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RESEARCH ARTICLE

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Safety and efficacy of the combination simeprevir-sofosbuvir in HCV genotype 1- and 4-mono-infected patients from the French ANRS CO22 hepather cohort

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Abstract

Background: Although real-life results of sofosbuvir/simeprevir have been extensively reported from the United States, data from other geographical areas are limited. In the French observational cohort, ANRS CO22 HEPATHER, 9432 patients were given the new oral antivirals from December 2013 to June 30, 2018. We report the results of sofosbuvir/simeprevir in genotypes 1- and 4-infected patients.

Methods: Demographics and history of liver disease were collected at entry in the cohort. Clinical, adverse events, and virological data were collected throughout treatment and post-treatment follow-up. The choice of treatment duration or addition of ribavirin was left up to the physician.

Results: Five hundred ninety-nine HCV (467 genotype 1 and 132 genotype 4) mono-infected, naïve for all oral-DAA's regimen patients were given sofosbuvir/simeprevir with ($n = 63$) or without ribavirin ($n = 536$) for 12 or 24 weeks; 56% had cirrhosis (4% decompensated) and 71% had prior treatment failure to interferon-based regimen. 7 patients (1.16%) were lost to follow-up. The overall SVR12 rate was 92.6%. The SVR12 was 90% in GT1a, 94.2% in GT1b and 91.6% in GT4 with no significant difference for genotype, treatment duration or ribavirin addition. Severity of liver disease was not associated with a lower SVR12 rate on multivariate analysis but was associated with a higher rate of severe side effects. Early treatment discontinuations were rare; no new safety signals were reported.

Conclusion: In this real life, observational, prospective cohort study, the 12-week sofosbuvir/simeprevir+/-ribavirin combination appears to be efficient and safe.

Trial registration: Trial registration with ClinicalTrials.gov [NCT01953458](https://clinicaltrials.gov/ct2/show/study/NCT01953458).

Keywords: Direct acting antivirals, Hepatitis C virus, Real life cohort, Simeprevir, Sofosbuvir

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Key points

- The combination of sofosbuvir and simeprevir results in an overall SVR12 of 92.6, 90% in patients with genotype 1a infection, 94.2% with genotype 1b and 91.6% with genotype 4.
- The safety of the sofosbuvir and simeprevir combination was acceptable with only 3% of early discontinuations and with no new safety warnings.
- The combination with sofosbuvir and simeprevir is no longer recommended but remains a potential therapeutic option in resource-limited settings or in countries where simeprevir is still available.

Background

Chronic hepatitis C virus (HCV) infection is a worldwide disease that is responsible for hepatic and extrahepatic morbidity and mortality [1, 2]. A sustained virological response (SVR) corresponds to a complete cure of infection. A SVR is also associated with a reduction in HCV-related complications such as cirrhosis, hepatocellular carcinoma, the need for transplantation and death [3–6]. A better understanding of the viral cycle and characterization of the non-structural proteins of the virus led to development of direct acting antivirals (DAAs) against HCV [7–9]. Approved in the Spring of 2011, second generation DAAs replaced first generation protease inhibitors, which were then removed from the market in 2014. NS5B polymerase inhibitors (sofosbuvir, dasabuvir), protease inhibitors (simeprevir, paritaprevir, grazoprevir, glecaprevir, voxilaprevir) and NS5A replication complex inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir, pibrentasvir and velpatasvir) have also been approved and evaluated [10–21]. A combination of pangenotypic drugs is now recommended to treat chronic HCV infection, while EASL guidelines no longer recommend the combination of sofosbuvir and simeprevir [22–24]. For the European Association for the Study of the Liver (EASL), antiviral therapy should be considered in all patients with chronic HCV infection because of the efficacy and safety profile of DAAs. Because of the long timelines for approval and in addition to clinical trials, preliminary real-life results of the combination of sofosbuvir/simeprevir have been extensively reported [25–30] from the United States (US) in patients with genotype 1 infection. However, real-life data from Europe or outside the US, and for genotype 4 are limited [31–33].

We report the real-life results of the French ANRS CO22 Hepather cohort for the sofosbuvir+simeprevir +/- ribavirin combination in patients with HCV genotypes 1 or 4 mono-infection.

Methods

Study design and participants

The ANRS CO22 HEPATHER cohort « Therapeutic option for hepatitis B and C: a French cohort » is a multi-center, national, prospective, observational cohort study of patients infected with hepatitis B or C virus ([ClinicalTrials.gov](https://clinicaltrials.gov) registry number: NCT01953458). The cohort has been extensively described elsewhere [34].

In summary, by December 31, 2015, 20,798 patients had been included in the cohort, including 14,195 HCV-positive patients. A total of 9432 patients were given treatment including at least one direct acting antiviral from December 2013 to June 30, 2018. We selected all patients with HCV genotype 1 or genotype 4 infection who initiated a combination of sofosbuvir (400 mg/d) and simeprevir (150 mg/d) with or without ribavirin (1–1.2 g/d) before October 31, 2014 ($n = 599$). Patients who were liver transplant recipients, previously treated with other DAAs (except first generation protease inhibitors) or involved in clinical trials, were excluded. Patients were divided into four groups according to the scheduled duration of treatment and whether the regimen included ribavirin. This was an observational and not a randomized controlled study and the choice of treatment combination, duration and addition of ribavirin was left up to the physician. The diagnosis of cirrhosis was based either on the results of liver biopsy, a fibrotest result > 0.7 or fibroscan greater than 14.5 kPa. The duration of chronic hepatitis was estimated by the date of contamination, if available.

Outcomes

The main endpoint criterion was SVR at 12 weeks (SVR12) defined as undetectable HCV RNA 12 weeks after the last treatment. Secondary endpoints were undetectable HCV RNA 4 weeks after the last treatment (SVR4), early treatment discontinuation and adverse events.

Statistical analyses

A post-hoc calculation showed that the present study achieved a reliability of 2.4% for an anticipated 90% SVR12 and had a power $> 80\%$ for detecting Odds-Ratio (OR) < 0.3 for factors associated with SVR12, assuming the exposure to these factors ranged between 20 to 75%. Missing SVR12 measurements were determined using SVR24 measurements, if available ($n = 52$), otherwise using the SVR4 measurement ($n = 6$). Patients who died before SVR12 and therefore could not be evaluated ($n = 4$) and patients who were lost of follow-up ($n = 7$) and had no measurement of the virological response after the end of therapy, were considered to be virological failures.

Proportions were compared using the Fisher exact test and/or continuous outcomes were compared using the

Kruskal-Wallis test. Comparisons with stratification for treatment duration or ribavirin use were tested using the Cochran-Mantel Haenszel (CMH) Chi-Square. Exact logistic regression models were used to assess independent baseline variables associated with SVR12 or serious side effects (including death). Predefined cut-offs were used to categorize all continuous factors. A univariate exact logistic model was estimated for each factor. Primary multivariate analysis included ribavirin (No vs Yes), treatment duration (12 vs. 24 weeks) and any factors with a *P*-value < 0.10 on univariate analysis. A backward selection was applied retaining variables with a *P*-value < 0.05. Statistical analyses were performed with SAS 9.4 software (SAS Institute Inc., Cary, North Carolina, USA).

Role of the funding source

The ANRS CO22 HEPATHER cohort is sponsored by Inserm-ANRS (French National Institute for Health and Medical Research – ANRS/France REcherche Nord&Sud Sida-hiv Hépatites). The sponsor contributed to the

study design and writing of this report. The sponsor had no role in data collection, data analysis or data interpretation. The other sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. FC had full access to all the data in the study and SP and FC had the final responsibility for the decision to submit for publication.

Results

Patient population

By October 31, 2014, 599 cohort participants with HCV genotypes 1 (*N* = 467) or genotype 4 (*N* = 132) infection had started treatment with the sofosbuvir/simeprevir combination including 536 (89%) who did not receive and 63 (11%) who did receive ribavirin based on the physician’s decision (Fig. 1). The duration of treatment was 12 weeks in 530 (530/599 = 88.4%) patients and 24 weeks in 69 (69/599 = 11.5%).

Patient characteristics are described in Table 1. Fifty-four percent were men, mean age 61 years old, 56% with cirrhosis, 4% with decompensated cirrhosis and

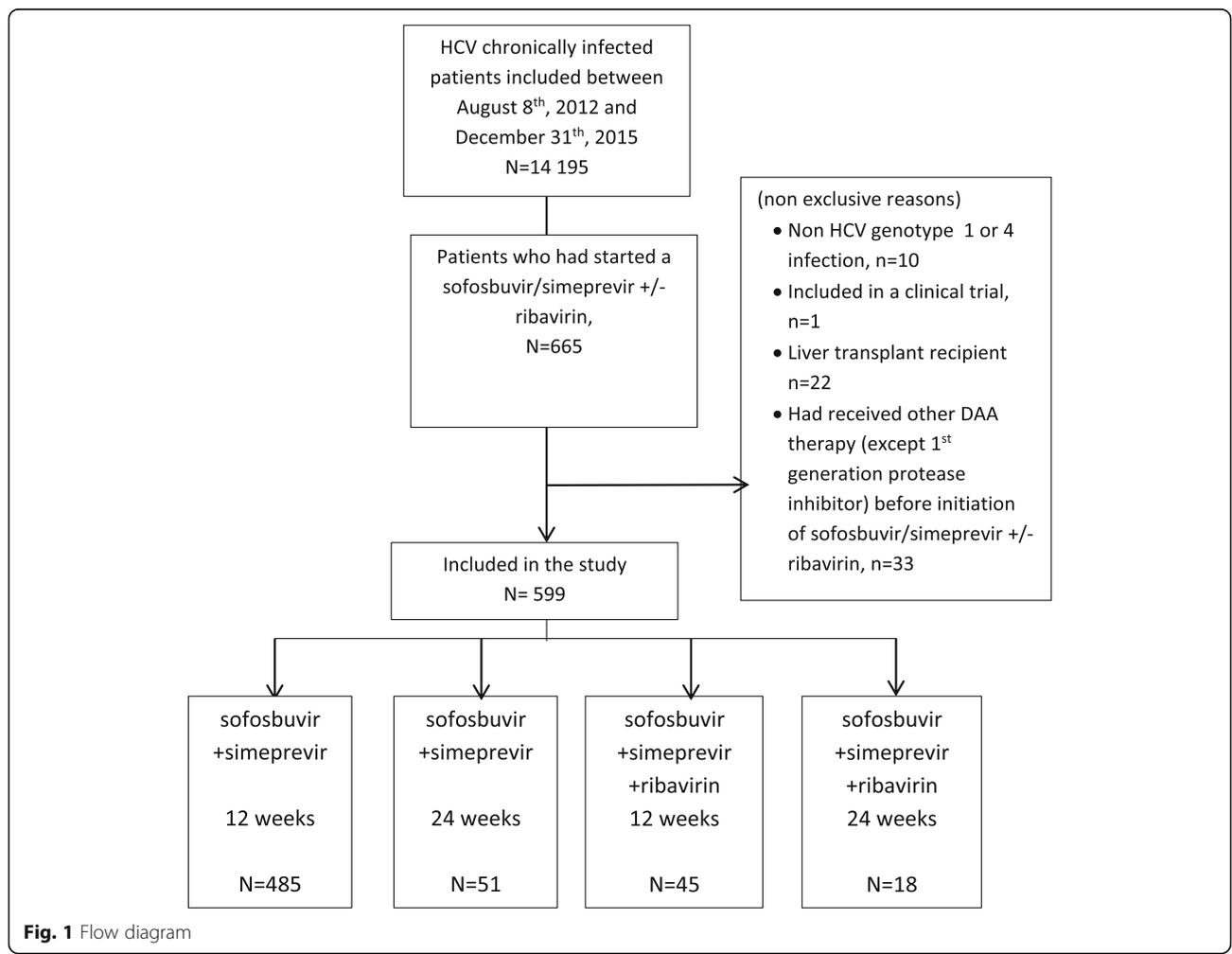


Fig. 1 Flow diagram

Table 1 Baseline characteristics of patients

	SOF SMV 12 weeks n = 485	SOF SMV 24 weeks n = 51	SOF SMV RBV 12 weeks n = 45	SOF SMV RBV 24 weeks n = 18	p value
Age (years), mean ± SD	61 ± 11	60 ± 10	59 ± 11	58 ± 13	0.2908
Gender Male n (%)	256 (53)	24 (47)	28 (62)	14 (78)	0.0866
BMI (kg/m ²) n (%)					
≥ 30	74 (15)	10 (20)	7 (16)	2 (11)	0.9531
< 18.5	12 (2)	2 (4)	0 (0)	0 (0)	
[25–30[163 (34)	14 (27)	17 (38)	7 (39)	
[18.5–25[233 (48)	25 (49)	21 (47)	9 (50)	
Chronic hepatitis duration (years), mean ± SD	16 ± 8	15 ± 7	16 ± 9	11 ± 8	0.0814
HCV genotype n (%)					
1a	110 (23)	11 (22)	14 (31)	6 (33)	0.2543
4	99 (20)	17 (33)	10 (22)	6 (33)	
1 not subtyped	25 (5)	1 (2)	3 (7)	0 (0)	
1b	251 (52)	22 (43)	18 (40)	6 (33)	
Diabetes n (%)	104 (21)	7 (14)	9 (20)	1 (6)	0.2710
Hypertension n (%)	194 (40)	25 (49)	18 (40)	4 (22)	0.2571
Cirrhosis n (%)	259 (54)	33 (65)	27 (60)	16 (89)	0.0117
• Child-Pugh score B or C	17 (7)	8 (24)	1 (4)	2 (13)	0.0083
• MELD ≥15	19 (8)	4 (13)	1 (4)	3 (19)	0.2444
• Elastography ≥14.5 kPa	131 (51)	15 (45)	14 (52)	10 (63)	0.7540
• Fibrotest ≥0.73	70 (27)	10 (30)	11 (41)	10 (63)	0.0175
• Liver biopsy > 2 years	148 (57)	20 (61)	14 (52)	7 (44)	0.6618
• Liver biopsy < 2 years	18 (7)	2 (6)	1 (4)	0 (0)	0.9306
Decompensated cirrhosis n (%)	16 (3)	6 (12)	2 (4)	0 (0)	0.0483
• Child-Pugh score B or C	6 (38)	4 (67)	1 (50)		0.5589
• MELD score, mean ± SD	9.7 ± 2.9	12.3 ± 3.9	12.5 ± 0.7		0.1793
Albumin (< 30 g/L) n (%)	12 (3)	5 (11)	1 (3)	1 (6)	0.0415
Prothrombin time (≤70%) n (%)	45 (10)	11 (22)	6 (14)	6 (33)	0.0037
AST (> 5 x ULN) n (%)	28 (6)	4 (8)	3 (7)	2 (12)	0.4951
ALT (> 5 x ULN) n (%)	31 (6)	2 (4)	1 (2)	1 (6)	0.7735
Haemoglobin (≤12 g/dL in women or ≤ 13 g/dL in men) n (%)	58 (12)	8 (16)	5 (11)	1 (6)	0.7365
Platelets < 100,000/mm ³	87 (19)	15 (30)	11 (25)	8 (47)	0.0109
Bilirubin conj ≥5 μmol/L	133 (52)	20 (63)	16 (57)	13 (100)	0.0021
Treatment history n (%)					
• Naïve patients	141 (29)	13 (25)	14 (31)	5 (28)	0.0618
• Experienced patients, last treatment PEG/RBV	324 (67)	35 (69)	25 (56)	10 (56)	
• Experienced patients, last treatment 1st generation PI/PEG/RBV	20 (4)	3 (6)	6 (13)	3 (17)	
Response profile in treatment experienced patients					
• Unknown	164 (48)	20 (53)	17 (55)	6 (46)	0.8370
• Responders	86 (25)	9 (24)	4 (13)	3 (23)	
• Not responders	94 (27)	9 (24)	10 (32)	4 (31)	

SOF Sofosbuvir, SMV Simeprevir, RBV Ribavirine, PI Protease inhibitor, SD Standard deviation, BMI Body mass index
P value inferior to 0.05 are in boldface

71% with interferon-based treatment failure (all were naïve for all oral DAAs regimens). Patients were infected with genotype 1a (23.5%), 1b (49.5%), 1 but unclassified (5%) or 4 (22%). The mean MELD score in the 312 with available data out of 335 patients with cirrhosis was 9.5 \pm 4.3 and 91.6% were Child-Pugh score A. Patients who received the 12-week combination of sofosbuvir/simeprevir differed from those who received the 24-week or ribavirin-containing regimens, with lower rates of cirrhosis (54% (259/478) vs 67% (76/114), $p = 0.0158$), decompensated cirrhosis (3% (16/485) vs 7% (8/114), $p = 0.1051$) and biochemical markers of liver severity: albumin < 30 g/L in 3% (12/437) vs 7% (7/101), $p = 0.0650$, prothrombin time \leq 70% in 10% (45/449) vs 21% (23/110), $p = 0.0031$, thrombocyte count < 100,000/mm³ in 19% (87/468) vs 31% (34/111), $p = 0.064$ and conjugated bilirubinemia \geq 5 μ mol/L in 52% (133/257) vs 67% (49/73), $p = 0.0233$.

Efficacy

Missing SVR12 measurements were determined using SVR24 measurements in 52 patients and SVR4 measurements in 6 patients. Four patients who died before reaching SVR12 and seven patients who were lost to follow-up with no virological response measurement at the end of therapy were considered virological failures.

A SVR12 was achieved in a total of 555 (92.6%) patients. SVR12 rates ranged from 89% in patients who received a 24-week sofosbuvir/simeprevir/ribavirin combination regimen to 98% in patients who received a 12-week sofosbuvir/simeprevir/ribavirin combination regimen (Table 2 and Fig. 2).

Although no significant difference was found between the 12- or 24-week regimen with or without ribavirin, the groups were not comparable because patients in the ribavirin and 24-week treatment groups had more severe disease.

The SVR12 rate in patients without cirrhosis was 94.9%, whatever the treatment.

The SVR12 rate in patients with cirrhosis was 90.7% in treatment-naïve and 89% in treatment-experienced patients. No significant difference was found between those who received a 24-week regimen and a 12-week regimen (42/49 (85.7% %) versus 262/286 (91.6%), respectively (CMH Chi Square stratified on ribavirin containing regimen: $p = 0.12$)). The SVR12 rate was not different between those who received a 12-week regimen with or without ribavirin (26/27 (96%) versus 236/259 (91%), respectively (CMH Chi Square stratified on ribavirin containing regimen: $p = 0.39$)).

The overall SVR12 was 90, 94.2 and 91.6% in patients with genotypes 1a, 1b and 4, respectively, and was not significant different among the groups (Table 3). The addition of ribavirin or not, and the duration of treatment (12 vs 24 weeks) did not influence the SVR12 rate.

There were no variables associated with SVR12 at the 0.05 level on univariate analysis (Table 3).

Age, sex, gender, BMI, genotype, prior treatment history, cirrhosis or not and treatment duration did not influence SVR12. No factor was associated with the absence of SVR12 on multivariate analysis.

Safety and tolerability

Early treatment discontinuation only occurred in 18 patients (3%). The rate of discontinuation for adverse events was 1.5%. The rate of discontinuation was higher in patients treated for 24 weeks or with ribavirin (Table 4). Nine of the patients who discontinued treatment (50%) achieved a SVR12. Eight (44%) had been treated for 8 weeks or more.

Four patients died during follow-up. One patient died from a subdural hematoma in the first week after initiating treatment, and one patient at week 8 from undetermined causes. Two patients died suddenly at week 12 from cardiac arrest, which was considered to be possibly treatment-related (sofosbuvir/simeprevir). Cardiovascular side effects (mainly bradyarrhythmias) have been associated with sofosbuvir treatment and may result in the implementation of a pace-maker [35] and associated with a risk of sudden, unexplained death [36].

Forty-three other serious adverse events occurred in 37 (9%) patients with no difference between treatment with or without ribavirin, but with a higher rate in the 24-week regimen ($p = 0.0453$). Two of these serious adverse events were considered to be possibly treatment-related (simeprevir): one malaise at week 12 and one drug-induced acute hepatitis at week 5.

The most common adverse events (\geq 10% in any subgroup) were asthenia, headache and pruritus.

Univariate analysis identified treatment duration, prothrombin time \leq 70%, decompensated cirrhosis, time since diagnosis \geq 15 years, MELD \geq 15 or cirrhosis at inclusion, cirrhosis, platelet count < 100,000/mm³, conjugated bilirubin \geq 5 μ mol/L and albumin < 30 g/L as potential predictors of serious adverse events. A prothrombin time \leq 70% (OR versus prothrombin time \geq 70%, 2.88 95%CI 1.24–6.48; $P = 0.0127$), MELD \geq 15 or cirrhosis (OR versus MELD < 15 and no cirrhosis, 3.13 95%CI 1.2–9.62; $P = 0.0154$) and a time since diagnosis \geq 15 years (OR versus time since diagnosis < 15 years, 2.19 95%CI 1.01–5.1; $P = 0.0465$) remained the only 3 factors independently associated with serious adverse events. It should be noted that age and gender were not associated with serious adverse events.

Discussion

Although the real-life results of the sofosbuvir/simeprevir combination have been extensively reported in US genotype 1-infected patients, data from other

Table 2 Virologic responses according to therapeutic regimens

	TOTAL N = 599		Fisher p value	CMH p value (stratification: 12 weeks vs 24 weeks)	CMH p value (stratification: RBV vs no RBV)			
	Sofosbuvir + simeprevir 12 weeks n = 485	Sofosbuvir + simeprevir + ribavirin 24 weeks n = 18						
Negative HCV RNA								
Week 12 n/N (%)	519/576 (90)	422/469 (90)	41/47 (87)	43/44 (98)	13/16 (81)	0.1312	0.2779	0.1514
Week 24n/N (%)	60/65 (92)		44/49 (90)		16/16 (100)	0.3219	0.1869	
Follow up week 4n/N (%)	277/570 (49)	318/341 (93)	30/31 (97)	39/40 (98)	13/13 (100)	0.7525	0.2341	0.3669
SVR 12 (imputed ^a) n/N (%)	555/599 (93)	449/485 (93)	46/51 (90)	44/45 (98)	16/18 (89)	0.3742	0.3197	0.2538
SVR 24 n/N (%)	459/473 (97)	374/385 (97)	38/40 (95)	37/38 (97)	10/10 (100)	0.7360	0.6713	0.6102
SVR 12 in non cirrhotic patients n/N (%)	244/257 (95)	206/219 (94)	18/18 (100)	18/18 (100)	2/2 (100)	0.5937	0.2887	0.2887
SVR 12 in cirrhotic patients n/N (%)	304/335 (91)	236/259 (91)	28/33 (85)	26/27 (96)	14/16 (88)	0.4043	0.3882	0.1293
SVR 12 in treatment naïve patientsn/N (%)	160/173 (92)	130/141 (92)	12/13 (92)	14/14 (100)	4/5 (80)	0.3637	0.6195	0.4809
SVR 12 in treatment experienced patients n/N (%)	395/426 (93)	319/344 (93)	34/38 (89)	30/31 (97)	12/13 (92)	0.6749	0.3874	0.3635
Last treatment								
PEG/RBV n/N (%)	365/394 (93)	300/324 (93)	32/35 (91)	24/25 (96)	9/10 (90)	0.8073	0.6462	0.6214
First generation PI/PEG/RBV n/N (%)	30/32 (94)	19/20 (95)	2/3 (67)	6/6 (100)	3/3 (100)	0.3750	0.2637	0.1122
Response profile								
Not respondersn/N (%)	108/117 (92)	87/94 (93)	8/9 (89)	9/10 (90)	4/4 (100)	0.6151	0.9339	0.9864
Responders ^b n/N (%)	99/102 (97)	84/86 (98)	8/9 (89)	4/4 (100)	3/3 (100)	0.4040	0.5154	0.1537
Unknown n/N (%)	188/207 (91)	148/164 (90)	18/20 (90)	17/17 (100)	5/6 (83)	0.4343	0.3647	0.5569
SVR 12 in Cirrhotic Treatment experienced patients n/N(%)	230/258 (89)	178/200 (89)	23/27 (85)	18/19 (95)	11/12 (92)	0.8219	0.3407	0.5044
SVR 12 in patients with genotype 1a n/N (%)	127/141 (90)	99/110 (90)	10/11 (91)	13/14 (93)	5/6 (83)	0.8660	0.9608	0.7862
SVR 12 in patients with genotype 1b infection n/N (%)	280/297 (94)	237/251 (94)	20/22 (91)	18/18 (100)	5/6 (83)	0.2403	0.6111	0.2015
SVR 12 in patients with genotype 4 infection n/N (%)	121/132 (92)	89/99 (90)	16/17 (94)	10/10 (100)	6/6 (100)	0.9150	0.2283	0.5850
SVR 12 in patients with genotype 1 not subtyped n/N (%)	277/29 (93)	24/25 (96)	0/1 (0)	3/3 (100)		0.0764	0.7290	0.0005

HCV Hepatitis C Virus, SVR Sustain virological response, PI Protease inhibitor, RBV Ribavirin, PEG Pegylated interferon.

^aImputed: missing SVR12 measurements were imputed using SVR24 measurement if available (n = 52), otherwise using SVR4 measurement (n = 6). We imputed a virological failure in patients who died before SVR12 and therefore could not be evaluated (n = 4) and in patients who were lost of follow up (n = 7) and had no measurement of the virological response after end of therapy. ^b responders = patients with negative HCV RNA on last treatment - includes one patient with sustained virological response who was re-infected

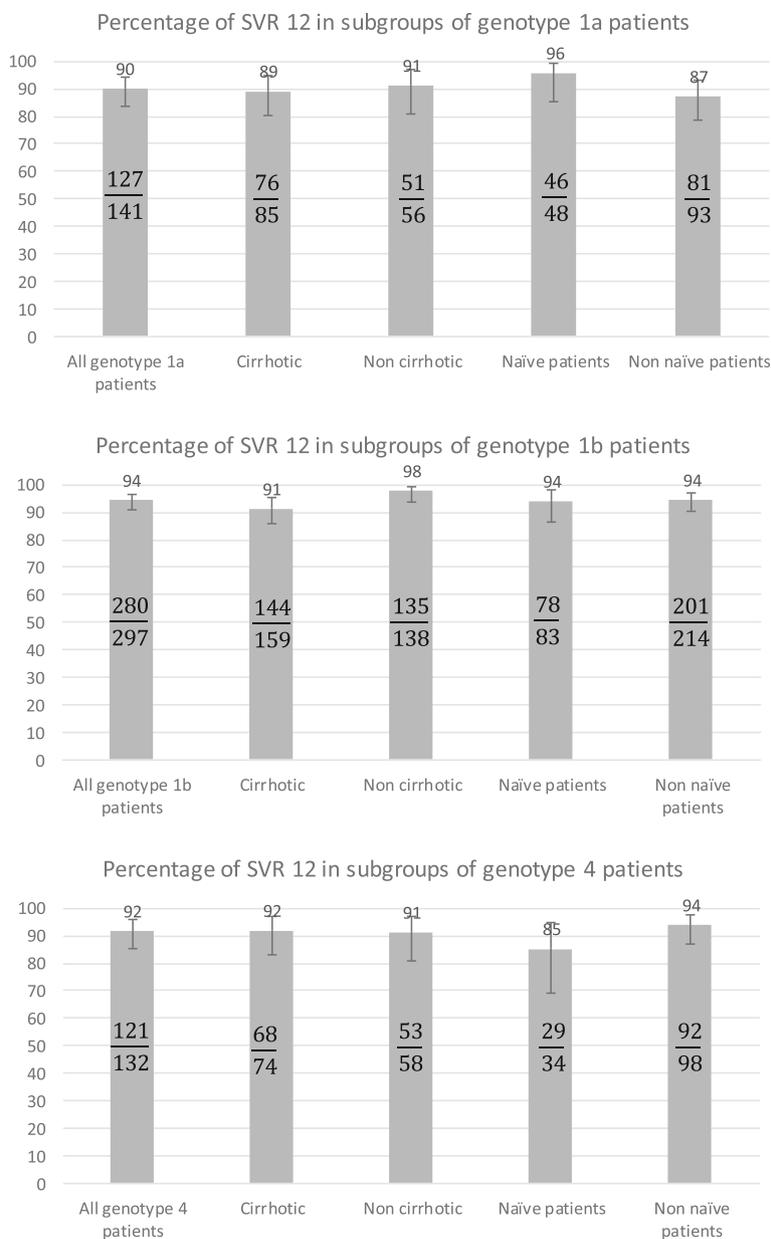


Fig. 2 Percentages of SVR12 in subgroups of patients by genotype

geographical areas or other genotypes are limited. In this real-life study, we analyzed the efficacy and safety of the sofosbuvir+simeprevir +/- ribavirin combination in patients with genotypes 1 or 4 infection from the French ANRS CO22 HEPATHER cohort, a real-life study. Most of these patients were “difficult-to-treat” since 56% had cirrhosis, 4% had decompensated cirrhosis, 71% had failed prior treatment with pegylated interferon and ribavirin and 5% associated with telaprevir or boceprevir. Only 7 patients (1.16%) were lost to follow-up with no available PCR after the end of treatment. The sofosbuvir/simeprevir combination resulted in a global SVR12

rate of 92.6%. Most patients (81%) received the sofosbuvir/simeprevir combination without ribavirin for 12 weeks with a SVR of 93%. No significant difference in SVR12 rate was found between 12 or 24 weeks of treatment, with or without ribavirin. However, it is not possible to conclude whether extending the duration of treatment or the addition of ribavirin is needed or not, especially in patients with cirrhosis or decompensated cirrhosis because of the small sample size and because patients had more severe liver disease in the ribavirin and 24- week regimen groups. The overall SVR12 was 94.2% in patients with genotype 1b infection (vs 90

Table 3 Variables associated with SVR12 in univariate and multivariate analysis

	n with SVR 12 / Total (%): Yes VS Reference	Univariate		Multivariate	
		OR (95% CI)	p-Value	OR (95% CI)	p-Value
Ribavirin containing regimen (reference: no RBV)	60/63 (95) VS 495/536 (92)	1.66 (0.5–8.61)	0.5936		
Treatment duration 24 weeks (reference: 12 weeks)	62/69 (90) VS 493/530 (93)	0.67 (0.28–1.85)	0.4654		
Cirrhosis (reference: no cirrhosis)	304/335 (91) VS 244/257 (95)	0.52 (0.25–1.06)	0.0734	1.07 (0.36–3.20)	1.0000
Conjugated bilirubin ≥ 5 $\mu\text{mol/L}$ (reference: < 5 $\mu\text{mol/L}$)	163/182 (90) VS 141/148 (95)	0.43 (0.15–1.1)	0.0835	0.58 (0.19–1.67)	0.3701
TP $\leq 70\%$ (reference: $> 70\%$)	59/68 (87) VS 458/491 (93)	0.47 (0.21–1.18)	0.1103	0.41 (0.14–1.22)	0.1148
Hemoglobin ≤ 12 g/dL for women or ≤ 13 g/dL for men (reference: > 12 g/dL or > 13 g/dL)	63/72 (88) VS 480/514 (93)	0.5 (0.22–1.23)	0.1338	0.59 (0.22–1.71)	0.3620
Platelets $< 100,000/\text{mm}^3$ (reference: $\geq 100,000/\text{mm}^3$)	108/121 (89) VS 429/458 (94)	0.56 (0.27–1.22)	0.1505	1.12 (0.39–3.38)	1.0000
Genotype 1b (reference: 1 not subtyped or 1a or 4)	280/297 (94) VS 275/302 (91)	1.62 (0.83–3.24)	0.1757	0.94 (0.39–2.26)	1.0000
Male (reference: Female)	303/322 (94) VS 252/277 (91)	1.18 (0.65–2.13)	0.6504	1.62 (0.68–3.94)	0.3192
Genotype 1a (reference: 1 not subtyped or 1b or 4)	127/141 (90) VS 428/458 (93)	0.64 (0.32–1.34)	0.2489		
Neutrophil $< 1500/\text{mm}^3$ (reference: $\geq 1500/\text{mm}^3$)	33/38 (87) VS 503/540 (93)	0.49 (0.17–1.69)	0.2641		
Chronic hepatitis duration ≥ 15 years (reference: < 15 years)	308/337 (91) VS 236/251 (94)	0.68 (0.33–1.34)	0.2980		
Albumin < 30 g/L (reference: ≥ 30 g/L)	16/19 (84) VS 479/519 (92)	0.45 (0.12–2.49)	0.3756		
Age > 65 years (reference: ≤ 65 years)	209/223 (94) VS 346/376 (92)	1.29 (0.65–2.7)	0.5478		
MELD ≥ 15 (reference: < 15)	31/35 (89) VS 454/491 (92)	0.63 (0.21–2.6)	0.5732		
Genotype 4 (reference: 1a or 1b or 1 not subtyped)	121/132 (92) VS 434/467 (93)	0.84 (0.4–1.89)	0.7409		
Viral load < 6 M at beginning of treatment (reference: ≥ 6 M)	502/542 (93) VS 42/44 (95)	0.6 (0.07–2.45)	0.7425		
ALAT > 5 ULN (reference: ≤ 5 ULN)	33/35 (94) VS 511/551 (93)	1.29 (0.31–11.5)	0.9999		
ASAT > 5 ULN (reference: ≤ 5 ULN)	34/37 (92) VS 508/547 (93)	0.87 (0.26–4.63)	0.9999		
Decompensated cirrhosis (reference: no decompensated cirrhosis)	22/24 (92) VS 533/575 (93)	0.87 (0.2–7.86)	0.9999		
Treatment experienced (reference: treatment naïve)	160/173 (92) VS 395/426 (93)	0.97 (0.48–2.07)	0.9999		
Genotype 1 not subtyped (reference: 1a or 1b or 4)	27/29 (93) VS 528/570 (93)	1.07 (0.25–9.63)	0.9999		
Previous treatment: PEG/RBV (reference: 1st generation PI/PEG/RBV or none)	365/394 (93) VS 190/205 (93)	0.99 (0.48–1.97)	0.9999		

SVR Sustain virological response, RBV Ribavirin, PEG Pegylated interferon, PI Protease inhibitor

and 91.6% for genotypes 1a and 4, respectively) but the difference was not statistically significant. There was no factor associated with treatment failure on univariate analysis.

Early treatment discontinuation was rare and no new safety signals were reported compared to previous studies. The severity of liver disease (MELD ≥ 15 or cirrhosis

at inclusion) was a risk factor for serious adverse events which support a causal relationship between adverse events and protease inhibitor exposure, as previously reported in the CUPIC study [37].

It is not possible to compare our results with those of other studies, clinical trials or real-world studies, because the rate of “difficult to treat” patients differed. The

Table 4 Adverse events

	Sofosbuvir + simeprevir		Sofosbuvir + simeprevir+ ribavirin		Fisher <i>P</i> -value	CMH <i>P</i> value (stratification: 12 weeks vs 24 weeks)	CMH <i>P</i> value (stratification: RBV vs no RBV)
	12 weeks	24 weeks	12 weeks	24 weeks			
Number of patients	485	51	45	18			
Treatment interruptions n (%)	6 (1)	4 (8)	5 (11)	3 (17)	0.0000	0.0003	0.0130
- Adverse event	3 (1)	2 (4)	3 (7)	1 (6)	0.0030	0.0074	0.2081
- Other reasons	3 (1)	2 (4)	2 (4)	2 (11)	0.0014	0.0169	0.0300
All adverse events - any n (%)	312 (64)	35 (69)	32 (71)	15 (83)	0.3185	0.1720	0.3247
(Maximum grade)							
- Grade 1	156 (32)	15 (29)	9 (20)	3 (17)	< 0.0001	0.0043	< 0.0001
- Grade 2	116 (24)	7 (14)	19 (42)	10 (56)			
- Grade 3	28 (6)	3 (6)	2 (4)	0 (0)			
- Grade 4	11 (2)	8 (16)	2 (4)	1 (6)			
- Grade 5	1 (0)	2 (4)	0 (0)	1 (6)			
Deaths	1 (0)	2 (4)	0 (0)	1 (6)	0.0096	0.8684	0.0003
Other serious adverse events	26 (5)	7 (14)	3 (7)	1 (6)	0.1241	0.7697	0.0453
Adverse Events (≥10% in any subgroup)							
- Asthenia	80 (16)	11 (22)	17 (38)	4 (22)	0.0074	0.0023	0.9114
- Headache	69 (14)	2 (4)	3 (7)	4 (22)	0.0457	0.7803	0.2836
- Pruritus	42 (9)	1 (2)	3 (7)	3 (17)	0.1653	0.5673	0.3966
- Hyperbilirubinaemia	28 (6)	5 (10)	7 (16)	5 (28)	0.0015	0.0018	0.1129
- Fatigue	33 (7)	2 (4)	0 (0)	2 (11)	0.1531	0.2982	0.9563
- Thrombocytopenia	20 (4)	7 (14)	2 (4)	3 (17)	0.0059	0.7737	0.0007
- Insomnia	24 (5)	2 (4)	3 (7)	2 (11)	0.4667	0.3140	0.9557
- Sleep disorder	21 (4)	2 (4)	1 (2)	3 (17)	0.1160	0.6041	0.3077
- Dry skin	7 (1)	0 (0)	1 (2)	2 (11)	0.0526	0.0711	0.6618
- Oedema peripheral	4 (1)	2 (4)	0 (0)	2 (11)	0.0117	0.5464	0.0028
- Eczema	3 (1)	2 (4)	0 (0)	2 (11)	0.0059	0.4760	0.0012
- Dyspnoea	1 (0)	2 (4)	1 (2)	2 (11)	0.0004	0.0586	0.0019
- Gastrointestinal disorder	4 (1)	0 (0)	0 (0)	2 (11)	0.0336	0.1701	0.2244
- Jaundice	0 (0)	1 (2)	2 (4)	2 (11)	0.0001	0.0003	0.0579

RBV Ribavirin

SVR12 rate in the real-world US TARGET cohort [25] including 59% of patients with cirrhosis (56% in our study) and around 50% of treatment-experienced patients (71% in our study) was 84%. In that study, in contrast to our results, the severity of liver disease and previous protease inhibitor treatments were associated with treatment failure in the model-adjusted estimates. In an Egyptian [32] and a US real-life study [38] the SVR rate was > 92%. In summary, our study shows a SVR-rate of nearly 95% in patients without cirrhosis, and 91% in those with cirrhosis, which is comparable to other real-life studies [31–33].

Even with a SVR rate of 91–95%, the role of simeprevir/sofosbuvir, is debatable with the current high turnover of DAAs. In the era of “second” wave DAAs

(sofosbuvir with ledipasvir, daclatasvir or velpatasvir and voxilaprevir, ombitasvir/paritaprevir/dasabuvir, grazoprevir/elbasvir, glecaprevir/pibrentasvir) with high SVR rates in both clinical trials and real-life studies [34] and access to shorter-duration pangenotypic regimens even in patients with cirrhosis, our real-world study suggests that the efficacy of the 12-week sofosbuvir/simeprevir combination is probably suboptimal despite an acceptable safety profile.

Conclusion

This study reports the real-life results of the French ANRS CO22 Hepather cohort for the sofosbuvir+simeprevir +/- ribavirin combination in patients with HCV genotypes 1 or 4 mono-infection. The overall SVR12

was 92.6, 90% in patients with genotype 1a infection, 94.2% with genotype 1b and 91.6% with genotype 4 with an acceptable safety profile. In the era of “second” wave DAAs this combination is no longer recommended in the most recent (2018) EASL guidelines but could remain a therapeutic option in low-income countries without access to pangenotypic drugs.

Abbreviations

BMI: Body mass index; DAA: Direct-acting antiviral; EASL: European Association for the Study of the Liver; HCV: Hepatitis C virus; PCR: Polymerase chain reaction; PEG: Pegylated interferon; PI: Protease inhibitor; RBV: Ribavirin; RNA: Ribonucleic acid; SD: Standard deviation; SMV: Simeprevir; SOF: Sofosbuvir; SVR: Sustained virological response

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Availability of data and materials

The data that support the findings of this study are available from ANRS-INSERM but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request and with permission of ANRS-INSERM.

Authors' contributions

Study concept and design: FC, CD, HF, VPZ, SP. Acquisition of data: HF, CD, SM, GH, DL, CD, CH, FZ, PMar, MB, JPZ, DT, LA, NGC, PC, JPB, GR, CG, XC, AA, OC, PMat, DG, DS, AT, VLR, VPZ, AD, FC, SP. Analysis and interpretation of data: AL, GH, HF, FC, SP. Drafting of the manuscript: AL, SP. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: GH, FC, CLN. Obtained funding: FC, HF, CD, VPZ, SP. Administrative, technical, or material support: FC, HF, CD, VPZ, SP. Study supervision: FC, HF, CD, VPZ, SP. Approval of the final version of the manuscript: all.

Ethics approval and consent to participate

Written informed consent was obtained from each patient before enrolment. The protocol was performed in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the “CPP Ile de France 3” Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM).

Consent for publication

not applicable.

Competing interests

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