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Sustained Virological Response Rates following Hepatitis C treatment with Direct-Acting Antivirals in patients with Decompensated Liver Cirrhosis

N. Nurdin[1], L. Corey[1], S. O'Toole[2], J. Sopena-Falco[2], D. Houlihan[2], E.R. Feeney[1]

1. Department of Infectious Diseases, St Vincents University Hospital, Dublin 4, Ireland.
2. Hepatology Department, St Vincents University Hospital, Dublin 4, Ireland.

Abstract

Aim

Direct acting antivirals (DAA) have revolutionised the management of Hepatitis C (HCV) with high sustained viral response (SVR) rates and improved morbidity and mortality. However, SVR rates individuals with decompensated liver disease are lower. We examined outcomes for SVR in patients attending the Irish National Liver Transplant Centre.

Methods

Audit of outcomes in patients with decompensated cirrhosis (defined as Child Pugh B or C) treated with DAA from 2014 until 2021. Chi2, Mann Whitney U and t-test were used for statistical analysis.

Results

59 patients were included; 71% male (n=42), mean age 52.2 years (SD±10) and 71%(n=42) treatment naïve. 68% (n=40) percent were Child Pugh B, mean MELD was 12.1 (SD±5.2). 98% of patients completed treatment and 5 percent died prior assessing SVR. 82% (n=46) of patients with end of treatment bloods achieved SVR. Lower SVR was associated with; older age (51 vs 56 years, p=0.019), genotype 3 infection (p=0.05), HCC at the time of treatment (28% vs 84%, p 0.001) and treatment regime (50% SVR rates SOF/LED p=0.012 vs 78% SOF/VEL; p=0.013).

Discussion

SVR rates in decompensated patients in Ireland remained high, and were comparable to other real world studies. Patients with HCC and genotype 3 are more challenging to treat.

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Introduction

The treatment of chronic hepatitis C virus (HCV) infection has been revolutionised with the availability of direct acting antiviral agents (DAA) specifically targeting HCV proteins[1]. Cure is the goal of treatment, with successful sustained virological response (SVR) at 12 weeks seen in over 95% of patients[2]. Consequently, since 2016 WHO has provided a roadmap for global elimination of HCV by 2030 based on DAA use; aiming for in a 90% reduction in incidence and a 65% reduction in mortality by 2030[3].

In contrast to older interferon-based regimens, SVR rates are maintained in patients with compensated liver cirrhosis with tailored DAA therapy[4], even in previously considered difficult to treat patients such genotype (GT)3 infection (>85%)[5, 6]. Treatment of patients with compensated liver cirrhosis has clear advantages with resulting improvement in liver disease, improved survival rates and a reduction in extrahepatic manifestations[7]. Despite a reduction in risk of hepatocellular carcinoma (HCC) with SVR, it remains higher than general population and as such ongoing HCC screening in patients with advanced fibrosis and/or cirrhosis is paramount[8].

Treatment outcomes in patients with decompensated liver cirrhosis are less well defined with variable rates reported in the literature. Early clinical trials, such as ASTRAL-4 [9] and SOLAR-1 [10], assessed treatment in decompensated liver disease patients, where most patients were genotype 1 and SVR rates were 83% up to 94% with the addition of ribavirin and 86 to 89% with treatment extended from 12 to 24 weeks respectively. Subsequent real world studies have been conducted; a cohort study by Krassenburg et al described SVR rate of 81% in 120 patients with CPT B/C[11] while Tada et al demonstrated SVR 12 rates of >92% are achievable in patients with decompensated liver cirrhosis in a real world setting[12]. However, in patients with decompensated liver cirrhosis, despite improvements seen in liver disease severity after achieving SVR, there is debate whether this translates to an improvement in clinical status[13] although research describes potential for delisting for transplantation, this is not consistently seen[14.] Therefore, the European Liver and Intestine Transplantation Association, ELITA, guidelines recommend treatment of HCV in patients with decompensated cirrhosis in MELD < 16, however if MELD score is 16-20 it is recommended that patients are treated and concurrently listed for liver transplant[15]. In patients with MELD > 20 an individualised risk benefit approach is recommended, considering local expected wait times for liver transplantation.

St Vincent's University Hospital (SVUH) is the National liver transplant centre for Ireland and since 2014 has had a program in place for the use of DAA for HCV treatment. Patients with decompensated cirrhosis were the first to access these agents as part of an early access programme for treating patients with end-stage liver cirrhosis. An audit was conducted to

assess the SVR rates in patients with decompensated liver cirrhosis attending SVUH and to explore factors associated with SVR.

Methods

A dedicated viral hepatitis service in St. Vincent's University Hospital was established in 2014 and is overseen by a hepatologist and an infectious diseases physician. Data on all patients attending the service is entered on a treatment database.

This audit was a retrospective analysis of all patients attending the viral hepatitis clinic from January 2014 to August 2021. Inclusion criteria were patients with HCV infection (defined as detectable HCV RNA) with decompensated liver cirrhosis defined as CPT B or C who were treated with DAA during this timeframe.

Data was collected using patient medical records as well as specialist pharmacy and nursing HCV treatment outcome databases.

Statistical analysis was performed using SPSS. Chi2 tests were used for qualitative variables and Mann Whitney U and Student's t-test for non-parametric and parametric quantitative variables respectively. A p value ≤ 0.05 was considered significant for each of the forementioned tests.

As this is an audit of service outcomes, ethical approval was not required for data collection and processing. Prior to undertaking the audit, approval was sought and granted from the St Vincent's Hospital Audit Committee. The authors have no conflicts of interest to declare.

Results

Patient Characteristics

59 patients with decompensated liver cirrhosis treated with DAA from January 2014 - August 2021 were included in the audit. 71% of patients were male, with a mean age of 52 (SD±10, 28 - 79) (see Table 1). As a cofactor for liver disease 20% of patients had a background of type 2 diabetes mellitus and alcohol excess was reported in 44% of patients. 30.5% were on methadone maintenance therapy at the time of treatment. Prior to DAA treatment, 10% of patients had a liver transplant and 12% had HCC at the time of HCV treatment.

Prior to initiation of DAA treatment, 68% of patients had a transient elastography (TE) with a mean score of 48.4kPa (SD±17.94, 8.2kPa – 75kPa). 58 of 59 patients had a TE >12.5kPa,

indicating cirrhosis, one patient had a TE of 8.2kPa; which was considered a false negative result as the patient had clinical features of cirrhosis and decompensation. 68% of patients were CPT B and 32% CPT C. Mean MELD score was 12.1 (SD±5.2; 6 – 32). HCV genotype was in keeping with the standard Irish genotype [16] 1 (51%), 2 (3%), 3 (39%), 4 (7%).

Table 1: Patient characteristics

Demographics	number of patients (n=59)
Male	42 (71%)
Age (mean)	52 (SD 10)
MELD	12.1 (SD±5.2)
Medical Co-morbidities	**Prevalence**
Type 2 diabetes mellitus	12 (20%)
Alcohol excess	26 (44%)
Methadone maintenance therapy	18 (30.5%)
Previous liver transplant	7 (12%)
Hepatocellular carcinoma at time of treatment	7 (12%)
Genotype	
1a	22 (37%)
1b	8 (14%)
2	2 (3%)
3	23 (39%)
4	4 (7%)

HCV Treatment

71% (n=42) of patients were treatment naïve, whereas 20% (n=12) had previously received treatment with interferon and ribavirin, 3% (n=2) received interferon monotherapy therapy alone, 3% (n=2) had previous DAA treatment (one patient received ombitasvir/paritaprevir/ritonavir/dasabuvir with one receiving sofosbuvir/simeprevir) and in 1.5% (n= 1) previous treatment data was unavailable.

DAA regimens used (see Table 2) in 69.4% of patients sofosbuvir/velpatasvir, 17% Sofosbuvir/ledipasvir, 12% sofosbuvir/daclatasvir and 1.6% ombitasvir/paritaprevir/ritonavir/dasabuvir. Ribavirin combination therapy was used in 69% of patients.

98% (n=58) of patients completed treatment, with one patient dying while on treatment. The majority of the cohort (78%) received 12 weeks of treatment and in 20.4% of patients the treatment was extended to 24 weeks.

Table 2: Treatment regime

Previous Treatment	**n= 59 (%)**
Treatment Naive	42 (71%)
Interferon + Ribavirin	12 (20%)
Interferon	2 (3%)
Ombitasvir/paritaprevir/ritonavir/dasabuvir	1 (2%)
sofosbuvir/simeprevir	1 (2%)
Other/Unknown	1 (2%)
Duration of treatment	
12 weeks	46 (78%)
24 weeks	14 (24%)
Addition of ribavirin	41 (69%)
Treatment Regimen	
Sofosbuvir/ledipasvir	10 (17%)
Sofosbuvir/velpatasvir	41 (69.4%)
Sofosbuvir/daclatasvir	7 (12%)
Ombitasvir/paritaprevir/ritonavir/dasabuvir	1 (1.6%)

Treatment Outcomes:

As per intention to treat analysis (ITT) SVR was achieved in 78% of patients; 83% within Child Pugh B group and 67% Child Pugh C (p=0.16). 5% (n=3) patients died prior to assessment of SVR at week 12 of treatment completion. Treatment was unsuccessful in the remaining 17% (n=10) with detectable HCV RNA at 12 weeks post end of treatment. As a result, 82% (n=48) of patients who finished treatment and had bloods at week 12 of end of treatment achieved SVR.

In relation to the three deaths, as described above, one patient died during their treatment (ombitasvir/paritaprevir/ritonavir/dasabuvir) and the two other deaths occurred following completion of therapy; one as a consequence of a new 6cm HCC, the other patient from complications of decompensated liver cirrhosis.

In the univariate analysis (see Table 3) patients who achieved SVR were younger (51 vs 56 years, (p=0.019). Patients with HCC at time of commencing HCV treatment were less likely

to achieve successful SVR (28% vs 84%, p=0.001). SVR rates also varied with treatment regime; patients treated with sofosbuvir/ledipasvir were less likely to achieve SVR (50%, p=0.012), whereas those treated with sofosbuvir/velpatasvir were more likely to achieve SVR (78%, p=0.013).

In relation to their genotype, there was a trend towards patients treated who were genotype 1 (87% SVR) and genotype 2 (100% SVR) achieving higher treatment success rates, compared to genotype 3 (65% SVR) and genotype 4 (50% SVR).

88.5% of patients with a history high-risk alcohol consumption achieved SVR compared to 68.8% in patients without high-risk alcohol intake (p = 0.07). Previous HCV treatment failure, concomitant methadone maintenance treatment, MELD score or addition of ribavirin in the treatment regime did not affect SVR rates.

Table 3: SVR rates and associated variables

Variable	**SVR (%)**	**P value**
Alcohol related liver disease	88.5	0.07
No alcohol related liver disease	68.8	
Methadone maintenance treatment	83.3	0.55
Not on methadone maintenance treatment	76.3	
HCC/HCV at the same time (n = 7)	28	0.001
No HCC/HCV at the same time	84	
Child Pugh B	83	0.165
Child Pugh C	67	
Treatment naïve	83	0.496
Previously treated	75	
Received ribavirin	75.6	0.971
Did not receive ribavirin	75	
Treatment Received	**SVR (%)**	**P value**
Sofosbuvir/ledipasvir	50	0.012
Sofosbuvir/velpatasvir	78	0.013
Sofosbuvir/daclatasvir	71	0.583
Genotype	**SVR (%)**	**P value**
Genotype 1	87	0.054
Genotype 2	100	0.444
Genotype 3	65	0.059
Genotype 4	50	0.332

Fifty percent of patients (n=5) with DAA failure (who did not achieve SVR following DAA treatment) were successfully retreated, 20% (n=2) declined further treatment, 10% (n=1) of patients died prior to retreatment, 10% (n=1) were deemed too sick for treatment and 10% (n=1) failed retreatment. 12% (n=7) of all patients received a liver transplant post treatment.

Discussion

In this single centre audit 82% of patients with decompensated cirrhosis patients who finished treatment achieved SVR, comparable to previously reported studies [11, 12]. This was an especially difficult to treat group as almost 40% were genotype 3 and 12% had concurrent HCC at the time of treatment.

Proposed reasons for treatment failure in patients with decompensated liver cirrhosis includes drug-drug interactions due impaired liver metabolism causing drug accumulation, patient non adherence as well as poor intestinal absorption secondary to portal hypertension [17]. Chronic kidney disease, commonly seen in patients with decompensated liver cirrhosis due to hepatorenal syndrome, cryoglobulinaemic vasculitis and immune mediated glomerulonephritis further causes treatment challenges with increased adverse events described[18].

Aforementioned, in 2014 St Vincent's Liver Unit was given approval for early access to DAA agents to treat patients with advanced liver cirrhosis, however, treatment options were initially limited to Sofosbuvir/Ledipasvir[19]. It was not until December 2016 sofosbuvir and velpatasvir became available, which is currently recommended as the treatment of choice in patients with decompensated liver cirrhosis [20]. Prior to this, sofosbuvir/ledipasvir was initially used as the primary therapy although initial evidence of its efficacy for genotype 3 was scarce. Currently, this is now known to be suboptimal in treating genotype 3 and is therefore recommended in genotypes 1, 4, 5 and 6 only[20].

Therefore in this audit treatment regimen significantly correlated with SVR, with SVR rate of 50% in patients receiving sofosbuvir/ledipasvir. Four patients with genotype 3-(mean MELD 10, range 9-11) were prescribed sofosbuvir/ledipasvir and consequently none of them achieved SVR (one died prior to SVR bloods as mentioned previously). If patients with genotype 3 are excluded from analysis (n=36) intention to treat SVR rates would have been 86.1%.

Twelve percent of patients in this audit had concurrent HCC, in this subgroup of patients, lower SVR rates were observed (28%). Previous reports have described lower SVR rates in patients with HCC[21]. Studies propose lower treatment success rates attributable to tumour microenvironment resulting in reduced penetration and increased vascularity of HCC resulting in drug redistribution [22]. Moreover, there is ongoing discussion on optimal timing of HCV treatment in patients with HCC as recommends that in patients without liver cirrhosis, treatment is deferred until HCC treatment is completed[20]. Ideally, patients would have their HCV treated prior to developing HCC. In patients with early HCC, guidelines recommend treatment of HCC prior to HCV DAA therapy to improve SVR rates. A case by case decision is recommended for HCV treatment in patients who meet criteria for liver transplant, considering regional average wait times for transplant and the patients stage of liver disease. In patients with advanced HCC, AGA guidelines emphasise evaluating cost/benefit of HCV treatment, with a consideration to not providing DAA therapy in patients with prognosis <2 years[23].

In this audit, older patients had lower SVR rates. Age has not been identified in previous studies to negative correlate with SVR rates and due to small sample size no multivariate analysis was performed. However, patients with HCC were older (mean age 56.5 years vs 51.7; p 0.239) and despite this did not achieve statistical significance we hypothesise that this was a confounding variable.

Despite high SVR rates in the initiate DAA failure group were obtained, just 50% underwent repeat DAA treatment, presumably due to the medically complex nature of this group of patients, with many refusing further treatment or dying before treatment could be instituted.

The retrospective nature of this audit and relatively small numbers are one of the main limitations in identifying risk factors associated with treatment failure. Furthermore, we cannot correlate SVR rates in our cohort with long-term clinical outcomes as this was not the aim of the study.

In conclusion, this audit highlights the strength of the early access programme at St Vincent's Hospital and subsequent HCV treatment over the following years in a challenging group due to their end-stage liver disease. EASL guidelines recommend that *"Patients with decompensated (Child-Pugh B or C) cirrhosis should be treated in experienced centres with easy access to liver transplantation",* given the challenges of treatment in this group and potential risk of complications[20].

Declarations of Conflict of Interest:
None declared.

Corresponding author:
Nadra Nurdin,
Department of Infectious Diseases,

St Vincents University Hospital,
Dublin 4,
Ireland.
E-Mail: nadranurdin@mater.ie

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