Research Article

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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*

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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

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* 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