Research Article

JOURNAL OF HEPATOLOGY

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

Michelle C.M. Cheung[1], Alex J. Walker[2], Benjamin E. Hudson[3], Suman Verma[4], John McLauchlan[5], David J. Mutimer[6], Ashley Brown[7], William T.H. Gelson[8], Douglas C. MacDonald[9], Kosh Agarwal[4], Graham R. Foster[10,*], William L. Irving[11], HCV Research UK

[1]*Liver Unit, Blizard Insitute, Queen Mary University of London, United Kingdom;* [2]*Faculty of Medicine & Health Sciences, University of Nottingham, United Kingdom;* [3]*University Hospitals Bristol NHS Trust, United Kingdom;* [4]*Institute of Liver Studies, King's College London, United Kingdom;* [5]*MRC-University of Glasgow Centre for Virus Research, United Kingdom;* [6]*Centre for Liver Research and NIHR Biomedical Research Unit, Queen Elizabeth Hospital, Birmingham, United Kingdom;* [7]*Department of Hepatology, St Mary's Hospital, Imperial College London, United Kingdom;* [8]*Department of Hepatology, Cambridge University Hospitals NHS Foundation Trust, United Kingdom;* [9]*UCL Institute for Liver and Digestive Health, University College London, United Kingdom;* [10]*Queen Mary University of London, United Kingdom;* [11]*NIHR Nottingham Digestive Diseases Biomedical Research Unit, United Kingdom*

See Editorial, pages 663–665

Background & Aims: 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 (IFN)-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 [1–4], although some concerns have been expressed that the rate of malignancy may not change or may, paradoxically, increase [5,6]. Previous studies of IFN-based therapies have demonstrated that HCV clearance improves liver fibrosis, even in cirrhosis [7]. Moreover, patients who achieved SVR had reduced mortality, complications of

Keywords: Hepatitis C virus; Sofosbuvir; Ledipasvir; Daclatasvir; Decompensated cirrhosis; MELD score.

Received 18 May 2016; received in revised form 10 June 2016; accepted 18 June 2016; available online 5 July 2016

* Corresponding author. Address: Queen Mary University of London, 4 Newark Street, London E1 4AT, United Kingdom. Tel.: +44 0207 882 7242; fax: +44 0207 882 2191.

E-mail address: g.r.foster@qmul.ac.uk (G.R. Foster).

Abbreviations: HCV, hepatitis C virus; DAA, direct-acting antiviral; MELD, model for 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.

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 IFN-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, extrahepatic 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 the national research ethics service (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 SVR after 24 weeks (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 <30 IU/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 $\geqslant$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 75×10^9/L.

Virological outcomes

SVR after 12 weeks (SVR12) was achieved in 329 out of 406 patients (81.0%), including 4 patients originally classified as

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	SVR24 - serious adverse events	SVR24 - 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, 7, -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)

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.

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 retreatment 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 retreatment.

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%, $p = 0.83$). Fig. 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 Fig. 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.

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%)†	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%)
Decompensation	46 (14.5%)	16 (5.0%)	52 (16.4%)	26 (29.2%)	-	-	-	-	-

*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.

†Figure updated from earlier publication.

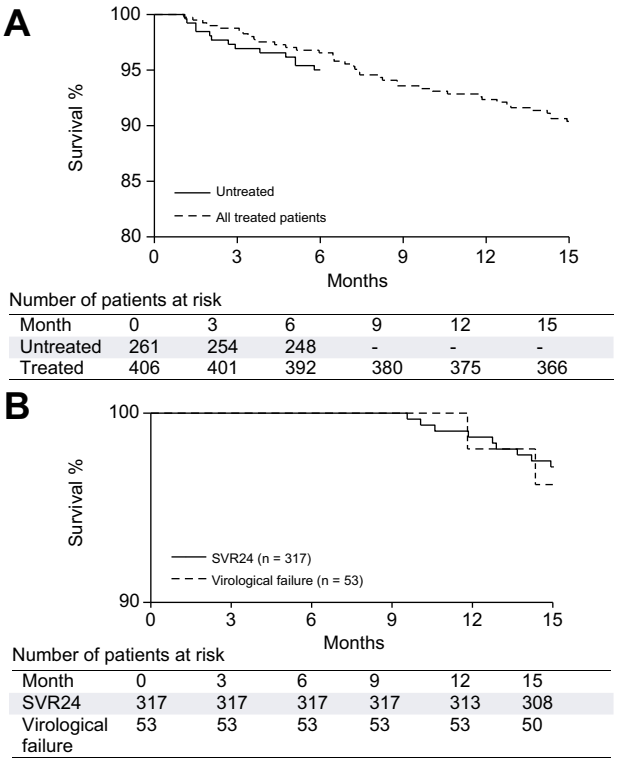

Fig. 1. Survival of patients over 15 months. (A) Survival in patients treated and untreated (log rank $p = 0.32$). (B) Survival in treated patients with SVR24 and virological failure (log rank $p = 0.38$). Note by definition no deaths occurred before month 9 (post-treatment week 24) in both groups.

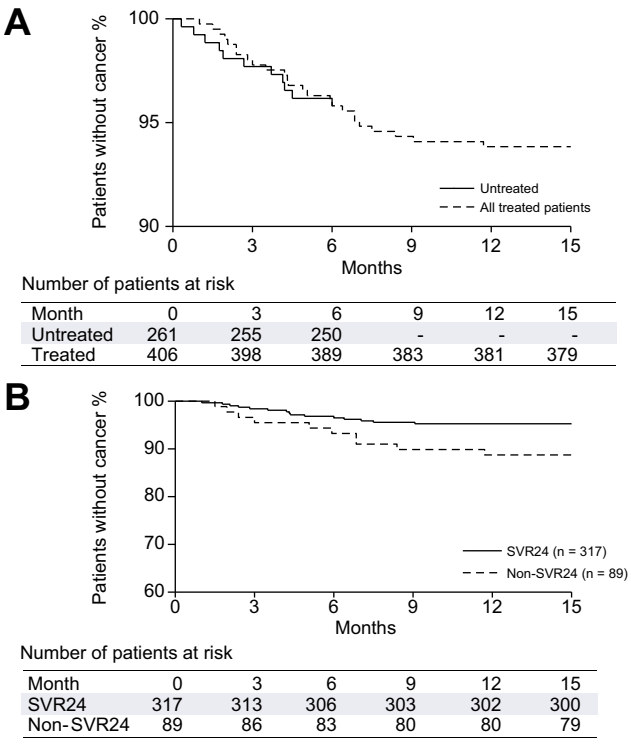

Fig. 2. Development of new hepatocellular carcinoma over 15 months. (A) New hepatocellular carcinoma in untreated and treated patients (log rank $p = 0.98$). (B) New hepatocellular carcinoma in patients with and without SVR24 (log rank $p = 0.02$).

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). Fig. 3 shows that adverse events were most frequent during the treatment period, and decreased over time.

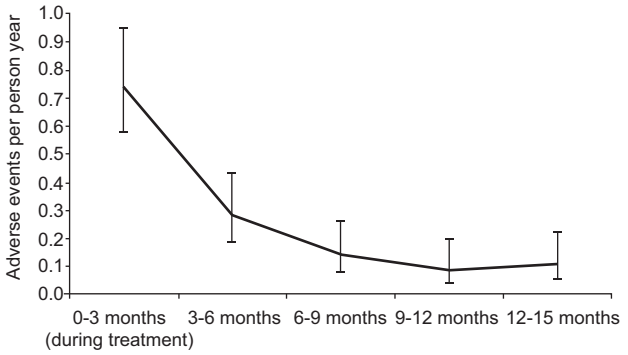

Fig. 3. Combined adverse event rate (death, liver transplant, HCC, decompensation, sepsis, all-cause hospitalisation) per person over time, for patients with SVR24 (n = 307). Error bars represent 95% confidence intervals.

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%

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 Fig. 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.

Discussion

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 IFN 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 IFN, 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.

Financial support

This study was supported by NHS England; Medical Research Foundation (Grant reference C0365); Gilead; Bristol-Myers Squibb.

Conflict of interest

Dr Cheung is funded by the National Institute for Health Research Doctoral Research Fellowship; Professor Mutimer has received honoraria from Gilead Sciences, AbbVie, Bristol-Myers Squibb, MSD and Janssen. Dr Agarwal has received speaker and consultancy fees from AbbVie, Achillion, Astellas, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis; Professor Foster has received speaker and consultancy fees from AbbVie, Achillion, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Idenix, Janssen, Merck, Novartis, Roche, Springbank; Professor Irving has received speaker and consultancy fees from Roche Products, Janssen Cilag and Novartis, educational grants from Boehringer Ingelheim, MSD and Gilead Sciences, and research grant support from GlaxoSmithKline, Pfizer, Gilead Sciences and Janssen Cilag.

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.

Acknowledgements

The authors would like to thank the patients, their families and all participating study studies for contributing data to this study. We are also grateful to HCV Research UK, in particular Elizabeth Holtham and Jennifer Benselin for collecting and collating data. HCV Research UK was supported by the Medical Research Foundation (grant reference C0365). AW was supported by the MRC-funded STOP-HCV consortium. We would like to acknowledge NHS England, Gilead Sciences and Bristol-Myers Squibb for supplying drugs for the EAP.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2016.06.019.

References

Author names in bold designate shared co-first authorship

[1] Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015;149:649–659.

[2] Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618–2628.

[3] Leroy V, Hezode C, Metivier S, Tateo M, Conti F, Nguyen-Khac E, et al. Daclatasvir plus sofosbuvir with or without ribavirin in patients with HCV infection and decompensated cirrhosis: interim analysis of a French multicentre compassionate use programme European association for the study of the liver. Barcelona, Spain: The International Liver Congress; 2016.

[4] Petersen J, Welzel T, Herzer K, Ferenci P, Gschwantler M, Cornberg M, et al. Daclatasvir plus sofosbuvir with or without ribavirin for the treatment of chronic HCV infection in patients with decompensated cirrhosis: results of a European Multicentre Compassionate Use Programme. European Association for the Study of the Liver. Barcelona, Spain: The International Liver Congress; 2016.

[5] Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. Unexpected early tumor recurrence in patients with hepatitis C virus - related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution. J Hepatol 2016;65:719–726.

[6] Buonfiglioli F, Conti F, Andreone P, Crespi C, Foschi G, Lenzi M, et al. Development of hepatocellular carcinoma in HCV cirrhotic patients treated with direct acting antivirals. European Association for the Study of the Liver. Barcelona, Spain: The International Liver Congress; 2016.
[7] Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303–1313.
[8] van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584–2593.
[9] Shiratori Y, Ito Y, Yokosuka O, Imazeki F, Nakata R, Tanaka N, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Ann Intern Med 2005;142:105–114.
[10] Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnù L, Mazzella G, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology 2007;45:579–587.
[11] Liver EAfSo. EASL recommendations on treatment of hepatitis C 2015. J Hepatol 2015;63:199–236.
[12] Panel AIHG. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62:932–954.
[13] Bunchorntavakul C, Reddy KR. Treat chronic hepatitis C virus infection in decompensated cirrhosis - pre- or post-liver transplantation? The ironic conundrum in the era of effective and well-tolerated therapy. J Viral Hepat 2016;23:408–418.
[14] **Foster GR**, **Irving WL**, Cheung MC, Walker AJ, Hudson BE, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64:1224–1231.
[15] Lok AS, Everhart JE, Wright EC, Di Bisceglie AM, Kim HY, Sterling RK, et al. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. Gastroenterology 2011;140:840–849, quiz e812.