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Health-Related Quality of Life in Chronic HCV-Infected Patients Switching to Pegylated-Interferon-Free Regimens (ANRS CO20 CUPIC Cohort Study and SIRIUS Trial)

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Author's contributions

Maria Patrizia Carrieri and Camelia Protopopescu designed the study and discussed the analysis plan. Camelia Protopopescu and Antoine Vilotitch conducted the statistical analysis. Maria Patrizia Carrieri and Camelia Protopopescu drafted the manuscript. All authors contributed to the interpretation of the results and commented on drafts of the manuscript. All authors read and approved the final manuscript.

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Running Heading

Health-Related Quality of Life in HCV Patients Switching to Pegylated-Interferon-Free Regimens

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Abstract

Objective We aimed to compare health-related quality of life (HRQL) during and after HCV treatment in patients receiving pegylated-interferon (PEG-IFN)-containing therapy (including boceprevir or telaprevir - ANRS CO20 CUPIC cohort) who subsequently switched to PEG-IFN-free regimens (sofosbuvir + ledipasvir with or without ribavirin (RBV) - SIRIUS trial).

Methods Two analyses were performed. The first compared physical (PCS) and mental (MCS) HRQL (MOS SF-12) scores during treatment between CUPIC and SIRIUS. The second compared PCS and MCS scores after treatment end between CUPIC and SIRIUS. The analyses used linear regression mixed models adjusted for pre-treatment HRQL scores, gender and age at each visit.

Results Among patients enrolled successively in both studies, 43 (corresponding to 212 HRQL assessments) and 43 (82 HRQL assessments) were eligible for the “during” and “post” treatment analyses, respectively. In the “during-treatment” analysis, we found both significantly higher PCS and MCS values during PEG-IFN-free treatment than for PEG-IFN-containing treatment. In the “post-treatment” analysis, results showed significantly higher MCS values after PEG-IFN-free treatment than after PEG-IFN-containing treatment. No significant difference was found for PCS in “post-treatment analysis”.

Conclusions These results highlight an improvement in both physical and mental HRQL during HCV treatment, but no major improvement in physical HRQL after treatment end, when comparing PEG-IFN-free regimens with PEG-IFN-containing regimens. This suggests that in the PEG-IFN-free regimens era, screening and comprehensive care of comorbidities and residual somatic symptoms during treatment, and especially after HCV clearance, are still needed to improve patient outcomes.

Key Points for Decision Makers

This study examines health-related quality of life (HRQL) in HCV-infected patients switching, after treatment failure, from a pegylated-interferon (PEG-IFN)-based HCV treatment (ANRS CO20 CUPIC cohort) to a PEG-IFN-free treatment (SIRIUS trial).

The results highlight a relative improvement in both physical and mental HRQL during HCV treatment, but no major improvement in physical HRQL after treatment end, when comparing PEG-IFN-free regimens with PEG-IFN-containing regimens. This suggests that in the PEG-IFN-free regimens era, screening and comprehensive care of comorbidities and residual somatic symptoms during treatment, and especially after HCV clearance, are still needed to improve patient outcomes.

1 Introduction

For several decades HCV chronic infection was regarded as an incurable disease, leading ineluctably to the death of a great many people from liver cirrhosis or liver cancer sequelae. Pegylated-interferon (PEG-IFN) plus ribavirin (RBV) was the first regimen to result in promising HCV clearance rates, although its effectiveness was strongly linked to HCV genotype and continuity of treatment (persistence). In 1999, the European Consensus Conference on Hepatitis C established that the gold standard for treatment of chronic hepatitis C was a combination of PEG-IFN and RBV [1]. However, increasing access to treatment and ensuring adherence to the treatment regimen were a challenge with this combination. The burden of anemia and/or influenza-like symptoms, as well as psychiatric side-effects such as depression, fatigue and anger [2, 3], represented a major barrier to initiation and continuity of treatment [4-6]. HCV-related fatigue and treatment-related side effects negatively affected health-related quality of life (HRQL) and were identified as predictive factors of treatment discontinuation [7].

The arrival of the first protease inhibitors - boceprevir and telaprevir - in 2012, which were administered in combination with PEG-IFN and RBV, improved rates of sustained virological response (SVR) in genotype 1 subjects [8], but increased toxicity (cytopenia, anemia, asthenia, myalgia, skin rash) [9] resulting in treatment discontinuation. This highlighted the need for appropriate somatic and psychiatric clinical management. These regimens were also associated with significant impairment of HRQL [10, 11].

One of the new Direct-Acting Antiviral Agents (DAA) against HCV is sofosbuvir (SOF), a nucleotide analog inhibitor of the NS5B polymerase enzyme, approved in June 2013 by the US Food & Drug Administration (FDA) [12] and in January 2014 by the European Medicines Agency (EMA) [13] for different treatment combinations. It may be used with PEG-IFN and RBV for 12 weeks or with RBV only for 12 or 24 weeks, according to the HCV genotype. SOF + RBV was the first interferon-free HCV treatment regimen available, and is also recommended for patients with severe fibrosis.

SOF is characterized by high efficacy and tolerance, which result in high response rates (depending on HCV genotype, extent of liver damage and previous treatment history) and few side-effects, especially when not combined with PEG-IFN. HRQL data for SOF regimens with and without PEG-IFN and/or RBV have recently been published. These data show that PEG-IFN-containing SOF regimens significantly impaired patients' HRQL (as captured by the Medical Outcomes Study 36-item Short-Form questionnaire (MOS SF-36)) [14]. Moreover, the addition of SOF to the treatment regimen did not add to the HRQL burden of PEG-IFN + RBV. In contrast, PEG-IFN-free regimens with SOF + RBV resulted in a slight impairment of HRQL, which was not related to treatment duration [14]. It has also been shown that other patient-reported outcomes, including work productivity, were more negatively affected in patients receiving SOF with PEG-IFN than in those on SOF regimens without PEG-IFN [15].

The objective of this study was to compare, for the first time, HRQL in patients receiving boceprevir or telaprevir triple combination PEG-IFN-containing therapy (ANRS CO20 CUPIC cohort study [8]) who subsequently switched to SOF combined with a NS5A inhibitor (ledipasvir (LDV)) PEG-IFN-free therapy with or without RBV (SIRIUS trial [16]). The comparison focuses specifically on patient HRQL during HCV treatment in a first analysis, and after the end of treatment in a second analysis.

2 Methods

2.1 Study Design

Analyses are based on data collected from HCV-chronic patients who consecutively participated in the following two studies conducted in France: the ANRS CO20 CUPIC cohort (in 2011-2012) and the SIRIUS trial (in 2013-2014).

ANRS CO20 CUPIC (ClinicalTrials.gov number NCT01514890) was a multicenter cohort study which started in February 2011. It included HCV genotype 1 patients with compensated cirrhosis who had failed to eradicate HCV after completing a previous standard PEG-IFN/RBV therapy, and who were subsequently provided with protease inhibitor-based HCV therapy in the context

of the French Early Access Program and the cohort's Temporary Authorisation for Use (ATU) for a new drug. The study prospectively followed 674 patients who received triple therapy with PEG-IFN, RBV and either boceprevir or telaprevir for 48 weeks, with approval from the French Health authorities [8]. Drug safety profiles and virological response to combined treatment were assessed [8].

SIRIUS (ClinicalTrials.gov identifier: GS-US-337-0121) is a phase II multicenter, randomized, double-blind trial [16], which evaluated the efficacy and safety of interferon-free SOF/LDV treatment with or without RBV, in treatment-experienced patients with compensated cirrhosis. Eligible patients were genotype 1 individuals with prior virological failure after both PEG-IFN + RBV regimen and triple combination therapy (containing either telaprevir or boceprevir). The 154 patients enrolled in SIRIUS were randomized into the following two arms: 24-week treatment with SOF/LDV as a fixed-dose combination (FDC) with placebo RBV (arm 1: "FDC + Placebo RBV", n=78 patients), and 12-week treatment with placebo, followed by 12-week treatment with FDC and RBV (arm 2: "Placebo -> FDC + RBV", n=76 patients).

Among the 154 patients enrolled in SIRIUS between 21st October and 28th November 2013, 47 were identified as having previously participated in the CUPIC cohort (CUPIC enrolment date between March 2011 and April 2012). According to SIRIUS eligibility criteria, none of these 47 patients had achieved sustained virological response (SVR) after treatment from CUPIC, and none had either hepatocellular carcinoma or decompensated hepatic disease. All these patients achieved SVR by the end of the treatment in SIRIUS trial. The analyses of this study will use data from these 47 patients.

2.2 Assessment of HRQL

In the CUPIC study, patient HRQL was assessed using the Medical Outcomes Study 12-item Short-Form questionnaire (MOS SF-12), a short version of the MOS SF-36 questionnaire [17], which has been widely used for studies on HCV-infected patients in France and other European countries [18, 19]. Patients answered the SF-12 at several time points during follow-up, as

follows: baseline (Week 0), during treatment (Weeks 4, 8, 12, 24, 36, and 48), and after treatment (Week 72, i.e., 24 weeks after treatment end).

A similar self-administered questionnaire including the MOS SF-36 questionnaire [17] was proposed to participants in the SIRIUS trial during and after the treatment period: at the baseline visit (Week 0), during treatment (Weeks 4, 12, 16, 24), and after the end of treatment (Weeks 28, 36, 48, i.e. respectively 4, 12 and 24 weeks after treatment end) [20].

Two HRQL aggregate scores - the physical component summary (PCS) for physical HRQL and the mental component summary (MCS) for mental HRQL - were calculated in both studies using the 12 items common to the SF-12 and the SF-36 questionnaires. These summary scores were calculated using the U.S. population norms to the mean of 50 and a standard deviation of 10, over a range of 0 to 100 points, with higher values denoting better HRQL.

2.3 Statistical Analyses

Given the repeated-measure design of the study and the presence of two arms in the SIRIUS trial with different treatment durations and follow-up schedules, for the purpose of standardization, analyses were restricted to the data collected at the following selected visits during CUPIC and SIRIUS follow-ups. Accordingly, we performed the following two analyses:

During-treatment analysis: This analysis aimed at comparing PCS and MCS during treatment in SIRIUS (using data at Weeks 4, 12, 16, 24) versus CUPIC (using data at Weeks 4, 8, 12, 24, 36, and 48), after adjustment for gender, age at each visit and pre-treatment HRQL values (baseline data). Patients with available HRQL scores at least once during treatment and at baseline, in at least one of the two studies, were included in this analysis. The baseline time point was set at Week 0. However for SIRIUS-arm 2 patients (who had taken the Placebo during the first 12 weeks), the baseline was set at Week 12 and only subsequent visits (at Weeks 16 and 24) were included in the “during-treatment” analysis. In addition, in order to maximize the sample size, we performed a last observation carried forward imputation for SIRIUS-arm 2 patients, using the score values at Week 0 as baseline values when the values at Week 12 were missing (this was the

case for 2 patients). A linear mixed-effects regression model - adjusted for baseline PCS and MCS values in CUPIC and SIRIUS - was used to verify whether PCS and MCS changed significantly during the PEG-IFN-free regimens (SIRIUS) with respect to the boceprevir/telaprevir PEG-IFN-containing regimens (CUPIC).

Post-treatment analysis: This second analysis aimed at comparing PCS and MCS after treatment end in SIRIUS (data at Weeks 36 and 48) and CUPIC (data at Week 72), after adjustment for gender, age at each visit and pre-treatment HRQL values (baseline data). To this end, we employed the same method used for the “during-treatment” comparison. Patients with available HRQL scores at least once after end of treatment and at baseline, in at least one of the two studies (CUPIC and SIRIUS), were included in this analysis. Nevertheless, the visit at 28 weeks in SIRIUS (i.e. 4 weeks after treatment end) was not included in this analysis, to keep a reasonable minimum delay of at least 12 weeks after the end of treatment.

In all analyses the computation of p-values and confidence intervals was based on the robust sandwich method.

The descriptive statistics (mean \pm standard deviation, median and interquartile range (IQR)) of PCS and MCS scores for each CUPIC and SIRIUS visit are reported in Table 1. The scores' distributions for both studies and for each visit are also described using boxplots in Fig. 1.

Stata software release 12.1 was used for all statistical analyses [21].

3 Results

Among the 47 patients enrolled in both studies (SIRIUS trial and CUPIC cohort), 42 were present in the CUPIC HRQL database (the remaining 5 patients did not respond to the HRQL questionnaire during the CUPIC follow-up). Overall, 43 patients were eligible for the “during-treatment” analysis, having available HRQL scores at least once during treatment and at baseline, in at least one of the two studies, for a total of 212 HRQL assessments (109 visits from CUPIC and 103 visits from SIRIUS). Forty-three patients were eligible for “post-treatment” analysis, having HRQL scores available at least once after end of treatment and at baseline, in at least one

of the two studies, for a total of 82 HRQL assessments (7 visits from CUPIC and 75 visits from SIRIUS, see flow chart in Fig. 2).

The “during-treatment” study group of 43 patients mainly included men ($n=35$ (81.4%)), median [IQR] age at baseline in CUPIC was 56 [50-63] years. Among these 43 patients, 33 had HRQL data during treatment and at baseline in CUPIC, and 41 had HRQL data during treatment and at baseline in Sirius (18 in “FDC + Placebo RBV” arm and 23 in “Placebo -> FDC + RBV” arm) (see Fig. 2).

The “post-treatment” study group of 43 patients had similar characteristics (in fact, 41 patients were common to both the “during-treatment” and “post-treatment” study groups). It included 36 men (83.7%), with a median [IQR] age at baseline in CUPIC of 56 [51-64] years.

In the “during-treatment” analysis (Table 2, model A), results showed significantly higher values for both PCS and MCS scores during PEG-IFN-free treatment (SIRIUS) than with PEG-IFN-containing treatment combined with telaprevir or boceprevir (CUPIC), after adjustment for baseline score values (before treatment), gender and age at each visit. The average increase in HRQL values during the follow-up of SIRIUS versus CUPIC - estimated by the coefficient in the multivariate linear regression mixed model - was 4.57 points (95% confidence interval (CI): [2.44; 6.71], p -value<0.0001) for the PCS score and 2.49 points (95% CI: [0.28; 4.69], $p=0.027$) for the MCS score.

In the “post-treatment” analysis (Table 2, model B), significantly higher MCS values were found after PEG-IFN-free treatment (SIRIUS), with an average increase of 3.95 points (95% CI: [0.38; 7.52], p -value=0.030) compared with after PEG-IFN-containing treatment (CUPIC), after adjustment for baseline PCS values, gender and age at each visit. However, for PCS score, there was a trend towards better HRQL when comparing PCS values after PEG-IFN-free treatment versus after PEG-IFN-containing treatment, but this increase of 2.07 points (95% CI: [-4.69; 8.84], p -value=0.548) was not statistically significant.

4 Discussion

To our knowledge, this is the first study to compare changes in HRQL in the same group of chronic HCV-infected patients switching from a PEG-IFN-containing regimen (including telaprevir or boceprevir) to a PEG-IFN-free regimen, while taking into account within-subject variability. The repeated-measure design of the study allowed us to control for pre-treatment values of HRQL while comparing HRQL values assessed during treatment and in post-treatment comparison.

This study has two main results. First, compared with PEG-IFN-containing regimens, we observed a significant improvement in both the physical and mental dimensions of HRQL during PEG-IFN-free treatment. Second, in the post-treatment analysis, a significant improvement was observed in the mental dimension of HRQL after completing PEG-IFN-free treatments compared with PEG-IFN-containing treatments. By contrast, no significant improvement was found for post-treatment values of physical HRQL.

The improvement observed during treatment in both physical and mental HRQL when moving from telaprevir/boceprevir-based triple combination therapy to the PEG-IFN-free SOF-based treatment is consistent with previous results [20] and may be due to the benefits of PEG-IFN-free treatment in terms of increased efficacy and fewer treatment-related side-effects. Moreover, the former can be considered the “worst case scenario” in terms of toxicity burden, while the latter has already proven itself to be quite well tolerated for most patients.

Results from the “post-treatment” analysis showed there was no significant difference between physical HRQL values after PEG-IFN-containing and PEG-IFN-free treatment completion. This may be attributable to fatigue, which is known to persist after completing PEG-IFN-containing regimens [22], and which may also continue for a substantial period (in our case 12 to 24 weeks) after completing PEG-IFN-free regimens, despite HCV clearance. In fact, recent data show that fatigue may decrease over time after post HCV clearance [23], which would suggest that even

with the advent of novel powerful and less toxic regimens, the management of physical health disturbances cannot be neglected, and needs to be incorporated into standard HCV care.

The significant improvement found in the mental HRQL dimension after the end of PEG-IFN-free regimens suggests that HCV clearance may have important benefits for patients including decreased anxiety and a reduced impact of HCV-related psychiatric symptoms on daily life. This improvement found here is consistent with previous research in HIV-HCV co-infected patients which highlighted that the low rates of suicide ideation exhibited by HCV-clearers were similar to those in people who had never been HCV co-infected [24]. This is an additional argument for promoting access to better tolerated treatment regimens for HCV-infected patients.

In addition, given that the minimal clinically important difference for the two summary scores (PCS and MCS) is generally in the range of 3 to 5 points [25-27], we can conclude that the statistically significant improvements observed in this study can also be interpreted as clinically important, except for the mental HRQL dimension during treatment. For the latter, the slight improvement of 2.49 points, albeit statistically significant, was not clinically significant. We suppose that depressive and anxiety symptoms (not measured in this study but known to be highly correlated with mental HRQL) may persist during any HCV treatment because of patient expectations about treatment outcomes, and also because of the burden of HCV on mental health [28].

5 Limitations

The main limitation of this study is the use of a generic scale for the assessment of HRQL, which is perhaps unable to capture specific dimensions of improvement (or absence of improvement) in chronically-infected HCV patients' quality of life. Although the sample size is rather limited and this may hide potential differences, we used robust estimates to compensate for this reduced power.

Moreover, the lack of comparable scales of self-reported symptoms and fatigue in both studies did not enable us to document the residual burden of some symptoms during and after PEG-IFN-containing and PEG-IFN-free regimens.

Finally, in this study we were not able to compare the specific dimensions (subdomains) of the SF-12 scale which could have captured specific aspects like fatigue or emotional problems. This was due to the fact that the HRQL questionnaire in CUPIC was based on SF-12 version 1, while the HRQL questionnaire in SIRIUS was based on SF-36 version 2. Consequently, although the PCS and MCS summary scores were comparable between versions 1 and 2 of the reduced SF-12 scale, this was not the case for the SF-12 scale's specific dimensions, which had different scoring algorithms in the two versions.

6 Conclusion

To conclude, our results highlight an improvement in both physical and mental HRQL during HCV treatment, but no major improvement in physical HRQL after treatment end, when comparing PEG-IFN-free regimens with PEG-IFN-containing regimens. Accordingly, these results may have important implications for clinical management of HCV chronically-infected patients. They suggest that in the PEG-IFN-free regimen era, screening and comprehensive care of comorbidities and residual somatic symptoms during and especially after HCV clearance, are still needed in order to improve patient outcomes.

Insert Fig. 1 about here.

Insert Fig. 2 about here.

Figures Legend

Fig. 1 Boxplots of PCS and MCS scores in CUPIC and SIRIUS, during and post treatment comparisons

Fig. 2 Flow chart for comparison of PCS and MCS scores in SIRIUS *versus* CUPIC, during- and post- treatment analyses (n=number of patients, N=number of observations)

Table 1. Descriptive statistics of PCS and MCS scores in CUPIC and SIRIUS, for the during- and post-treatment analyses

	CUPIC (PEG-IFN regimens)		FDC + Placebo RBV (SIRIUS arm 1)		Placebo->FDC + RBV (SIRIUS arm 2)	
	n	mean ± SD median (IQR)	n	mean ± SD median (IQR)	n	mean ± SD median (IQR)
PCS score						
Baseline [§]	33	43.4 ± 6.6 43.2 (38.7-49.5)	19	46.7 ± 6.3 46.2 (42.6-51.0)	24	47.1 ± 7.7 48.2 (40.1-54.0)
During-treatment						
Week 4	30	41.0 ± 5.8 40.8 (38.0-45.9)	14	45.5 ± 4.6 46.0 (41.6-49.4)		
Week 8	24	43.2 ± 6.0 43.0 (39.8-47.5)				
Week 12	24	40.2 ± 5.5 41.2 (36.9-43.5)	17	46.6 ± 7.7 44.6 (39.5-54.0)		
Week 16			16	46.8 ± 7.3 45.8 (41.5-53.8)	21	47.2 ± 7.6 48.3 (44.6-52.1)
Week 24	14	37.8 ± 6.6 39.1 (34.5-43.8)	17	45.8 ± 7.7 46.4 (42.0-50.2)	18	47.0 ± 6.9 47.9 (43.3-52.7)
Week 36	9	41.4 ± 6.2 42.0 (36.2-44.9)				
Week 48	8	41.6 ± 3.6 42.1 (39.9-44.3)				
Post-treatment						
Week 36			18	45.7 ± 8.4 44.0 (38.6-53.4)	19	46.0 ± 7.7 46.1 (39.3-53.4)
Week 48			18	47.9 ± 7.5 49.2 (43.9-54.8)	20	51.2 ± 5.2 51.9 (49.0-55.0)
Week 72	7	42.9 ± 7.3 42.8 (36.7-50.4)				
MCS score						
Baseline [§]	33	42.3 ± 5.8 41.2 (38.6-45.4)	19	42.4 ± 10.1 44.0 (34.1-49.3)	24	40.8 ± 12.2 39.7 (29.8-51.9)
During-treatment						

Week 4	30	42.0 ± 5.6 42.7 (40.1-46.1)	14	44.6 ± 9.8 42.9 (35.2-53.5)		
Week 8	24	41.2 ± 5.6 41.3 (36.8-45.2)				
Week 12	24	42.5 ± 6.0 42.3 (39.6-46.6)	17	44.6 ± 10.4 44.6 (37.3-53.5)		
Week 16			16	44.8 ± 11.1 43.7 (38.2-54.5)	21	42.4 ± 9.4 42.9 (34.7-46.5)
Week 24	14	39.9 ± 4.3 38.0 (37.0-41.5)	17	44.7 ± 10.2 43.4 (38.1-52.0)	18	44.4 ± 13.1 43.7 (32.9-56.9)
Week 36	9	41.0 ± 4.2 39.5 (39.2-42.5)				
Week 48	8	43.0 ± 6.9 42.4 (37.8-48.3)				
Post-treatment						
Week 36			18	46.8 ± 9.1 47.0 (40.5-52.0)	19	45.2 ± 10.9 48.3 (31.9-54.4)
Week 48			18	47.5 ± 11.0 48.7 (39.9-54.4)	20	49.7 ± 6.8 50.1 (46.5-53.5)
Week 72	7	42.6 ± 5.2 40.8 (38.8-47.4)				

PEG-IFN = pegylated-interferon; FDC (fixed dose combination) = LDV (ledipasvir) + SOF (sofosbuvir); RBV = ribavirin;

PCS = physical component summary score; MCS= mental component summary score; SD = standard deviation; IQR = interquartile range

[§]Baseline = Week 0 for CUPIC and SIRIUS arm 1, and Week 12 for SIRIUS arm 2

Table 2. Comparison of PCS and MCS scores, SIRIUS *versus* CUPIC, linear mixed-effects regression models, during- and post-treatment multivariate analyses

	PCS score		MCS score	
	Adjusted coefficient [95% CI]*	p-value*	Adjusted coefficient [95% CI]*	p-value*
Model A. During-treatment analysis (n=43 patients, N=212 observations)				
CUPIC ¹ (ref.)				
SIRIUS ²	4.57 [2.44;6.71]	<0.0001	2.49 [0.28;4.69]	0.027
PCS score at baseline [§]	0.30 [0.13;0.47]	0.001		
MCS score at baseline [§]			0.60 [0.46;0.75]	<0.0001
Female gender	0.74 [-3.25;4.72]	0.717	-0.21 [-5.06;4.64]	0.933
Age [#] (years)	-0.09 [-0.20;0.03]	0.131	-0.05 [-0.18;0.08]	0.470
Intercept	32.76 [21.25;44.26]	<0.0001	19.20 [9.42;28.98]	<0.0001
Model B. Post-treatment analysis (n=43 patients, N=82 observations)				
CUPIC ¹ (ref.)				
SIRIUS ²	2.07 [-4.69;8.84]	0.548	3.95 [0.38;7.52]	0.030
PCS score at baseline [§]	0.45 [0.25;0.64]	<0.0001		
MCS score at baseline [§]			0.49 [0.34;0.64]	<0.0001
Female gender	-1.69 [-6.09;2.70]	0.450	-1.55 [-8.22;5.11]	0.648
Age [#] (years)	-0.11 [-0.33;0.10]	0.312	-0.14 [-0.29;-0.003]	0.055
Intercept	31.59 [16.98;46.19]	<0.0001	31.93 [20.14;44.72]	<0.0001

*robust p-values and confidence intervals (CI); PCS = physical component summary score;

MCS= mental component summary score;

¹ PEG-IFN (pegylated-interferon)-containing regimens

² PEG-IFN-free regimens

[§]Baseline = Week 0 for CUPIC and SIRIUS arm 1, and Week 12 for SIRIUS arm 2

[#] Time-varying variable

Compliance with Ethical Standards**Funding**

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Conflict of Interest

Zobair Younossi: research support and consultant for Gilead Sciences.

Hélène Fontaine: speaker fees from MSD, Janssen, Roche, BMS.

Christophe Hézode: consultancy fees from Abbott, MSD, Roche, Janssen, BMS, Gilead, and speaker fees from MSD, Janssen, Roche, BMS.

The other authors (Maria Patrizia Carrieri, Camelia Protopopescu, Antoine Vilotitch, Ventzislava Petrov-Sanchez, Fabienne Marcellin, Fabrice Carrat, and Marc Bourlière) declare that they have no conflict of interest.

Informed Consent

Written informed consent was obtained from all patients included in the study.

Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committees (the “Ile de France IX” Ethics Committee, Créteil, France, for CUPIC and the “Comité de Protection des Personnes Sud Méditerranée”, CHU Nice, France, for SIRIUS) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

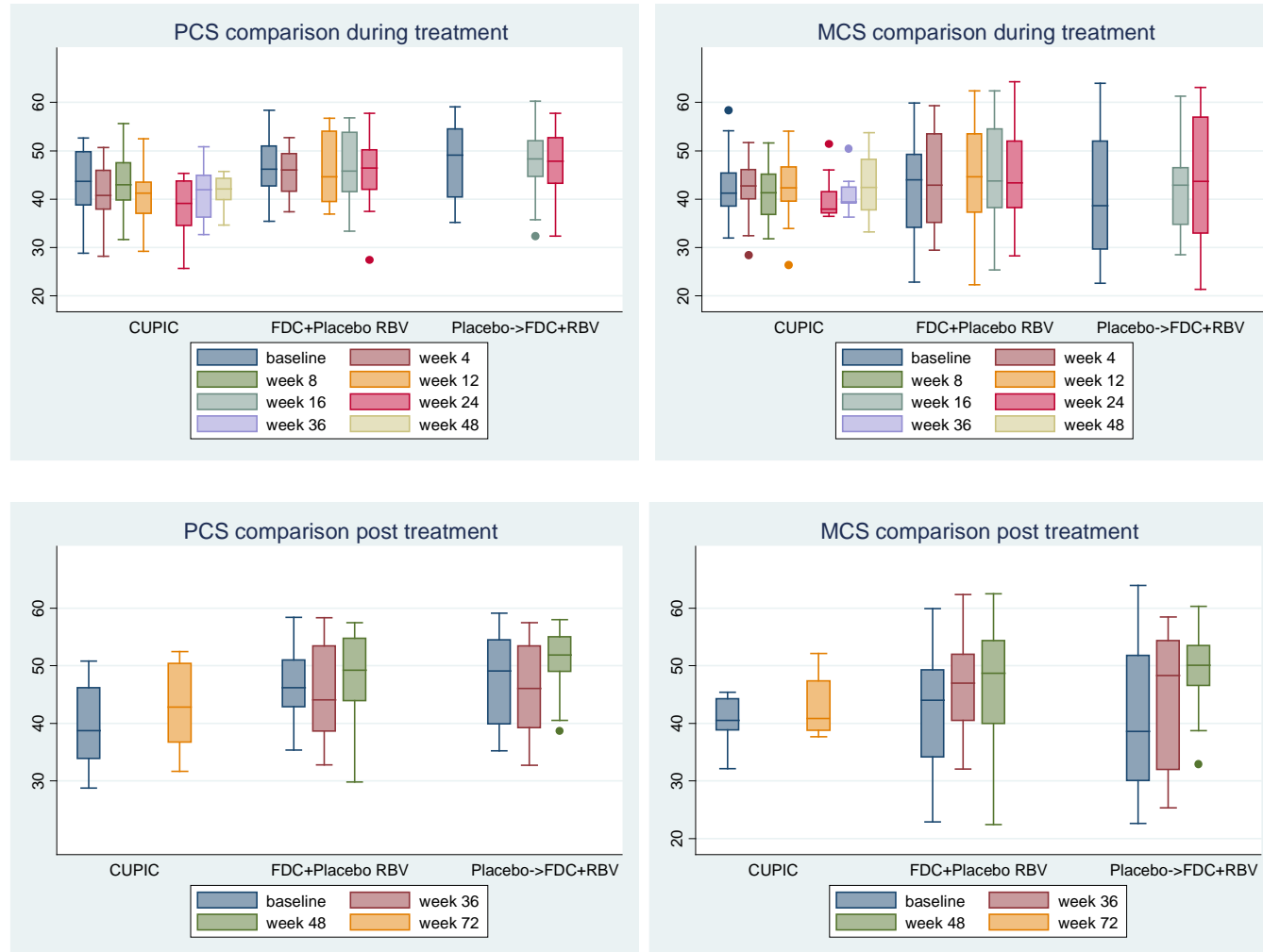
References

1. Palumbo E. PEG-interferon in acute and chronic hepatitis C: a review. *American journal of therapeutics*. 2009;16(6):573-8. doi:10.1097/MJT.0b013e3181960819.
2. Marcellin F, Preau M, Dellamonica P, Ravaux I, Kurkdji P, Protopopescu C et al. Adding HCV treatment to HIV treatment in HIV-HCV coinfectd patients: the impact on the different dimensions of fatigue and self-reported side effects. *Journal of pain and symptom management*. 2007;34(4):413-21. doi:10.1016/j.jpainsymman.2006.12.014.
3. Marcellin F, Roux P, Winnock M, Lions C, Dabis F, Salmon-Ceron D et al. Using patient-reported outcomes to improve the management of co-infection with HIV and HCV: the ANRS CO13 HEPAVIH cohort. *Expert review of gastroenterology & hepatology*. 2014;8(4):351-8. doi:10.1586/17474124.2014.888949.
4. Bonner JE, Esserman DA, Golin CE, Evon DM. Self-efficacy and adherence to antiviral treatment for chronic hepatitis C. *Journal of clinical gastroenterology*. 2015;49(1):76-83. doi:10.1097/MCG.0000000000000055.
5. Brett Hauber A, Mohamed AF, Beam C, Medjedovic J, Mauskopf J. Patient preferences and assessment of likely adherence to hepatitis C virus treatment. *Journal of viral hepatitis*. 2011;18(9):619-27. doi:10.1111/j.1365-2893.2010.01343.x.
6. Broers B, Helbling B, Francois A, Schmid P, Chuard C, Hadengue A et al. Barriers to interferon-alpha therapy are higher in intravenous drug users than in other patients with acute hepatitis C. *Journal of hepatology*. 2005;42(3):323-8.
7. Guadagnino V, Trotta MP, Carioti J, Caroleo B, Antinori A, Nocchiero Study G. Does depression symptomatology affect medication compliance during the first weeks of anti-HCV therapy in intravenous drug users? *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 2006;38(2):119-24. doi:10.1016/j.dld.2005.10.008.
8. Hezode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *Journal of hepatology*. 2013;59(3):434-41. doi:10.1016/j.jhep.2013.04.035.
9. Chopra A, Klein PL, Drinnan T, Lee SS. How to optimize HCV therapy in genotype 1 patients: management of side-effects. *Liver international : official journal of the International Association for the Study of the Liver*. 2013;33 Suppl 1:30-4. doi:10.1111/liv.12080.

10. Marcellin F, Fournier I, Carrieri MP, Poizot-Martin I, Cotte L, Anrs HC et al. From first-generation hepatitis C virus protease inhibitors to direct-acting antivirals: self-reported symptoms as a warning signal for potential adverse events (ANRS HC26, ANRS HC27 trials). *Eur J Gastroenterol Hepatol*. 2016;28(6):733-4. doi:10.1097/MEG.0000000000000612.
11. Vera-Llonch M, Martin M, Aggarwal J, Donepudi M, Bayliss M, Goss T et al. Health-related quality of life in genotype 1 treatment-naïve chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. *Alimentary pharmacology & therapeutics*. 2013;38(2):124-33. doi:10.1111/apt.12354.
12. Gilead Sciences I. U.S. Food and Drug Administration Approves Gilead's Sovaldi™ (Sofosbuvir) for the Treatment of Chronic Hepatitis C. Business Wire (English): Regional Business News.
13. Gilead Sciences I. European Commission Grants Marketing Authorization for Gilead's Sovaldi® (Sofosbuvir) for the Treatment of Chronic Hepatitis C Infection. Business Wire (English): Regional Business News.
14. Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E et al. Minimal impact of sofosbuvir and ribavirin on health related quality of life in chronic hepatitis C (CH-C). *Journal of hepatology*. 2014;60(4):741-7. doi:10.1016/j.jhep.2013.12.006.
15. Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E et al. Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2014;12(8):1349-59 e13. doi:10.1016/j.cgh.2013.11.032.
16. Bourliere M, Bronowicki JP, de Ledinghen V, Hezode C, Zoulim F, Mathurin P et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). *The Lancet Infectious diseases*. 2015;15(4):397-404. doi:10.1016/S1473-3099(15)70050-2.
17. Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. *Qual Life Res*. 2001;10:405–13;15–20.
18. daCosta DiBonaventura M, Yuan Y, Wagner JS, L'Italien GJ, Lescrauwaet B, Langley P. The burden of viral hepatitis C in Europe: a propensity analysis of patient outcomes. *Eur J Gastroenterol Hepatol*. 2012;24(8):869-77. doi:10.1097/MEG.0b013e3283551dee.

19. Vietri J, Prajapati G, El Khoury AC. The burden of hepatitis C in Europe from the patients' perspective: a survey in 5 countries. *BMC Gastroenterol.* 2013;13:16. doi:10.1186/1471-230X-13-16.
20. Younossi ZM, Stepanova M, Pol S, Bronowicki JP, Carrieri MP, Bourliere M. The impact of ledipasvir/sofosbuvir on patient-reported outcomes in cirrhotic patients with chronic hepatitis C: the SIRIUS study. *Liver international : official journal of the International Association for the Study of the Liver.* 2015. doi:10.1111/liv.12886.
21. Stata Statistical Software. Release 12 ed: StataCorp; 2011.
22. Younossi Z, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. *Hepatology.* 2007;45(3):806-16. doi:10.1002/hep.21565.
23. Gerber L, Estep M, Stepanova M, Escheik C, Weinstein A, Younossi ZM. Effects of Viral Eradication With Ledipasvir and Sofosbuvir, With or Without Ribavirin, on Measures of Fatigue in Patients With Chronic Hepatitis C Virus Infection. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2016;14(1):156-64 e3. doi:10.1016/j.cgh.2015.07.035.
24. Fressard L, Spire B, Préau M, Sagaon Teyssier L, Suzan-Monti M, Mora M et al., editors. Suicide risk in people living with HIV: the possible role of HCV co-infection and experience of discrimination. *AIDS IMPACT*; 2015; Amsterdam.
25. Younossi Z, Henry L. Systematic review: patient-reported outcomes in chronic hepatitis C--the impact of liver disease and new treatment regimens. *Alimentary pharmacology & therapeutics.* 2015;41(6):497-520. doi:10.1111/apt.13090.
26. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Ann Med.* 2001;33(5):350-7.
27. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. *Hepatology.* 2005;41(4):790-800. doi:10.1002/hep.20659.
28. Fletcher NF, McKeating JA. Hepatitis C virus and the brain. *Journal of viral hepatitis.* 2012;19(5):301-6. doi:10.1111/j.1365-2893.2012.01591.x.

Fig. 1 Boxplots of PCS and MCS scores in CUPIC and SIRIUS, during and post treatment comparisons

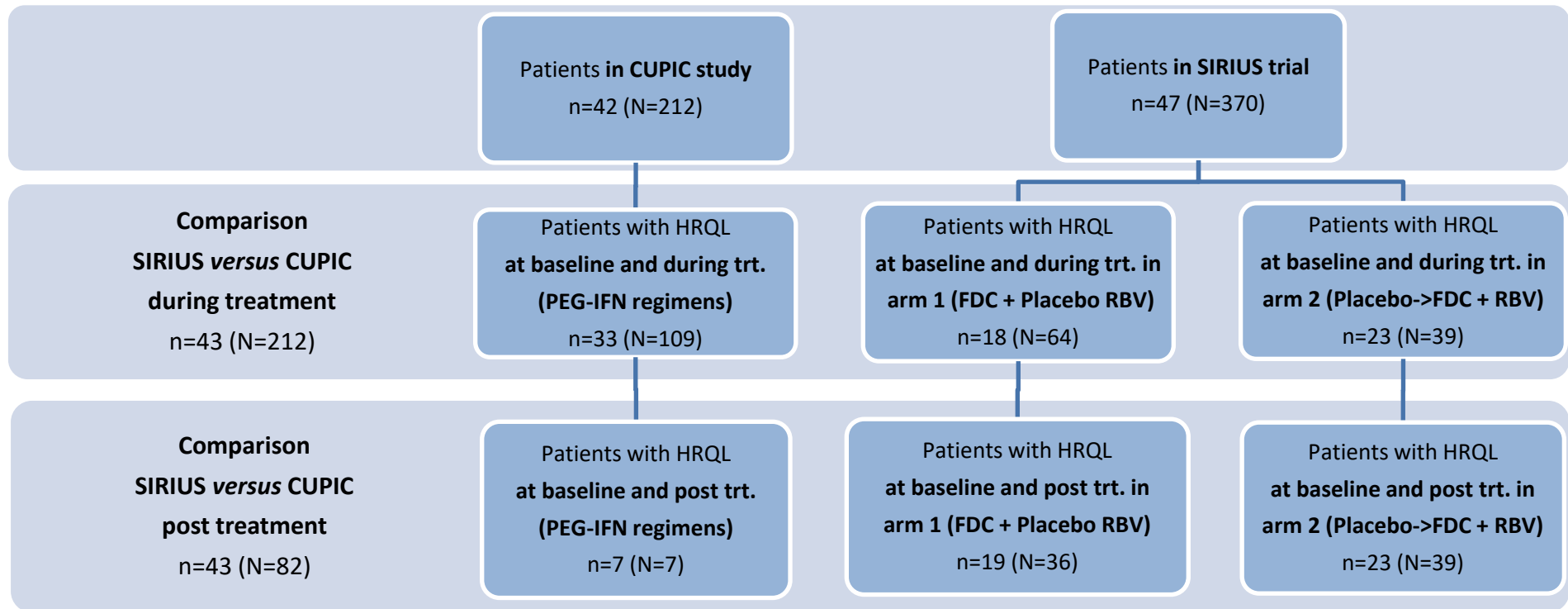


PCS = physical component summary score; MCS = mental component summary score;

FDC (fixed dose combination) = LDV (ledipasvir) + SOF (sofosbuvir); RBV = ribavirin

The boxes display the lower and upper quartiles of the scores by group at each visit, and the median (the line drawn across the boxes). The length of the boxes thus represents the interquartile range (IQR). The lines (whiskers) are drawn to span all data points within 1.5 IQR of the nearest quartile. All data points beyond the whiskers are shown individually.

Fig. 2 Flow chart for comparison of PCS and MCS scores in SIRIUS *versus* CUPIC, during- and post- treatment analyses (n=number of patients, N=number of observations)



PCS = physical component summary score; MCS= mental component summary score;

PEG-IFN = pegylated-interferon; FDC (fixed dose combination) = LDV (ledipasvir) + SOF (sofosbuvir); RBV = ribavirin