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Article type : SuperFast

Changes in Patient-Reported Outcomes in Direct Acting Antiviral-Naïve Chronic Hepatitis C Patients with or without Cirrhosis: The Impact of Sofosbuvir and Velpatasvir with or without Voxilaprevir

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/apt.14423](https://doi.org/10.1111/apt.14423)

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Running Title: Voxilaprevir and health related quality of life

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Word Count (Body of the manuscript): 2531

Abstract: 248

Tables: 1

Figures: 3

Ethical approval: The study was approved by the institutional review boards. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Abbreviations:

DAA – direct-acting anti-viral agents; GT- genotype; HCV- hepatitis C virus; PRO – patient-reported outcome; SVR12- sustained virologic response at 12 weeks after treatment; RBV – ribavirin; SOF – sofosbuvir; VEL - velpatasvir; VOX – voxilaprevir.

ABSTRACT

Background: Chronic hepatitis C infection leads to impairment of patient-reported outcomes (PROs). Treatment with direct-acting antiviral regimens results in short- and long-term improvement of these outcomes. **Aim:** Assess PROs in patients treated with a newly developed direct-acting antiviral, a fixed-dose combination of sofosbuvir/velpatasvir (SOF/VEL) with/without voxilaprevir (VOX). **Methods:** The PRO data was collected from participants of POLARIS-2 and POLARIS-3 clinical trials (DAA-naïve, all HCV genotypes). Participants self-administered SF-36v2, FACIT-F, CLDQ-HCV and WPAI:SHP instruments at baseline, during treatment, and in follow-up. **Results:** Of 1,160 patients, 611 received SOF/VEL/VOX and 549 received SOF/VEL (52.8±11.0 years, 55.9% male, 75.4% treatment-naïve, 33.9% cirrhotic). The SVR-12 rates were 95-98%. During treatment, improvements in most PRO scores were significant (all but one $p<0.01$) and ranged from, on average, +2.3 to +15.0 points (on a 0-100 scale) by the end of treatment. These improvements were similar between SOF/VEL/VOX and SOF/VEL arms (all $p>0.05$). After treatment discontinuation, patients treated with both regimens achieved significant and clinically meaningful PRO gains (+2.7 to +16.7 by post-treatment week 12, +3.9 to +20.1 by post-treatment week 24; all but one $p<0.001$). Multivariate analysis showed that depression, anxiety and cirrhosis were the most consistent independent predictors of PRO impairment while no association of PROs with the treatment regimen choice was found (all $p>0.05$). **Conclusions:** The pan-genotypic regimens with SOF/VEL with or without VOX not only have excellent efficacy and safety but also significantly positively impact patients' experience during treatment and after achieving sustained virologic response in DAA-naïve patients with HCV.

Key Words: HCV, health utility, PROs, fatigue, work productivity, activity.

INTRODUCTION

In the past decade, treatment of hepatitis C infection with different combinations of direct-acting antiviral agents (DAAs) has been revolutionized. The most recent advances in this field have led to 8- to 12 week-long treatment with single-pill all-oral pan-genotypic regimens with over 95%

sustained virologic response (SVR) rates [1-16]. In fact, these high rates of response have been documented even in difficult-to-treat HCV subpopulations, including those with genotype 3, cirrhosis, and prior DAA experience [2,4,6-16]. Furthermore, the regimens have been shown to be simple, safe, and also associated with improved patient-reported outcomes (PROs) such as health-related quality of life (HRQL), fatigue, and daily functioning during and after treatment [17-35].

A relatively new addition to the landscape, 8- or 12 week-long regimens containing sofosbuvir (SOF), velpatasvir (VEL) and voxilaprevir (VOX) have been shown to result in excellent efficacy and safety [1,16]. Prior studies reported significant improvements in multiple aspects of patients' well-being in different patient populations treated with SOF/VEL alone [29-33]. However, the effect of the addition of VOX, a pan-genotypic NS3/4A protease inhibitor, on on-treatment and post-treatment PROs is not well understood. Therefore, the aim of the current study was to assess treatment-emergent changes in PROs of DAA-naïve patients with chronic HCV who received the new SOF/VEL/VOX regimen and to compare those to PROs of patients who received SOF/VEL only.

METHODS

In this study, we used the PRO data collected from participants of POLARIS-2 (clinicaltrials.gov #NCT02607800) and POLARIS-3 (#NCT02639338) studies; both studies were randomized open-label phase 3 clinical trials of SOF/VEL/VOX in DAA-naïve (treatment-naïve or treatment-experienced with an IFN-based regimen) patients with chronic HCV infection. In POLARIS-2, DAA-naïve patients of all HCV genotypes with or without cirrhosis (excluding patients with genotype 3 and cirrhosis) were randomized 1:1, stratified by HCV genotype, cirrhosis status, and treatment history, to receive either a fixed-dose combination of SOF, VEL, and VOX (400/100/100mg) once daily for 8 weeks or SOF/VEL (400/100 mg) once daily for 12 weeks. In POLARIS-3, DAA-naïve patients with HCV genotype 3 and cirrhosis were also randomized 1:1 to receive these regimens, stratified by treatment history. In both studies, eligibility criteria included being of at least 18 years of age, willingness and ability to give an informed consent, having no clinically significant illness or health condition other than chronic HCV infection, no history of hepatic decompensation, the absence of HBV or HIV co-infection,

no recent alcohol or drug abuse, and no history of noncompliance during previous treatment with an IFN-based regimen, if any [1,16]. In both studies, the presence of cirrhosis in participants was ascertained by a prior liver biopsy (Metavir score=4), or a combination of APRI (>2) and Fibrotest (>0.75), or by transient elastography (>12.5 kPa).

The trials were conducted in the U.S., Canada, Australia, New Zealand, Germany, France, and the United Kingdom in 2015-2017. Other details of the trials' design and safety and efficacy outcomes of both trials have been published [1]. Using medical history collected at screening, we identified patients with pre-treatment history of depression or mood disorders, clinically overt fatigue, anxiety or panic disorders, insomnia or sleep disorders, and type 2 diabetes mellitus (DM). Treatment-related adverse events reported by the investigators were summarized by the body system or organ class.

Patient-Reported Outcomes

Patient-reported outcomes were prospectively collected as exploratory endpoints in both POLARIS-2 and POLARIS-3 studies: the participants self-administered four PRO instruments (the Short-Form-36 (SF-36), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), the Chronic Liver Disease Questionnaire-HCV Version (CLDQ-HCV), and the Work Productivity Activity Index: Specific Health Problem (WPAI:SHP) [36-40]) on the first day of treatment (the baseline level), at treatment week 4, the last day of treatment, and during week 4, 12 and 24 follow-up visits. For the current analysis, PRO data from the POLARIS-2 and POLARIS-3 studies are pooled and analyzed by the treatment group.

The SF-36 includes 8 independent HRQL domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. It also includes 2 summary HRQL scores – Physical (PCS) and Mental (MCS) Component Summary [36]. The FACIT-F includes 5 HRQL domains – Physical Well-Being, Emotional Well-Being, Social Well-Being, Functional Well-Being, Fatigue Scale, and one summary score [37]. The CLDQ-HCV includes 4 HRQL domains – Activity/Energy, Emotional, Worry, and Systemic Symptoms, accompanied by a summary score [38-39]. Finally, the WPAI:SHP includes Work Productivity Impairment and Activity Impairment scores; the former is a sum of Presenteeism

and Absenteeism scores [40]. Thus, the four PRO instruments assess a total of 25 PRO domain and summary scores. In addition, we also used SF-36 to calculate the preference-based utility score (SF-6D) using a previously published non-parametric algorithm [41]. The use of those four PRO instruments in clinical trials in patients with HCV has been previously described [17-35]. With the exception of WPAI:SHP, all instruments presume positive scoring of the included PROs (i.e., greater scores are supposed to reflect better health status). For presentation purposes, we additionally transformed changes in PROs from their original scales to a universal 0-100 scale.

Statistical Analysis

Clinico-demographic parameters, baseline, on-treatment, and post-treatment PRO scores were summarized as N (%) or mean $\pm$ standard deviation and compared between the two treatment arms using chi-square test or a Mann-Whitney non-parametric test. Also, at all study time points, we calculated the changes (decrements or improvements) in the PRO scores with reference to patients' own baseline levels, and used Wilcoxon sign rank test to identify significant changes. Only p-values not exceeding 0.05 were considered potentially statistically significant.

Independent predictors of PRO scores at baseline, during treatment and in follow-up were assessed using multiple linear regression models. Potential predictors included location (USA vs. non-USA), age, gender, race, BMI, anti-HCV treatment history, history of psychiatric comorbidities, clinically overt fatigue, and type 2 diabetes, and the presence of cirrhosis; those potential predictors were subjected to bidirectional stepwise selection with $p=0.20$ for entry and 0.05 for stay. At post-baseline time points, we also assess the association of the treatment regimen used with the treatment-emergent changes in the PRO scores; for that purpose, adjustment for the baseline PRO levels was added.

All analyses were run using SAS 9.4 (SAS Institute, Cary, NC). The study was separately approved by each site's Institutional Review Board.

RESULTS

A total of 1,160 DAA-naïve patients with chronic HCV were included. Of these, 549 were treated with SOF/VEL and 611 with SOF/VEL/VOX. The cohort from the two studies was 52.8 ± 11.0 years old, 56% male, 82% white, 56% enrolled in the U.S., 75% treatment-naïve and 34% cirrhotic. Clinico-demographic parameters of patients assigned to different treatment regimens were generally similar except for a slightly greater proportion of Asian patients in the SOF/VEL/VOX group and genotype imbalance as per the design of the original studies (**Table 1, Supplementary Table 1**). Consistent with prior reports, during treatment, there was a higher rate of mild gastrointestinal adverse events in the SOF/VEL/VOX group: 29.6% vs. 14.8% ($p < 0.0001$). The SVR-12 rates were 95%-98% in both treatment arms in the two studies [1].

Patient-reported outcomes during treatment

Regardless of the regimen, significant improvements in nearly all studied PRO scores were observed soon after treatment initiation. In particular, by treatment week 4, improvements from the baseline scores were statistically significant in both treatment arms for 20 out of 26 PRO domains, and the average magnitude of such improvement ranged from +1.7 to +12.5 points on a universal 0-100 PRO scale (**Figure 1A**). The same or greater improvements were sustained throughout treatment duration: with reference to patients' own baseline levels, the PRO scores improved in 22/26 domains in both treatment arms, and the average improvement ranged from +2.3 to +15.0 points (**Figure 1B**). No differences in treatment-emergent changes in the PRO scores were seen between SOF/VEL and SOF/VEL/VOX treatment arms at any time point during treatment (all $p > 0.05$).

In a subgroup analysis of patients with cirrhosis (N=193 treated with SOF/VEL, N=200 with SOF/VEL/VOX), PRO improvements were equivalent or more pronounced in those with cirrhosis as compared to those without cirrhosis: from +2.7 to +17.9 points by the end of treatment ($p < 0.05$) (**Figure 2**).

Patient-reported outcomes after treatment

After treatment cessation, regardless of the regimen, all PRO gains were sustained or further improved (**Figure 3**). In particular, by post-treatment week 4, all but one PRO improvement became statistically significant, and the average PRO improvement ranged from +2.6 to +16.4

points. By post-treatment week 12, the same improvements were noted ranging from +2.7 to +16.7 points (**Supplementary Figure 1A**). Finally, by post-treatment week 24, these PRO gains ranged increased ranging from +3.9 to +20.1 points (**Supplementary Figure 1B**). In fact, by week 24 follow-up, the only PRO domain that did not improve was the Absenteeism component of WPAI:SHP which remained at the baseline level at all time points (all $p>0.05$).

In patients with cirrhosis, post-treatment PRO improvements were again similar or more pronounced in comparison to those without cirrhosis, ranging from +4.5 to +18.7 points by post-treatment week 12, from +4.4 to +23.5 points by post-treatment week 24.

Predictors of patient-reported outcomes

In multivariate analysis, independent predictors of lower baseline PRO scores included older age, female gender, being enrolled outside the U.S., as well as history of anxiety, depression, clinically overt fatigue, sleep disorders, cirrhosis, and DM (**Supplementary Table 2**). After additional adjustment for the baseline PRO levels, no association of the treatment regimen used (SOF/VEL vs. SOF/VEL/VOX) with on-treatment or post-treatment PRO scores was found (all $p>0.05$). On the other hand, having baseline comorbidities or cirrhosis was associated with greater PRO improvements during or after treatment (**Supplementary Table 3**).

In a separate multivariate analysis of patients with cirrhosis, independent predictors of lower PROs included history of depression, anxiety and insomnia. Similarly, to the entire cohort, no association of the treatment regimen with treatment-emergent PROs (after adjustment for the baseline levels) was found (all $p>0.05$).

DISCUSSION

In this study, we have shown that treatment of chronic hepatitis C with SOF/VEL/VOX, a new pan-genotypic regimen, positively impacts patients' experience during treatment and after achieving SVR. These data support the comprehensive benefit of this regimen for patients with chronic HCV infection [1,16,42].

Although historically, clinical outcomes, such as SVR, have been emphasized as the primary endpoints of clinical trials, PROs are now being increasingly recognized as important endpoints in studies involving patients with HCV. Indeed, SVR has been accepted as a surrogate for the clinical benefit of treatment which should ultimately lead to improvement in patients' survival [43-44]. In contrast, PROs can be considered a surrogate for patients' experience, and, thus, their improvement are of utmost importance from patients' perspective. In this context, it is critical that the new regimens for HCV are not only assessed for their efficacy and safety, but also for their impact on PROs.

It has previously been shown that SOF/VEL improves PROs during treatment after achieving SVR (32, 33). The current study confirms the benefit of this combination treatment for HCV patients and extends this benefit to patients who were treated with the new three drug combination regimen of SOF/VEL/VOX. Although subjects treated with SOF/VEL/VOX started with slightly lower (not statistically significant) baseline PRO scores than those patients treated SOF/VEL group, the improvement of PRO scores was similar throughout treatment and post-treatment. Nevertheless, there may be some differences in PRO changes according to the type of regimen which did not reach statistical significant or meet the minimal clinically important difference (MCID) thresholds.

Furthermore, it is important to note that the PRO improvements which were seen early after the initiation of treatment, coincided with early virologic response, and became more prominent by the end-of-treatment. Additionally, it is also important to note that most improvements in PRO scores were not only statistically significant but also clinically relevant meeting the threshold for MCID in PRO scores [45-46]. Lastly, achieving SVR-12 was associated with improvement in almost all PRO domains that were measured, and those improvements were sustained or increased further during week 24 of follow-up.

Furthermore, despite the higher rate of gastrointestinal adverse events recorded during treatment with the SOF/VEL/VOX regimen, the addition of VOX to SOF/VEL did not negatively impact PROs in a clinically meaningful manner. Furthermore, comparison of treatment-emergent changes in PROs between those who had or did not have gastrointestinal side effects did not reach statistically significant differences (all $p > 0.05$ at the end of treatment).

Consistent with prior reports, independent predictors of lower baseline PRO scores in this study were primarily related to the presence of co-morbidities such as anxiety, depression and clinically overt fatigue. At the same time, patients with comorbidities also enjoyed the greatest improvement of their PROs after clearance of their HCV infection. Furthermore, the PRO improvements in patients with cirrhosis were even more prominent in comparison to the score changes seen in non-cirrhotic patients. This suggests that observed PRO improvements may be partially related to viral suppression and/or viral eradication, which is seen in all patients, but also may be related to improvement in liver function which would primarily manifest in patients with cirrhosis and extrahepatic manifestations of HCV infection. This is especially important since patients with HCV and cirrhosis are not only at the highest risk for developing adverse clinical outcomes but also experience severe impairment of their PROs.

The study limitations include the clinical trial-related selection bias in the study cohort, the open label design, differing study durations for the studied regimens, and a relatively short follow-up duration. Nevertheless, duration of treatment with interferon and ribavirin free regimens does not seem to impact PROs [29-33]. Despite these limitations, the strengths of the study include a large, multinational, and prospectively followed cohort of patients with HCV, and the use of four fully validated instruments to assess a number of different PRO domains which cover multiple aspects of patients' well-being. Indeed, the observed synchronous improvement of PROs in 25 out of 26 studied domains (absenteeism was the only domain not to improve, possibly due to a relatively short follow up; studies are ongoing to further investigate this issue) provide an indirect evidence for the validity and robustness of the findings.

Nevertheless, to establish generalizability, the findings need to be further validated in a real-life setting with more diverse patient populations. This is especially important since being from outside the United States was a predictor for lower PRO scores at baseline and of some treatment-emergent changes in PROs. In this context, studies are needed to understand the drivers of these cultural differences. However, we must emphasize that, regardless of these differences, patients who achieved SVR saw a significant increase in their PROs which also exceeded the minimal clinically importance difference. We would also suggest that adding

qualitative data to assessing PROs should be considered given the considerable favorable patients' input recorded during follow-up. Comments have been made as early as four weeks after treatment initiation correlating with virus suppression and included phrases as: “feeling sharper”, “lifting of brain fog”, “have more energy”. All reports recorded in the quantitative surveys but bear consideration as another way to strengthen the discussion as to why treatment should be considered for all.

In summary, these data show that the new pan-genotypic regimens of SOF/VEL/VOX or SOF/VEL are not only associated with high efficacy but also with substantial improvement in PRO scores. These improvements were seen across regimens and genotypes and were more prominent in patients with cirrhosis and other comorbidities. In this context, the comprehensive benefit of these regimens includes not only high SVR rates but also improvement of patients' experience during treatment and after achieving SVR.

Acknowledgement Page:

Funding Source: This study was funded by Gilead Sciences. **Role of the funding source:** Research funding was used to support data analysis for this manuscript. None of the authors received any funding for their contribution to writing this manuscript.

(i). Guarantor of the article: Zobair M. Younossi, MD takes responsibility for the integrity of the work as a whole, from inception to published article.

(ii). Authors' contributions: ZY designed and supervised the study, and prepared the final version of the manuscript; MS managed the data and run statistical analysis, MS, LH and IY prepared the draft of the manuscript; IJ, TA, EG, EL, GF, SR, AT, BW, TW, BP critically reviewed the manuscript.

(iii) All authors have reviewed and approved the final version of the submitted manuscript.

Conflict of Interest: ZMY has received research funding or research consultant to Gilead Sciences. IMJ has served as a consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and Trek, and has served as a speaker for Gilead and Merck. TA has served on advisory boards for AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences,

Janssen, Merck, and Roche; and has served as a speaker for AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and Roche. EJG has served on advisory boards for AbbVie, Boehringer Ingelheim, Gilead, Janssen, Novartis, Roche, and Tibotec; has conducted research for Gilead; and has served as a speaker for Gilead, Novartis, Roche, and Tibotec. EJJ has served as a consultant for AbbVie, Achillion, Bristol-Myers Squibb, Enanta, Gilead Sciences, Janssen, Merck, Novartis, Santaris, Regulus, and Theravance; has conducted research for AbbVie, Achillion, Boehringer Ingelheim, Bristol-Myers Squibb, Enanta, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Roche, Salix, Santaris, Tacere, and Theravance; and has served as a speaker for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck. GRF declares no conflicts of interest. SKR has served as a consultant for Gilead, MSD, and AbbVie; and has served on advisory boards for Gilead, MSD and AbbVie. AJT has served on advisory boards for Gilead, AbbVie, Merck, BMS, Novartis and Roche; has conducted research for Gilead, AbbVie, BMS, Merck, Spring Bank, Arrowhead, and Novartis; and has served as a speaker for Gilead, AbbVie, BMS, and Merck. BEW has served as a consultant for Gilead, AbbVie, BMS, and Intercept; has served on advisory boards for Gilead, AbbVie, BMS, and Intercept; has conducted research for Gilead, and AbbVie; and has served as a speaker for Gilead. TMW has been a member of the speaker's bureau and/or has served on advisory boards for Abbvie, Bristol-Myers-Squibb, Gilead, Janssen, and Novartis. BP has served as a consultant for Gilead, Merck, and J&J; has served on advisory boards for Gilead, Merck, and J&J; has conducted research for BMS, BI, Gilead, Merck, and J&J; and has served as a speaker for Gilead, Merck, and J&J.

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Figure Legends

Figure 1. Treatment-emergent changes in summary PROs by (A) treatment week 4 and (B) the end of treatment. All changes are on a universal 0-100 scale (mean with 95% confidence interval).

Figure 2. Treatment-emergent changes in PROs in patients with vs. without cirrhosis treated with SOF/VEL or SOF/VEL/VOX. All changes are on a universal 0-100 scale (mean with 95% confidence interval).

Figure 3. Treatment-emergent changes in PROs during and after treatment with SOF/VEL and SOF/VEL/VOX. (A) Physical Component Summary (PCS) of SF-36; (B) Mental Component Summary (MCS) of SF-36; (C) Fatigue Scale of FACIT-F; (D) CLDQ-HCV total score; (E) Work Productivity Impairment of WPAI:SHP; (F) Activity Impairment of WPAI:SHP.

Table 1. Clinical and demographic characteristics of POLARIS-2 and -3 participants by the treatment regimen.

	SOF/VEL	SOF/VEL/VOX	p	All
N	549	611		1160
Age, years	52.8 ± 11.4	52.8 ± 10.7	0.51	52.8 ± 11.0
Male gender	320 (58.3%)	329 (53.8%)	0.13	649 (55.9%)
White	462 (84.2%)	491 (80.4%)	0.09	953 (82.2%)
Black	48 (8.7%)	48 (7.9%)	0.58	96 (8.3%)
Asian	31 (5.6%)	59 (9.7%)	0.0108	90 (7.8%)
Employed at baseline	301 (57.2%)	322 (56.1%)	0.71	623 (56.6%)
Enrolled in the U.S.	315 (57.4%)	333 (54.5%)	0.32	648 (55.9%)
BMI, kg/m ²	27.1 ± 5.1	27.2 ± 5.7	0.49	27.2 ± 5.4
History of type 2 DM	58 (10.6%)	78 (12.8%)	0.24	136 (11.7%)
Anti-HCV treatment-naïve	417 (76.0%)	458 (75.0%)	0.69	875 (75.4%)
HCV genotype 1	232 (42.3%)	233 (38.3%)	0.17	465 (40.2%)
HCV genotype 2	53 (9.7%)	63 (10.3%)	0.70	116 (10.0%)
HCV genotype 3	198 (36.1%)	202 (33.2%)	0.30	400 (34.5%)
HCV genotype 4	57 (10.4%)	63 (10.3%)	0.98	120 (10.4%)
HCV genotype 5	0 (0.0%)	18 (3.0%)	<0.0001	18 (1.6%)
HCV genotype 6	9 (1.6%)	30 (4.9%)	0.0020	39 (3.4%)
Baseline HCV RNA > 800,000 IU/mL	383 (69.8%)	416 (68.1%)	0.54	799 (68.9%)
Baseline ALT > 1.5 ULN	286 (52.1%)	296 (48.4%)	0.21	582 (50.2%)
Cirrhosis	193 (35.2%)	200 (32.7%)	0.38	393 (33.9%)
Baseline albumin, g/dL	4.30 ± 0.31	4.29 ± 0.37	0.99	4.29 ± 0.35
Baseline APRI	1.24 ± 1.45	1.16 ± 1.30	0.25	1.19 ± 1.38
Baseline Fibrotest score	0.51 ± 0.29	0.50 ± 0.29	0.46	0.50 ± 0.29
Baseline hemoglobin, g/dL	14.51 ± 1.42	14.49 ± 1.42	0.88	14.50 ± 1.42
Baseline INR	1.04 ± 0.24	1.02 ± 0.12	0.57	1.03 ± 0.18
Baseline platelet count, 10 ⁶ /mL	208.8 ± 82.4	206.5 ± 76.8	0.96	207.6 ± 79.5

History of anxiety or panic disorder	98 (17.9%)	103 (16.9%)	0.66	201 (17.3%)
History of depression or mood disorder	122 (22.2%)	135 (22.1%)	0.96	257 (22.2%)
History of clinically overt fatigue	97 (17.7%)	105 (17.2%)	0.83	202 (17.4%)
History of insomnia or sleep disorder	85 (15.5%)	119 (19.5%)	0.07	204 (17.6%)

DM – diabetes mellitus; APRI – AST to platelet ratio; INR – International Normalized Ratio

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract-pg. 3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found- pg 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported pg 4
Objectives	3	State specific objectives, including any prespecified hypotheses- pg 4
Methods		
Study design	4	Present key elements of study design early in the paper -pg-4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection- pg 4-5
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up pg 4-5
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed
		<i>Case-control study</i> —For matched studies, give matching criteria and the number

		of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. pg 5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group pg 4-7
Bias	9	Describe any efforts to address potential sources of bias NA
Study size	10	Explain how the study size was arrived at pg 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why pg 7
Statistical methods	12	<p>(a) Describe all statistical methods, including those used to control for confounding pg 7</p> <p>(b) Describe any methods used to examine subgroups and interactions pg 7</p> <p>(c) Explain how missing data were addressed pg 5-6</p> <p>(d) <i>Cohort study</i>—If applicable, explain how loss to follow-up was addressed pg 4-7</p> <p><i>Case-control study</i>—If applicable, explain how matching of cases and controls was addressed</p> <p><i>Cross-sectional study</i>—If applicable, describe analytical methods taking account of sampling strategy</p> <p>(e) Describe any sensitivity analyses</p>

Continued on next page

Results

Participants	13*	<p>(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed pg 7</p> <p>(b) Give reasons for non-participation at each stage- NA</p> <p>(c) Consider use of a flow diagram- NA</p>
Descriptive data	14*	<p>(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders pg 7-8 Table 1</p> <p>(b) Indicate number of participants with missing data for each variable of interest NA</p> <p>(c) <i>Cohort study</i>—Summarise follow-up time (eg, average and total amount) pg 7-8</p>
Outcome data	15*	<p><i>Cohort study</i>—Report numbers of outcome events or summary measures over time pg 7-9 Figures 1-3 and Table 2</p> <p><i>Case-control study</i>—Report numbers in each exposure category, or summary measures of exposure</p>

Cross-sectional study—Report numbers of outcome events or summary measures

Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included pg 7-9 Figures 1-3 and Table 2
		(b) Report category boundaries when continuous variables were categorized- pg 7
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period- NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses- NA
Discussion		
Key results	18	Summarise key results with reference to study objectives- pg 9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias- pg 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – pg 10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results- pg 10-11
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based- pg 13

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Title:

Sofosbuvir and velpatasvir with or without voxilaprevir in direct-acting antiviral-naïve chronic hepatitis C: patient-reported outcomes from POLARIS 2 and 3.

Date:

2018-01

Citation:

Younossi, Z. M., Stepanova, M., Jacobson, I. M., Asselah, T., Gane, E. J., Lawitz, E., Foster, G. R., Roberts, S. K., Thompson, A. J., Willems, B. E., Welzel, T. M., Pearlman, B., Younossi, I., Racila, A. & Henry, L. (2018). Sofosbuvir and velpatasvir with or without voxilaprevir in direct-acting antiviral-naïve chronic hepatitis C: patient-reported outcomes from POLARIS 2 and 3.. *Aliment Pharmacol Ther*, 47 (2), pp.259-267. <https://doi.org/10.1111/apt.14423>.

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