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Sofosbuvir plus velpatasvir for 8 weeks in patients with acute hepatitis C: The HepNet acute HCV-V study

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Background & Aims: EASL guidelines recommend 8 weeks of treatment with sofosbuvir plus velpatasvir (SOF/VEL) for the treatment of acute or recently acquired hepatitis C virus (HCV) infection, but only 6- and 12-week data are available. Therefore, the aim of this study was to evaluate the safety and efficacy of a shortened 8-week SOF/VEL treatment for acute HCV monoinfection.

Methods: In this investigator-initiated, prospective, multicentre, single-arm study, we recruited 20 adult patients with acute HCV monoinfection from nine centers in Germany. Patients received SOF/VEL (400/100 mg) as a fixed-dose combination tablet once daily for 8 weeks. The primary efficacy endpoint was the proportion of patients with sustained virological response 12 weeks after the end of treatment (SVR12).

Results: The median HCV RNA viral load at baseline was 104,307 IU/ml; the distribution of HCV genotypes was as follows: GT1a/1b/2/3/4: n = 12/1/1/3/3. Thirteen (65%) of the 20 patients were taking medication for HIV pre-exposure prophylaxis. SVR12 was achieved in all patients who complied with the study protocol (n = 18/18 [100%], per protocol analysis), but the primary endpoint was not met in the intention-to-treat analysis (n = 18/20 [90%]) because two patients were lost to follow-up. One serious adverse event (unrelated to study drug) occurred during 12 weeks of post-treatment follow-up.

Conclusions: The 8-week treatment with SOF/VEL was well tolerated and highly effective in all adherent patients with acute HCV monoinfection. Early treatment of hepatitis C might effectively prevent the spread of HCV in high-risk groups.

Clinical Trial Number: NCT03818308.

Impact and implications: The HepNet acute HCV-V study (NCT03818308), an investigator-initiated, single-arm, multicenter pilot study, demonstrates the efficacy and safety of 8 weeks of daily treatment with the fixed-dose combination sofosbuvir/velpatasvir (400/100 mg) in patients with acute hepatitis C virus (HCV) infection. All patients who completed therapy and were followed-up achieved sustained virologic response. Thus, an 8-week treatment with SOF/VEL can be recommended for patients with acute HCV monoinfection and early treatment might effectively prevent the spread of HCV in high-risk groups.

Introduction

Hepatitis C virus (HCV) infection is one of the leading global health problems. According to the WHO, there are an estimated 58 million chronically infected people worldwide and about 1.5 million new infections per year, resulting in an annual rate of more than 250,000 deaths (https://www.who.int/news-room/fact-sheets/detail/hepatitis-c).

Direct-acting antivirals are now available, and combination therapy of NS5A inhibitors with either a protease inhibitor or polymerase inhibitor results in sustained virologic response

Keywords: acute HCV infection; direct-acting antivirals; hepatitis C elimination; recently acquired infection.

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(SVR) in more than 95% of individuals with chronic hepatitis C.[1] Therefore, it is theoretically possible to eradicate HCV infection globally, and the WHO has accordingly set elimination targets of a 90% reduction in HCV incidence by 2030 compared to 2015 baselines, resulting in a 65% reduction in HCV-related mortality.[2] However, despite these successes in treating chronic hepatitis C, major challenges in the cascade of care must be overcome if we are to achieve HCV elimination. One of the main barriers is early diagnosis and treatment of high-risk groups, such as people who inject drugs or men who have sex with men, who contribute significantly to the ongoing transmission of HCV. As a result, more new acute HCV infections than cured chronic infections are observed in certain high-exposure risk populations, particularly because of high transmission and reinfection rates in these high-risk groups.[3,4] Thus, if people with high-risk behaviors are not treated immediately and treatment programs are not scaled up, they will transmit HCV to many more individuals, and re-infections of already cured individuals will continue to occur.[5–7]

Since there is currently no prophylactic HCV vaccine, early treatment of high-risk groups is likely to be an important aspect of elimination strategies.[8,9] Indeed, early treatment of acute hepatitis C has been shown to be safe and almost always to prevent chronic progression in numerous studies, including those conducted when interferon-alfa was still used for treatment.[10–17] However, many studies on this topic have also been heterogeneous, with mixed populations of HCV-monoinfected or HCV/HIV-coinfected people and inconsistent definitions of acute HCV infection, with people often classified as having recently acquired and early chronic hepatitis C (*e.g.* infection for less than 12 months).[14,15] Nevertheless, based on available data, the EASL guidelines recommend early treatment of HCV infection (acute or recently acquired) with pan-genotypic DAA therapy for 8 weeks with either glecaprevir/pibrentasvir (GLE/PIB) or sofosbuvir/velpatasvir (SOF/VEL).[1] The efficacy of 8 weeks of GLE/PIB should be >95% based on data in individuals with chronic hepatitis C[18] and a study reported high SVR rates of 96% even with 6 weeks of GLE/PIB in people with recent HCV infection without any safety concerns.[15] For SOF/VEL, 6- and 12-week treatment regimens have been studied[14] but not 8-week regimens as recommended by the EASL guidelines.[1] In addition, treatment of acute HCV infection is not included in the marketing authorization label. Thus, the acute HCV-V study fills an important gap and provides data on the safety and efficacy of 8 weeks of SOF/VEL in people with acute hepatitis C without HIV coinfection.

Patients and methods

Study design and patients

The investigator-initiated HepNet acute HCV-V study was designed as a phase II, national, multicentre, prospective, single-arm pilot study and was coordinated by the HepNet Study-House, a project of the German Liver Foundation, funded by the German Center for Infection Research (DZIF). The trial was conducted at nine clinical sites in Germany. Each patient included in the study gave written informed consent. Detailed inclusion and exclusion criteria are listed in table S1. Briefly, eligible patients were at least 18 years of age with an acute HCV monoinfection, confirmed by HCV RNA levels >10^3 IU/ml at the time of the screening. Acute HCV infection was defined as documented seroconversion to HCV antibody within 4 months before screening or documented conversion to HCV RNA positivity 4 months before screening or a known or suspected exposure to HCV with raised alanine aminotransferase (ALT) concentration more than 10x the upper limit of normal within 4 months preceding screening. Key exclusion criteria were presence of cirrhosis, clinical hepatic decompensation, solid organ transplantation, infection with HIV, uncontrolled drug abuse and clinically significant illness that might interfere with study treatment, assessment, or compliance with the protocol. Other causes of liver disease were excluded by standard clinical and laboratory criteria. Coinfection with HIV, significant illnesses other than HCV and any contraindication to the intake of SOF/VEL were exclusion criteria.

Procedures

After screening for inclusion and exclusion criteria, patients received SOF/VEL (dose 400/100 mg) once daily for 8 weeks in an open label one-arm trial design with a subsequent 12 weeks follow-up. Study visits occurred at screening, baseline, week 2, week 4, week 8 (end of treatment) of antiviral treatment and 12 weeks after the end of therapy. Blood and serum samples were obtained at each study visit and HCV RNA was quantified in the central laboratory of Hannover Medical School using the Hologic Aptima® HCV Quant Assay with a lower limit of quantification (LLOQ) of 10 IU/ml. Biochemical responses (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase) and HCV genotype were assessed by the local laboratory of each center in serum samples using standard assays on automated platforms.

Outcomes

The primary efficacy endpoint was defined as the proportion of patients with HCV RNA below the LLOQ 12 weeks after stopping treatment. Secondary endpoints were virologic and biochemical kinetics at baseline, week 2, week 4, week 8, and week 12, and the proportion of patients achieving ALT normalization (ALT below the upper limit of normal; ULN) at 8 weeks of therapy and 12 weeks after the end of therapy. In addition, the safety and tolerability of SOF/VEL were evaluated based on an analysis of documented adverse events and serious adverse events. The study procedures and safety assessment are described in detail in the study protocol.

Ethics

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee (Hannover Medical School ethics committee, vote no. 8282_AMG_M_2019). The protocol was registered at ClinicalTrial.gov (NCT03818308).

Statistical analyses

This study was planned as a pilot trial with 20 patients and under the assumption that the proportion of patients who achieve a response will be close to 100% based on previous acute HCV-IV study data.[12] The study is considered successful if the lower bound of the 95% Wilson CI is greater than 83%. The study had a power of 82% if the true response rate is greater than 98%. Baseline characteristics are reported as absolute and relative frequencies for categorical data and mean and SD for continuous data (except quantitative HCV RNA and liver enzymes). The primary analysis was conducted within the intention-to-treat (ITT) population (all patients who received at least one dose of study drug). The sensitivity analysis was conducted in the per protocol (PP) population (all patients that completed the study in

accordance with the study protocol). Safety was assessed in all patients who received at least one dose of study drug. All analyses were performed with SAS version 9.4.

Patients with missing values for the primary endpoint SVR12 were counted as treatment failures for the ITT analysis. These patients were hence counted as patients who did not show a sustained viral response. All other missing virology values were imputed with locally assessed data. Patients with HCV RNA viral loads greater than or equal to the LLOQ were counted as HCV RNA positive and patients with HCV RNA viral loads below the LLOQ were counted as HCV RNA negative.

Results

Study cohort

Between March 2019 and June 2021, 31 patients were screened, and 20 patients entered the study. Eleven patients were ineligible at screening: five patients had HCV RNA viral load <10^3 IU/ml at screening, five patients had no sufficient evidence of acute HCV infection, as defined in the inclusion criteria, and one patient had to be excluded due to COVID-19 restrictions at the respective study site (Fig. S1). Enrolled patients were predominantly men (95%), had a mean age of 37.4 years (SD 9.3) and most had HCV genotype 1a infection (60%). Two-thirds of the patients (n = 13 [65%]) were taking oral HIV pre-exposure prophylaxis with emtricitabine/tenofovir disoproxil and most patients had a primary acute HCV infection (95%) (Table 1). The exact route of transmission was not assessed in our study and information about any risk behavior could only be assumed due to concomitant medications like pre-exposure prophylaxis and drug substitutes.

Within the 4 months preceding screening, 10 patients had a documented seroconversion to HCV antibody (anti-HCV) positivity, four patients had a documented conversion to HCV RNA positivity and 10 patients had a known or suspected exposure to HCV with a documented peak ALT of more than 10x the ULN (median 719 U/L, IQR 590–988). In addition to anti-HCV seroconversion or new detection of HCV RNA, four patients also experienced peak ALT more than 10x the ULN with a documented infection event.

Median HCV RNA viral load at baseline was 104,307 IU/ml (IQR 7,842–1,726,734). Two patients had a viral load that was below the LLOQ at baseline but with HCV RNA >10^3 IU/ml at screening visit (measured at local study sites according to inclusion criteria). We did not exclude these individuals because it has been reported that chronic HCV infection can develop despite intermittent HCV RNA negativity.[19] Centrally measured HCV RNA levels were 1,426 IU/ml and 331 IU/ml for these two patients at screening. Four (20%) patients had jaundice with bilirubin concentration more than 1.5x the ULN at screening. Median ALT levels were 249 U/L (IQR 165–463).

Treatment efficacy

The mean time between first diagnosis of acute hepatitis C and start of antiviral therapy was 43.2 days (SD 25.6). In the ITT analysis (n = 20), HCV RNA levels were <10 IU/ml (LLOQ) in 19 patients (95%) after 4 weeks of antiviral treatment, in 19 patients (95%) at the end of therapy (treatment week 8), and in 18 patients (90%) after the 12-week follow-up period. The primary endpoint (ITT analysis, SVR12 100%, Wilson interval >83%) was not met, as the rate of SVR12 in the ITT analysis was 90% (95% Wilson interval CI [69.9%–97.2%]). During the study, two patients were lost to follow-up: one patient after week 4 of antiviral treatment and one patient during the 12-week follow-up period. Of note, both patients had HCV RNA levels below the LLOQ at their last study visit. In the PP analysis (n = 18), excluding the two patients lost-to-follow-up, HCV RNA levels were <10 IU/ml (LLOQ) in 17 patients (94%) after 4 weeks of treatment, and in all 18 patients at the end of treatment and 12 weeks after end of treatment. Thus, SVR12 was 100% (95% Wilson interval CI [82.41–100.00%]) in the PP analysis (Fig. 1).

Table 1. Baseline characteristics.

	Patients (n = 20)
Men	19 (95%)
Age [years]	37.4±9.3
BMI [kg/m^2]	22.8 ±2.8
HCV RNA [IU/ml]	10,4307 (7,842–1,726,734)
<50,000	8 (40%)
<10	2 (10%)
HCV genotype	
1a	12 (60%)
1b	1 (5%)
2	1 (5%)
3	3 (15%)
4	3 (15%)
Patients with oral HIV pre-exposure prophylaxis	13 (65%)
Patients with substitution treatment	2 (10%)
Patients with confirmed HCV reinfection	1 (5%)
Liver enzymes	
Alanine aminotransferase [U/L]	249 (165–463)
Aspartate aminotransferase [U/L]	133 (71–219)
Bilirubin [U/L]	12.0 (8.0–17.1)
Gamma-glutamyltransferase [U/L]	93 (52–160)

Values as median (interquartile range) or mean ± SD.

Biochemical response was rapid, with ALT concentrations declining into the normal range in 17 (85%) of 20 patients within the first 4 weeks of treatment, in 16 (80%) of 20 patients within the 8-week treatment period, and in 17 (85%) of 20 patients by follow-up week 12 (Fig. 1). One patient had abnormal ALT concentration during the whole study (ALT declined from baseline to week 2 by 62%, from 241 IU/ml to 91 IU/ml) but with persistently high ALT concentrations between 90 IU/ml and 131 IU/ml up to the end of follow-up. Bilirubin was above the ULN in four of 20 patients at baseline and normalized in all patients during the 8-week treatment period.

The individual HCV RNA and biochemical kinetics during the entire study period are displayed in Table S2.

Treatment safety

Treatment of acute hepatitis C with SOF/VEL was well tolerated. By 12 weeks post treatment, 28 adverse events were reported in total. Only six of these were reported as possible or probable drug-related adverse events, with very mild symptoms that occurred during medical treatment: 2/20 [10%] patients reported skin irritations (one twice), 1/20 [5%] patients reported sleeping disorders, 1/20 [5%] patients reported flatulence and 1/20 [5%] patients reported headache. There was only one serious adverse event that was classified as unrelated to the study drug; this patient presented with unusual behavior at the study site and was hospitalized due to toxicity to various agents (suspected intoxication with ketamine, benzodiazepines, and amphetamines based on external history). Overall, there were no significant changes in creatinine clearance, serum lipase concentration, or other safety-related biochemical or hematologic measures during or after therapy.

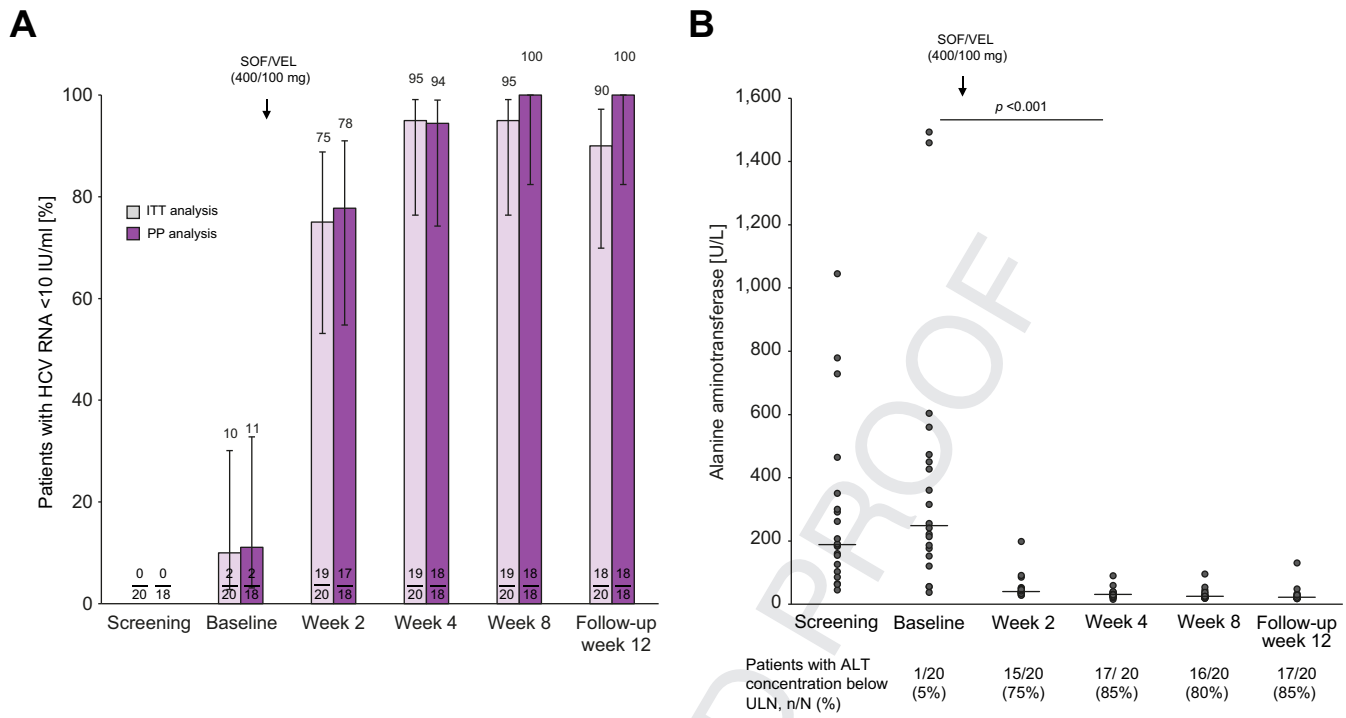

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Fig. 1. Virological and biochemical response. (A) Response to antiviral treatment by patients with serum HCV RNA levels <10 IU/ml LLOQ in ITT and PP analysis. Two patients were lost to follow-up. Percentage of patients ±95 Wilson confidence interval. (B) Decline of ALT by scatter plot with median line; ULN; Friedman test with *post hoc* analysis (n = 20). ALT, alanine aminotransferase; DZIF, German Center for Infection Research; GLE/PIB, glecaprevir/pibrentasvir; HCV, hepatitis C virus; ITT, intention-to-treat; LLOQ, lower limit of quantification; PP, per protocol; SOF/VEL, sofosbuvir/velpatasvir; ULN, upper limit of normal.

Discussion

There is still some controversy about whether patients with acute hepatitis C should be treated early because treatment may be unnecessary, leading to avoidable costs and side effects, as 20-50% of patients spontaneously eliminate HCV. However, studies have shown that an unrestricted access to early treatment leads to a substantial decline in new HCV infections in high-risk settings.[8] In addition, it has been suggested that immediate treatment of acute HCV infection can actually be cost-effective.[20] Therefore, we believe early treatment of acute HCV infection is an important tool to achieve WHO elimination goals. Current guidelines indeed recommend treatment of patients with acute or recently acquired HCV infection,[1] although this is not included in the marketing authorization label of any EMA- and FDA-approved DAAs. Thus, safety and efficacy data in this setting remain important for possible indication expansion.

Our prospective study supports the EASL recommendation of 8 weeks SOF/VEL for patients with acute or recently acquired HCV infection. It is important to note that we only enrolled patients with acute HCV infection based on a very strict definition. This subsequently restricted our recruitment target to only 20 patients, which is a limitation of this study. Nevertheless, the definition of acute HCV infection in our and other studies cannot always reliably exclude chronic HCV infection. Fourteen patients had documented anti-HCV seroconversion or conversion to HCV RNA positivity, but in six patients with a 10-fold ALT elevation and known/suspected HCV exposure, we cannot be 100% certain of acute HCV infection because of the absence of HCV RNA testing in the past. Because of this limited sample size, the study narrowly failed to meet the primary endpoint (100% SVR, Wilson interval >83%), although no relapse occurred, because two patients were lost to follow-up. Nevertheless, it is important for the consideration of the extension of approval that we also have safety data on DAA therapy in patients with acute infection. From this study and the earlier acute HCV-IV study in 20 patients with acute HCV treated with sofosbuvir/ledipasvir,[12] we can conclude that treatment with sofosbuvir plus a NS5A inhibitor is safe in patients with acute hepatitis C and high ALT, some even with elevated bilirubin. Importantly, early treatment with SOF/VEL was not only safe in patients with severe hepatitis activity, but also resulted in very rapid improvement of liver enzymes within a few weeks. Thus, early treatment likely shortened the duration of symptomatic disease, which could have major relevance for individual patients.

The high efficacy of 100% in the PP analysis in this study is not surprising and confirms the results of other studies[12,13,15–17] showing that a short duration of therapy is feasible in recently infected patients. Nevertheless, this confirmation is important because there was theoretical concern that 8 weeks of SOF/VEL was not sufficient, as 12 weeks is the standard treatment for patients with chronic hepatitis C and 6 weeks of therapy was associated with a higher relapse rate in a randomized trial of 188 patients with recently acquired hepatitis C that was published by Matthews *et al.* last year.[14] However, it is important to note that unlike the authors of this paper,[14] we did not include HIV-coinfected patients nor those with a duration of infection longer than 6 months, who still fall within the definition of recently acquired infection but do not meet the criteria for acute

HCV infection. These patients may respond differently but must also be considered when making a clear recommendation for 8 weeks of SOF/VEL. One additional factor that may be associated with a suboptimal response after shorter treatment in this setting is very high baseline HCV RNA.[21]

Therefore, to avoid consideration of all these variables that might mitigate against shortened therapy in acute or recently acquired HCV infection, we propose that the word "chronic" simply be removed from the label of pan-genotypic DAA therapies so that all patients with HCV infection can be treated immediately, regardless of the stage of infection. This would greatly simplify treatment decisions, which is critical to achieving elimination goals. In addition, immediate treatment of acute HCV infection may reduce the risk of losing patients during follow-up, which is quite common in high-risk groups and in acute HCV infection.[11] Even in our controlled trial with patients being treated by experienced centers and close monitoring, the lost-to-follow-up rate was still 10%. However, it is quite possible that all patients, including the lost-to-follow-up cases, have eliminated HCV, since they have received the therapy for a few weeks and even 4 weeks DAA therapy may be effective in a substantial number of patients.[22]

Finally, another important issue for HCV elimination that needs to be discussed in this context is the development of a prophylactic HCV vaccine,[23] which we believe is also an important concept for reaching HCV elimination goals. The development of such a vaccine is challenging due to the lack of suitable animal models. Prospective trials in high-risk persons have been shown to be feasible but require huge efforts and resources and take quite some time.[24] Therefore, a controlled human infection model such as those used for Influenza A or SARS-CoV-2 infections[25–27] would be a possibility for testing an early-stage HCV vaccine, and this is currently being discussed by renowned experts as a great opportunity to accelerate HCV vaccine development.[28] It is essential for the discussion to have an effective and safe back-up treatment as early as possible in case the tested vaccine fails to prevent HCV infection. Therefore, the data from this study are also relevant to this discussion.

In conclusion, our data confirm that early treatment of acute HCV infection is safe and effective, and this supports current guideline recommendations for the treatment of acute or recently acquired HCV infection. These data are important as they support simplification of the treatment cascade, *e.g.* by removing “chronic” from the label of current pan-genotypic DAA regimens, and the consideration of controlled human infection models to accelerate HCV vaccine development.

Abbreviations

ALT, alanine aminotransferase; HCV, hepatitis C virus; ITT, intention-to-treat; LLOQ, lower limit of quantification; PP, per protocol; SVR, sustained virologic response; ULN, upper limit of normal.

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Conflicts of interest

The authors declare no conflict of interest concerning the content of this manuscript. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors’ contributions

The study was designed and protocol was written by MC, BM, HW, MvK and MPM; the study was coordinated by MC, BM, JK, PD; patients were recruited and treated by MC, BM, PI, CDS, CC, HJS, JSzW, SS, KD, TM; data analysis and statistics were performed by MvK, MC, BM, JK. Drafting of the manuscript were done by MC, BM, PI, MvK, JK, PD and HW, critical revision of the manuscript was performed by all authors. MC, BM, MvK and JK has access to all data and can vouch for integrity of data analysis.

Data availability statement

All data is available from the corresponding authors upon special request.

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Supplementary data

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Supplemental information

Sofosbuvir plus velpatasvir for 8 weeks in patients with acute hepatitis C: The HepNet acute HCV-V study

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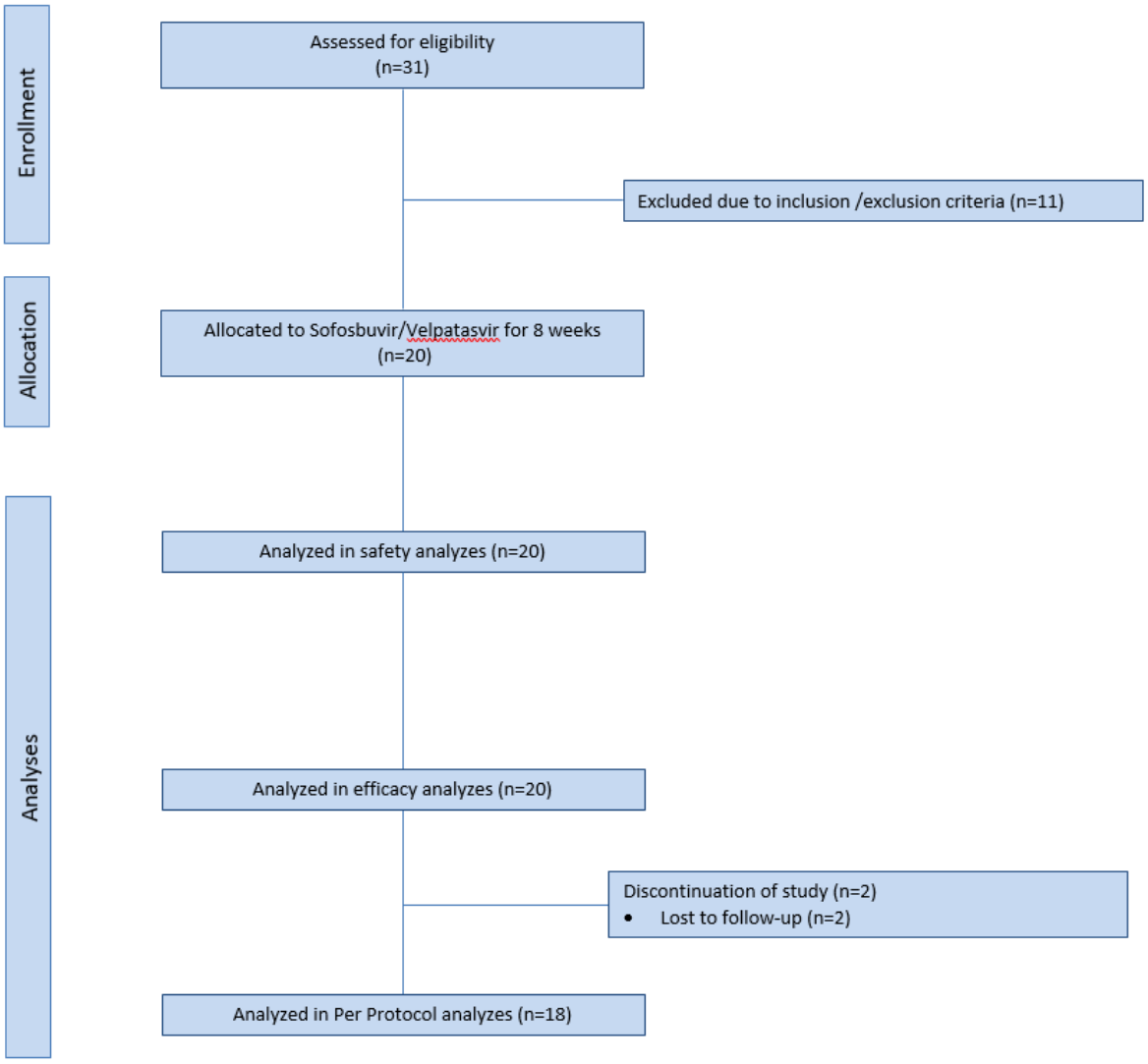

Fig. S1. Consort chart of patient population

Table S1. Detailed inclusion and exclusion criteria

Inclusion criteria:

1. Willing and able to provide written informed consent
2. Male or female, age ≥ 18 years
3. HCV RNA > 10^3 IU/mL at screening
4. Confirmation of acute HCV infection documented by either:
   a. Documented seroconversion to HCV antibody (anti-HCV) positivity within the 4 months preceding screening
   b. Documented conversion to HCV RNA positivity within the 4 months preceding screening
   c. or known or suspected exposure to HCV within the 4 months preceding screening with 10 times elevated serum ALT level at screening or 4 months preceding screening without evidence of confounding liver disorders
5. Body mass index (BMI) ≥18 kg/m2
6. Subjects must have the following laboratory parameters at screening:
   a. INR ≤ 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR
   b. HbA1c ≤10%
   c. Creatinine clearance (CLcr) ≥ 30 mL/min, as calculated by the Cockcroft-Gault equation (using actual body weight)
7. A negative serum pregnancy test is required for female subjects (unless surgically sterile or women ≥ 54 years of age with cessation for 24 ≥ months of previously occurring menses). Complete abstinence from intercourse. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) is not permitted.

   Or

   Consistent and correct use of 1 of the following methods of birth control listed below, in addition to a male partner who correctly uses a condom, from the date of Screening until the end of FU:

   - intrauterine device (IUD) with a failure rate of < 1% per year
   - tubal sterilization
   - vasectomy in male partner
   - hormone-containing contraceptive:
     - implants of progestogen-only hormonal contraception associated with inhibition of ovulation
     - injectable progestogen-only hormonal contraception associated with inhibition of ovulation
     - oral contraceptives (either combined or progestogen-only hormonal contraception associated with inhibition of ovulation)
     - contraceptive vaginal ring
     - transdermal contraceptive patch
8. Subject must be able to comply with the dosing instructions for study drug administration and be able to complete the study schedule of assessments.

Exclusion criteria:

1. Subject has been treated with any investigational drug or device within 42 days of the Screening visit or within 5 half-lives for investigational drugs, whichever is longer
2. Co-Infection with HIV
3. Clinically-significant illness (other than HCV) or any other major medical disorder that, in the opinion of the investigator, may interfere with subject treatment, assessment or compliance with the protocol.
4. Solid organ transplantation
5. Gastrointestinal disorder or post-operative condition that could interfere with the absorption of the study drug (for example, gastric bypass or severe ulcerative colitis).
6. Clinical signs of hepatic decompensation (i.e., clinical ascites, encephalopathy or variceal hemorrhage).
7. Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy.
8. Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 2 years. Subjects with psychiatric illness that is well-controlled on a stable treatment regimen for at least 12 months prior to screening or has not required medication in the last 12 months may be included.
9. Significant drug allergy (such as anaphylaxis or hepatotoxicity).
10. Pregnant or nursing female
11. Clinically-relevant drug or alcohol abuse that significantly impairs patient compliance. Uncontrolled users of intravenous drugs will not be permitted to enroll in the study.
12. Clinical relevant(not controlled) liver disease of a non-HCV etiology (e.g., hemochromatosis, autoimmune hepatitis, alcoholic liver disease, Wilson's disease, alpha1 antitrypsin deficiency, cholangitis)
13. Use of any prohibited concomitant medications within 21 days before the Baseline/Day 1 visit. The use of amiodarone is prohibited from 60 days prior to Day 1 through the end of treatment
14. Known hypersensitivity to SOF/VEL or formulation excipients.

Table S2. Individual virologic and biochemical kinetics during the study

Patient		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Sex		male	male	male	female	male	male	male	male	male	male	male	male	male	male	male	male	male	male	male	male
Age [y]		42	28	39	31	42	47	31	59	37	31	35	29	25	38	42	26	48	28	45	29
Genotype		1a	1a	1a	1b	2	1a	1a	3	4	4	1a	1a	1a	1a	4	1a	3	3	1a	1a
	SCR	6,33	4,96	4,52	4,80	7,27	3,18	4,09	2,52	3,01	6,99	7,82	5,41	4,25	6,39	3,15	4,37	5,54	3,55	6,06	7,03
	BL	3,89	4,85	4,59	5,46	6,81	1,38	3,84	ND	5,48	7,05	6,90	5,24	5,14	6,47	ND	3,96	5,69	3,90	4,83	7,47
HCV RNA	W2	-	ND	ND	ND	ND	ND	ND	ND	ND	1,52	1,46	ND	ND	ND	ND	ND	1,48	ND	ND	1,73
[log_{10} IU/ml]	W4	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	-	ND	ND	ND	ND	ND	ND	ND	ND
	W8	-	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	FU12	-	-	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SCR	103	292	351	160	262	65	155	45	86	183	126	300	1045	186	63	729	191	465	779	207
Alanine	BL	474	177	316	1494	121	55	152	38	560	451	1459	361	604	256	56	222	214	427	241	186
amino-	W2	-	29	36	86	35	40	42	32	38	53	199	51	34	29	49	38	34	42	91	46
transferase	W4	16	32	31	21	23	39	37	34	26	29	59	-	23	26	40	31	26	32	90	30
[U/L]	W8	-	28	22	21	20	35	44	-	19	28	54	28	19	24	37	21	21	22	96	26
	FU12	-	-	21	19	19	33	22	31	20	23	22	49	20	25	21	18	18	22	131	29
	SCR	44	78	142	107	116	40	101	32	33	86	75	139	413	104	35	323	95	116	430	97
Aspartate	BL	196	125	140	1106	62	38	97	30	349	238	977	154	293	142	35	62	107	199	108	80
amino-	W2	-	22	30	32	36	36	20	27	28	35	185	37	29	34	32	25	29	31	50	45
transferase	W4	14	26	27	23	26	31	32	29	26	43	39	-	34	43	38	27	27	27	45	33
[U/L]	W8	-	26	25	21	24	32	27	-	18	34	45	-	25	37	37	26	25	22	52	29
	FU12	-	-	26	25	23	29	19	24	24	29	24	44	26	31	23	23	25	30	87	30
	SCR	90	60	82	97	88	88	80	80	75	92	91	83	80	87	84	71	80	68	68	81
	BL	81	57	66	88	71	88	74	85	76	91	83	88	99	95	93	63	77	73	81	88
Creatinine	W2	-	65		80	88	80	79	80	76	95	76	88	100	87	100	73	80	71	79	103
[µmol/L]	W4	79	62	59	97	88	80	75	90	74	96	84	-	78	116	88	64	79	67	70	88
	W8	-	68	82	88	71	71	73	-	72	106	84	82	73	97	89	57	80	71	72	95
	FU12	-	-	79	88	80	80	77	87	82	100	77	100	85	78	78	60	88	75	86	92
	SCR	96	91	360	25	64	78	45	101	39	34	43	154	198	146	91	112	50	159	691	114
Gamma-	BL	158	93	282	135	71	49	37	75	49	40	354	161	135	165	60	54	49	128	485	92
glutamyl-	W2	-	49	151	82	47	40	33	53	33	29	195	72	57	74	39	36	28	61	352	51
transferase	W4	39	35	95	40	35	30	18	41	18	19	71	-	32	40	32	34	17	35	316	25
[U/L]	W8	-	26	30	15	31	23	18	-	12	13	38	-	18	21	24	18	10	20	334	15
	FU12	-	-	24	12	31	17	15	26	11	9	18	13	12	35	19	18	7	16	388	13

Hemoglobin [g/L]	SCR	134	135	153	146	145	154	157	158	154	159	141	136	142	142	162	156	145	142	149	153
	BL	123	140	158	148	137	146	152	156	146	156	137	141	155	136	156	142	146	139	150	161
	W2	-	145	149	141	137	150	160	161	150	159	139	143	148	139	160	143	144	143	151	172
	W4	145	154	159	134	132	149	145	155	151	155	139	-	156	134	154	152	140	131	152	153
	W8	-	155	145	143	153	149	151	-	146	156	147	156	143	127	161	157	130	132	151	161
	FU12	-	-	153	139	131	148	154	146	152	156	135	143	143	140	159	147	139	135	148	167
Platelet count [10^3/µL]	SCR	219	261	347	199	134	234	220	283	176	259	307	345	213	298	222	228	245	238	110	184
	BL	215	212	362	177	167	206	168	329	140	237	208	329	244	321	217	236	246	232	203	180
	W2	-	238	352	246	228	229	206	280	192	234	336	331	243	300	221	296	271	236	175	206
	W4	344	229	406	174	131	237	189	300	178	204	294	-	249	286	219	256	239	230	175	155
	W8	-	226	402	198	154	237	191	-	183	231	265	293	225	303	214	284	298	236	156	160
	FU12	-	-	374	181	135	228	182	297	161	234	339	233	258	342	213	270	233	252	203	155
Bilirubin [µmol/L]	SCR	54	80	14	10	5	10	14	10	9	7	10	10	23	5	10	35	11	10	34	17
	BL	38	23	17	10	5	10	12	7	12	7	17	12	28	6	12	13	8	8	11	26
	W2	-	14	10	9	5	9	21	6	5	9	10	5	29	6	9	23	6	12	8	24
	W4	10	10	14	10	7	10	-	6	7	12	7	-	27	12	13	13	10	10	9	9
	W8	-	4	12	9	14	15	14	-	3	10	15	-	15	10	12	15	8	8	5	10
	FU12	-	-	9	17	3	12	10	6	10	9	3	22	13	8	12	12	7	9	12	9

HCV, hepatitis C virus; RNA, ribonucleid acid; SCR, screening; BL, baseline; W2, week 2; W4, week 4; W8, week 8; FU12, follow up week 12