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Outcomes a year after successful direct acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis

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Key words

Hepatitis C virus, sofosbuvir, ledipasvir, daclatasvir, decompensated cirrhosis, MELD score

Abbreviations

HCV - Hepatitis C virus

DAA – Direct acting antiviral

MELD – Model of End Stage Liver Disease

SVR - Sustained virological response

EAP - Expanded access programme

HCVRUK – Hepatitis C Research UK

Sof - Sofosbuvir

LDV - Ledipasvir

DCV - Daclatasvir

RBV - Ribavirin

OLT - orthotopic liver transplant

HCC - hepatocellular carcinoma

CI – confidence intervals

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Authors' contributions

The study was designed and led by GRF and WI. MC, BH, SV managed patients in the study, collated the data and assisted in the analysis. MC and AW performed the data and statistical analysis. WI and JM supervised sample collection, data management and assisted with study design and implementation. DJM, AB, WG, DCM and KA led the recruitment and data collection. All authors participated in data analysis and participated in the preparation of the manuscript.

Abstract

Direct-acting antivirals have become widely used for patients with chronic hepatitis C virus infection with decompensated cirrhosis. Virological responses are excellent and early improvements in liver function, at least in a proportion of patients, have been observed but the longer term impact of viral clearance on end-stage liver disease complications is unclear.

Methods: Prospective study of patients with decompensated cirrhosis who received 12 weeks of all-oral direct-acting antivirals through the English Expanded Access Programme. Endpoints were deaths, liver transplantation, hepatocellular carcinoma, serious decompensation events, sepsis or hospitalisations, and MELD scores between start of therapy to 15 months post treatment start. An untreated cohort of patients was retrospectively studied over 6 months for comparison.

Results: Amongst 317/406 patients who achieved sustained virological response at 24 weeks post-treatment, there were 9 deaths (3%), 17 new liver cancers (5%), 39 transplantations (12%) and 52 with serious decompensations (16%), over 15 months.

When compared to the first six months from treatment start and to untreated patients, there was a reduction in incidence of decompensations [30/406 (7%) in months 6-15 and 72/406 (18%) in months 0-6 for treated patients vs 73/261 (28%) in untreated patients). There was no significant difference in liver cancer incidence (10/406 (2.5%) in months 6-15 and 17/406 (4%) in months 0-6 for treated patients vs 11/261 (4%) in untreated patients).

Conclusions: This study suggests that antiviral therapy in patients with decompensated cirrhosis led to prolonged improvement in liver function, with no evidence of paradoxical adverse impact nor increase in liver malignancy.

Lay summary

This is a report of a large group of patients in England who have hepatitis C virus (HCV) infection with advanced liver disease. They have been treated with new anti-HCV drugs, which cured the infection in the majority. This study looks at their outcomes a year following treatment, in terms of deaths, cancers and other complications of advanced liver disease. We conclude that in most patients anti-HCV treatment is beneficial even in advanced liver disease.

Introduction

All-oral, interferon-free direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection has allowed successful treatment of patients with advanced liver disease. Worldwide, large numbers of HCV-infected patients with decompensated cirrhosis have received antiviral therapy and although sustained virological response (SVR) rates are slightly reduced compared to patients with compensated disease, over 80% of treated patients still achieve viral clearance. Early analysis of patients who responded to therapy showed associated improvements in MELD and Child Pugh scores [1] [2-4], although some concerns have been expressed that the rate of malignancy may not change or may, paradoxically, increase [5, 6]. Previous studies of interferon-based therapies have demonstrated that HCV clearance improves liver fibrosis, even in cirrhosis [7]. Moreover, patients who achieved SVR had reduced mortality, complications of cirrhosis and hepatocellular carcinoma compared to untreated patients or those who failed to achieve SVR [8-10]. However such studies involved patients with relatively 'early' cirrhosis and it remains unclear whether these long term benefits will be seen in patients treated for more advanced disease. Although there is little data on long term outcomes, international guidelines recommend that patients with decompensated cirrhosis should be urgently treated with interferon-free DAA therapy, regardless of eligibility for liver transplantation [11, 12].

Chronic HCV infection is the main indication for liver transplantation in the Western world, and universally recurs causing accelerated disease progression in the liver graft. Given the shortage of donor organs and costs of liver transplantation, DAA treatment may reduce the need for transplantation in patients with advanced cirrhosis and allow

alternative uses for scarce organs. Pooled analysis of over 800 patients with decompensated cirrhosis showed that 60% of patients had an improvement in MELD score from baseline following therapy, but 23% deteriorated, at post treatment weeks 4 to 12 [13]. The magnitude of improvement varied with a median of 2 MELD points. It is unclear whether this early change is clinically meaningful. Perhaps more importantly, minor reductions in MELD may adversely affect access to liver transplantation, if a patient no longer meets transplant criteria but is insufficiently improved with a reduced quality of life (so called 'MELD purgatory'). In such cases, therapy may not be beneficial.

We recently published data on the virological and clinical outcomes of patients with decompensated cirrhosis treated on the English Expanded Access Programme (EAP) with 12 weeks of sofosbuvir and a NS5A inhibitor with or without ribavirin [14]. Consistent with other studies, the majority of patients successfully achieved viral clearance associated with MELD improvements by post treatment week 12. To assess the impact of antiviral therapy in patients with decompensated cirrhosis, the study compared treated patients to a retrospective cohort of patients with decompensation who were untreated for 6 months prior to the availability of DAAs. Treated patients had fewer decompensations, reduced deterioration in MELD, and overall adverse events, although there were no significant differences in rates of death, liver transplantation or hepatocellular carcinoma [14]. To address the longer-term benefits of successful HCV clearance, here we report the outcomes in the same patient cohort followed up for one year after completion of therapy.

Patients and Methods

Patients who received DAA therapy through the English EAP were enrolled into the HCV Research UK (HCVRUK) registry for prospective data collection. Patients who started treatment between 1 April and 11 November 2014 were studied. Details of the EAP treatment and patient selection criteria were previously published [14]. In brief, treatment consisted of 12 weeks of sofosbuvir with ledipasvir or daclatasvir, with or without ribavirin. Treatment choice was according to local multidisciplinary meeting decisions by experienced clinicians. Eligible patients included those with past or current decompensated cirrhosis (with ascites, variceal bleed or encephalopathy), Child Pugh score B7 or above, extra-hepatic HCV manifestations or exceptional circumstances which were determined by panel review. Presence of hepatocellular carcinoma was not an indication for treatment in the EAP unless one of the above criteria was also met.

An untreated cohort of patients with decompensated HCV cirrhosis were studied for 6 months to compare early outcomes with patients who underwent treatment on the EAP. They were not studied beyond 6 months of follow-up as data was retrospectively collected. Untreated patients were registered in HCVRUK either at least 6 months prior to the national start date of the EAP (1 April 2014), or 6 months before initiation of treatment for those patients who subsequently received DAAs. Further details on this comparator cohort have been described [14].

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee. Ethics approval for HCVRUK was given by NRES Committee East Midlands – Derby 1

(Research Ethics Committee reference 11/EM/0314) and informed consent was obtained from each patient included in the study. Patients in the EAP who declined data collection (N=13) were treated but were excluded from this analysis.

Outcome measures

Data on virological response and clinical outcomes at 12 weeks post treatment on consenting patients treated in the EAP was previously published [14]. Here we focus on the clinical outcomes in patients with decompensated cirrhosis followed for up to a year post completion of therapy (total follow up 15 months since start of therapy). Data was collected for the period post treatment week 12 to month 12 (month 6 to 15), via standardised electronic forms. Sites were individually re-contacted by the central study team with any missing or invalid responses, to ensure completeness and accuracy of collected data. This data was combined with earlier data from treatment start to month 6.

Viral loads at 24 weeks post treatment end or later were collected. We assessed the proportion of patients who achieved SVR24, and those with late relapse after initial undetectable viral load at post treatment week 12. All who relapsed were offered retreatment with 24 weeks therapy.

The following primary clinical endpoints were collected: deaths, liver transplantations and hepatocellular carcinoma at 15 months (3 months on treatment, 12 months post-treatment). Endpoints were calculated as 15 months from treatment start date, to account for premature treatment discontinuations.

For patients who achieved SVR24, the following secondary endpoints were measured: serious adverse events (decompensation, sepsis, hospitalisation for any cause) between month 6 and 15, MELD scores at 15 months (for non-transplanted patients only). For patients who did not attend clinic at month 15, laboratory data from visits within 1 month of the timepoint were included. Patients who did not achieve SVR24 were not included. SVR24 was defined as undetectable HCV RNA (measured at local laboratories with a lower limit of quantification of <30iu/mL) at 24 weeks post-treatment. Where there was no result available at post-treatment week 24 but subsequent viral load was detectable, it was assumed that the patient had not achieved SVR24. MELD scores were calculated using results provided by local accredited laboratories. Serious adverse event was defined as life-threatening, requiring hospitalisation or prolonged existing hospitalisation, resulting in persistent or significant disability, incapacity or death.

Statistical analysis was performed using Graphpad Prism 5. The following statistical tests were performed: chi-squared test (for comparison of proportions), T-test (for comparison of means) and log rank test (for comparison of survival).

Results

Patient population

A total of 480 patients received antiviral therapy through the EAP between the start of the programme on 1 April 2014 to 11 November 2014 – 467 (97.3%) patients consented to provide data to the HCVRUK registry and 406 (87%) patients had decompensated cirrhosis and/or Child Pugh score ≥B7, without previous liver transplantation, at treatment start. Sixty-one (13%) patients were treated for extrahepatic HCV disease or aggressive HCV recurrence in liver grafts.

Table 1 shows the demographics and baseline liver disease of patients with decompensation. The majority (295/406, 72.7%) were Child Pugh B; 41 patients (10.1%) were Child Pugh C. The remaining 70 patients (17.2%) had Child Pugh A disease at baseline but a past history of liver decompensation. Most patients had significant portal hypertension represented by a median platelet count of $75x10^9$/L.

Virological outcomes

SVR12 was achieved in 329 out of 406 patients (81.0%), including 4 patients originally classified as non-SVR12 because no virology result was available, but who on further follow up, were shown to be HCV RNA negative. Four patients relapsed after having a HCV RNA negative result at post treatment week 12 and a further 8 died in the follow-up period after achieving SVR12. Therefore 317 (78.1%) patients achieved SVR24. Of note there were no late relapses after post treatment week 12 amongst patients without baseline decompensated cirrhosis.

Amongst the 89 patients who did not achieve SVR24, 53 had virological failure (49 known before post treatment week 12 and 4 late relapsers), 14 patients died before reaching post treatment week 12, and another 12 between post treatment 12-24 weeks. Ten patients had no available viral results at post treatment week 24 although clinical outcomes data was still provided. See supplementary table 1 for SVR24 according to genotype and treatment regimen.

Of the 53 patients with virological failure, 21 had viral relapse by post treatment week 4, 24 patients by post treatment week 12, and 4 relapsed after post treatment week 12. Three patients did not clear virus by the end of therapy and one patient without a known virological result at post treatment week 12 subsequently had documented relapse.

Forty-five of the patients with viral relapse were offered re-treatment with a 24 week course of the same drug regime (switching NS5A inhibitor was not supported by the funders of the EAP), the outcomes of which will be reported separately. Eight patients declined re-treatment.

Outcomes after 15 months in patients with decompensated cirrhosis

Mortality

In the 406 patients with decompensated cirrhosis there were 40 deaths over 15 months (9.9%) – 9 patients died who achieved SVR24 (2.8%), which was not statistically different to patients with known virological failure (3/53, 5.7%, p=0.28) (Table 2). Although virological failure was predominantly seen in genotype 3 infected patients, the

proportion who died did not differ between genotypes – there were 9 deaths amongst 24 genotype 1 infected patients without SVR24, compared to 21 deaths amongst 60 genotype 3 infected patients without SVR24 (37.5% vs 35.0%, p=0.83). Figure 1 shows the survival rates over the study period.

Development of Liver Cancer

At treatment baseline, 29 of 406 total patients had a history of HCC (median days between diagnosis and DAA start was 287 days). Eighteen of these patients achieved SVR24 (Table 1). Two patients with pre-existing liver cancer history developed a new HCC (at 20 and 26 weeks from treatment start), both achieved SVR24. There were no recurrent HCCs amongst patients with previous cancer who did not achieve SVR24.

Amongst 317 patients who achieved SVR24, 17 (5.4%) developed a liver cancer (Table 2) over the follow up period of 15 months (15 de novo and 2 recurrent). Five of the 17 (29.4%) new liver cancers developed in patients who achieved SVR24 occurred early, within 3 months of commencing treatment. There was a reduction (of borderline significance) in new cancer rates over 15 months between patients with and without SVR24 (17/317, 5.4% vs 10/89, 11.2%, p=0.049) in patients with decompensated cirrhosis (hazard ratio 0.33, 95% CI 0.13 - 0.87) (see figure 2). This compares with 11/261 (4.2%) in untreated patients over 6 months.

Other outcomes

Table 2 shows the outcomes for patients followed up for 15 months. Amongst the 317 patients who achieved SVR24, 39 (12.3%) received a liver transplant. Forty-six patients experienced serious decompensation between months 0-6 (14.5%) which was markedly reduced in months 6-15 (16/317, 5.0%) (p=0.00006). Supplementary table 2 shows the details of these events with incidences of decompensations, sepsis and all-cause hospitalisations which were graded as serious adverse events.

For patients who achieved SVR24, 135 (42.6%) experienced at least one serious adverse event (death, transplant, liver cancer, decompensation, sepsis or hospitalisation), therefore the transplant-free, adverse-event free survival over 15 months was 57.4%. The group with adverse events contained a significantly higher proportion of patients with Child Pugh C disease at baseline – 24/135 (17.8%) for patients with adverse events and 5/182 (2.7%) for patients without adverse events (p<0.0005) (see Table 1). Figure 3 shows that adverse events were most frequent during the treatment period, and decreased over time.

Earlier we published on the baseline characteristics of the untreated and treated patients, showing that the two cohorts were similar apart from a higher proportion of patients using alcohol (of any amount) at baseline amongst untreated patients [14]. Supplementary table 3 illustrates that after excluding active alcohol users, adverse outcomes remained less frequent in treated compared to untreated patients. Amongst untreated patients who subsequently received DAAs when they became available, and were studied as the treated cohort at least six months later, there were numerically but not statistically significantly lower incidences of liver cancers and decompensations following treatment.

We previously proposed a model using baseline age and albumin to predict adverse outcomes at 6 months. Table 3 shows the proportion of patients without adverse outcomes at month 15 based on age and serum albumin at treatment start, however these baseline factors did not discriminate the likelihood of developing adverse events or not. We did not include MELD score change into the model due to the limited number of available comparative scores.

MELD scores for patients with decompensated cirrhosis who achieved SVR24

The mean MELD score change from baseline at month 6 was -0.83 +/- 0.14 (improvement) and +0.51 +/- 0.4 at month 15 (deterioration) ($p<0.0001$) based on 282 patients with available comparative scores at month 6 and 74 patients at month 15. Supplementary figure 1 shows the waterfall plots for MELD score changes between baseline and month 6 and month 15 for non-transplanted patients who achieved SVR24. MELD improvement was observed in patients with higher baseline score (see supplementary table 4) but even in for those with baseline MELD >15 the margin of improvement was smaller at 15 months than at 6 months. Supplementary table 5 shows that based on the small number of available results, there were no patients with baseline MELD <9 who worsened to above 15; for the majority group with baseline MELD 10-14 there were similar proportions who improved or deteriorated but 48.8% had no significant change in MELD at month 15.

Discussions

The availability of highly effective all-oral antiviral regimens for patients with chronic HCV infection has transformed the treatment options for infected patients and most patients can now achieve viral clearance. For patients with advanced liver disease it is unclear whether viral eradication is beneficial and there are some reports suggesting that it may be harmful. Indeed the definition of benefit following viral clearance, whether it is patient survival, access to transplantation or avoidance of complications, is debatable.

To evaluate the potential risks and benefits of antiviral therapy in patients with end stage liver disease we examined medium term outcomes in the English Expanded Access Programme. This involved a well-studied, prospectively enrolled cohort of patients managed by experienced clinicians in a limited number of centres. Data collection was to clinical trial standards although external audit was not performed. Although observational studies in non-clinical trial conditions may be confounded by subject or clinician non-compliance, the patient cohort in this study all had advanced liver disease requiring regular medical intervention and the treating centres were all experienced in data handling techniques and were provided with support and resources from the central administration. We therefore believe that our dataset is likely to be accurate and complete with minimal errors from reporting or attendance failure.

One limitation of the study is the choice of control subjects – untreated patients with decompensated cirrhosis were selected based on the same criteria as treated patients, from the same registry, but were not otherwise matched. Treated and untreated patients

had similar demographics and baseline liver disease, apart from the proportion of active alcohol users which was higher in untreated patients. Excluding patients using any amount of alcohol at baseline, who had additional risks for disease progression and potentially poorer engagement with medical input, treated patients remained with fewer decompensations and total adverse events compared to untreated [14]. Although patients during treatment were followed-up more closely, all patients were regularly reviewed due to their advanced liver disease. The study evaluated serious adverse events which were actively monitored for (all patients were offered HCC surveillance) or resulted in hospitalisations. Therefore reporting of such events between treated and untreated patients were not likely to be biased by differences in the frequency of routine follow-up. The majority of the untreated cohort subsequently received DAAs when they became available, and about half were included in the treated cohort. Thus the same patients were studied at least six months later, during their treatment period, and there was no increase in the incidences of decompensations and liver cancers.

Recent studies highlighting the possibility of an increased incidence or recurrence of liver malignancy in patients with decompensated cirrhosis who achieve viral clearance with DAA regimens has led some to question the value of treating such patients [5, 6]. In the English EAP, patients with liver cancer were not indicated for treatment unless they had decompensated cirrhosis. We did not see any evidence of an increase in liver cancer during therapy and the following 12 months. Nearly a third of the newly detected liver cancers occurred in the first 3 months of therapy, suggesting this was growth from cancers which were radiologically undetectable at treatment baseline, rather than de novo development. There is potential bias that in a cohort of patients with

decompensated cirrhosis, development or detection of liver cancer is masked by death driven by advanced liver disease. We observed a reduction in cancer rates in patients with SVR compared to virological failure, but the relatively short duration of follow up and the low incidence of such events prevent a clear conclusion at this stage.

In the interferon era, antiviral therapy in patients with cirrhosis was associated with reduced hepatocellular carcinoma [9]. Large cohorts such as HALT-C have demonstrated that reduced cancer development may be an effect of interferon, which has anti-tumour properties, rather than viral clearance alone, although this was only observed after four years from treatment [15]. The magnitude of the impact of clearing HCV with DAAs on liver cancers may require data pooling from studies with longer follow-up, and may differ depending on the degree of cirrhosis or whether there is previous history of HCC. The reduction in liver cancer rates from 4% in 261 untreated patients over 6 months to 1.9% over 9 months after achieving viral clearance in 317 successfully treated patients reassures us that induction of liver cancer in our patients did not occur.

The long term benefits of viral eradication on liver function and the complications of portal hypertension remain unclear. However in our cohort there was a marked reduction in liver related serious adverse events in those patients who cleared virus, with decreasing adverse events rates over time. We speculate that patients will continue to benefit long term although further data will be required to confirm this.

The value of antiviral therapy in patients with decompensated cirrhosis will remain a subject for debate until very large cohorts have been evaluated for extended periods of

time. Our data on 12 months follow up after treatment of a large English cohort indicates that there are benefits for many patients, although in patients with Child Pugh C disease viral clearance may have the least impact on liver complications. In our view it is important that liver transplantation remains available for patients with very advanced disease who achieve viral clearance, as such patients may not improve to a level commensurate with a high quality of life.

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* Author names in bold designate shared co-first authorship

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Tables 1-3

Table 1. **Baseline characteristics of patients according to treatment outcomes.** Virological failure included all patients with a detectable viral load at post treatment week 24 or before, including re-treated patients. Non-SVR24 included in addition patients who died before post treatment week 24 or without available viral load. Serious adverse events included all deaths, transplants, HCCs, decompensations, sepsis and hospitalisation to month 15.

Baseline characteristic	All decompensated	SVR24	Non-SVR24	Virological failure	SVR 24 – serious adverse events	SVR 24 – no serious adverse events
All N (%)	406	317 (78.1%)	89 (21.9)	53 (13.1)	135 (42.6%)	182 (57.4%)
Sof/LDV	18 (4.4)	12 (3.8)	6 (6.7)	4 (7.5)	7 (5.2%)	5 (2.7%)
Sof/LDV/RBV	228 (56.2)	187 (59.0)	41 (46.1)	30 (56.6)	78 (57.8%)	109 (59.9)
Sof/DCV	11 (2.7)	7 (2.2)	4 (4.5)	1 (1.9)	5 (3.7%)	2 (1.1%)
Sof/DCV/RBV	149 (36.7)	111 (35.0)	38 (42.7)	18 (34.0)	45 (33.3%)	66 (36.3%)
Genotype 1	198 (48.8)	174 (54.9)	24 (27.0)	11 (20.8)	75 (55.6%)	99 (54.4%)
Genotype 3	171 (42.1)	111 (35.0)	60 (67.4)	39 (73.6)	45 (33.3%)	66 (36.3%)
Other genotypes	37 (9.1)	32 (10.1)	5 (5.6)	3 (5.7)	15 (11.1%)	17 (9.3%)
Age (years) median, range	54, 28-79	54, 28-79	52, 30-74	52, 33-72	54, 33-76	55, 28-79
Bilirubin (µmol/L) median, range	29, 4-433	28, 4-311	34, 7-433	33, 7-148	30, 4-311	26, 6-90
Albumin (g/L) median, range	31, 17-55	31, 17-49	29, 21-55	30, 21-40	31, 17-45	32, 17-49
Platelets ($x10^9$/L) median, range	75, 3-321	75, 3-321	76, 20-277	76, 20-277	74, 20-237	76, 3-321
MELD median, range	12, 7-32	11, 7-32	13, -25	12, 8-23	12, 7-32	11, 7-21
Child Pugh B	295 (72.7)	225 (71.0)	70 (78.7)	42 (79.2)	88 (65.3%)	137 (75.3%)
Child Pugh C	41 (10.1)	29 (9.1)	12 (13.5)	5 (9.4)	24 (17.8%)	5 (2.7%)
Baseline HCC	29 (7.1)	18 (5.7)	11 (12.4)	9 (17.0)	13 (9.6%)	5 (2.7%)

Footnote: Since the earlier publication [4], 3 additional patients were confirmed as transplanted prior to DAA therapy, including one registered for therapy pre-transplant, grafted then initiated treatment. These patients were re-defined as post-transplant at treatment baseline, therefore 406 instead of 409 patients were included in this study.

Table 2. **Deaths, hepatocellular carcinomas (HCC), orthotoptic liver transplants (OLT) and decompensations over 15 months for all treated patients according to treatment outcomes, compared to patients untreated for HCV** (data for untreated patients derived from [4]). Note all deaths up to post treatment week 24 were defined as non-SVR24. Decompensation events were recorded for patients with SVR24 only.

Adverse Event	Untreated N=261	All treated N = 406		
	Month 0-6	Month 0 - 6	Month 6 - 15	**Overall**
Died	13 (5.0%)	14 (3.4%)	26 (6.4%)	**40 (9.9%)**
HCC	11 (4.2%)ǂ	17 (4.2%)	10 (2.5%)	**27 (6.7%)**
OLT	10 (3.8%)	29 (7.1%)	17 (4.2%)	**46 (11.3%)**
Decompensation	73 (28.0)	72 (17.7%)	30 (7.4%)	**87 (21.4%)**

Adverse Event	SVR24 N = 317			Non-SVR24 N=89			Virological failure N = 53		
	Month 0 - 6	Month 6 - 15	**Overall**	Month 0 – 6	Month 6 - 15	**Overall**	Month 0 – 6	Month 6 - 15	**Overall**
Died	0 (0.0%)	9 (2.8%)	**9 (2.8%)**	14 (15.7%)	17 (19.1%)	31 (34.8%)	0 (0%)	3 (5.7%) *	**3 (5.7%)**
HCC	11 (3.5%)	6 (1.9%)	**17 (5.4%)**	6 (6.7%)	4 (4.5%) **	**10 (11.2%)**	3 (5.7%)	3 (5.7%)	**6 (11.3%)**
OLT	27 (8.5%)	12 (3.8%)	**39 (12.3%)**	2 (2.2%) ***	5 (5.6%)	**7 (7.9%)**	1 (1.9%)	5 (9.4%)	**6 (11.3%)**
Decomp-ensation	46 (14.5%)	16 (5.0%)	**52 (16.4%)**	26 (29.2%)	-	-	-	-	-

Footnote:

* denotes two patients who did not have known virological outcomes at 24 weeks post-treatment but had reported deaths, one of the two patients (marked by **) also had a new liver cancer

*** denotes a patient transplanted by month 6 who did not have a known virological outcome at 24 weeks post-treatment

ǂ figure updated from earlier publication

Table 3. **Proportion of patients without adverse events (death, transplantation, liver cancer, decompensation, sepsis or hospitalisations) according to baseline characteristics** (total 182 patients out of 317 who achieved SVR24).

		N	No adverse events (n)	
Age <65	Albumin >/= 35	74	47	63.5%
Age <65	Albumin <35	212	120	56.6%
Age >/=65	Albumin <35	21	10	47.6%
Age >/=65	Albumin >/= 35	10	5	50.0%

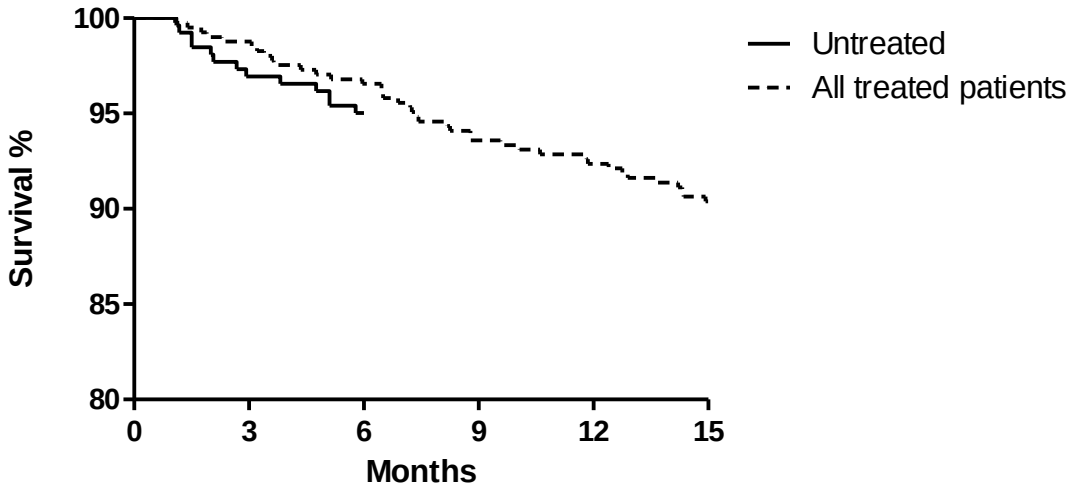
Figure legends

Fig. 1. Survival of patients over 15 months. (A) Survival in patients treated and untreated (log rank p=0.32). (B) Survival in treated patients with SVR24 and virological failure (log rank p=0.38). Note by definition no deaths occurred before month 9 (post-treatment week 24) in both groups.

Fig. 2. Development of new hepatocellular carcinoma over 15 months. (A) New hepatocellular carcinoma in untreated and treated patients (log rank p=0.98). (B) New hepatocellular carcinoma in patients with and without SVR24 (log rank p=0.02)

Fig. 3. Combined adverse event rate (death, liver transplant, HCC, decompensation, sepsis, all-cause hospitalisation) per person over time, for patients with SVR24 (n=307). Error bars represent 95% confidence intervals.

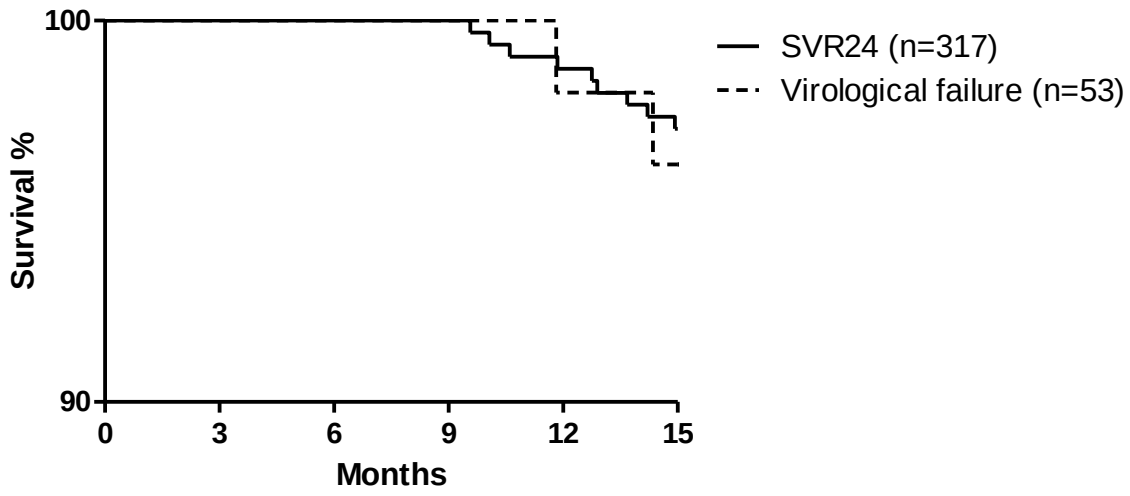
Figure



Number of patients at risk

Month	0	3	6	9	12	15
Untreated	261	254	248	-	-	-
Treated	406	401	392	380	375	366

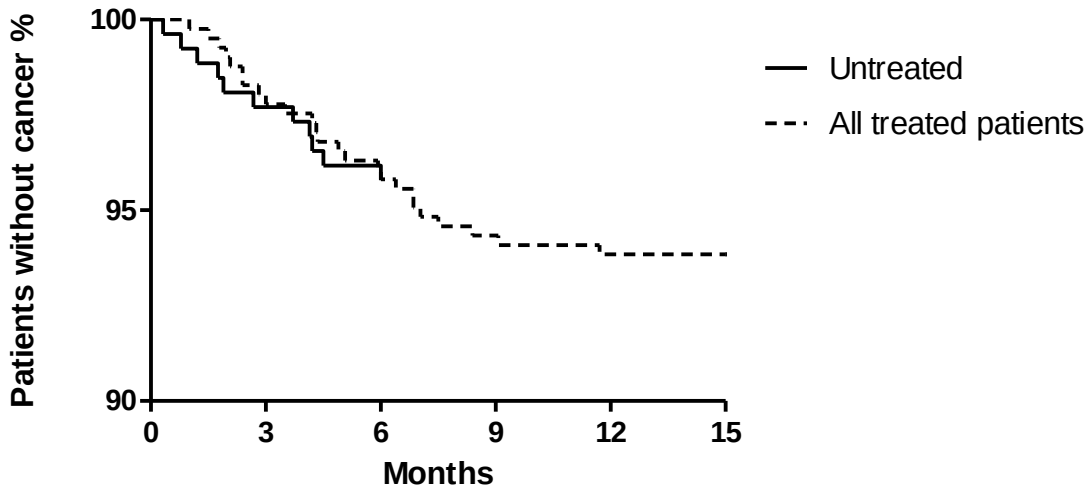
Figure



Number of patients at risk

Month	0	3	6	9	12	15
SVR24	317	317	317	317	313	308
Virological failure	53	53	53	53	53	50

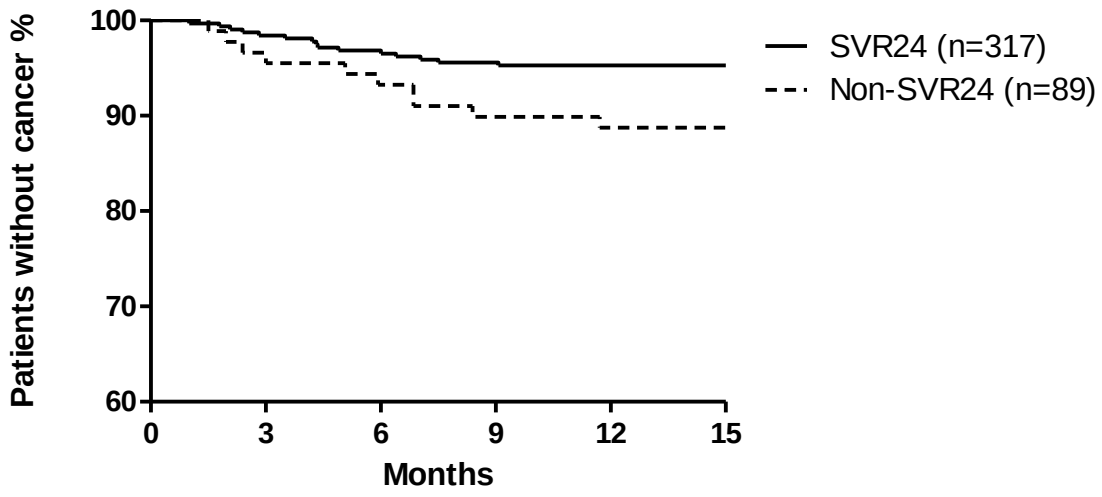
Figure



Number of patients at risk

Month	0	3	6	9	12	15
Untreated	261	255	250	-	-	-
Treated	406	398	389	383	381	379

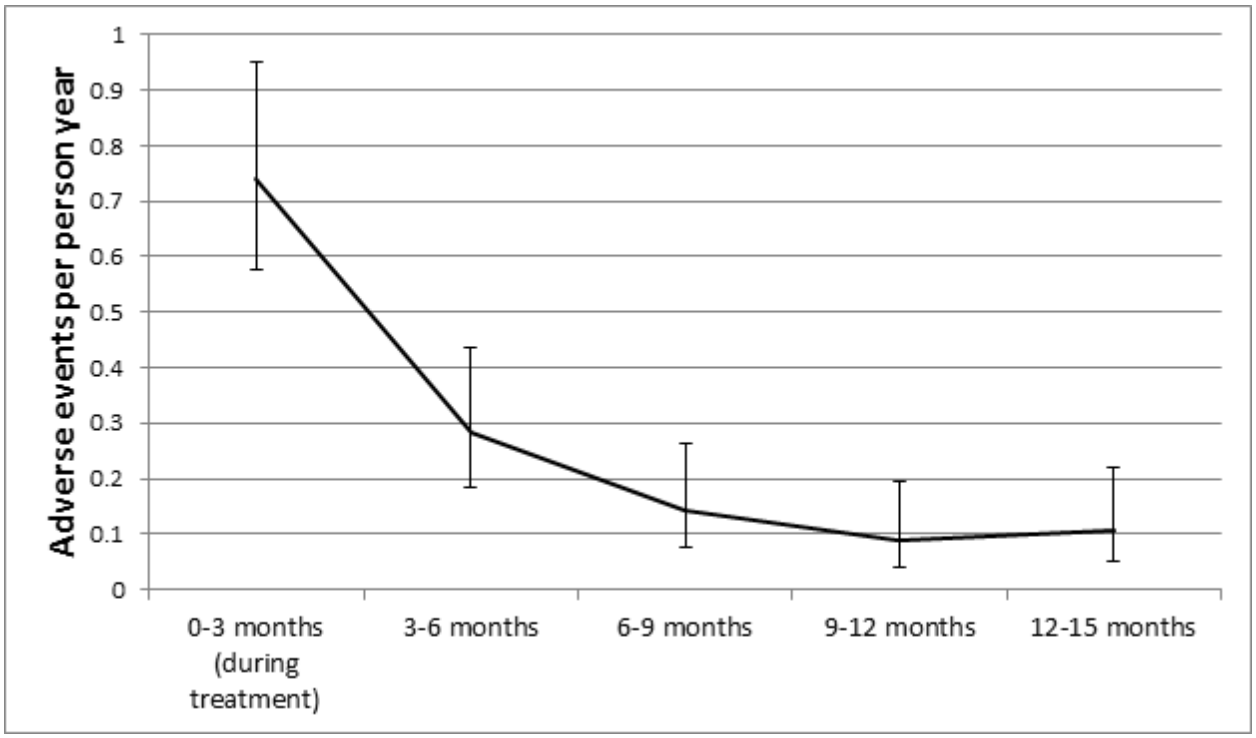
Figure



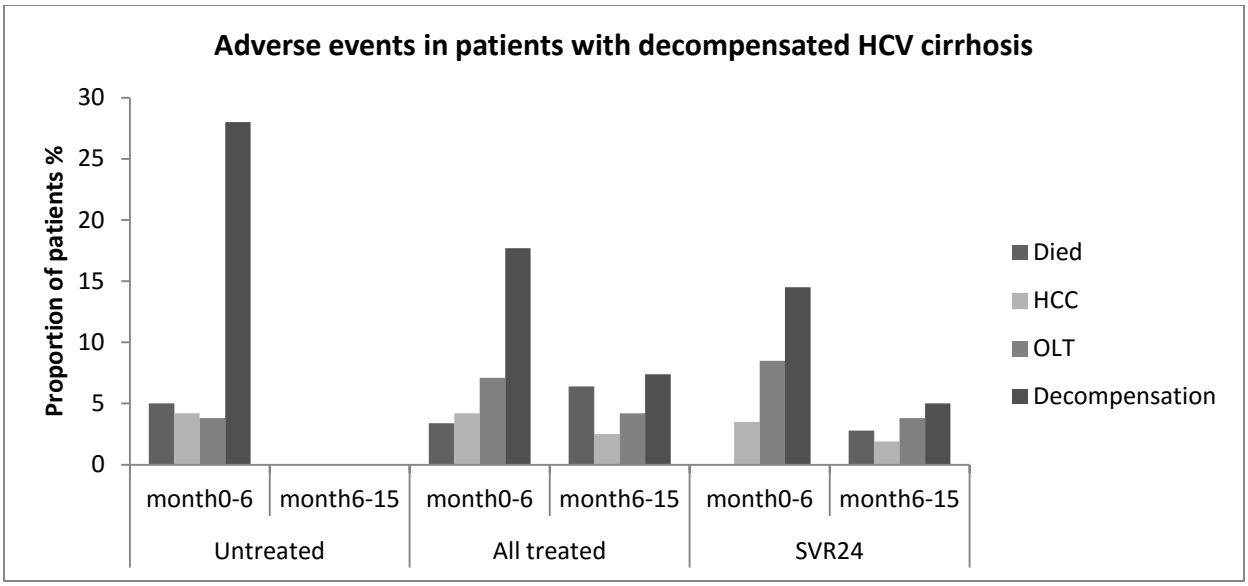
Number of patients at risk

Month	0	3	6	9	12	15
SVR24	317	313	306	303	302	300
Non-SVR24	89	86	83	80	80	79

Figure


Adverse events per person year
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0-3 months (during treatment)
3-6 months
6-9 months
9-12 months
12-15 months

*Graphical Abstract



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