, that deaths and transplants were most likely to occur (10 of 29 who did not improve versus 11 of 76 who did improve, p=0.022). In our study, 10% of patients died and 19% were transplanted (with four transplants occurring post treatment due to lack of clinical improvement and physician discretion during the 12 week follow-up post end of treatment and despite having achieved negative end of treatment hepatitis c PCR (Figure 1)). As would be expected in the patients who died, there was worsening of MELD scores (median of 16 to median of 23) from baseline to death (Table 7). However, it was noteworthy that MELD scores at baseline did not predict mortality and were not significantly different from those patients who successfully completed the 24-week sofosbuvir and daclatasvir treatment. Moreover, there was an equal mortality rate in patients who had baseline MELD scores between 15 and 19 versus those with MELD scores greater than or equal to 20. Thus in this group of patients with decompensated cirrhosis, deaths were due to a rapidly progressive liver failure that appeared to be largely unpredictable based on pre-treatment status. There was no significant change in Child-Pugh score in these patients, which may be related to the significant increase in creatinine that was noticed in the patients immediately pre-death (baseline median (IQR) creatinine 94 (86 – 105) µmol/L to 127 (108-162) µmol/L pre-death. Additionally, it may be a reflection of the baseline high Child-Pugh score and also potentially due to it being a discrete variable as opposed to the continuous variable MELD score.

Fourteen patients underwent rescue transplantation for the indication of liver failure during the nine-month study period. The univariate analysis identified a number of factors that may predict liver transplantation (MELD, Child-Pugh score, platelet count) although on multivariate analysis, the only remaining factor was MELD score. Baseline MELD score was found to be significantly higher in the transplant group compared to those who successfully

completed treatment (19.5 vs 16), furthermore, a baseline MELD of 20 or more was highly predictive of the need for transplantation, with an odds ratio of 14. Although these patients underwent liver transplantation prior to completion of the direct acting antiviral treatment, they did not appear to be transplanted due to deterioration in MELD status whilst on treatment (Table 8) but rather because of the pre-existing severity of their disease and a lack of improvement on treatment, at physician discretion. The majority of patients continued the direct acting antivirals post-transplant and although the study was not powered to assess post-transplant response to treatment, 86% of patients went on to achieve SVR12 in this setting. This may not be unexpected given prior studies showing 30-day therapy may eliminate hepatitis c viraemia followed by removal of the virus's reservoir in the liver during transplantation successfully eradicating the virus.

This study also raises the issue of whether to treat these patients pre- or post-transplant. The International Liver Transplantation Society guidelines suggest that treatment should be considered pre-transplantation in patients with MELD scores less than 20 whilst in those patients with baseline MELD scores greater than 30, treatment is recommended post-transplantation[18]. There is controversy regarding this middle cohort of patients. In the study by Belli and colleagues, after 60 weeks follow up, one third of patients were inactivated and 20% were delisted from transplantation post SVR12[19]. As discussed above, we also found a baseline above 20 was unlikely to lead to clinically significant improvement in patients treated pre-transplantation. Thus given that there was low SVR12 in the decompensated cirrhotics with the current direct acting antiviral regimens, it may be reasonable to consider treatment post-transplantation in these difficult-to-treat patients. Longer-term follow up of these patients will allow us to make further conclusions regarding their outcome.

In conclusion, this paper provides new information on the response to direct acting antiviral therapy in patients with advanced decompensated disease meeting current criteria for liver transplantation. It emphasises the importance of treating cirrhotic patients earlier rather than at the decompensated stage with high MELD whereby the SVR12 is lower, there is a higher rate of incomplete therapy (from death or rescue liver transplantation), lower tolerability to ribavirin, and also ongoing decompensation despite achieving SVR12. We have found SVR12 rates of 70%, which is significantly lower than the 95% consistently quoted in patients with compensated disease treated with sofosbuvir /NS5A inhibitor therapy. Although the direct acting antiviral regimen used in this study is not the current choice of therapies in genotype 1 infection, we would argue that recent results with newer regimens such as

sofosbuvir/velpatasvir are not dissimilar to our data in Child-Pugh C patients. The paper does not allow us to answer the question of whether to treat before or after transplant. Improvements in MELD scores are consistent with the literature and the SVR12 rates suggests that many patients (20-30%) who are treated at a very late stage of disease will go to transplant with viraemia, which will require treatment post-transplant to prevent severe recurrent disease. This applies to all current regimens including sofosbuvir / ledipasvir, sofosbuvir / daclatasvir and sofosbuvir /velpatasvir. Emerging regimens will allow treatment of potential NS5a-resistant viruses in the post-transplant period. However, such regimens are not as yet freely available worldwide. Thus the timing and overall approaches to therapy in patients with advanced decompensated liver disease remains challenging.

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Tables

Table 1: Patient Baseline demographics

Variable	Number (percent)
Age, years	56 (51-61)
Male gender, n (%)	79 (73)
Race, n (%)	
Caucasian	97 (90%)
Unknown	4 (4%)
Ascites	89 (82%)
Mild	51 (47%)
Moderate-severe	38 (35%)
Encephalopathy	74 (69%)
Albumin, g/L	29 (26-32)
Creatinine, µmol/L	81 (63 – 102)
ALT, U/L	57 (37-98.5)
Child Pugh score	10(9-11)
MELD score	16 (15-18)
HCV viral load, IU/mL	413, 554 (60, 320 - 853, 170)
HCV genotype	
1a	41 (38%)
1b	6 (6%)
1 unspecified	8 (7%)

2	3 (3%)
3	47 (44%)
4	3 (3%)
Previous treatment	42 (40%)
History of hepatocellular carcinoma	25 (23%)
Diabetes mellitus	14 (13%)

Results are expressed as median (IQR) unless otherwise specified.

Table 2: Per protocol analysis of patients completing 24-week treatment according to baseline characteristics (n = 78).

	Treatment completion group baseline characteristics (n=78)	End of treatment negative PCR (n=73)	End of treatment positive PCR (n=5)	Comparison of end of treatment PCR negative and positive groups p-value*
Age, years	56 (50-60)	56 (51-60)	51 (49-52)	0.15
Gender Male/Female (Male%)	56/22 (71.79)	52/21 (71.23)	4/1 (80)	1.00
Genotype 1/2/3/4	35/2/38/3	33/2/35/3	2/0/3/0	1.00
Previous hepatitis c treatment Yes/No	31/47 (39.74)	28/45 (38.36)	3/2 (60.0)	0.38

(Yes%)				
Viral load, IU/ml	398107 (50000-794328)	361500 (50000-713000)	1584893 (794328-2183920)	0.085
MELD score	16(15-18)	16 (15-18)	15(15-16)	0.24
Child-Pugh score	10(9-11)	10(9-11)	9(8-10)	0.39
ALT, U/L	59 (35-94)	56 (35-89)	136(112-191)	0.004
Albumin, g/L	29(27-32)	28(26-32)	30(29-31)	0.15
Bilirubin, µmol/L	56 (41-69)	50 (41-69)	59(47-60)	0.99
Platelets, x 10^9 /L	66(43-94)	67 (43-94)	50(44-63)	0.49
Creatinine, µmol/L	75.5 (63-101)	76(63-102)	63(59-78)	0.233
Hepatocellular carcinoma Never/ Current/Previous	62/8/8	58/8/7	4/0/1	0.69

*T-test, Wilcoxon rank-sum test Chi square/Fisher's exact test. Results are expressed as median (IQR) unless otherwise specified.

Table 3: Per protocol analysis of patients completing 24-week treatment according to baseline characteristics (n = 78) and according to treatment outcome (SVR12 and relapse).

	SVR12 (n = 56)	Treatment relapse (non SVR12) (n = 12)	Comparison of SVR12 and Relapse groups p-value*

Age, years	56(50.5-61)	53.5(48.5-58.5)	0.40
Gender Male/Female (Male%)	39/17 (69.64)	9/3 (75)	1.00
Genotype 1/2/3/4	27/2/24/3	4/0/8/0	0.63
Previous hepatitis c treatment Yes/No (Yes%)	23/33 (41.07)	4/8 (33.33)	0.75
Viral load, IU/mL	387053 (39811-654344)	246818 (74400-909722)	0.95
MELD score	16(15-17)	16(15.5-18)	0.59
Child-Pugh score	10(9-11)	10(9-11)	0.71
ALT, U/L	55(34.5-91)	60(40-92.5)	0.612
Albumin, g/L	28(26.5-30.5)	33(25-35)	0.21
Bilirubin, µmol/L	55(41-68.5)	55(40.5-68)	0.92
Platelets,X 10^9 /L,	68 (44-96)	61.5(36.5-92)	0.40
Creatinine, µmol/L	72.5 (61.5-100.5)	85 (69-100.5)	0.385
Hepatocellular carcinoma Never/ Current/ Previous	44/6/6	10/1/1	1.00

*T-test, Wilcoxon rank-sum test Chi square/Fisher's exact test. All results expressed as median (IQR) unless otherwise specified. ALT, alanine aminotransferase.

Table 4: Change in MELD score, Child-Pugh score and alanine aminotransferase from baseline to end of treatment (per protocol).

Treatment group (n=78)	HCV PCR negative group (n=73)	p-value	HCV PCR positive group (n=5)	p-value
Baseline MELD End of treatment MELD	16 (15-18) 14 (12-17)	0.001	15 (15-16) 14 (11-15)	0.22
Baseline Child-Pugh End of treatment Child-Pugh	10(9-11) 8(7 - 10)	0.001	9 (8-10) 8 (7 - 8)	0.040
Baseline ALT, U/L End of treatment ALT	56 (35-89) 27 (20-31)	0.001	136 (112-191) 42 (31-49)	0.080

All results expressed as median (IQR). P-values calculated using Wilcoxon matched pairs signed rank test. HCV, hepatitis c virus; PCR, polymerase chain reaction; ALT, alanine aminotransferase.

Table 5: Change in MELD score, Child-Pugh and alanine aminotransferase from baseline to week 12 post treatment according to treatment response (SVR12 versus relapse) (Per-protocol).

End of treatment PCR negative group (n=68**)	SVR12 group (n=56)	p-value	Relapse group (n=12)	p-value
Baseline MELD score SVR12 MELD	16 (15- 17) 14 (12 - 17)	0.0001	16 (15.5- 18) 12.5(11 - 17)	0.065
Baseline Child-Pugh SVR12 Child-Pugh	10(9- 11) 8 (6 – 9.5)	0.0001	10 (9- 11) 9(7.5 – 9.5)	0.074

Baseline ALT, U/L SVR12 ALT	55(34.5- 91) 27 (18 - 31)	0.0001	60 (40-92.5) 57.5 (39 - 96)	0.97

NB: One follow-up missing and four patients transplanted during 12weeks post-end of treatment excluded. All results presented as Median (IQR). ALT, alanine aminotransferase. P-values calculated using Wilcoxon matched pairs signed rank test.

Table 6: Comparison of change in severity of ascites and encephalopathy from baseline compared to 12 weeks post-treatment in SVR12 (n=56) and relapse (n = 12) groups.

	Baseline (n = 68)	SVR12 (n = 56)	Change from baseline to SVR12 p-value	Relapse (12 weeks post treatment) (n = 12)	Change from Baseline to relapse p-value
Ascites none/mild/severe	13/33/22	26/22/8	0.013	4/4/3*	0.29
Encephalopathy None/ Grade1-11/ Grade111	43/23/2	39/17/0	0.051	6/6/0	0.54

* Data on ascites missing in n = 1 relapse patient. P-values calculated using Friedman test.

Table 7: Characteristics of patients who died on treatment (n=11).

	Baseline	Pre-death	Change from Baseline to pre-death (p-value*)	Comparison of Baseline characteristics death and treatment completion groups (p-

				value^)
MELD score	16(15-18)	23 (18-24)	0.037	0.82
Child-Pugh score	11(10-11)	11(11-12)	0.47	0.22
ALT, U/L	57(41-79)	33(27-54)	0.059	0.78
Viral load, IU/mL	618066 (408708-995760)	n/a	n/a	0.20
Hepatitis c PCR positive, n	11	3 *	0.031	
Creatinine, µmol/L	94 (86-105)	117.5 (90-162)	0.014	0.128
Albumin, g/L	31(25-39)	31 (24-35)	0.563	0.60
Bilirubin, µmol/L	59 (40-78)	107 (39-116)	0.110	0.55
INR	1.5 (1.3-1.8)	1.8 (1.7-1.9)	0.061	n/a

Results expressed as median (IQR) unless otherwise specified. ALT, alanine aminotransferase; INR, international normalised ratio. * Hepatitis c PCR results for two patients missing. * p-value calculated using Wilcoxon matched pairs signed rank test or McNemar's test. ^ p-value calculated using Wilcoxon rank-sum test.

Table 8: Characteristics of patients undergoing rescue transplantation for liver failure during the nine-month study (baseline vs immediately pre-transplant) (patients transplanted for hepatocellular carcinoma indication excluded)(n=14).

	Baseline	At time of transplant	Change from baseline to pre-	Comparison between baseline characteristics

			transplant (p-value*)	in transplant and treatment completion group (p-value^)
MELD score	19.5(16-22)	19.5 (15-23)	0.85	0.01
Child-Pugh score	11(11-12)	10 (9-12)	0.15	0.002
ALT, U/L	45(34-69)	26 (18-38)	0.064	0.33
Viral load, IU/mL	462500 (234763-1156523)	n/a	n/a	0.24
Hepatitis c PCR positive, n	14	3	0.01	n/a
Creatinine, µmol/L	88 (63-114)	93 (77-144)	0.382	0.405
Albumin, g/L	29.5(26-32)	n/a	n/a	0.54
Bilirubin, µmol/L	70 (44-83)	n/a	n/a	0.084
Platelets, x 10^9 /L	44.5 (38-68)	n/a	n/a	0.019

Results are expressed as median (IQR) unless otherwise specified. ALT, alanine aminotransferase; INR, international normalised ratio. * p-value calculated using Wilcoxon matched pairs signed rank test or McNemar's test. ^ p-value calculated using Wilcoxon rank-sum test.

Figures

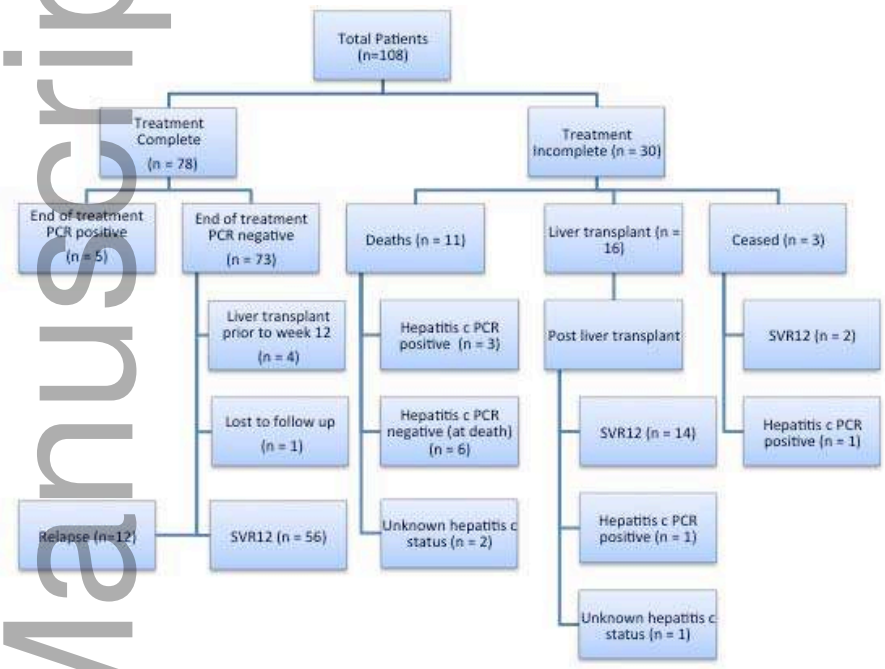

Figure 1: Flow diagram of patients throughout the nine-month study period. PCR, Polymerase Chain Reaction; SVR12, sustained virologic response. Overall SVR12 in study 70%.

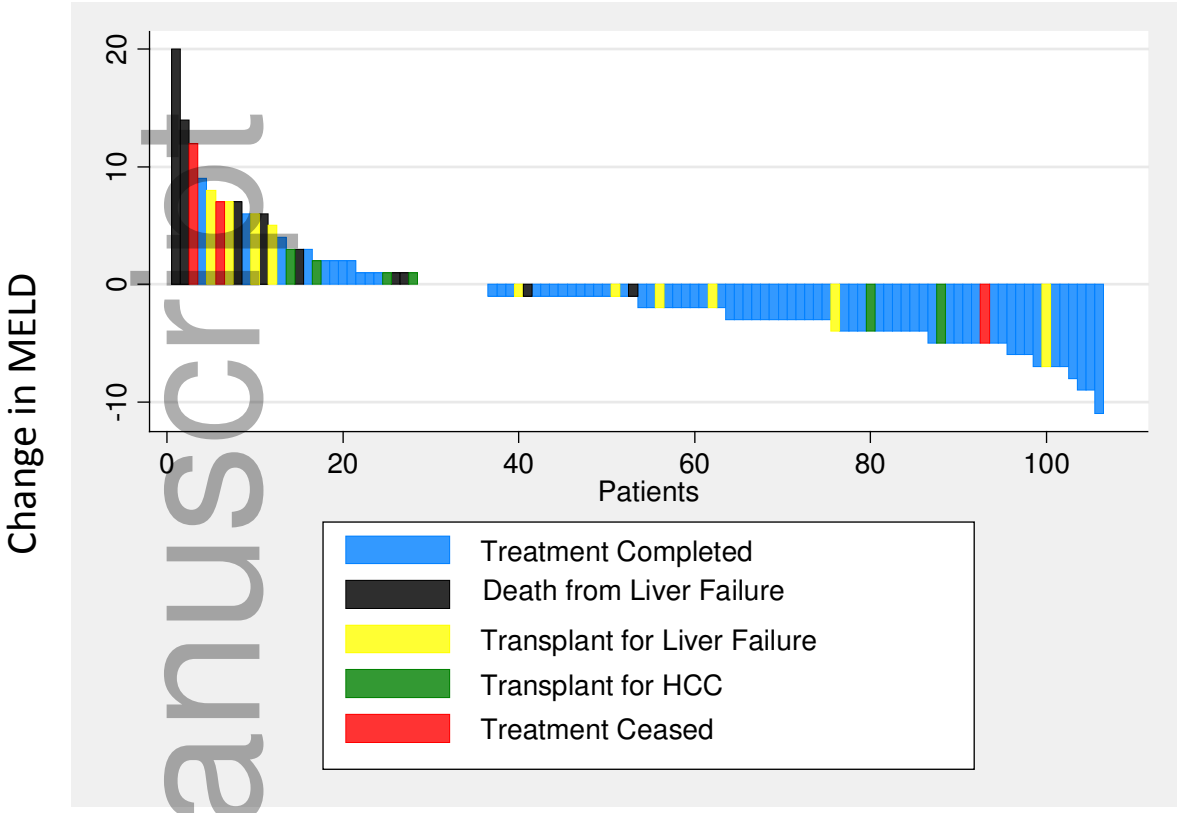

Figure 2: Waterfall plot of change in MELD for each patient from baseline to treatment completion, liver transplant or death. HCC, hepatocellular carcinoma.

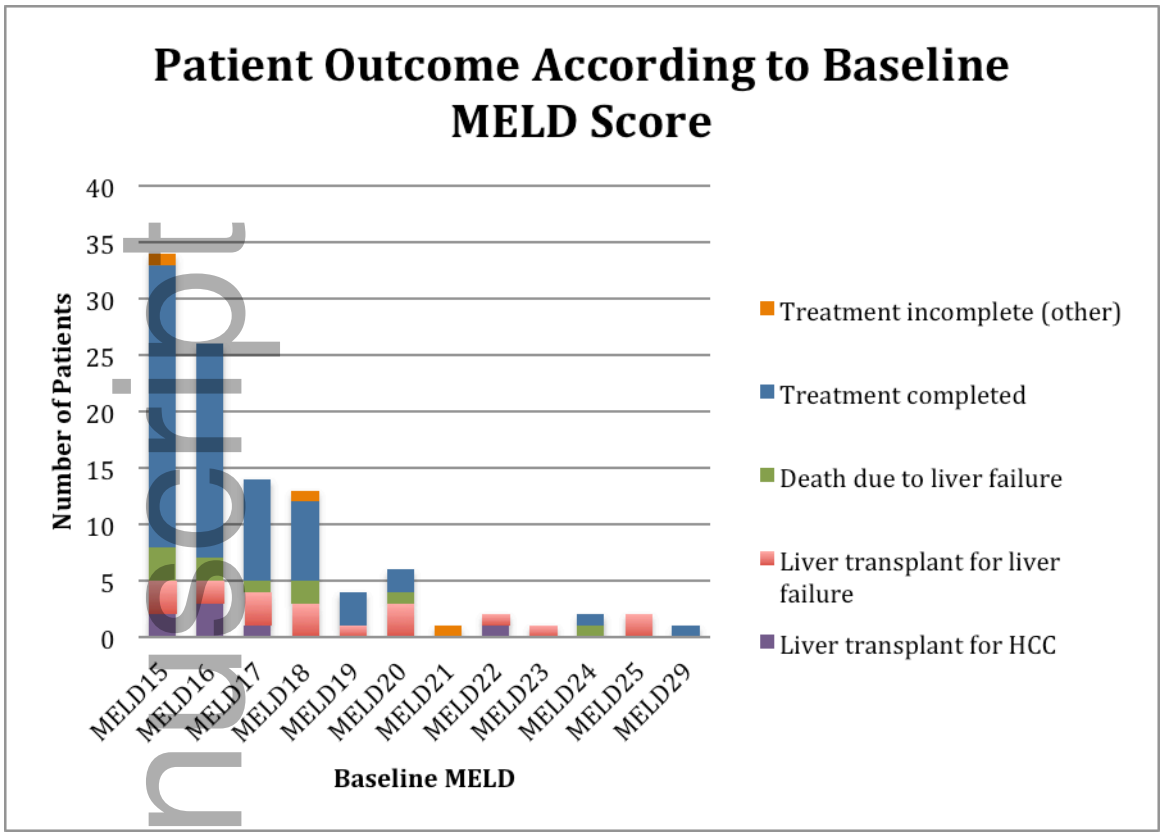

Figure 3: Graph illustrating the outcome (transplant, death, treatment completion/incompletion) at final follow up in the 108 patients according to baseline MELD score. HCC, hepatocellular carcinoma.