ORIGINAL ARTICLE

Real-world experience with daclatasvir plus sofosbuvir ± ribavirin for post-liver transplant HCV recurrence and severe liver disease

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SUMMARY

Optimizing therapy of post-transplant HCV recurrence remains important, especially in advanced liver disease. We evaluated daclatasvir (DCV) plus sofosbuvir (SOF), with or without ribavirin (RBV), in patients with post-liver transplant recurrence in a real-world European cohort at high risk of decompensation or death within 12 months. Recommended treatment was DCV 60 mg plus SOF 400 mg once daily for 24 weeks; RBV use/shorter treatment duration was at physicians' discretion. Patients ($N = 87$) were 70% male, 93% white, and mostly infected with HCV genotypes 1b (48%), 1a (32%), or 3 (9%); 37 (43%) had cirrhosis (16 decompensated), five had fibrosing cholestatic hepatitis. Sustained virologic response at post-treatment week 12 (SVR12) was 94% (80/85) in a modified intention-to-treat analysis: 95% (58/61) without RBV and 92% (22/24) with RBV, with no virologic failures. SVR12 was 100% (80/80) in an as-observed analysis excluding five nonvirologic failures. Four patients (5%) discontinued therapy for adverse events (AEs); 16 (18%) experienced serious AEs. One patient died on treatment and five during follow-up. Most AEs were associated with advanced liver disease and unrelated to therapy. No clinically significant drug–drug interactions were observed. DCV + SOF ± RBV was well tolerated and achieved high SVR12 (94%) in patients with post-transplant HCV recurrence, including patients with severe liver disease.

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Introduction

Chronic hepatitis C virus (HCV)-related end-stage liver disease is one of the most common indications for liver transplantation (LT) worldwide [1–3]. Unfortunately, post-transplant HCV recurrence with liver graft reinfection is near-universal in patients who are viremic at time of transplant and is associated with increased risk of accelerated disease progression and graft failure [4]. Viral eradication with effective early treatment has proven to be the best way to improve patient and graft survival [5]. However, post-transplant patient management is complicated by the severity of the liver disease, associated comorbidities, and by use of immunosuppressants [6,7].

All-oral combinations of direct-acting antivirals have markedly improved treatment of post-transplant HCV recurrence. High rates of sustained virologic response at post-treatment week 12 (SVR12) have been demonstrated with several regimens, with safety profiles superior to those of peginterferon-based treatment [3,8–14]. However, some regimens have been associated with significant drug–drug interactions and/or a higher risk of complications in patients with advanced disease, limiting their utility in the post-transplant setting [7,15]. Data on direct-acting antiviral regimens in patients with advanced liver disease remain limited.

Daclatasvir (DCV), a potent pangenotypic NS5A inhibitor, and sofosbuvir (SOF), a potent pangenotypic nucleotide analog NS5B inhibitor, are both approved for treatment of HCV recurrence after LT [16,17]. Neither agent has clinically relevant interactions with immunosuppressive medications, and both can be used safely in patients with hepatic impairment [18,19]. The all-oral combination of DCV + SOF with ribavirin (RBV) was well tolerated and achieved 94% SVR12 after 12 weeks of treatment in patients with post-liver transplant HCV recurrence in the ALLY-1 study [13]. Similar findings outside of clinical trials have been reported and provide a body of real-world evidence to support and validate the clinical development program [20–22].

In Europe, a compassionate use program (CUP) was initiated to provide premarket access to DCV, in combination with SOF and with or without RBV, for patients with urgent need of HCV treatment and no therapeutic alternatives. This program has contributed real-world data regarding the clinical profile of this combination in a diverse population with minimal entry restrictions. We report here on findings from patients with HCV recurrence after LT who received DCV + SOF ± RBV, including many with severe liver disease.

Patients and methods

Patients and treatment

The European CUP for DCV enrolled adults ≥18 years of age with chronic HCV infection (any genotype) who were at high risk of hepatic decompensation or death within 12 months if left untreated, or in urgent need of viral clearance due to extrahepatic manifestations, comorbidities, or post-transplant HCV recurrence, and who had no alternative therapeutic options. Patients were enrolled at 100 centers in Germany, Austria, the Netherlands, Sweden, and Norway between April 2014 and April 2015. Human immunodeficiency virus/HCV or hepatitis B virus (HBV)/HCV coinfection, hepatocellular carcinoma, fibrosing cholestatic hepatitis (FCH), and decompensated cirrhosis were permitted. There were no restrictions on Child-Pugh or Model for End-Stage Liver Disease (MELD) scores. Patients with creatinine clearance (CrCl) ≤30 ml/min, pregnancy, or not using required contraception were excluded. The current analysis includes the subset of EU CUP patients with recurrent HCV infection after LT, regardless of liver disease severity. Findings from the overall cohort have been reported previously [23].

Cirrhosis status was evaluated initially at each site. To maximize consistency across sites, disease stage was reassessed using a predefined algorithm and cirrhosis diagnosed according to data from liver biopsy (Metavir >F3, Ishak >4, or the equivalent at any time prior to screening), FibroScan (>14.6 kPa at any time prior to screening), or FIB-4 score (>3.25 at baseline).

Recommended treatment was DCV 60 mg plus SOF 400 mg once daily for 24 weeks; RBV could be added and/or shorter treatment undertaken at physician's discretion. Written informed consent was obtained before enrollment. This program was conducted in accordance with the Declaration of Helsinki and approved by national health authorities for all participating countries. Ethics committee approval was managed in accordance with local legislation regulating CUPs.

Efficacy and safety assessments

All assessments were conducted locally using standard local practices and recommendations provided in the program protocol. Recommended program visits for safety assessments and collection of blood samples for laboratory analyses were at baseline, on-treatment weeks 4, 12, and 24, and post-treatment weeks 12 and (optional) 24. Serum HCV RNA determinations were conducted at

each center using HCV RNA assay methods selected according to local preferences and practice standards.

Endpoints

Sustained virologic response at post-treatment week 12, defined as HCV RNA below the assay lower limit of quantification (LLOQ), target detected or target not detected (TND), at post-treatment week 12 was the primary measure of treatment efficacy. Virologic failure was defined as relapse (HCV RNA >LLOQ during any post-treatment visit in patients with HCV RNA <LLOQ, target detected or TND, at the end of treatment), virologic breakthrough (HCV RNA ≥LLOQ on treatment following confirmed HCV RNA <LLOQ, target detected or TND, or a ≥1 $\log_{10}$ increase in HCV RNA from nadir), or other on-treatment virologic failure (HCV RNA never <LLOQ, or HCV RNA ≥LLOQ at the end of treatment, not meeting the definition of virologic breakthrough). Safety was assessed as graded adverse events (AEs) and clinical laboratory abnormalities [24], serious AEs, discontinuations due to AEs, and deaths.

Statistical analyses

Enrollment was based on the clinical need for treatment. The primary efficacy population [modified intention-to-treat (mITT) population] included patients who received ≥1 dose of the program regimen excluding those without virologic failure who were lost to follow-up, withdrew informed consent, or withdrew for undocumented reasons. Patients with missing data who died or discontinued treatment due to AEs were considered to have experienced nonvirologic failure.

Efficacy outcomes were also assessed in the full intention-to-treat population (all patients who received ≥1 dose of program regimen) and in patients with HCV RNA data available at post-treatment week 12, excluding those who failed due to nonvirologic reasons (as-observed population). Safety analyses were based on the intention-to-treat population.

Proportions with SVR12 and two-sided 95% confidence intervals were calculated by treatment group. Outcomes for patients with missing HCV RNA data at post-treatment week 12 were imputed from the next available post-treatment visit (next-observation-carried-backward). Patients with missing HCV RNA data following virologic failure were imputed as failures in all analysis. Patients with missing data caused by death or treatment discontinuation were imputed as failures in the intention-to-treat and mITT analyses.

Results

Patients

Eighty-seven of 485 patients enrolled in the CUP had post-liver transplant HCV recurrence. In this group, 70% were male with a median age of 58 years (range: 39–75 years), 93% were white, and 69% were HCV treatment-experienced (Table 1). The most common HCV genotypes were 1b (48%), 1a (32%), and 3 (9%), and 47% had HCV RNA ≥2×10^6 IU/ml at baseline. Cirrhosis was present in 37 patients (43%), among whom 16 (43%) had decompensated disease (Child-Pugh B or C), and eight (22%) had MELD scores >15. Low platelet counts (<100×10^9/l) and low albumin (<35 g/l) were present in 27 (31%) and 13 (15%) patients, respectively. Five patients (6%) had hepatocellular carcinoma, five (6%) were coinfected with HBV, and 40 (46%) had moderate or severe renal impairment (CrCl <60 ml/min/1.73 m^2).

The median time between LT and initiation of program treatment was 3.7 years (range: 0.3–22 years). Five patients had FCH at treatment initiation, as per physician's assessment. Frequently used immunosuppressive agents included tacrolimus (72% of patients), cyclosporine (21%), and everolimus (11%); 49% received mycophenolate and 16% prednisone or prednisolone.

Treatment assignments were not randomized; 62 patients (71%) were treated with DCV + SOF and 25 (29%) with DCV + SOF + RBV. Patients treated with DCV + SOF + RBV had a higher proportion of non-genotype 1 HCV infections (24% vs. 6% with DCV + SOF), a higher proportion with prior treatment experience (76% vs. 66%), and a higher proportion with cirrhosis (52% vs. 39%). However, the proportions with decompensated cirrhosis (Child-Pugh class B or C) or MELD scores >15 were higher in DCV + SOF recipients than for DCV + SOF + RBV (50% vs. 31%, and 29% vs. 8%, respectively). None of the four Child-Pugh class C patients received RBV.

Ten (40%) of the 25 patients treated with DCV + SOF + RBV initiated therapy with the standard RBV dose (1000 or 1200 mg/day), while 15 (60%) initiated with a reduced dose (range: 200–800 mg/day). Five (20%) patients treated with DCV + SOF + RBV discontinued RBV while continuing DCV + SOF therapy. Nine patients had RBV dose reductions (six standard-dose initiations and three reduced-dose initiations).

Seventy-nine of the 87 patients (91%) who started therapy completed 24 weeks of treatment (Fig. 1). One patient died during treatment, four discontinued

Table 1. Baseline characteristics.

Parameter	DCV + SOF *n* = 62	DCV + SOF + RBV *n* = 25	All patients *N* = 87
Age, median years (range)	58 (40–75)	58 (39–74)	58 (39–75)
Male, *n* (%)	46 (74)	15 (60)	61 (70)
Body mass index, median kg/m^2 (range)*	26 (17–38)	25 (21–35)	25 (17–38)
Race, *n* (%)			
White	59 (95)	22 (88)	81 (93)
Other	3 (5)	3 (12)	6 (7)
HCV genotype, *n* (%)			
1a	21 (34)	7 (28)	28 (32)
1b	33 (53)	9 (36)	42 (48)
1 Subtype unknown	4 (6)	2 (8)	6 (7)
3	4 (6)	4 (16)	8 (9)
4	0	2 (8)	2 (2)
Unknown	0	1 (4)	1 (1)
HCV RNA			
Median $\log_{10}$ IU/ml (range)	6.3 (0–7.5)	6.2 (0–7.2)	6.2 (0–7.5)
≥2 000 000 IU/ml, *n* (%)	31 (50)	10 (40)	41 (47)
Not reported, *n* (%)	0	1 (4)	1 (1)
Cirrhosis status, *n* (%)			
Present†	24 (39)	13 (52)	37 (43)
Absent‡	32 (52)	11 (44)	43 (49)
Indeterminate	6 (10)	1 (4)	7 (8)
Child-Pugh class, *n* (%)§			
A	12 (50)	9 (69)	21 (57)
B	8 (33)	4 (31)	12 (32)
C	4 (17)	0	4 (11)
MELD score, *n* (%)§			
<10	11 (46)	7 (54)	18 (49)
10–15	6 (25)	5 (38)	11 (30)
>15	7 (29)	1 (8)	8 (22)
FCH, *n* (%)	4 (6)	1 (4)	5 (6)
Hb, median mmol/l (range)*	8 (5–12)	8 (6–11)	8 (5–12)
ALT, median IU/l (range)*	55 (9–347)	49 (14–235)	53 (9–347)
Albumin			
Median g/l (range)	41 (20–49)	41 (24–47)	41 (20–49)
<35 g/L, *n* (%)	6 (10)	7 (28)	13 (15)
Not reported, *n* (%)	12 (19)	1 (4)	13 (15)
Platelet count $\times 10^9$/l			
Median (range)	127 (40–446)	136 (30–294)	134 (30–446)
≥100, *n* (%)	42 (68)	17 (68)	59 (68)
≥50 to <100, *n* (%)	17 (27)	5 (20)	22 (25)
<50, *n* (%)	2 (3)	3 (12)	5 (6)
Not reported	1 (2)	0	1 (1)
CrCl, ml/min/1.73 m^2, *n* (%)			
≥90	2 (3)	3 (12)	5 (6)
60–89	10 (16)	12 (48)	22 (25)
30–59	27 (44)	9 (36)	36 (41)
<30§	3 (5)	1 (4)	4 (5)
Not reported	20 (32)	0	20 (23)
Prior HCV therapy, *n* (%)	41 (66)	19	60 (69)
HBV/HCV coinfection, *n* (%)¶	3 (5)	2	5 (6)
Hepatocellular carcinoma, *n* (%)	4 (6)	1	5 (6)
Time since LT, median, years (range)	4.2 (0.3–22)	2.2	3.7 (0.3–22)

Table 1. Continued.

Parameter	DCV + SOF *n* = 62	DCV + SOF + RBV *n* = 25	All patients *N* = 87
Immunosuppressive therapy, *n* (%)			
Tacrolimus	43 (69)	20 (80)	63 (72)
Cyclosporine	15 (24)	3 (12)	18 (21)
Everolimus	6 (10)	4 (16)	10 (11)
Sirolimus	2 (3)	0	2 (2)
Mycophenolate	29 (47)	14 (56)	43 (49)
Prednisone/prednisolone	11 (18)	3 (12)	14 (16)

ALT, alanine aminotransferase; CrCl, creatinine clearance; DCV, daclatasvir; FCH, fibrosing cholestatic hepatitis; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; LT, liver transplant; MELD, Model for End-Stage Liver Disease; RBV, ribavirin; SOF, sofosbuvir.

*Body mass index not reported for four patients; Hb data not reported for one patient; ALT data not reported for one patient.

†Cirrhosis diagnosed by liver biopsy (Metavir >F3, Ishak >4, or the equivalent), *n* = 2; FibroScan (>14.6 kPa), *n* = 19; or FIB-4 score (>3.25), *n* = 16.

‡Absence of cirrhosis diagnosed by liver biopsy (Metavir ≤F3, Ishak ≤4, or the equivalent), *n* = 13 (≤F2, *n* = 10; F3, *n* = 3); FibroScan, *n* = 25 (range: 4.4–9.6); or FIB-4 score, *n* = 5 (range: 0.6–1.31).

§Percentages are based on patients with cirrhosis.

¶Patients with CrCl <30 ml/min/1.73 m^2 (range: 24–26.8 ml/min/1.73 m^2) were exceptionally allowed in the program following individual patient risk–benefit assessment to permit compassionate use access.

treatment due to AEs, and two discontinued as per medical decision or patient request. The remaining patient discontinued treatment after receiving DCV + SOF for 13 weeks; in this patient, DCV was added to ongoing SOF + RBV therapy and treatment was stopped after completion of a combined 24 weeks of SOF.

Two patients, one per treatment group, were excluded from the mITT population: one (HCV genotype 1, treatment-experienced, Child-Pugh A, MELD score 13) chose to discontinue treatment after 16 weeks and was subsequently lost to follow-up, and one (HCV genotype 1, treatment-experienced, cirrhosis status indeterminate) was lost to follow-up after 24 weeks of treatment. For both patients, HCV RNA was <LLOQ at their last available visit.

Efficacy outcomes

In the primary mITT analysis, SVR12 was achieved by 94% of patients overall (80/85): 95% (58/61) with DCV + SOF and 92% (22/24) with DCV + SOF + RBV (Fig. 2). No virologic failures were observed. There were five nonvirologic failures comprising four patients with decompensated cirrhosis who died during (*n* = 1) or after (*n* = 3) treatment from causes related to advanced liver disease, and one patient lost to follow-up after discontinuing treatment due to acute kidney injury with lactic acidosis. After excluding nonvirologic failures (as-observed analysis), SVR12 was 100% (80/80). In the intention-to-treat analysis (all treated patients), SVR12 was 94% (58/62) with DCV + SOF and 88% (22/25) with DCV + SOF + RBV.

High SVR12 was observed across baseline subgroups. Differences between subgroups were driven by nonvirologic failures, mostly associated with progression or complications of advanced liver disease (Fig. 3). In the mITT analysis, subgroups with comparatively lower SVR12 rates were primarily those associated with advanced liver disease, such as Child-Pugh class B or C, MELD scores >15, and low platelet counts. When nonvirologic failures were excluded in the as-observed analysis, the SVR12 rate was 100%, demonstrating consistent virologic responses across the broad range of virologic and disease characteristics represented by patients enrolled in the program. Although patient numbers were small in some categories, SVR12 in the as-observed analysis was achieved by 100% of patients, regardless of the severity of liver disease (including patients with decompensated disease or MELD scores as high as 29), extent of renal impairment (including severe renal insufficiency), HCV genotype (genotypes 1, 3, and 4), baseline HCV RNA level, prior HCV therapy, or presence of HBV/HCV coinfection.

Five patients were reported as having FCH at treatment initiation, as per physician's assessment. Of them, four received treatment with DCV + SOF for 24 weeks;

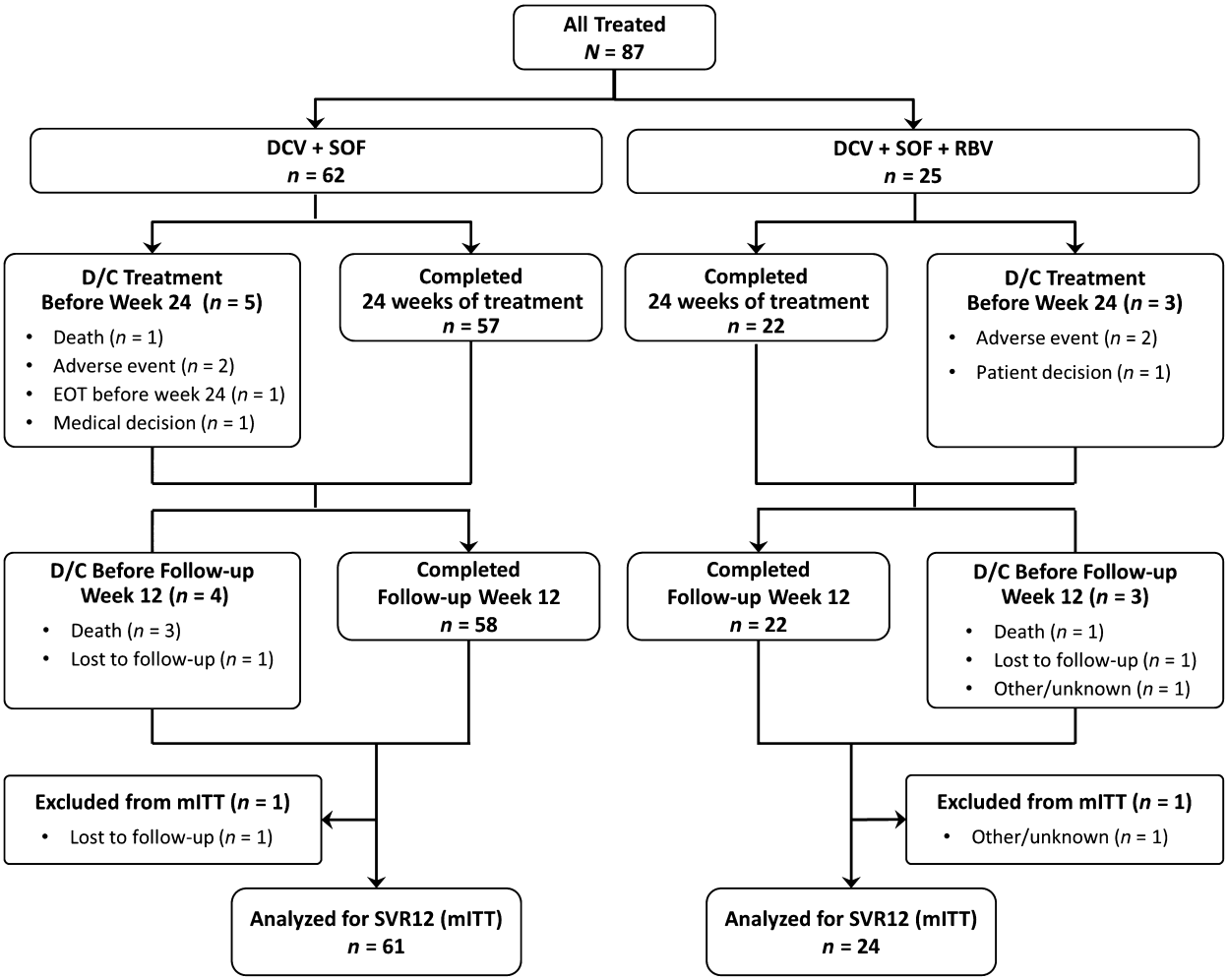

Figure 1 Patient disposition. Patient disposition by treatment group and reasons for noncompletion of 24 weeks of therapy and discontinuation of follow-up are shown. Deaths after post-treatment week 12 ($n = 2$) are not shown. Patients who discontinued treatment prematurely could remain in follow-up. Discontinuations before follow-up week 12 include patients who stopped treatment prematurely and did not continue follow-up (on-treatment death, lost to follow-up) and those who discontinued after completing treatment. In the DCV + SOF + RBV group, the mITT population includes one patient lost to follow-up; patient discontinued treatment due to adverse events and was imputed as a failure. D/C, discontinuation; DCV, daclatasvir; EOT, end of treatment; mITT, modified intention-to-treat; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at post-treatment week 12.

the remaining patient, initially treated with DCV + SOF + RBV, discontinued RBV on day 29 due to anemia but continued DCV + SOF for 24 weeks. Virologic responses were consistent with those of the overall population; HCV RNA was ≤LLOQ in all five patients by week 12 and remained undetectable until end of treatment. Four of the five patients achieved SVR12 and one died after completing treatment. The patient who died (71-year-old Child-Pugh B male with genotype 1b infection) showed an early improvement in liver function parameters, but alkaline phosphatase and gamma-glutamyl transpeptidase levels increased sharply after week 12, reaching levels >10× the upper limit of their respective reference ranges by week 24. This patient was anemic, thrombocytopenic, and borderline neutropenic before and during treatment, and died of abdominal abscess and pneumonia 16 weeks post-treatment.

Changes in liver function

Median platelet counts and levels of alanine aminotransferase (ALT), total bilirubin, and albumin showed improvements between baseline and post-treatment week 12. ALT levels decreased by a median 28 IU/l [interquartile range (IQR) 47], total bilirubin decreased by a median 2.9 μmol/l (IQR 7.7), albumin increased by a median 2.0 g/l (IQR 4.0), and platelet counts increased by a median 14 × 10^9/l (IQR 43; Figure S1). Among 29

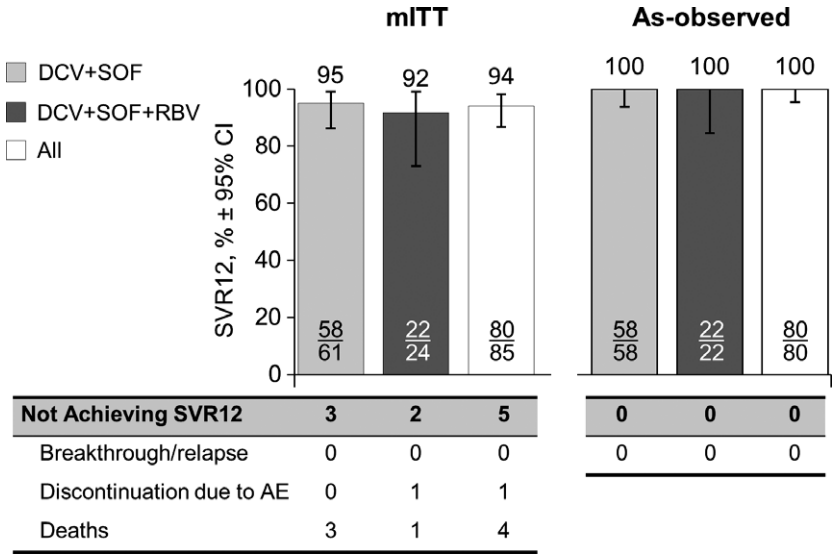

Figure 2 Efficacy outcomes. SVR12 rates and 95% CIs are shown by treatment group for the mITT and as-observed populations. Patients who did not achieve SVR12 are indicated by category of treatment failure. AE, adverse event; CI, confidence interval; DCV, daclatasvir; mITT, modified intention-to-treat; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at post-treatment week 12.

patients with paired MELD data at baseline and post-treatment week 12, 15 (52%) showed improvements. In all 10 Child-Pugh class B or C patients, most of whom had a baseline MELD score ≥15, scores decreased by 210 points (Fig. 4). Among patients with Child-Pugh class B ($n = 6$) or C ($n = 1$) cirrhosis who had paired Child-Pugh data at baseline and post-treatment week 24, six showed an improvement in score with a shift to Child-Pugh class A; the Child-Pugh class of one patient with Child-Pugh class B cirrhosis remained unchanged at post-treatment week 24.

Safety

Five patients discontinued treatment prematurely due to AEs, including one who died during the treatment period (Table 2). AEs leading to discontinuation of DCV + SOF included seborrheic dermatitis (considered treatment-related) and sepsis (considered unrelated). Events leading to discontinuation of DCV + SOF + RBV included spontaneous bacterial peritonitis with hepatic decompensation (considered unrelated) and acute kidney injury with lactic acidosis (considered treatment-related).

Sixteen patients experienced serious AEs during treatment: 10 receiving DCV + SOF (16%) and six receiving DCV + SOF + RBV (24%). Most serious AEs were related to complications of advanced liver disease, infections, or renal disease, and three were reported as treatment-related: two cases (one per treatment group) of renal impairment (one with lactic acidosis), and one case of acute pancreatitis associated with *Clostridium difficile* colitis, acute kidney injury, and pancytopenia (DCV + SOF + RBV). Serious AEs were slightly more frequent in patients with cirrhosis (19% vs. 14% in noncirrhotic patients), particularly in cirrhotic patients with more advanced liver disease. A full list of serious AEs during treatment and the follow-up period is provided in Table S1.

In total, six patients died during the program, consisting of one on-treatment death and five additional deaths during the follow-up period, before ($n = 3$) or after ($n = 2$) post-treatment week 12. All but one of the patients who died were cirrhotic (one with FCH), and most were Child-Pugh class B or C with a MELD score >10 (including two with scores >15); the remaining patient was reported as having hepatocellular carcinoma and died due to anal carcinoma after achieving SVR12. One patient (genotype 1b, treatment-experienced, Child-Pugh B, MELD score 29) died during the first week of treatment due to sepsis (considered unrelated to therapy). Causes of death during the follow-up period included abdominal abscess/pneumonia in a patient with FCH, sepsis due to *Candida glabrata*, spontaneous bacterial peritonitis with hepatic encephalopathy, anal carcinoma, and cardiogenic/septic shock. The individual characteristics of patients who died are provided in Table S2.

The most common AEs of any grade were anemia and nonspecific events such as fatigue, diarrhea, dyspnea, and sleep disorders (Table 2). Anemia was more frequently reported in those patients who received treatment with RBV [nine patients (36%) versus two patients (3%) without RBV], and in most cases was associated with RBV dose reduction ($n = 3$) or discontinuation ($n = 5$). Three additional patients reduced RBV dose for other reasons; all showed decreased CrCl levels. No cases of HBV reactivation were reported.

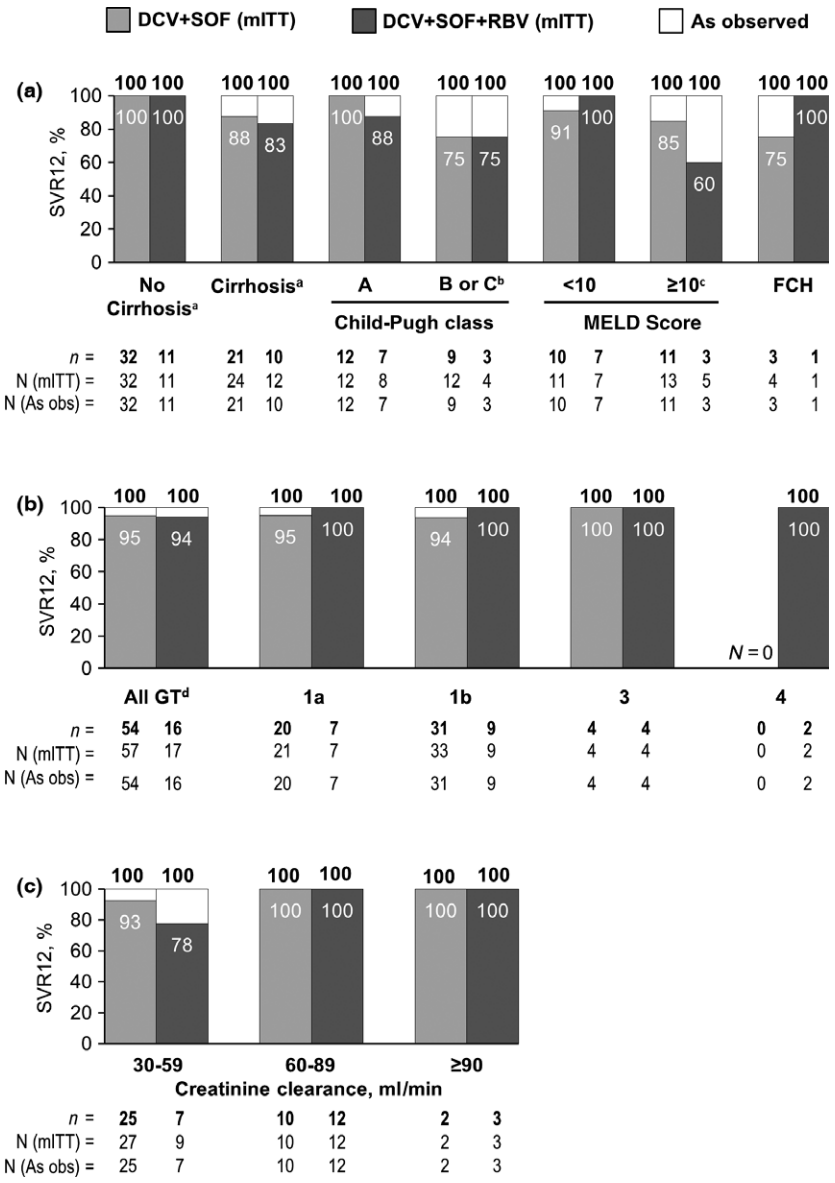

Figure 3 SVR12 (mITT and as-observed) by baseline subgroup; (a) liver disease status; (b) HCV genotype; (c) creatinine clearance. SVR12 rates in patients stratified are shown by baseline subgroup; (a) liver disease status; (b) HCV genotype; (c) creatinine clearance (mITT and as-observed). AE, adverse event; CrCl, creatinine clearance; DCV, daclatasvir; FCH, fibrosing cholestatic hepatitis; GT, genotype; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; mITT, modified intention-to-treat; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained virologic response at post-treatment week 12. Panel b excludes one patient of unknown genotype (discontinuation due to AE) and panel C excludes three patients with CrCl <30 ml/min (all achieved SVR12). [a]Excludes six patients with indeterminate cirrhosis status (all SVR12). [b]Four patients were Child-Pugh class C (three achieved SVR12 and one died during follow-up). [c]Six patients had MELD scores of 16–20 (four achieved SVR12, one died, one discontinued due to an AE), one patient had a MELD score between 21 and 25 (achieved SVR12), and one patient had a MELD score >25 (died). [d]Includes four patients of unknown or other genotype 1 subtype (three achieved SVR12, one died).

Overall, treatment-emergent grade 3 or 4 laboratory abnormalities were infrequent, with decreases in hemoglobin levels the most common abnormality observed (12%). Four patients showed grade 3 or 4 increases in creatinine levels; however, overall median CrCl levels remained stable while on treatment (Fig. 5). Three patients reduced SOF dose (200 mg) due to renal insufficiency; all had CrCl <30 ml/min/1.73 m^2 at baseline.

There were no reports of graft rejection. Changes to immunosuppressive drug dosages during treatment were reported in 14, 2 and 2 patients treated with tacrolimus, cyclosporine, and everolimus, respectively. Most adjustments were modest and none were reported as caused by drug interactions with the treatment regimens.

Discussion

Patients with post-transplant HCV recurrence can lose the benefits of liver transplantation rapidly due to accelerated progression of liver disease and/or graft failure [4,10]. Therefore, optimizing HCV therapy in this population remains an important objective. In our cohort—which includes transplanted patients with decompensated cirrhosis and other complications—94% of patients treated for 24 weeks with DCV + SOF ± RBV achieved SVR12, with no virologic failures (100% SVR12 after excluding nonvirologic failures). The regimen was well tolerated regardless of liver disease severity, and no

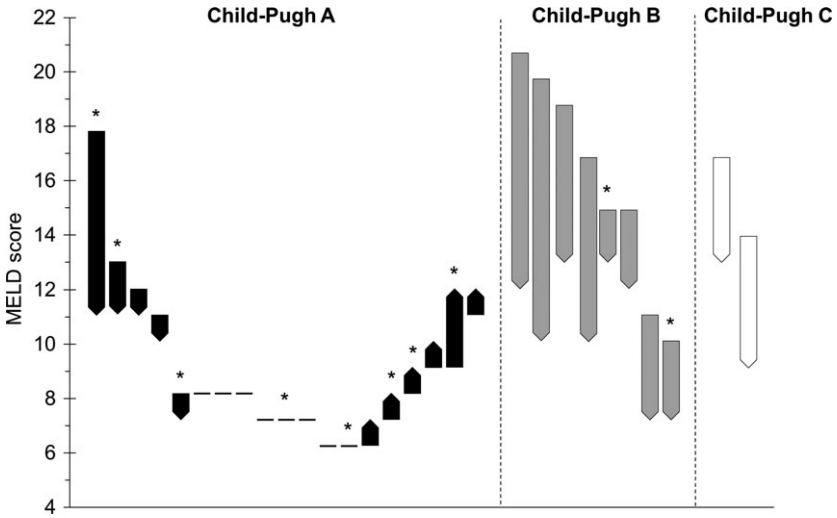

Figure 4 Changes in MELD scores from baseline to post-treatment week 12 by Child-Pugh class. Data show the magnitude and direction of change for individual patients from baseline to post-treatment week 12; the asterisks indicate patients who received additional ribavirin. MELD, Model for End-Stage Liver Disease.

clinically significant drug–drug interactions were observed.

The 94% overall rate of SVR12 in liver transplant patients is consistent with the 91% SVR12 observed in the entire CUP cohort of 485 patients [23], and with other real-world analyses of DCV + SOF ± RBV in post-transplant recurrence and/or advanced liver disease [20–22]. Our findings are also comparable to the 94% SVR12 rate achieved with DCV + SOF + RBV for 12 weeks in patients with post-liver transplant HCV recurrence in a phase 3 clinical trial (ALLY-1) [13], despite the inclusion of patients with a broader range of liver disease severity and other medical complications such as FCH or renal insufficiency. In our cohort, 43% of patients had cirrhosis, among whom 43% had decompensated (Child-Pugh B or C) disease, 22% had a MELD score >15, and 31% had low platelet counts. However, none of these indicators of advanced liver disease appeared to adversely affect virologic response, as indicated by the absence of virologic failures in this analysis. By comparison, earlier studies evaluating combinations of interferon-free regimens in the post-transplant setting—mainly in genotype 1-infected patients—have shown lower response rates in patients with decompensated cirrhosis [8]. Notably, although most patients in our cohort had HCV genotype 1a or 1b infection, other genotypes such as genotypes 3 and 4 were also represented.

Fibrosing cholestatic hepatitis is typically associated with rapid progression of cholestasis and fibrosis and is often fatal. Five patients with FCH were enrolled in the program; four achieved SVR12 and one died after completing treatment. In the four surviving patients, improvements in disease parameters were observed in parallel with virologic responses. This observation, although limited to a small number of patients, is consistent with previous reports [8,25,26], suggesting that DCV + SOF ± RBV regimens may be of benefit in patients with FCH due to the mortality rate in transplant recipients with this condition.

Defining the role of RBV in the management of HCV remains an open question. In the post-transplant setting, not using RBV could potentially improve regimen tolerability, especially in the context of advanced liver disease or renal impairment. Previous results suggest that an incremental benefit of including RBV without adding toxicity is most evident with shorter treatment durations but could be less relevant when treatment is extended to 24 weeks [13,22,27,28]. In our cohort, the potential effect of adding RBV cannot be fully assessed due to a nonrandomized treatment assignment and the limited number of patients who received RBV. However, the absence of virologic failures in either group suggests that RBV might not be necessary when treatment with DCV + SOF is extended to 24 weeks, offering a potential therapeutic option for those patients who do not tolerate RBV. Similarly, the results from the ANRS CULPIT cohort questioned the benefit of additional RBV in terms of efficacy outcomes, even for shorter treatment durations, when SVR12 rates of 100% and 97% were demonstrated in transplant recipients with any stage fibrosis who received DCV + SOF without RBV for 12 or 24 weeks, respectively [19]. Of note, nearly all patients in this post-transplant cohort, as well as in our cohort, received 24 weeks of therapy, which complicates the interpretation of data from patients who received treatment for 12 weeks due to the limited number of patients. However, taken collectively recent data

Table 2. On-treatment safety summary.

Patients, *n* (%)	DCV + SOF *n* = 62	DCV + SOF + RBV *n* = 25	All patients *N* = 87
Total AEs	34 (55)	17 (68)	51 (59)
Serious AEs	10 (16)	6 (24)	16 (18)
Treatment-related serious AEs*	1 (2)	2 (8)	3 (3)
AEs leading to discontinuation†	3 (5)	2 (8)	5 (6)
Death‡	1 (2)	0	1 (1)
Graft rejection events	0	0	0
RBV discontinued	–	5 (20)	5 (6)
RBV dose reduced	–	6 (24)	6 (7)
AEs (any grade) in ≥5% of all patients			
Anemia	2 (3)	9 (36)	11 (13)
Fatigue	7 (11)	1 (4)	8 (9)
Diarrhea	2 (3)	2 (8)	4 (5)
Dyspnea	2 (3)	2 (8)	4 (5)
Sleep disorders	2 (3)	2 (8)	4 (5)
Treatment-emergent grade 3 or 4 laboratory abnormalities, *n/N* (%)			
Hemoglobin <90 g/l	5/61 (8)	5/24 (21)	10/85 (12)
ALT >5 × ULN	1/61 (2)	0/24	1/85 (1)
AST >5 × ULN	1/60 (2)	0/24	1/84 (1)
Total bilirubin >2.5 × ULN	1/61 (2)	1/24 (4)	2/85 (2)
Creatinine >1.9 × ULN	4/61 (7)	0/24	4/85 (5)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCV, daclatasvir; RBV, ribavirin; SOF, sofosbuvir; ULN, upper limit of normal.

On-treatment safety includes events occurring during the treatment period and the first 7 days after stopping treatment.

Five additional deaths occurred during follow-up (before or after post-treatment week 12): abdominal abscess/pneumonia (*n* = 1); sepsis due to *Candida glabrata* (*n* = 1); spontaneous bacterial peritonitis with encephalopathy (*n* = 1); cardiogenic/septic shock (*n* = 1); and anal carcinoma (*n* = 1).

*Reported as treatment-related: renal impairment (*n* = 1); pancreatitis with *Clostridium difficile* colitis and pancytopenia (*n* = 1); fluid overload with lactic acidosis (*n* = 1).

†Reported as treatment-related: fluid overload with lactic acidosis (*n* = 1); seborrheic dermatitis (*n* = 1); dyspnea (*n* = 1).

‡On-treatment death due to sepsis (considered non-treatment-related).

suggest that the addition of RBV to a regimen of DCV + SOF may not be a mandatory requirement in the context of achieving SVR in liver transplant recipients, although further investigations are required to fully evaluate the contribution of RBV to efficacy outcomes.

The safety profile of the treatment regimen was favorable and consistent with that observed in clinical trials [13,28]. There were no events of graft rejection and no evidence of novel safety events attributable to the treatment regimen, even in patients with advanced liver disease or concomitant medical conditions. Consistent with other studies in patients with advanced liver disease, most serious AEs, treatment discontinuations, and deaths were attributable to continued disease progression and were more common in patients with Child-Pugh class B or C cirrhosis at program entry [8,14]. Safety outcomes were similar with or without RBV, except for higher frequencies of reduced hemoglobin and anemia in patients receiving RBV.

Biochemical indicators of liver function showed incremental improvements after initiation of therapy, consistent with previous studies in patients with advanced disease [8,13,14]. Similarly, MELD scores improved by post-treatment week 12 in all patients with available data who had scores ≥10 at baseline. Together, these results confirm that HCV clearance generally engenders progressive improvement of liver disease. However, some improvements are modest and gradual and patients with advanced disease remain at high risk of serious adverse outcomes and death even after viral clearance, emphasizing the need to start treatment at early stages of HCV recurrence after liver transplantation, and to carefully evaluate the benefit of treatment in the more advanced stages.

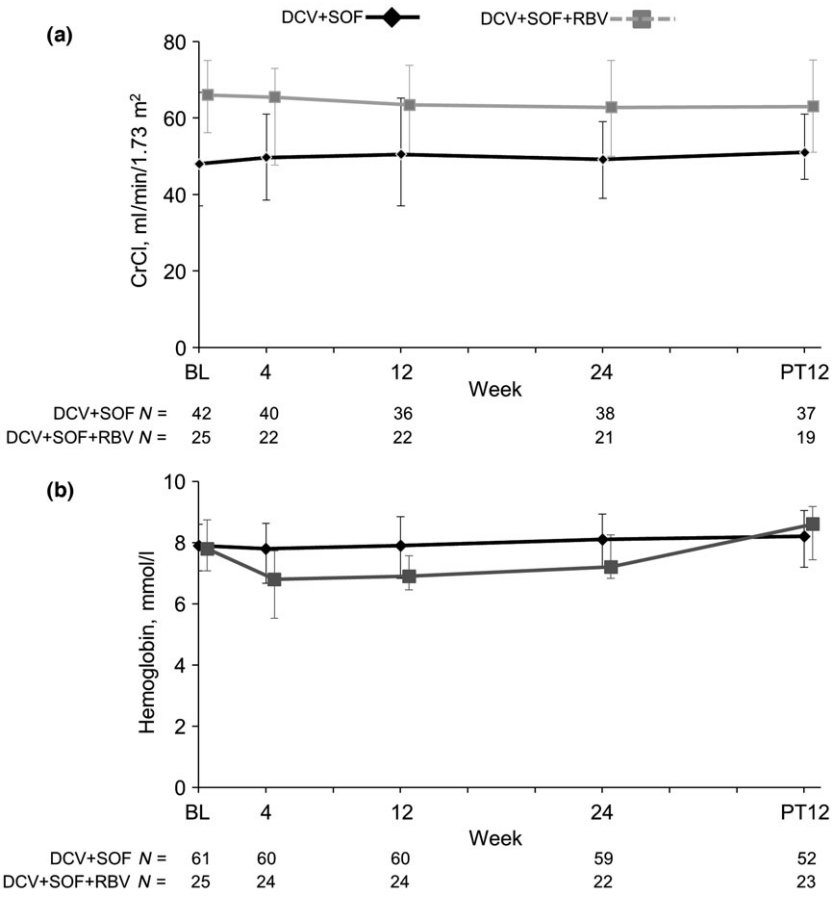

Figure 5 Changes in (a) creatinine clearance, and (b) hemoglobin from baseline to post-treatment week 12. Data indicate medians + interquartile range (25th-75th percentiles). BL, baseline; CrCl, creatinine clearance; DCV, daclatasvir; PT12, post-treatment week 12; RBV, ribavirin; SOF, sofosbuvir.

Renal function has been identified as a major prognostic factor following liver transplantation. In our cohort, renal impairment had no evident effect on SVR12 rates. Overall, HCV therapy had minimal impact on CrCl levels between baseline and post-treatment week 12 for either treatment group. Comparable findings have been observed previously with recipients of DCV + SOF in the pre- and postrenal transplant setting [29]. However, clinical data regarding use of DCV + SOF in patients with severe renal impairment are limited and further decreases in CrCl requiring SOF dose adjustments have been observed, suggesting that close monitoring of renal function in these patients is warranted [30].

Unlike some direct-acting antiviral regimens, which contain HCV NS3 inhibitors or ritonavir that have inhibitory effects on cytochrome P450 3A4 and may subsequently be prone to drug–drug interactions with cyclosporine and tacrolimus [31], neither DCV nor SOF has clinically important drug–drug interactions with the immunosuppressive agents used most commonly in liver transplantation [15,18,19]. Thus, the DCV + SOF regimen was compatible with the range of immunosuppressive regimens used in this cohort. Some patients required generally modest dosage adjustments of immunosuppressive agents during treatment, most likely reflecting changes in drug metabolism due to improvements in hepatic function after viral clearance, as previously reported [8,20,32].

Several limitations should be considered in the interpretation of these results, including the relatively small numbers in some subgroups and incomplete collection of immunosuppressant pharmacokinetic trough concentrations. Treatment assignment was not randomized, and the contribution of RBV to efficacy outcomes cannot be fully evaluated. However, the absence of virologic failures suggests that RBV may not be necessary in some patients when treatment is extended to 24 weeks. Laboratory data were compiled from tests run at each center, and inconsistencies may have resulted from differences in the assay technologies that were used. As is common with real-world cohorts, safety events may have been underreported due to the limited requirements for data capture; consequently, the potential contribution of drug-related toxicity to disease progression and deaths cannot be fully assessed. Despite these considerations,

this cohort comprises a unique population that has contributed valuable real-world data in a population usually underrepresented in clinical trials, and for whom data are scarce.

In summary, this program provides real-world evidence that the DCV + SOF combination, administered for 24 weeks with or without RBV to post-transplant patients with HCV recurrence, was well tolerated and demonstrated high response rates with no virologic failures across a diverse spectrum of genotypes and severity of liver disease. Our results provide further encouraging real-world evidence in a difficult-to-cure population for whom limited therapeutic options are available.

Authorship

MJJE: involved in program design, data analysis and interpretation and drafting of the manuscript. KH, TW, US, HH, HK, TB, PF, MPR, AI and SZ: involved in data acquisition and interpretation. YZ: involved in data analysis and interpretation. All authors: critically reviewed and revised the manuscript for content and approved the final draft for publication.

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Conflicts of interest

KH—grants: Astellas, Biotest, Chiesi, and Novartis; consultant/speaker for AbbVie, Biotest, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Novartis, and Roche. TMW—consultant: Novartis, Janssen, Gilead, AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb. US—speaker: Bristol-Myers Squibb, Janssen, MSD, and AbbVie. HH—consultant: Janssen, MSD, Gilead, AbbVie, Bristol-Myers Squibb. HK—grants: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen-Cilag, MSD; consultant: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Hexal, Janssen-Cilag, MSD, ViiV Healthcare; speaking and teaching: AbbVie, Bristol-Myers Squibb, Gilead, Janssen-Cilag, MSD, Roche. TB—grant: Gilead, Bristol-Myers Squibb, Roche, Tibotec, Vertex, Janssen, Merck, Boehringer Ingelheim, Novartis, AbbVie; consultant: Gilead, Bristol-Myers Squibb, Roche, Tibotec, Vertex, Janssen, Novartis, Abbott, Merck, AbbVie; speaking and teaching: Gilead, Bristol-Myers Squibb, Roche, Tibotec, Vertex, Janssen, Merck, Novartis, Bayer, AbbVie. PF—consultant: Idenix, Gilead, Merck, Janssen, Salix, AbbVie, Bristol-Myers Squibb; patent held/filed: Rottapharm| Madaus; speaking and teaching: Gilead, Roche. MP-R—grant: Bayer, Roche, Gilead, Merck, AbbVie; consultant: Bayer, Boehringer Ingelheim, Jennerex, Eli Lilly, AbbVie; advisory committee or review panel: Bayer, Gilead, Janssen, Bristol-Myers Squibb, AbbVie; speaking and teaching: Bayer, Roche, Gilead, Merck, Eli Lilly, AbbVie. AI— no conflicts: YZ—employee: Bristol-Myers Squibb. MJJE—employee: Bristol-Myers Squibb. SZ—consultant: AbbVie, Bristol-Myers Squibb, Gilead, Merck, Janssen.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Changes in disease parameters from baseline to post-treatment week 12.

Table S1. Serious adverse events during the on-treatment and follow-up period and adverse events leading to discontinuation by liver disease stage.

Table S2. Characteristics of patients who died.

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