Efficacy of direct acting antivirals: UK real world data from a well-characterised predominantly cirrhotic HCV cohort

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Running Title: UK real world DAA data

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Abstract

Direct acting antivirals (DAAs) have revolutionised the management of chronic hepatitis C virus (HCV) infection. We describe UK real world DAA experience. Individuals commencing HCV treatment containing a DAA regimen (Mar 2014 – Nov 2016), participating in the National HCV Research UK (HCVRUK) Cohort Study were recruited from 33 specialist UK HCV centres. Data were prospectively entered at sites onto a centralised database. Data are reported as median (Q1-Q3). Of the 1448 treated patients, 1054 (73%) were males, median age being 54 yrs (47-60), 900 (62%) being infected with genotype 1 and 455 (31%) genotype 3. The majority, 887 (61%) had cirrhosis, and 590 (41%) were~~being~~ treatment-experienced. DAA regimens utilised: genotype1 sofosbuvir (SOF)/Ledipasvir/± Ribavirin (RBV) (625/900,69%) and Ombitasvir/ Paritaprevir/Dasabuvir/±RBV (220/900, 24%), and in genotype 3 SOF/ Daclatasvir ±RBV (256/455, 56%) and SOF/pegylated interferon/RBV (157/455, 35%). Overall, 1321 (91%) achieved sustained virological response (SVR12), genotype 1 vs. 3, 93% vs. 87%, p <0.001. Prior treatment, presence of cirrhosis and treatment regimen did not impact SVR12. Predictors of treatment failure were genotype 3 infection, OR 2.015 (95% CI: 1.279-3.176, p=0.003), and male gender, OR 1.878 (95% CI: 1.071-3.291, p=0.028). Of those with hepatic decompensation at baseline (n=39), 51% (n=20) recompensated post treatment, lower baseline serum creatinine being associated with recompensation (p=0.029). There were two liver-related deaths, both having decompensated disease. This real world UK data, comprising of a predominantly cirrhotic HCV genotype 1/3 cohort, confirms DAA efficacy with an

overall 91% SVR12, with 51% recompensating post treatment. Genotype 3 infection was a predictor of treatment failure.

Introduction

Worldwide, chronic hepatitis C virus (HCV) is a major health burden with 71 million infected individuals. (1) There are estimated to be 214,000 people with HCV infection in the United Kingdom (UK). (2)

The advent of direct acting antivirals (DAA) has revolutionised the management of HCV infection. Regimens~~This~~ include~~s~~ ombitasvir/ paritaprevir/ritonavir+dasabuvir OBV/PTVr/DSV) (3), sofosbuvir/ledipasvir (SOF/LDV) (4), sofosbuvir/velpatasvir (SOF/VEL) (5), grazoprevir/elbasvir (6) and the recently licensed glecaprevir/ pibrentasvir (GLE/PIB) (7) and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX). (8) Sustained virological response (SVR) rates of ~95% can now be achieved in clinical trials, even with advanced cirrhosis (3-5,9), prior treatment failures (3,5,8) and genotype 3 infection. (7,10) HCV cure is associated with an approximately 70% decreased incidence of hepatocellular cancer (HCC) and hepatic decompensation, ~60% lower risk of cardiovascular events and bacterial infections (11) and reduction in overall mortality. (11-12) Benefits are seen even in those with decompensated cirrhosis (12-14) though SVR12 rates vary from 82% to 96% (13) with the newer regimens (SOF/VEL) (15).

Most of the safety and efficacy DAA data have been obtained from well-controlled and regulated clinical trials. As apparent from the interferon-based studies, SVR rates observed in clinical trials do not always mirror those seen in a non-trial setting. (16-17) It is imperative therefore to generate real world DAA data to ensure that

clinical trial results can be extrapolated to a non-trial setting.

HCV Research UK is a consortium of leading stakeholders in the UK, with a remit to address critical gaps in our understanding of the natural history of HCV-related liver disease, effectiveness and long-term impact of antiviral treatment and genetic factors influencing prognosis. (18) The HCVRUK clinical database and bio-bank were established in 2012. (18) We have recently published real world data on a decompensated cirrhosis HCVRUK cohort treated with DAA (UK Early Access Programme [EAP]) (13-14).

Here we report on UK real world DAA experience amongst HCVRUK registered patients who were treated outside of the EAP.

Patients and methods

Between March 2012 and April 2017, more than 12,000 patients with past or current HCV infection (>95%) were enrolled into HCVRUK through attendance at one of 58 specialist UK HCV clinics. All adults and children attending a participating clinic and willing and able to give informed consent were eligible for inclusion. Exclusion criteria were an inability/unwillingness to give informed consent and or being incarcerated at the time of the clinic visit. (18)

The current study comprised recruitment (Mar 2014 – Nov 2016) of patients receiving a DAA-containing- regimen other than telaprevir and boceprevir.

Individuals participating in the current study were recruited from 33 specialist UK HCV centres (see supplementary file for site details). Data were collected through a standardised follow up data collection form and included: socio-demographics, laboratory data, presence/ absence of cirrhosis, presence of diabetes mellitus,

details of hepatic decompensation, liver prognostic scores, viral genotype and viral load (VL), HCV treatment history, treatment regimens and outcomes, co morbidity and co-medications. Data were prospectively entered at enrolling sites onto a centralised database by trained clinical staff.

Ethical approval for the study was obtained (NRES Committee East Midlands- Derby 1,reference no 11/EM/0314), each recruited patient signing an informed consent. Those who declined consent were still offered DAA therapy but their data were not collected.

Patients were assessed at baseline, week 4, week 8, week 12 (end of treatment [EOT]) and then week 12 after EOT. SVR12 was defined as the absence of detectable virus (at any level) 12 weeks after EOT. Patients whose VL became undetectable at any stage during therapy but returned after the EOT were classed as responder-relapsers. Cirrhosis was defined as one or more of the following:

- Liver stiffness measurement (LSM) > 12 kPa
- APRI score ≥2 (19) and AST/ALT ratio >1
- Presence of hepatic decompensation (jaundice [bilirubin ≥ 50 μmol/L, variceal bleed, hepatic encephalopathy or ascites) currently or in the past.
- Imaging suggesting nodular liver with splenomegaly and collaterals
- A consistent liver biopsy

Presence or absence of cirrhosis and hepatic decompensation were recorded. Reporting severity of ascites and hepatic encephalopathy was not a requirement. Hence we only assessed the MELD (20) and UKELD (21) prognostic scores.

There were no standardised criteria for assessment of hepatic recompensation. Clinicians recorded if patients were decompensated at time of initiation of DDA therapy (yes/no) and then at follow up post HCV treatment (yes/no). Those that were decompensated at time of DAA therapy but not during follow up were deemed to have recompensated.

This study was conducted prior to development of national HCV treatment guidelines and therefore use of ribavirin was not standardised and was left to the discretion of treating Hepatologists. However, those with genotype 3 infection and cirrhosis (including prior or current hepatic decompensation) were likely to receive ribavirin.

As this study describes real world treatment outcome data, consistent with other real world manuscripts an untreated cohort was not included.

All data were anonymised under a unique study number prior to analysis. For the current study, number of patients with missing data are only specified if it involved ≥ 5% of the cohort.

Statistical analysis

Data are presented as median (Q1-Q3) or number (%) and all reported p values are two-tailed. The Mann-Whitney U test was used to compare non-normally distributed continuous variables and categorical data were compared using the χ^2 test. Univariate analysis was performed to assess predictors of virological failure. Variables with p value <0.10 in univariate analysis were entered into a multivariate binary logistic regression model to determine predictors associated with failure to achieve SVR12. Data were analysed using SPSS (Chicago, IL, USA) v23.

Results

From Mar 2014 – Nov 2016, 1450 patients receiving HCV therapy containing a non telaprevir/boceprevir based DAA regimen were registered with HCVRUK. Of these two were excluded (unknown genotype and age) with 1448 being eligible for inclusion into the study. Ethnicity data were unavailable in 16/1448 (1%) and of the remainder, 1232/1432 (86%) were Caucasian. Table 1 shows baseline data in the whole cohort and stratified by genotype 1 and 3 infection.

The cohort was predominantly male (n=1054, 73%); median age of 54 yrs (47-60) with 13% (n= 183) aged ≥65yrs of age. Genotype distribution was as follows: 900 (62%) genotype 1 (1a 610 (68%), 1b 152 [17%]; in 138 [15%] subtype unknown), 455 (31%) genotype 3 and 93 (7%) other genotypes (not analysed further).

Cirrhosis prevalence was 61% (n= 887). The diagnosis of cirrhosis was made as follows (some having more than one modality): radiologically, n=687 (77%); LSM > 12kPa, n= 435 (49%); histologically, n=242 (27%); biochemically, n= 85 (10%); and clinically, n= 167 (19%). In 63 (7%), the method for cirrhosis diagnosis was~~had~~ not ~~been~~ specified. Of those with cirrhosis, 12% (n=104) had a history of hepatic decompensation, prior to (n=95) or at treatment baseline (n=39).

Of the treatment experienced patients (n=590 [41%]), 95% had previously failed ~~received~~ an interferon-based ± telaprevir/boceprevir regimen (table 1).

Treatment regimens and outcomes in the whole cohort and stratified by genotype 1 and genotype 3

In genotype 1 patients, the predominant regimens were SOF/LDV±RBV (625/900, 69%) and OBV/PTVr/DSV±RBV (220/900 24%) (table 1). RBV was administrated in 366/625 (59%) receiving SOF/LDV. This included 81% with and 21% without cirrhosis One hundred and ninety out of 220 (86%) on OBV/PTVr/DSV received ribavirin (98% with 78% without cirrhosis). Duration of treatment with SOF/LDV±RBV was eight weeks in 17% (109/625) and 12 weeks in 73% (454/625. For OBV/PTVr/DSV±RBV, 74%(162/220) received 12 weeks treatment. Overall, 66% (556/845) of the genotype 1 cohort received RBV with 73% (616/845) receiving 12 weeks of treatment. Therefore additional treatment outcome analysis (with vs. without RBV and < 12 wks vs. >12 wks treatment) were not performed.

Commented [WI1]: I am not sur eof the logic of "therefore" further analysis wasn't performed. Is this because the %s receiving RBV and the %s being treated for 12 weeks were too high to allow meaningful analysis? I would have thought having 34% and 27% in the respective minority groups would have been OK for further analysis. Perhaps just state categorically "Additional treatment analysis …. Etc etc. Or leave the sentence out completely.

In genotype 3, regimens used were SOF/DAC±RBV (n=256/455, 56%) and SOF/Peg/RBV (n=157/455, 35%). Only five patients (1%), (all on SOF/DAC) did not receive ribavirin. For SOF/PEG/RBV and SOF/DAC±RBV, 88% (138/157) and 80% (204/256) respectively, received 12 weeks treatment.

Fig 1 shows the SVR12 rates in the whole cohort and stratified by genotype 1 and 3, SVR12 rates being significantly higher in genotype 1, 93% vs. 87% (p<0.001).

Baseline data and treatment outcomes in genotype 1a patients stratified by presence or absence of cirrhosis and if treatment-naive or treatment-experienced

Of the n=610 patients with genotype 1a, n=302 (50%) had cirrhosis and n=229 (38%) were treatment-experienced. Overall those without cirrhosis were younger than those with cirrhosis (51 [45-57] yrs vs. 55 [50-62] yrs) p<0.001). Comparing non-cirrhotic treatment-naive versus non-cirrhotic treatment-experienced patients there were no significant differences in baseline data (age, platelet count, INR and serum

bilirubin, ALT, albumin, sodium and creatinine, [data not shown]), except the non-cirrhotic treatment-naïve patients had a higher ALT (55 IU/L [33-94] vs. 40 IU/L [37-42]), p = 0.029. Similarly comparing genotype 1a patients with cirrhosis treatment-naive versus cirrhotic treatment-experienced, there were no differences in baseline data except the cirrhotic treatment experienced patients were older, (57 yrs [51-63] vs. 54 yrs [50-60]), p=0.008.

Fig 2a shows SVR12 rates in genotype 1a patients stratified by absence or presence of cirrhosis and if treatment-naive or treatment-experienced. There were no statistical differences, SVR12 rates being ≥ 91% in all subgroups (fig 2a)

Baseline data and treatment outcomes in genotype 1b patients stratified by presence and absence of cirrhosis and if treatment-naive or treatment-experienced

A similar analysis of 152 patients with genotype 1b infection, of whom 81 (53%) had cirrhosis and 71 (47%) were treatment-experienced showed that the non-cirrhotic patients were younger than the cirrhotic (53 yrs [42-61] vs. 60 yrs [51-67]), p=0.003. Comparing baseline data in non-cirrhotic treatment naive with non-cirrhotic treatment-experienced patients, the latter were older (59 yrs [47-65] vs. 48 yrs [39-59]), p=0.038. There were no significant differences in baseline data comparing cirrhotic treatment-naive and treatment-experienced patients (data not shown)

Figure 2b shows SVR12 data in genotype 1b patients stratified by absence and presence of cirrhosis and if treatment-naive or treatment-experienced. There were no statistical differences with SVR12 rates ≥93% in all subgroups.

There were no differences in overall SVR12 rates in genotype 1a and 1b patients: 569/610 (93%) vs.144/152 (95%) p=0.512).

Treatment outcomes in genotype 1 patients stratified by regimen utilised

In non-cirrhotic and cirrhotic treatment-naive and treatment-experienced patients there were no significant differences in SVR12 rates when stratified by treatment regimen utilised (SOF/LDV±RBV vs. OBV/PTVr/ DSV ±RBV) (Fig 2c and 2d respectively)

Baseline data and treatment outcomes in Genotype 3 patients stratified by presence and absence of cirrhosis, if treatment-naive or treatment-experienced and by treatment regimen

Of the 455 patients with genotype 3 infection, 365 (80%) had cirrhosis, and 181 (40%) were treatment-experienced. Overall, those without cirrhosis were younger than those with cirrhosis (49 yrs [26-78] vs. 53 yrs [25-81]), p = 0.004. In genotype 3 non-cirrhotics comparing treatment-naive and treatment-experienced patients, there were no statistical differences in baseline variables (data not shown). In those with cirrhosis, comparing treatment-naive and treatment-experienced patients, again there were no differences in baseline variables (data not shown) except the latter were significantly older (55 yrs [51-61] vs. 51 yrs [45-57]), p < 0.001).

Fig 3a shows SVR12 data in patients with genotype 3 stratified by presence and absence of cirrhosis and if treatment-naive or treatment-experienced. Non-cirrhotic treatment-naïve patients had numerically higher SVR12 rates compared to cirrhotic treatment-experienced (93% vs. 82%, p=0.069) (Fig 3a).

Fig 3b shows SVR12 rates in genotype 3 non-cirrhotic patients (treatment-naive and treatment-experienced) depending on regimen utilised (SOF/DAC±RBV vs. SOF/Peg/RBV). No statistically significant differences in SVR12 rates were observed. Fig 4c shows SVR12 rates in genotype 3 cirrhotics (treatment-naive and treatment-experienced) depending on treatment regimen. SVR12 rates were numerically higher in the treatment-naive group treated with SOF/Peg/RBV compared to SOF/DAC±RBV (95% vs. 86%, p=0.054) (Fig 3c).

Taking genotype 3 as a whole, SVR12 rates were numerically higher with SOF/Peg/RBV vs. SOF/DAC±RBV (90% [142/157] vs. 216/256 [84%], p=0.078).

Factors predicting failure to achieve SVR12

Of the 127/1448 (9%) who did not achieve SVR12, there were 66 (52%) responder-relapsers, 10 (8%) non-responders, and the remainder (n=50, 39%) were either lost to follow up (n=43) or died (n=7)**.** Treatment relapses were significantly higher in genotype 3 vs. genotype 1 (38/455 [8%] vs. 23/900 [3%]), p<0.001. Table 2 shows univariate analysis of demographic and baseline variables in those that failed to achieve SVR12. Since 99% with genotype 3 and 86% with genotype 1 treated OBV/PTVr/ DSV received ribavirin, the effect of ribavirin on non-SVR12 could only be analysed in those receiving SOF/LDV (table 2). Factors predicting non-response on univariate analysis were male gender, genotype 3 infection, serum albumin, serum bilirubin, platelet count, UKELD score and history of hepatic decompensation prior to and at baseline ($p < 0.1$ for all). Of the 104 with past or current hepatic decompensation, 98 (94%) received ribavirin. The UKELD score was a composite of other variables and there was collinearity between hepatic decompensation prior to

and at baseline. Therefore the following variables with p values <0.1 on univariate analysis were entered onto a multivariate binary logistic regression model: male gender, genotype 3 infection, serum albumin, serum bilirubin, platelet count and hepatic decompensation at baseline. Predictors of failure to achieve SVR 12 were genotype 3 infection, OR 2.015 (95% CI: 1.279-3.176, p=0.003) and male gender, OR 1.878 (95% CI: 1.071-3.291, p=0.028) (table 2b).

Factors predicting failure to achieve hepatic recompensation post HCV treatment

There were 39/1448 (3%) patients who had hepatic decompensation at baseline prior to commencing DAA therapy: ascites (n=21), jaundice (n=6), variceal bleeding (n=5), hepatic encephalopathy (HE) (n=2), ascites and jaundice (n=2), ascites and HE (n=2), and ascites, jaundice and HE (n=1). Of these, 30 (77%) achieved SVR12, seven (18%) being responder-relapsers and two (5%) dying from VB, one during and the second after completing treatment. Both had no prior history of variceal bleeding. Of the 39 treated patients with hepatic decompensation at baseline, 20 (51%) recompensated post treatment (18 achieved SVR12, two responder relapsers). Table 3 shows baseline data in the cohort with decompensated disease at baseline and stratified by those that did and did not achieve recompensation post HCV treatment. Those that failed to achieve recompensation post HCV treatment were likely to be older (55 yrs vs.53 yrs), male (74% vs. 26%), have lower serum albumin (30 g/L vs. 33 g/L) and ALT (46 IU/L vs. 68 IU/L) and higher serum creatinine (72 µmol/L vs. 58 µmol/L). Only the difference~~s~~ in serum creatinine achieved statistical significance (p=0.029)(table 3). Due to the small sample size a multiple logistic regression analysis was not performed.

Three patients (all men, two with genotype 1 and one with genotype 3 infection) had de novo hepatic decompensation post DAA therapy. Two achieved SVR12, one being a responder relapser. In addition to the two deaths with variceal bleeding, there were five additional deaths: non-liver related in four with cause of death being unavailable in one.

Overall, 63 patients in this real world cohort (4%) had HCC at baseline and nine (<1%) patients developed de novo HCC. Detailed ~~HCC~~ data on factors associated with HCC development are~~is~~ being reported separately.

Discussion

HCVRUK has~~is~~ one of the largest real world HCV clinical databases and bio-banks, recruiting patients from secondary and tertiary centres across almost all UK geographical areas. Other strengths include data collection in a prospective and standardised manner at baseline and longitudinally, inclusion of patients with both genotype 1 and 3 and <4% of the cohort being lost to follow up. In contrast other real world series have been retrospective (16, 22-27), had a small sample size (22,24), or a relatively easy to treat cohort, e.g. genotype 1b (22), or treatment naive, non-cirrhotic patients (28-29). Almost two-thirds of our cohort had genotype 1 infection, higher than that reported nationally (genotype 1, 50.1%, genotype 3, 38.4%) (30), probably reflecting, until recently, the relatively limited availability of genotype 3 treatment options.

The current study focused on a difficult to treat cohort with about two thirds having cirrhosis, 41% being treatment-experienced and about a third having genotype 3 infection. Despite this, overall SVR12 rates were 91%. Predictors of failure to achieve

SVR12 were male gender and genotype 3 infection. The significantly lower cure rates in genotype 3 patients compared to genotype 1 were due to an almost three fold higher relapse rate (8% vs. 3%, p<0.0001) in the former. The 80% prevalence of cirrhosis in genotype 3 patients likely contributed to this (31-32) though data on resistance-associated variants (RAS) were unavailable. Though lowest SVR12 rates (77%) were seen in those with hepatic decompensation at time of antiviral treatment, about 50% achieved hepatic recompensation post treatment.

In our genotype 1 cohort, subtype ~~(~~1a or 1b~~)~~, prior treatment history and presence of cirrhosis did not impact SVR12: genotype 1a vs. 1b non-cirrhotic treatment-naive 93% vs. 93%, non-cirrhotic treatment-experienced 91% vs. 93%, cirrhotic treatment-naive 94% vs. 97%, and cirrhotic treatment-experienced 95% vs. 95%. Cure rates were also independent of the regimen utilised (Fig 2c and 2d). Our genotype 1 SVR12 results are consistent with clinical trial data (3-4) and the recent Spanish real world cohort (33). In the latter study (16% genotype 1a, ~ 50% cirrhotic/treatment-experienced), SVR12 rates with SOF/LDV±RBV vs. OBV/PTVr/DSV ±RBV were 97% vs. 96% respectively with no differences being observed based on subtypes or fibrosis stage (33). Similar efficacy in a real world setting with SOF/LDV ±RBV vs. OBV/PTVr/DSV±RBV have also been reported by other real world series from the United States (16,25,29,34). However, unlike Fox (25) and Backus et al (29) we did not observe cirrhosis to be associated with lower SVR 12 rates in genotype 1 patients.

Until the advent of the newer DAAs (SOF/VEL, GLE/PIB, SOF/VEL/VOX (5, 7-8), genotype 3 has traditionally been a more difficult to treat group with cure rates

dependant on fibrosis stage, treatment regimens and prior treatment history (31-32). Our data corroborates this as genotype 3 cirrhotic treatment-experienced patients had numerically lower SVR12 rates compared to non-cirrhotic treatment-naïve patients (82% vs. 93%p =0.069) (Fig 4a). Also overall SVR12 rates were numerically higher with SOF/Peg/RBV vs. SOF/DAC±RBV regimens (90% vs. 84%, p=0.078). Our overall SVR12 rates with SOF/Peg/RBV (90%) are consistent both with real world (American Veterans Association [VA]) (87%) and trial data (ALLY 3+ [88%] and the BOSON study). (16,31,32) In the latter study, SVR12 rates reported were: non-cirrhotic treatment naive (96%), non-cirrhotic treatment experienced (94%), cirrhotic treatment naive (91%) and cirrhotic treatment experienced (86%).(32)

Interestingly we also observed male gender to be a predictor of non-SVR12 despite there being no statistically significant difference in men vs. women as regards prevalence of genotype 3 infection (32% vs. 31%), cirrhosis (60% vs. 64%) and prior treatment failure (41% vs. 39%), (p>0.290). We do however accept that treatment compliance data were unavailable. Since most HCV studies have a male preponderance, it is unlikely that the association between gender and SVR12 can be tested in an evenly distributed male vs. female cohort.

Older age was not a predictor of treatment failure; 93% of genotype 1 and genotype 3 patients above the age of 65 yrs achieved SVR12, consistent with real world American VA data (SVR12 89.8% vs. 93.8% if aged < 55 yrs vs. 75 yrs respectively). (23)

We observed more advanced liver disease as reflected by serum albumin and bilirubin, UKELD scores and presence of hepatic decompensation to be associated

with non-SVR12 on univariate but not multivariate analysis, most likely due to the dominant role played by genotype 3. Our SVR12 rates (77%) in those with hepatic decompensation at baseline are consistent with UK EAP (81.6%) (13) and clinical trial data (SOLAR 1, SOLAR 2 and ALLY-1) (35-37).

About 50% of our decompensated cohort recompensated post DAA, all but two achieving SVR12. Those likely to benefit were younger, female, have lower serum creatinine and better synthetic function. Only serum creatinine achieved statistical significance most likely due to multiple testing on a small sample size. Nonetheless our results are consistent with the EAP data (13) and the recent study by El-Sherif et al (38) confirming that those with more advanced disease are less likely to recompensate post DAA therapy. El- Sherif et al found presence of ascites, hepatic encephalopathy, serum albumin < 35 g/L or ALT < 60 IU/L and BMI > 25 kg/m^2 to be associated with an increased risk of not achieving reduction to Child Pugh A disease, independent of response to DAA therapy (38). Two (5%) of our decompensated patients died during DAA therapy, consistent with clinical trial data (15).

Though overall only 43/1448 (3%) of the study cohort were lost to follow-up, they accounted for 34% of the virological failures (43/127), higher than that reported in being consistent with the recent Spanish real world study (9%) (33).

Our study did have limitations. This was a predominantly Caucasian cohort and hence our results cannot be extrapolated to other ethnic groups. Also, data on DAA related adverse events, severity of decompensating events and RAS were not available. However, HCVRUK has commenced RAS analysis on all patients failing a DAA containing regimen who are undergoing re treatment and this is being reported

separately. Finally, our definition of recompensation was not standardised and this may have led to bias.

In conclusion, this real world UK data comprising a well-characterised cohort of difficult to treat genotype 1 and genotype 3 HCV patients confirms efficacy of DAA with SVR12 rates mirroring clinical trial data. Genotype 3 infection was a predictor of not achieving SVR12. Though about 50% of patients with advanced disease recompensated post DAA therapy, identifying those with decompensated most likely to benefit from antiviral treatment remains challenging.

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Figure Legends

Fig 1 SVR12 rates in whole cohort and in those with genotype 1 and Genotype 3

Fig 2a SVR12 rates in genotype 1a stratified by absence (NC) or presence (C) of cirrhosis and if treatment-naive (TN) or treatment-experienced (TE)

Fig 2b SVR12 rates in genotype 1b stratified by absence (NC) or presence (C) of cirrhosis and if treatment-naive (TN) or treatment-experienced (TE)

Fig 2c SVR 12 rates in genotype 1 non-cirrhotic patients, (treatment-naive and treatment-experienced) depending on regimen used

Fig 2d SVR 12 rates in genotype 1 cirrhotic patient (treatment-naive and treatment-experienced) depending on regimen used

Fig 3a. SVR12 rates in genotype 3 stratified by absence (NC) or presence (C) of cirrhosis and if treatment-naive (TN) or treatment-experienced (TE)

Fig 3b: SVR 12 rates in genotype 3 non-cirrhotic patients (treatment-naive and treatment-experienced) depending on regimen used

Fig 3c SVR12 rates in genotype 3 cirrhotic patients (treatment naive and treatment-experienced) depending on regimen used

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Table 1: Baseline data in whole cohort and stratified by genotype 1 and 3

	Total cohort n= 1448	**Genotype 1 n= 900**	**Genotype 3 n= 455**
Age (yrs)	54 (47-60)	54 (47-61)	52 (46-59)
Male	1054 (73%)	656 (73%)	332 (73%)
BMI (kg/m^2)	26.6 (23.5-30.1)	26.2 (23.3-30)	27.2 (23.7-30.7)
Viral load (IU/ml)	Log 6 (5.5-6.6)	Log 6 (5.6-6.6)	Log 5.8 (5.3-6.5)
Liver stiffness measurement (LSM) kPa[▪]	12 (6.9-21)	9.9 (6.3-16.8)	15.9 (11.9-27.4)
Platelets (10^9/L)	161 (107-219)	177 (124-232)	133 (90-176)
Bilirubin (µmol/L)	11 (8-16)	11 (8-16)	12 (9-18)
ALT (IU/L)	67 (41-109)	60 (39-96)	80 (49-123)
Albumin g/L	39 (36-42)	39 (36-42)	39 (35-42)
INR	1.1 (1-1.2)	1.1 (1-1.1)	1.1 (1-1.2)
Sodium (mmol/L)	140 (138-141)	140 (138-141)	139 (138-141)
Creatinine (µmol/L)	70 (61-80)	70 (62-80)	69 (60-79)
Cirrhosis **Prior or baseline decompensation**	887 (61%) 104 (12%)	465 (52%) 45 (10%)	365 (80%) 54 (15%)
MELD score	6 (6-7)	6 (6-7)	6 (6-7)
UKELD score	47 (45-49)	46 (45-48)	47 (45-50)
Treatment-naive **Treatment-experienced**	858 (59%) 590 (41%)	533 (59%) 367 (41%)	274 (60%) 181 (40%)
Prior treatments **Peg INF±RBV** **Peg INF±RBV+ telapevir/boceprevir** **Standard INF±RBV** **Other regimens***	 433 (73%) 74 (13%) 51 (9%) 32 (5%)	 235 (64%) 74 (20%) 37 (10%) 21 (6%)	 161 (89%) 11 (6%) 9 (5%)
Current DAA regimen **OBV/PTVr/DSV±RBV** **SOF/LDV±RBV** **SOF/DAC±RBV** **SOF/PEG/RBV** **Other regimens**	 221 (15%) 673 (46%) 260 (18%) 184 (13%) 110 (7%)	 220 (24%) 625 (69%) 55 (6%)	 256 (56%) 157 (34%) 42 (9%)

▪ Overall 879 (61%) had valid LSM. This included 557 with genotype 1 and 276 with genotype 3 had valid LSM readings

*Other regimens included sofosbuvir (SOF) and simeprevir

Normal values: platelet, bilirubin 0-21 µmol/l, ALT 0-41 iu/L, albumin 35-52g/L, INR 0.8-1.2, sodium, creatinine 62-106 µmol/L,

Table 2a: Univariate analysis of demographic and baseline variables in those without SVR12

	Odds Ratio	95% CI upper	lower	p value
Male gender	1.581	1.005	2.489	0.048
Age (yrs)	0.997	0.978	1.015	0.714
Age ≥65 yrs	0.702	0.379	1.299	0.260
BMI (kg/m2)	1.006	0.966	1.048	0.765
Viral load (baseline) (IU/L)	1	1	1	0.92
Cirrhosis (baseline)	1.213	0.828	1.777	0.322
Treatment experienced	1.204	0.834	1.737	0.321
Genotype 1a	0.630	0.428	0.928	0.019
Genotype 1b	0.549	0.263	1.148	0.111
Genotype 3	2.175	1.506	3.140	<0.001
LSM (kPa)	1.013	0.997	1.030	0.124
Ribavirin non use **	1.44	0.707	2.936	0.315
Sodium (mmol/L)	0.969	0.916	1.026	0.285
Creatinine (µmol/L)	0.995	0.985	1.005	0.324
Albumin (g/L)	0.930	0.897	0.964	<0.001
Bilirubin (µmol/L)	1.021	1.009	1.034	0.001
ALT (IU/L)	1.001	0.999	1.004	0.227
INR	1.080	0.628	1.859	0.781
Platelets (109/L)	0.996	0.994	0.999	0.007
MELD	1.108	0.934	1.314	0.238
UKELD	1.099	1.031	1.171	0.004
Hepatic decompensation				
Decompensated at baseline	3.138	1.435	6.860	0.004
Decompensated prior to baseline	2.192	1.212	3.964	0.009

** only assessed in genoptpe 1 patients receiving receiving SOF/LDV

Table 2b. Multivariate analysis of variables in those without SVR12

Variable	B	S.E.	Wald	df	P value	Hazard Ratio	95% CI	
							Lower	Upper
Male gender	**0.630**	**0.286**	**4.842**	**1**	**0.028**	**1.878**	**1.071**	**3.291**
Genotype 3 (compared to genotype 1a)	**0.701**	**0.232**	**9.112**	**1**	**0.003**	**2.015**	**1.279**	**3.176**
Serum albumin	-0.038	0.024	2.498	1	0.114	0.963	0.919	1.009
Serum bilirubin	0.011	0.008	1.856	1	0.173	1.011	0.995	1.028
Platelet count	0.000	0.002	0.003	1	0.959	1.000	0.997	1.003
Baseline hepatic decompensation	-0.760	0.481	2.501	1	0.114	0.468	0.182	1.199

Table 3: Demographic and baseline data in those with hepatic decompensation at baseline and stratified by those that did and did not recompensate post HCV treatment

	Hepatic decompensation at baseline n=39	**Recompensated post HCV treatment n=20**	**No recompensation post HCV treatment n=19**	**p value**
Male **Female**	23 (59%) 16 (41%)	9 (45%) 11(55%)	14 (74%) 5 (26%)	0.069
Age median **≥65 yrs**	55 (51-62) 5 (13%)	53 (48-61) 3 (13)	55 (53-64) 2(11%)	0.243 0.676
BMI (kg/m^2)	26.7 (23.4-32.8)	26.7 (23.4-31.4)	26.9 (20.9-33.2)	1
Viral load (baseline) (IU/ml)	Log 5.7 (4.9-6.2)	Log 5.4 (4.6-5.9)	Log 5.99 (5.2-6.5)	0.64
Treatment experienced	14 (36%)	6 (20%)	8 (42%)	0.431
Genotype **1** **3**	 16 (41%) 23 (59%)	 7 (35%) 13 (65%)	 9 (47%) 10 (53%)	 0.433 0.433
Sodium (mmol/L)	138 (133-140)	138 (134-139)	139 (132-141)	0.756
Creatinine (µmol/L)	60 (53-79)	58 (51-66)	72 (59-93)	**0.029**
Albumin (g/L)	31 (26-36)	33 (29-36)	30 (26-36)	0.266
Bilirubin (µmol/L)	32 (17-43)	35 (23-53)	26 (14-42)	0.243
ALT (IU/L)	49 (38-83)	68 (37-85)	46 (39-79)	0.546
INR	1.3 (1.2-1.5)	1.4 (1.2-1.6)	1.3 (1.18-1.4)	0.272
Platelets (10^9/L)	84 (66-118)	88 (66-120)	84 (57-118)	0.965
MELD score	7 (6-8)	7 (6-9)	8 (6-8)	0.946
UKELD score	52 (49-55)	52 (49-56)	52 (46-55)	0.854