

Sofosbuvir-Daclatasvir Is Suboptimal in Patients with Genotype 2 Chronic Hepatitis C Infection: Real-life Experience from the HEPATHER ANRS CO22 Cohort

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Sofosbuvir-based regimens are suboptimal in patients with genotype 2 chronic hepatitis C infection: real-life experience from the HEPATHER ANRS CO22 cohort

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Short title: Real-life sofosbuvir data in G2 HCV patients

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Disclosures

Dr V de Lédinghen has received consulting and lecturing fees from Gilead, AbbVie, Echosens, Intercept Pharma, SuperSonic Imagine, Indivior, Spimaco, Pfizer.

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Structured summary

Background

Sofosbuvir plus daclatasvir with or without ribavirin has demonstrated a high efficacy and an acceptable safety profile in clinical trials of patients infected with genotype 2 hepatitis C virus (HCV), however, there are currently no real-world data available for this regimen.

Aims

To evaluate the real-life safety and efficacy of sofosbuvir/daclatasvir with or without ribavirin in genotype 2 HCV patients in the French cohort ANRS CO22 HEPATHER (NCT01953458).

Methods

In this ongoing, national, multicentre, prospective, observational study, we observed patients with HCV genotype 2 infection who initiated treatment with sofosbuvir (400 mg/d) plus daclatasvir with or without ribavirin (1–1.2 g/d). Patients were divided into two treatment groups: sofosbuvir/daclatasvir with or without ribavirin (12 weeks/24 weeks). The primary endpoint was a sustained virological response at week 12 following the end of therapy.

Results

Overall, 88% and 91% of patients achieved a sustained virological response following 12- and 24 weeks of treatment with sofosbuvir/daclatasvir with or without ribavirin, respectively. The most common adverse events were asthenia (29%), headache (15%) and fatigue (20%) **and ribavirin addition was associated with a higher rate of adverse events and treatment discontinuation.**

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Conclusions

Sofosbuvir/daclatasvir with or without ribavirin was associated with lower rates of sustained virological response in the real-life setting compared with the clinical setting, and demonstrated suboptimal efficacy for the treatment of patients with genotype 2 chronic HCV.

Keywords

Hepatitis C, genotype 2, direct-acting antivirals, HEPATHER, real-world, sofosbuvir, daclatasvir

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Introduction

Direct-acting antiviral agents (DAAs) have transformed the treatment of hepatitis C virus (HCV), increasing sustained virologic response (SVR) rates with the associated reduction of HCV-related complications such as liver failure, hepatocellular carcinoma and liver-related death (1). DAA-based combinations are now recommended by the European Association for the Study of the Liver (EASL) for the treatment of chronic infection with all HCV genotypes (2). Genotype 2 accounts for approximately 8% of patients with chronic HCV in Europe, and approximately 13–15% of all HCV infections in the United States. Previous studies have shown 11% of patients with HCV in France are infected with genotype 2 (3). Genotype 2 infection has, historically, been 'easy-to-treat' due to favourable SVR rates of about 80% with the treatment of pegylated interferon (PegIFN) and ribavirin (RBV) (4). Now, due to the introduction of DAAs, SVR rates for patients with genotype 2 have increased to >95% (5). Today, several DAA combinations are available for the treatment of patients infected with genotype 2 (2) (1). Sofosbuvir (NS5B inhibitor) in combination with daclatasvir (NS5A inhibitor) was recommended in the EASL guidelines 2018 (2) and remains recommended as an alternative regimen by the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA). This combination has demonstrated a high efficacy in patients with HCV genotype 2, with previous clinical trials reporting SVR rates of up to 97%(6, 7)(1, 2) 12 weeks after treatment (SVR12), including patients co-infected with human Immunodeficiency virus (HIV) (7) (6). Previous reports have also indicated that this combination is well tolerated in patients with genotype 2 infection; most common adverse events were fatigue, nausea, and headache, and no patients discontinued treatment due to adverse events (7) (8).

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Real-world data of DAAs in patients with genotype 2 chronic infection are limited; however, available data for DAAs appear to show similar SVR rates in the real-world setting versus the clinical trial setting. Sofosbuvir plus ribavirin has shown almost the same SVR12 rates in both the clinical and real-life settings (91% versus 94%, respectively, in patients without cirrhosis) (5). Real-world data has shown sofosbuvir/velpatasvir with or without ribavirin in genotype 2 patients matches the clinical setting, with SVR rates reaching ≥95% (9) (10). Only a few real-world studies have been published with glecaprevir/pibrentasvir (11) (12) and currently, there are few published studies that have examined sofosbuvir with daclatasvir in in the real-life setting. Since the generic sofosbuvir/daclatasvir combination remains highly prescribed in low income countries, it seems relevant to report our real world results.

The French ANRS CO22 HEPATHER is a large multicentre study aiming to identify prognosis factors, including response to treatment, in patients infected with hepatitis B virus (HBV) and HCV in a real-life setting. The objective of the current prospective study was to examine the real-life efficacy and safety of the combination of sofosbuvir plus daclatasvir with or without ribavirin in HCV genotype 2-infected patients within the French ANRS CO22 HEPATHER cohort.

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Patients and Methods

Study design and participants

ANRS CO22 HEPATHER cohort (NCT01953458) is an ongoing, national, multicentre, prospective, observational study taking place across 32 investigator sites in France. This study aims to obtain real-world data on the efficacy and safety of hepatitis treatments in patients treated in 'real-life'. The study aimed to include a large population of approximately 25,000 patients (15,000 patients with HCV, 10,000 patients with HBV; of all genotypes), with a long-term follow-up of 7 or 8 years. Patients were recruited by their respective participating centre. Details of the cohort have been previously published (13).

All patients with HCV genotype 2 infection who initiated treatment with either sofosbuvir (SOF) plus ribavirin (RBV, 0.2 – 1.2 g/d), or a combination of SOF plus daclatasvir (DCV) with or without RBV (0.2 – 1.2 g/d) were included in this analysis. Patients were divided into four treatment groups: SOF/RBV (12 weeks), SOF/RBV (24 weeks), SOF/DCV with or without RBV (12 weeks) and SOF/DCV with or without RBV (24 weeks) but only results of the SOF/DCV combination should be detailed. Genotype and subtype were determined by means of sequencing of the non-structural (NS) 5B region of the HCV genome followed by phylogenetic analysis. Analysis of NS5A and NS5B resistance-associated substitutions (RASs) at baseline and at the time of failure was performed in patients treated with the DCV regimen by means of population sequencing (sensitivity of the Sanger method: 20–30%). Cirrhosis was defined by concordant reports of either a platelet count < 150 G/L or a prothrombin time < 70% or the results of liver biopsy, a fibrotest result > 0.75, a liver stiffness (FibroScan) result greater than 12.5 KPa, a fibrometer result >0.98 , a hepascore result >0.84, performed less than 1 year before and up to 3 months after inclusion. Obesity

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was defined by a BMI ≥ 30 kg/m^2. Due to the observational nature of the study, not all these data were available.

Outcomes

In this report, we focus on the primary endpoint of SVR at 12 weeks (SVR12) defined by the undetectability of HCV RNA 12 weeks after the last treatment intake. Secondary endpoints include the undetectability of HCV RNA, 4 and 24 weeks after last treatment intake (SVR4 and SVR24, respectively), resistance analysis, premature treatment discontinuations, and adverse events.

Statistical analyses

Descriptive analyses, including means, frequencies and percentages (with 95% confidence intervals [CIs] for SVR12) were used to summarise the data. A univariable analysis was performed to verify the association between SVR12 and treatment duration, patient demographics/clinical characteristics and whether the regimen contained DCV. A multivariable analysis was also performed to examine any potential relationships between SVR12 and treatment duration, gender, obesity, and presence/absence of DCV.

Fisher's exact tests and Cochran–Mantel–Haenszel statistics (stratified by: 12 versus 24 weeks, and regimen with RBV versus regimen without RBV) were used to compare treatment discontinuations and adverse events. A level of significance (α) of 5% was set for all analyses. Collected data were stratified based on presence/absence of cirrhosis. Most analyses were performed considering all patients included in the study as a single group. The analyses were divided into SOF/DCV with or without RBV (12 weeks or 24 weeks), for analysis of SVR type association, for description of treatment outcomes, and description of the most common adverse events.

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Results

Patient population

Between 6 August 2012 and 31 October 2016, 12,101 patients infected with chronic HCV were enrolled in the HEPATHER cohort, including 737 (6.1%) patients infected with HCV genotype 2. By 31 October 2016, 304 patients with genotype 2 in this cohort had started either a SOF/RBV (n=233) or a SOF/DCV (n=45) with or without RBV combination regimen. Overall, 278/304 (91.4%) patients completed treatment, with premature treatment discontinuation having occurred in 5% (14/278: 7 drug intolerance, 3 anaemia, 2 kidney failures, 1 asthma, 2 patient's request) of patients (Figure 1).

Across the four groups, the mean age of patients ranged from 61.1 – 67.1 years; 103 patients (37.1%) had cirrhosis, and 150 patients (54.0%) were treatment naïve (Table 1). Baseline characteristics were similar between treatment groups, with the exception of the following: a larger proportion of treatment-naïve patients in the groups receiving 12 weeks (n= 34) compared with 24 weeks of therapy (n = 11), and a larger proportion of patients with cirrhosis, lower haemoglobin levels and lower platelet counts in the groups receiving 24 weeks of therapy versus 12 weeks. HCV subtype distribution is detailed in Supplementary appendix 1.

Efficacy

Overall, 88% (30/34) of patients achieved an SVR12 following 12 weeks of SOF/DCV with or without ribavirin. In those patients treated for 24 weeks, the SVR12 was similar (91%; [10/11]). **Treatment failed in five patients receiving SOF/DCV without RBV.** Known relapses occurred 12 weeks following the end of treatment in two patients treated with SOF/DCV

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(12-week duration) without RBV. No significant difference in SVR12 was observed by univariable analysis between the 12 and 24-week treatment durations (p=0.9999, Table 3).

No significant difference was observed in SVR12 rates for treatment-naïve patients versus treatment-experienced patients across all treatment groups (p=0.0753). Whether or not the regimen contained daclatasvir also showed no significant difference (p=0.9999, Table 3).

In patients without cirrhosis, the SVR12 in patients treated with SOF/DCV with or without RBV was 94% (15/16) following 12 weeks of treatment; for those treated for 24 weeks, the SVR12 was 100% (4/4). No significant difference was observed between treatment groups (p=0.9999).

In patients with cirrhosis the SVR12 was 80% (12/15) when treated with SOF/DCV with or without RBV for 12 weeks; for those patients treated for 24 weeks with this regimen, the SVR12 rate was 86% (6/7). No significant difference was observed between treatment groups (p=0.9712).

Sex and obesity significantly affected SVR12 rates across all treatment groups when examined by multivariable analysis. Female patients achieved higher SVR12 rates across all treatment groups than males (92% vs 83%, p=0.0275), and patients with obesity had lower SVR12 rates across all treatment groups than those without (80% vs 90%, p=0.0481). Other patient variables demonstrated no impact on SVR12 (detailed in Table 4).

Resistance

Resistance analysis at baseline was conducted for 42 patients who received a DCV regimen and is detailed in Supplementary appendix 2. The resistance profile of the five patients in

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whom treatment with the SOF/DCV with or without RBV regimen failed is detailed in Supplementary appendix 3.

Safety and tolerability

The highest frequency of adverse events was observed in patients treated with RBV-including regimen with significant differences noted between treatment groups for any adverse event ($p<0.05$). The most common adverse events (≥10% in any subgroup) were asthenia (20%), and headache (13%). Adverse events ≥ grade 3 occurred in 12% (4/12) of patients treated with SOF/DCV with or without RBV for 12 weeks, and 18% (2/18) of patients treated with this regimen for 24 weeks. **Anemia, intolerance and treatment discontinuations were more frequent in the RBV group ($p<0.05$).**

Nine percent (3/34) of patients experienced a serious adverse event following treatment with SOF/DCV with or without ribavirin for 12 weeks; similarly, 9% (1/11) patients treated for 24 weeks experienced a serious adverse event. No significant difference was observed between treatment groups regarding serious adverse events. No treatment-related deaths were reported for any of the treatment groups.

Discussion

In this real-world analysis, we examined the efficacy and safety of the DAA combination SOF plus DCV with or without RBV in patients with genotype 2 HCV from the French ANRS CO22 HEPATHER cohort. SOF and DCV with or without RBV has shown a high efficacy and acceptable safety profile in clinical trials, however few comparisons have been made between clinical trial and real-world outcomes with this regimen (8) (6). Clinical trial patients are selected using strict criteria and are closely monitored throughout treatment, however data suggest that there is little difference in the performance of conventional

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regimens in real-world clinical practice (e.g., SVR12 rates of 91% versus 94% in patients without cirrhosis in previous studies with SOF/RBV) in patients with genotype 2 HCV (5).

In the current analysis, an SVR12 rate of around 90% was achieved with no significant difference noticed between 12 or 24-week durations of treatment, treatment-naïve or treatment-experienced patients, or whether the regimen contained DCV. These results show that treatment with SOF/DCV with or without RBV in the real-life setting is suboptimal compared with the clinical trial setting where reported SVR12 rates reach up to 97%.(6) Similarly, the results are suboptimal compared with real-world data from the TRIO study of SOF/velpatasvir with or without RBV for the treatment of patients with genotype 2 HCV, which showed virologic responses matching the clinical setting, with SVR rates reaching ≥95%.(14) However, generic oral directly acting agents are associated with high SVR rates in patients with HCV infection in a real-life clinical scenario (15, 16).

The difference between efficacy rates reported from clinical trials and the SVR rates reported from this real-world setting of HCV treatment regimens could be attributable to several factors. With the addition of DCV demonstrating no significant difference in efficacy across all treatment groups (p=0.9999), it is likely that the combination of SOF plus DCV with or without RBV in patients is inherently insufficiently effective in genotype 2 patients. However, other factors may contribute to these disappointing findings.

Resistance is another potential cause of the suboptimal results of this study. Analysis of NS5A and NS5B RASs at baseline and the time of failure in patients treated with DCV regimens are difficult to interpret due to the large number of patients with non-amplified NS5A domain (and therefore do not explain the suboptimal results). However, the amino acid mutation L31M was observed at baseline in 2/5 (40%) patients in whom the DCV

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treatment regimen failed. In the baseline analysis, 28.6% (12/42) of patients had a known L31M mutation, and a previous study reported that 23.1% of patients with genotype 2b had this mutation (17). Since the L31M mutation has been reported to confer resistance to DCV (18) this could have had some impact on the suboptimal SVR12 rates following treatment with SOF/DCV with or without RBV observed in the real-life setting. Furthermore, negative effects of atypical subtypes may also have had an effect of the SVR rates observed in this real-life analysis. Within the genotypes, subtypes with nucleotide identities of 75–86% may occur, individual isolates of each given subtype can typically differ by 8–10% and in each patient these subtypes can differ further. Variation at the genotype level affects the outcome of antiviral therapies (19). Within this analysis, patients with at least 17 HCV subtypes were included, which could have potentially impacted the virologic responses seen.

Known relapses occurred 12 weeks following treatment in two patients treated with SOF/DCV with or without RBV (12-week duration. Extending treatment duration compared with standard treatment, or adding ribavirin (cumulative ribavirin dose) have been demonstrated to improve SVR rates in slow responders; this is considered likely due to a lower rate of viral relapse associated with the time of being HCV negative during treatment (20). However, in the current analysis, no such effect was seen since for both regimens no significant difference in SVR12 was observed by univariable analysis between the 12 and 24-week treatment durations.

In subtype analysis, higher SVR12 rates were consistently seen in females compared with males, across treatment groups, however, previous studies have shown sex does not usually impact SVR rates in patients with genotype 2 (21). Further, an association was seen between

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obesity and treatment failure by multivariable analysis, with a lower SVR12 rate observed in patients with obesity. This is consistent with other studies since obesity has been reported to negatively influence virologic decline suggesting that the combination studied here is failing to perform effectively in patients with negative baseline factors.

Both clinical trials and this real-world study of SOF with DCV with or without RBV have demonstrated a low rate of discontinuation due to AES (6) (8). Asthenia and headache were the most common AEs and were clearly manageable for all patients in this study; and serious AEs were infrequent. Similar results are seen in patients treated with generics (16).

Limitations

Conclusions regarding that extension of treatment duration, prior treatments or addition of DCV have an impact on virologic response are limited by the small sample sizes and the uneven distribution of patients who were treatment naïve, and the number of patients who had cirrhosis.

Strengths

The response rates reported in this study are typical of those seen in the clinic, and the patient distribution is representative of the real-life setting leading to robust and consistent results.

Conclusions

To our knowledge, this study is the first to show the safety and efficacy of SOF/DCV with or without RBV for the treatment of patients with HCV infected with genotype 2 in a real-world setting. Our results show that this combination is suboptimal and shows that the addition of

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DCV demonstrates no significant difference to SVR rates. However, it is a first-line cheap generic combination which remains frequently prescribed in low income countries.

Statement of interests

The ANRS CO22 cohort is sponsored by the French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis (INSERM-ANRS). The sponsor contributed to the study design and writing of this report but had no role in data collection, data analysis and data interpretation. Other funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

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Table 1 – Demographics and baseline characteristics of patient cohort

	SOF+RBV 12 weeks	SOF+RBV 24 weeks	SOF/DCV±RBV 12 weeks	SOF/DCV±RBV 24 weeks	P-value
	N=188	N=45	N=34	N=11	
Age, mean ± SD years	61.1 ± 11.7	67.1 ± 10	62.4 ± 11.5	64.2 ± 11.5	0.0284
Gender Male, n (%)	101 (54)	15 (33)	16 (47)	5 (45)	0.0968
BMI (kg/m^2), n (%)					
<18.5	4 (2)	0 (0)	1 (3)	0 (0)	0.1598
18.5–25	81 (44)	18 (40)	13 (38)	4 (36)	
25–30	65 (35)	9 (20)	11 (32)	3 (27)	
≥30	34 (18)	18 (40)	9 (26)	4 (36)	
Chronic hepatitis duration (years), mean ± SD	13 ± 9.5	11.9 ± 9.4	14.4 ± 7.9	13.5 ± 9.9	0.5524
Diabetes (%)	37 (20)	10 (22)	9 (26)	3 (27)	0.6917
Hypertension (%)	68 (36)	22 (49)	14 (41)	7 (64)	0.1577
Cirrhosis,* n (%)	56 (30)	25 (56)	15 (48)	7 (64)	0.0014
MELD score, mean ± SD	8.5 ± 4.3	10 ± 5.1	7.9 ± 2.7	11.5 ± 6.2	0.2837
MELD score (≥15), n (%)	3 (6)	3 (13)	1 (8)	1 (17)	0.4760
Child-Pugh score B or C	2 (4)	2 (8)	0 (0)	1 (14)	0.3074
Liver biopsy > 2 years	17 (30)	10 (40)	4 (27)	3 (43)	0.7443
Liver biopsy < 2 years	4 (7)	1 (4)	0 (0)	0 (0)	0.8813
Fibrosis stage **(Liver biopsy)**					
F0	0 (0)	0 (0)	1 (2)	0 (0)	0.9575
F1	0 (0)	0 (0)	1 (2)	0 (0)	
F1/F2	0 (0)	0 (0)	2 (4)	0 (0)	
F3	1 (7)	0 (0)	4 (7)	1 (4)	
F3/F4	3 (20)	0 (0)	4 (7)	2 (8)	
F4	11 (73)	7 (100)	44 (79)	22 (88)	
Prothrombin time (≤70%), n (%)	15 (9)	5 (12)	1 (3)	2 (20)	0.2803

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AST (>5 x ULN), n (%)	7 (4)	0 (0)	1 (3)	1 (10)	0.2698
ALT (>5 x ULN), n (%)	19 (10)	3 (7)	4 (12)	0 (0)	0.7447
Albumin (<30g/L), n (%)	1 (1)	3 (8)	0 (0)	0 (0)	0.0533
Conjuguated Bilirubin (>5µmol/L), n (%)	36 (42)	14 (58)	15 (60)	6 (67)	0.1771
HCV-RNA <60,000,000 IU/mL (%)	164 (90)	38 (88)	31 (91)	9 (90)	0.9801
Haemoglobin (<12g/dL in women or <13g/dL in men), n (%)	25 (13)	8 (18)	9 (27)	8 (73)	0.0001
Platelets (<100 G/L), n (%)	18 (10)	13 (30)	3 (9)	2 (20)	0.0065
Treatment naïve, n (%)	112 (60)	16 (36)	18 (53)	4 (36)	0.0187

*Including 5 patients with decompensated cirrhosis. SOF/RBV 12 weeks (n=1), SOF/RBV 24 weeks (n=2), SOF/DCV±RBV 24 weeks (n=2)

†Previous treatments in non-naïve patients were: PR (n=106), PR+BOC or TVR (n=2), DAA (n=2), Other (n=18)

SOF: Sofosbuvir - RBV: Ribavirin - DCV: Daclatasvir - SD: Standard Deviation – BMI: Body Mass Index – ULN: Upper limit of Normal – AST: Aspartate Aminotransferase – ALT: Alanine Aminotransferase

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Table 2 – Virological response according to treatment with SOF/DCV with or without RBV for 12- and 24-week treatment durations

Negative HCV RNA	SOF/DCV ±RBV 12 weeks	SOF/DCV ±RBV 24 weeks	P-value
Week 4	19/31 (61)	7/10 (70)	0.3736
Week 12	32/33 (97)	8/10 (80)	0.1849
Week 24		7/7 (100)	0.9999
SVR4	30/33 (91)	10/11 (91)	0.9999
SVR12	30/34 (88)	10/11 (91)	0.9841
SVR24	24/28 (86)	9/10 (90)	0.4769
SVR12 in non-cirrhotic patients	15/16 (94)	4/4 (100)	0.9999
SVR12 in cirrhotic patients	12/15 (80)	6/7 (86)	0.9712
SVR12 in naïve patients	15/18 (83)	4/4 (100)	0.6325
SVR12 in treatment experienced patients	15/16 (94)	6/7 (86)	0.7902

SOF: Sofosbuvir - RBV : Ribavirin - DCV : Daclatasvir - HCV : Hepatitis C Virus - SVR : Sustained Virological Response

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Table 3 – Association between treatment duration, whether the regimen contained daclatasvir, sex, obesity, liver function, treatment history and sustained virologic response, by univariable and multivariable analysis

		Univariable		Multivariable	
Variable	**n with SVR12 / Total (%)**	**OR (95% CI)**	**P-Value**	**OR (95% CI)**	**P-value**
Treatment duration[†]					
24 weeks	49/56 (88)	0.97 (0.38-2.79)	0.9999	1.02 (0.38-3.09)	0.9999
12 weeks	195/222 (88)			Ref	
DCV containing regimen[†]					
Yes	40/45 (89)	1.14 (0.4-3.99)	0.9999	1.21 (0.42-4.33)	0.9372
No	204/233 (88)			Ref	
Sex, male					
Yes	114/137 (83)	0.42 (0.18-0.94)	0.0344	0.4 (0.17-0.91)	0.0275
No	130/141 (92)			Ref	
Obese					
Yes	52/65 (80)	0.45 (0.2-1.04)	0.0637	0.41 (0.18-0.99)	0.0481
No	188/209 (90)			Ref	
ALT (>5 x ULN)				NS	
Yes	26/26 (100)	5.82 (1.24-.)	0.0525		
No	213/247 (86)				
Treatment history				NS	
Treatment experienced	107/128 (84)	0.48 (0.21-1.07)	0.0753		
Treatment naïve	137/150 (91)				

[†]Treatment duration and daclatasvir containing regimen were included in the multivariable model irrespective of the p-value in the univariable analysis. Other variables with p-value < 0.1 in the univariable analysis were included in a multivariable model and selected according to a backward selection. NS: not significant.

SOF: Sofosbuvir - RBV : Ribavirin - DCV : Daclatasvir - SVR : Sustained Virological Response – OR : Odds Ratio – CI : Confidence Interval – ULN : Upper limit of Normal – ALT : Alanine Aminotransferase

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Table 4 – Association of sustained virological response and baseline demographics and clinical characteristics by univariable analysis

		Univariable	
Variable	**n with SVR12 / Total (%) (Yes VS No)**	**OR (95% CI)**	**P-Value**
Hypertension	93/111 (84) VS 151/167 (90)	0.55 (0.25-1.2)	0.1444
Suspicion of cirrhosis	86/103 (83) VS 153/170 (90)	0.56 (0.26-1.24)	0.1674
Diabetes	55/59 (93) VS 189/219 (86)	2.18 (0.72-8.87)	0.2163
Age at inclusion ≥ 65 years	112/123 (91) VS 132/154 (86)	1.69 (0.75-4.05)	0.2380
VL D0 < 6 000 000	214/242 (88) VS 23/28 (82)	1.66 (0.46-4.96)	0.4891
MELD ≥ 15	13/16 (81) VS 201/226 (89)	0.54 (0.13-3.16)	0.5551
AST > 5 ULN	11/11 (100) VS 226/259 (87)	2.21 (0.45-inf)	0.6071
Age at diagnosis ≥ 15 years	104/120 (87) VS 135/152 (89)	0.82 (0.37-1.82)	0.7216
Conjugated bilirubin ≥ 5 µmol/L	62/71 (87) VS 66/73 (90)	0.73 (0.22-2.36)	0.7462
Albumin < 30 g/L	3/4 (75) VS 211/237 (89)	0.37 (0.03-20.15)	0.7605
Haemoglobin < 12 or 13 g/dL	43/50 (86) VS 199/226 (88)	0.83 (0.33-2.42)	0.8421
Neutrophil < 1500 /mm3	22/26 (85) VS 213/243 (88)	0.78 (0.24-3.31)	0.8451
PT ≤ 70%	20/23 (87) VS 209/233 (90)	0.77 (0.2-4.32)	0.8945
Platelets < 100 G/L	31/36 (86) VS 207/236 (88)	0.87 (0.3-3.09)	0.9591
Decompensated cirrhosis	4/5 (80) VS 240/273 (88)	0.55 (0.05-27.9)	0.9635
French ethnicity	141/160 (88) VS 103/118 (87)	1.08 (0.49-2.36)	0.9742
Overconsumption of alcohol at inclusion	0/0 (100) VS 244/277 (88)	---	

SVR : Sustained Virological Response – OR : Odds Ratio – CI : Confidence Interval – ULN : Upper limit of Normal – AST : Aspartate Aminotransferase – VL D0 : Viral Load at Day 0 – PT : Prothrombin Time

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Table 5 – Treatment discontinuation, adverse events and serious adverse events according to treatment with SOF/RBV versus SOF/DCV with or without RBV for 12- and 24-week treatment durations

	SOF + DCV ± RBV		Fisher P-value	CMH P-value (stratification: 12 vs 24w)	CMH P-value (stratification: RBV vs no RBV)
	12 weeks	24 weeks			
Number of patients	34	11			
All AEs not taken into account (missing start and end dates)					
All adverse events - any	15 (44)	6 (55)	0.0146	0.0548	0.0102
(maximum grade)					
NA			0.0683	0.1147	0.0969
Grade 1	4 (12)	3 (27)			
Grade 2	7 (21)	1 (9)			
Grade 3	4 (12)	2 (18)			
Grade 4					
Serious adverse events	3 (9)	1 (9)	0.5402	0.7490	0.3276
Adverse events (≥10% in any subgroup)					
Asthenia	9 (26)		0.2116	0.4884	0.8883
Headache	5 (15)	1 (9)	0.9858	0.9884	0.8421
Fatigue	1 (3)		0.0746	0.0430	0.0958
Dyspnoea			0.0687	0.0197	0.2452
Insomnia			0.1156	0.0234	0.4572
Pruritus			0.0065	0.0280	0.0042
Anaemia	1 (3)	2 (18)	0.2996	0.9036	0.3313
Hyperglycaemia	1 (3)		0.0290	0.2565	0.0068
Sleep disorder		2 (18)	0.0967	0.8390	0.8948
Leukopenia			0.0368	0.0884	0.0118
Treatment interruptions		3 (27)	0.0024	0.7088	0.0005
Intolerance		2 (18)	0.0054	0.7458	0.0005
Other		1 (9)	0.2251	0.8594	0.2717

CMH : Cochran–Mantel –Haenszel statistics – SOF: Sofosbuvir - RBV : Ribavirin - DCV : Daclatasvir – AE : Adverse Event – NA : Non Available

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Figure legends

Figure 1 – Patient disposition and participant numbers per treatment group

Supplementary appendix table 1 – HCV subtype distribution of patient cohort

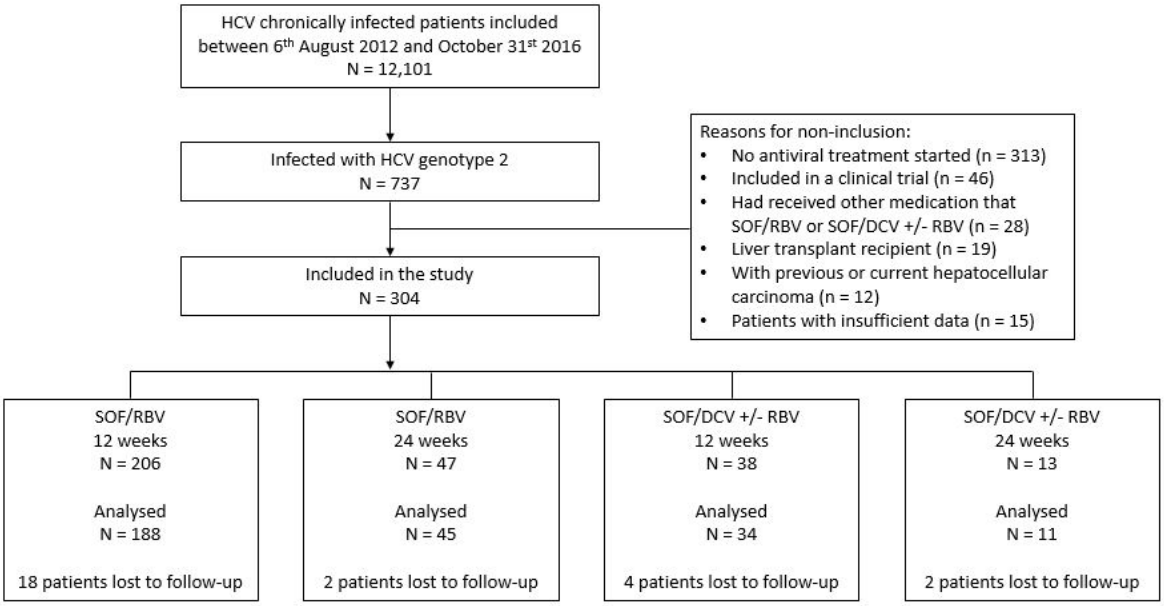
Supplementary appendix table 2 – resistance analysis at baseline of 42 patients

Supplementary appendix table 3 – resistance profile of the five patients who failed with the DCV regimen

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Figures

Figure 1 – Patient disposition



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Appendices

Supplementary appendix table 1 – HCV subtype distribution of patient cohort

Subtypes	Patients
	N=263
2a/2b/2c/2i/2k/2l, n	30/15/41/39/13/34
2d/2e/2f/2j/2m/2p/2q/2r, n	3/1/1/3/3/1/1/1
2k/1b variant, n	4
Undeterminate subtype, n	55
1a/1b, n	2/1
Non-amplified, n	15

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Supplementary appendix table 2 – resistance analysis at baseline (N=42)

	NS5A RAS	NS5B RAS
	N=42	N=42
Wild type, n	6	39
L31M, n	12	-
C92S, n	3	-
C92S/L31M, n	1	-
F28C, n	1	-
Non-amplified, n	19	3

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Supplementary appendix table 3 – resistance profile of the five patients in whom the SOF/DCV with or without ribavirin regimen failed

Subtype	NS5A RAS Baseline	NS5B RAS Baseline	NS5A RAS Failure	NS5B RAS Failure
$2_{undeterminate}$	Non-amplified	Wild type	Non-amplified	Not done
2a	L31M	Wild type	L31M	Wild type
2i	L31M	Wild type	L31M	Wild type
$2_{undeterminate}$	Non-amplified	Wild type	Non-amplified	Wild type
2b	Non-amplified	Wild type	Not available	Not available

SOF: Sofosbuvir - DCV : Daclatasvir

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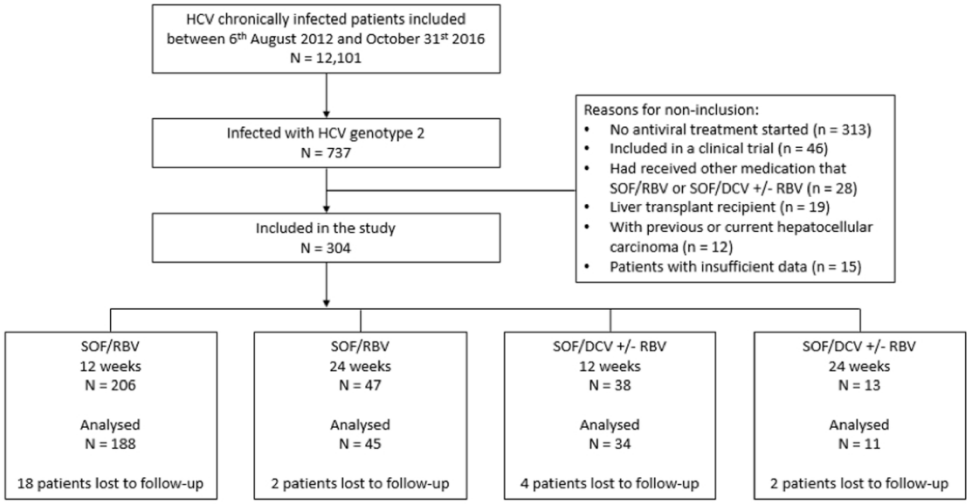


Figure 1

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