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EASL JOURNAL OF HEPATOLOGY

Improvement of health-related quality of life and work productivity in chronic hepatitis C patients with early and advanced fibrosis treated with ledipasvir and sofosbuvir

Zobair M. Younossi[1,2,*], Maria Stepanova[2,3], Nezam Afdhal[4], Kris V. Kowdley[5], Stefan Zeuzem[6], Linda Henry[3], Sharon L. Hunt[2], Patrick Marcellin[7]

[1]*Center for Liver Diseases, Department of Medicine, Inova Fairfax Hospital, Falls Church, VA, United States;* [2]*Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, United States;* [3]*Center for Outcomes Research in Liver Diseases, Washington, DC, United States;* [4]*Hepatology, Beth Israel Deaconess Medical Center, Boston, MA, United States;* [5]*Digestive Diseases Institute, Virginia Mason Clinic, Seattle, WA, United States;* [6]*Department of Medicine, J.W. Goethe University Hospital, Frankfurt, Germany;* [7]*Viral Hepatitis Research Unit in Hôpital Beaujon, Clichy, France*

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Background & Aims: New interferon-free anti-HCV regimens are highly efficacious with a favorable safety profile. We assessed health-related quality of life (HRQL) and work productivity in patients with different stages of hepatic fibrosis treated with sofosbuvir + ledipasvir.

Methods: Four questionnaires [Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), Short Form-36 (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Work Productivity and Activity Index:Specific Health Problem (WPAI:SHP)] were administered at baseline, during, and after treatment with sofosbuvir + ledipasvir + ribavirin or sofosbuvir + ledipasvir (ION-1,2,3 clinical trials). Metavir fibrosis stage was determined from pre-treatment liver biopsies.

Results: There were 1005 patients included (stage F0: n = 94; F1: n = 311; F2: n = 301; F3: n = 197; F4: n = 102). At baseline, patients with more advanced fibrosis had more HRQL impairments, predominantly related to physical functioning (stage 0 *vs.* stage 4 by up to 0.126 on a normalized 0–1 scale p <0.0001). During and post-treatment, HRQL remained lower in patients with advanced fibrosis. After achieving sustained virologic response, significant improvements from baseline in most HRQL domains were observed regardless of fibrosis stage (by 0.024–0.103 on a 0–1 scale; all p >0.05 across fibrosis stages). In multivariate analysis, advanced fibrosis was independently associated with impairment of HRQL and work productivity (beta up to −0.056 in comparison with none-to-mild fibrosis, p <0.05). However, improvement of HRQL and work productivity after viral clearance was not related to the stage of fibrosis (all p >0.05).

Conclusions: Although advanced hepatic fibrosis is associated with HRQL and work productivity impairment, viral eradication with sofosbuvir + ledipasvir leads to HRQL improvement regardless of fibrosis stage. HCV patients with early fibrosis experience similar improvement of patient reported outcomes as those with advanced fibrosis.

Keywords: HCV; Patient reported outcomes; Health-related quality of life; Work productivity; Fatigue; Fibrosis; Direct acting antivirals; Ribavirin.

Received 7 October 2014; received in revised form 6 February 2015; accepted 3 March 2015; available online 17 March 2015

☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2015.05.004.

* Corresponding author. Address: Betty and Guy Beatty Center for Integrated Research, Claude Moore Health Education and Research Building, 3300 Gallows Road, Falls Church, VA 22042, United States.

E-mail address: zobair.younossi@inova.org (Z.M. Younossi).

Abbreviations: HRQL, health-related quality of life; CLDQ-HCV, Chronic Liver Disease Questionnaire-Hepatitis C Virus; SF-36, Short Form-36; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; WPAI:SHP, Work Productivity and Activity Index:Specific Health Problem; CH-C, chronic hepatitis C; HCV, hepatitis C virus; SOF, sofosbuvir; LDV, ledipasvir; RBV, ribavirin; SVR, sustained virologic response; PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PCS, physical component summary; MCS, mental component summary; PWB, physical well-being; EWB, emotional well-being; SWB, social well-being; FWB, functional well-being; FS, fatigue scale; AE, activity/energy scale; EM, emotional scale; WO, worry scale; SY, systemic scale; WI, work productivity impairment; AI, activity impairment; HU, health utility.

Introduction

Since the discovery of hepatitis C virus (HCV) in 1989, there has been an explosion of knowledge about the molecular biology, pathogenicity and infectivity of this virus [1–3]. Our knowledge about the clinical impact of HCV has also evolved from estimating that only very few individuals with HCV infection will develop advanced liver disease to the current understanding that HCV is one of the most significant causes of chronic liver disease, cirrhosis, hepatocellular carcinoma and liver failure [4,5].

In addition to HCV-related liver disease, HCV infection is associated with a number of extrahepatic manifestations. These include mixed type 2 cryoglobinemia, porphyria catenae tarda, type 2 diabetes, fatigue and neuropsychiatric problems [4]. In fact,

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prevalence of psychiatric disorders is high among HCV patients possibly related to their underlying risk factors [6–9]. Furthermore, a number of cognitive impairments in patients with hepatitis C infection have been reported. Those included impairments in attention, concentration and information processing speed [6–9]. On the other hand, patients who achieved sustained virologic response (SVR) have been reported to enjoy improvements in verbal learning, memory, and visuospatial memory [10]. Although the exact mechanism that would link the presence of HCV infection with central nervous system (CNS) dysfunction is unclear, it has been suggested that certain cerebral metabolite abnormalities, which are observed in patients with chronic HCV infection and seem to be reversed in patients who cleared the virus (including choline-containing compounds and myo-inositol in basal ganglia), could be consistent with an inflammatory state within the brain accompanied by altered serotonergic and dopaminergic neurotransmission [11,12].

As a result of the effect of HCV on the liver as well as other organ systems (the extrahepatic manifestations of HCV), HCV has been widely reported to have a profound negative impact on health-related quality of life (HRQL), work productivity and other patient reported outcomes (PROs) [13–19]. In addition to this HRQL burden of HCV infection, the previous anti-HCV treatment with interferon and ribavirin (RBV), both with well-established side effects, further impacted patients' HRQL [14,20–22]. On the other hand, successful clearance of the virus after treatment has been reported to result in certain HRQL improvement in patients with chronic hepatitis C (CH-C) [23–27]. We have recently reported that a number of patient-reported outcomes (PROs), including HRQL, fatigue and work productivity improved in patients without cirrhosis after achieving SVR with interferon and RBV containing regimens [28]. However, it is important to note that in the absence of well-established cirrhosis or significant fibrosis, CH-C patients may still have substantial impairment in their overall well-being and HRQL. This impairment is probably predominantly driven by the extrahepatic manifestation of HCV such as fatigue, CNS and other organ manifestations.

Historically, histologic severity of liver disease has been used to prioritize treatment of patients with HCV infection [26]. Although histologic stage can be a reasonable but imperfect surrogate to predict clinical outcomes, a comprehensive approach to assessing outcomes in patients with HCV infection must consider not only the clinical outcomes but also patient experience. Therefore, our purpose was to determine if CH-C patients with early stage of liver disease experience a significant improvement in their HRQL and work productivity when treated with a sofosbuvir + ledipasvir (LDV/SOF) regimen as compared to those with advanced liver fibrosis treated with the same regimen.

Materials and methods

We assessed HRQL and work productivity data collected as secondary endpoints in the ION-1, ION-2, and ION-3 phase 3 clinical trials of anti-HCV treatment with LDV/SOF with and without the addition of RBV [29–32]. In these trials, treatment-naive or experienced patients with chronic HCV infection (genotype 1 only) were randomized to receive 400 mg of sofosbuvir plus 90 mg of ledipasvir once daily with or without weight-based RBV twice daily (1000 or 1200 mg/day) for 8, 12, or 24 weeks. For the purpose of our HRQL study, we used the medical history collected at screening to identify patients with pre-treatment history of anxiety, depression, fatigue, insomnia, and type 2 diabetes.

Health-related quality of life, work productivity and health utilities

HRQL and health utilities were reported using four different well-validated instruments [32–37]. After consent, all instruments were self-administered in the clinic room prior to initiation of any study-related activities at baseline, then at treatment weeks 2, 4, 8, 12, and 24 (where applicable), and at post-treatment week 4 and 12 follow-up visits. Both site staff and patients were blinded to patients' HCV RNA levels and other lab samples were collected during and after treatment.

The generic SF-36 questionnaire [32] is used to assess eight HRQL domains (ranging 0–100, higher values correspond to a better health status): physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The two summary scores summarize the physical and mental health components of SF-36: the Physical Component Summary score (PCS) and Mental Component Summary score (MCS). In this study, the SF-36 scales and summary scores were calculated using the QualityMetric Health Outcomes Scoring Software 4.5 (Lincoln, RI, USA) and the 2009 U.S. population norms.

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire [34] is another extensively validated 40-item HRQL and fatigue questionnaire. The scoring scheme includes physical (PWB, range 0–28, higher score indicates better well-being), emotional (EWB, 0–24), social (SWB, 0–28) and functional (FWB, 0–28) well-being domains, and the fatigue subscale domain (FS, 0–52). The five domains together add up to the total FACIT-F score (range 0–160).

The Chronic Liver Disease Questionnaire – Hepatitis C Virus (CLDQ-HCV) [35] is a widely used and validated disease-specific HRQL instrument developed specifically for assessment of HRQL in HCV patients. It includes four HRQL domains: activity and energy (AE), emotional (EM), worry (WO), and systemic (SY), all ranging 1 to 7 with higher values representing better HRQL. These domains are averaged to the total CLDQ-HCV score.

The Work Productivity and Activity – Specific Health Problem (WPAI:SHP) [36] is another validated instrument where participants are asked to evaluate impairment in their daily activities and work productivity associated with a specific health problem (HCV infection). The work productivity impairment domain is a sum of impairment in work productivity due to absenteeism and due to decreased productivity while working (presenteeism); this domain is assessed only in employed patients. The activity impairment domain is assessed in all participants regardless of their employment status and represents impairment in daily activities other than work. In this instrument, all domains range between 0 and 1, and, unlike other instruments, a greater impairment score indicates poorer health status (more impairment).

Health utility scores, which are preference-based measures for health typically used for calculation of quality-adjusted years of life in economic analyses, were assessed using the SF-6D metric which was derived from the SF-36 instrument by a non-parametric Bayesian model [37]. In general, health utility scores range between 0 and 1 (higher is better). However, in the Bayesian model used in this study, the minimal possible utility value was 0.2031.

Assessment of hepatic fibrosis

During pre-treatment screening, liver biopsies were collected (either performed for the purpose of screening or a recent biopsy made no more than 2 years before the study was used). Hepatic fibrosis was assessed using the Metavir scoring system [37]: F0: absent, F1: portal fibrosis, F2: portal fibrosis with few bridges, F3: bridging fibrosis, and F4: cirrhosis. For the purpose of this study, patients were classified into none-to-mild fibrosis (F0–F2) and advanced fibrosis (F3–F4). Patients with history of clinical hepatic decompensation (e.g., ascites, jaundice, encephalopathy, or variceal hemorrhage) were excluded from the study.

Statistical analysis

Age, gender distribution, other demographic and clinical parameters, HRQL domains, work productivity and health utility scores were summarized and compared between those with none-to-mild fibrosis and advanced fibrosis using Wilcoxon non-parametric test for pairwise comparison (continuous) or chi-square test for heterogeneity (categorical). The decrements/improvements in HRQL, work productivity and utility scores from patients' own baseline were calculated at all-time points, and then tested for significance using Wilcoxon sign rank test for matched pairs. Similar comparisons were made between five Metavir-assessed stages of fibrosis using non-parametric Kruskal-Wallis test. Independent predictors of HRQL, work productivity and health utilities at different time points were assessed in a series of multiple linear regressions using

stepwise selection with a significance level of 0.2 for entry and 0.05 for staying. All analyses were run in SAS 9.3 (SAS Institute, Cary, NC). The study was separately approved by each site's Institutional Review Board.

Results

Of 1952 participants of ION-1, ION-2, and ION-3 trials (29–32), only 1005 with available liver biopsy results were used. Of these, 94 patients were Metavir F0, 311 were F1, 301 were F2, 197 were F3, and 102 were F4; 706 had none-to-mild fibrosis and 299 had advanced fibrosis. The study cohort was 67.0% male, age (mean ± SD) 54.7 ± 9.1 years, 82.0% Caucasian, 66.1% treatment-naive, and 97.2% enrolled in the U.S. At baseline, 64.6% of the studies' participants reported being employed. During treatment, 34.0% of patients developed anemia (71.8% among those receiving RBV-containing regimens, and 6.5% in RBV-free arms) [29–31].

Baseline demographics and clinical parameters of the study participants with advanced *vs.* none-to-mild fibrosis are summarized in Table 1 (Supplementary Table 1 by individual Metavir stages). Expectedly, patients with more advanced stages of fibrosis were older (by approximately 1 year per each additional Metavir stage, $p = 0.0043$), predominantly treatment- experienced (65.7% F4 *vs.* 27.7% F0, $p < 0.0001$), had higher BMI (28.9 ± 5.2 in F3–4 *vs.* 27.7 ± 5.0 in F0–2, $p = 0.0001$) and ALT (above 1.5 upper limits of the norm in 64.55% F3–4 *vs.* 47.88% F0–2 patients, $p < 0.0001$). Furthermore, patients with advanced fibrosis reported history of clinically overt fatigue substantially more frequently (26.5% F4 *vs.* 5.3% F0, $p < 0.0001$). Treatment-related anemia was observed more frequently in patients with cirrhosis (48.0% *vs.* 32.4% in F0–3, $p = 0.0015$), but did not differ between the other stages of fibrosis ($p > 0.05$). The rates of SVR-12 were not different between the stages of fibrosis ($p > 0.05$) (Table 1, Supplementary Table 1).

Baseline HRQL, work productivity and health utilities, and hepatic fibrosis

HRQL assessed at the first day of treatment in patients with advanced *vs.* none-to-mild fibrosis are summarized in Table 2 and Fig. 1 (Supplementary Table 1 by individual Metavir stages). Expectedly, most of the HRQL domains were lower in patients with advanced fibrosis; in particular, the GH domain of SF-36 was lower by 7.4% on a 0–100% scale ($p < 0.0001$) when compared to those with none-to-mild fibrosis. In fact, the only exceptions were HRQL domains related to emotional well-being and mental health which were similar regardless of the severity of fibrosis.

HRQL, work productivity and health utilities in patients with different stages of hepatic fibrosis during and after treatment with LDV/SOF+RBV

Of the study cohort, 423 (42.1%) patients were treated with an RBV-containing regimen: 136 for 8 weeks, 196 for 12 weeks and 91 for 24 weeks. Changes in HRQL, work productivity and health utilities during and post-treatment in patients receiving

Table 1. Demographic and clinical presentation of the study cohort (n (%) or mean ± SD).

	Advanced fibrosis	None-to-mild fibrosis	*p* value
N	299	706	
Age, years	56.3 ± 7.1	54.0 ± 9.8	0.0106
Male gender	199 (66.56%)	474 (67.14%)	0.86
Caucasian	242 (80.94%)	543 (76.91%)	0.16
Enrolled in the U.S.	290 (96.99%)	687 (97.31%)	0.78
Treatment-naive	160 (53.51%)	504 (71.39%)	<0.0001
Baseline BMI	28.9 ± 5.2	27.7 ± 5.0	0.0001
Baseline hemoglobin, g/dl	14.89 ± 1.40	14.82 ± 1.33	0.45
Baseline HCV load $>10^6$	264 (88.29%)	579 (82.01%)	0.0133
ALT >1.5 x upper limit of norm	193 (64.55%)	338 (47.88%)	<0.0001
Cirrhosis	102 (34.11%)	0 (0.00%)	<0.0001
Pre-treatment history of:			
Anxiety	69 (23.08%)	151 (21.39%)	0.55
Depression	88 (29.43%)	184 (26.06%)	0.27
Fatigue	70 (23.41%)	83 (11.76%)	<0.0001
Insomnia	71 (23.75%)	154 (21.81%)	0.50
Type 2 diabetes	48 (16.05%)	86 (12.18%)	0.10
Treated with an RBV-containing regimen	137 (45.82%)	286 (40.51%)	0.12
Treatment duration			
8 weeks	57 (19.06%)	235 (33.29%)	<0.0001
12 weeks	171 (57.19%)	368 (52.12%)	0.14
24 weeks	71 (23.75%)	103 (14.59%)	0.0005
Developed anemia (Δ Hgb ≥2 g/dl)	113 (37.79%)	228 (32.34%)	0.10
SVR-12	288 (96.32%)	682 (96.60%)	0.83

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Table 2. Baseline HRQL and work productivity (mean ± SD) in patients with and without advanced fibrosis.

Instrument/domain	Advanced fibrosis (N = 299)	None-to-mild fibrosis (N = 706)	*p* value
SF-36			
Physical functioning	76.2 ± 24.8	82.6 ± 23.3	<0.0001
Role physical	74.4 ± 29.1	79.6 ± 26.7	0.0017
Bodily pain	70.1 ± 26.2	74.3 ± 25.2	0.0190
General health	62.0 ± 22.2	69.4 ± 20.9	<0.0001
Vitality	59.8 ± 25.2	63.7 ± 22.4	0.0453
Social functioning	78.6 ± 26.7	83.0 ± 23.7	0.0170
Role emotional	83.7 ± 24.1	84.5 ± 24.1	0.36
Mental health	73.9 ± 19.5	75.7 ± 18.1	0.15
Physical summary	48.4 ± 9.5	51.2 ± 8.9	<0.0001
Mental summary	50.3 ± 10.7	50.9 ± 9.8	0.55
FACIT-F			
Physical well-being	22.7 ± 5.6	23.6 ± 5.4	0.0022
Social well-being	17.3 ± 4.7	18.7 ± 4.2	<0.0001
Emotional well-being	21.3 ± 6.4	22.2 ± 5.8	0.06
Functional well-being	19.8 ± 6.4	21.2 ± 5.9	0.0019
Fatigue scale	37.8 ± 12.4	39.9 ± 11.9	0.0037
Total FACIT-F	118.6 ± 29.3	125.5 ± 27.0	0.0003
CLDQ-HCV			
Activity/energy	5.18 ± 1.46	5.47 ± 1.33	0.0039
Emotional	5.37 ± 1.29	5.56 ± 1.22	0.0232
Worry	5.25 ± 1.31	5.56 ± 1.29	0.0001
Systemic	4.93 ± 1.30	5.15 ± 1.29	0.0083
Total CLDQ-HCV	5.18 ± 1.20	5.43 ± 1.14	0.0008
WPAI:SHP			
Work productivity impairment	0.142 ± 0.235	0.103 ± 0.203	0.0234
Absenteeism	0.019 ± 0.076	0.027 ± 0.127	0.86
Presenteeism	0.123 ± 0.193	0.076 ± 0.147	0.0044
Activity impairment	0.207 ± 0.277	0.158 ± 0.252	0.0019
Health utility score			
SF-6D	0.690 ± 0.147	0.724 ± 0.147	0.0040

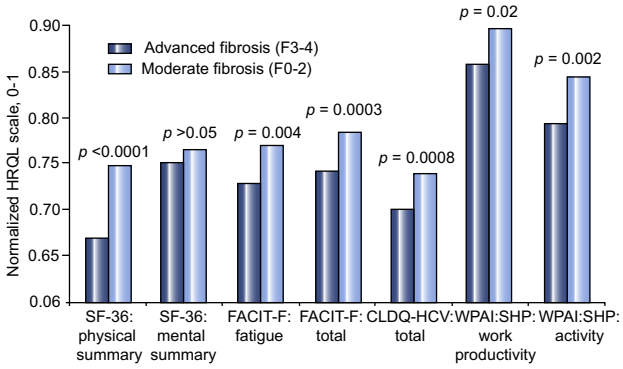

Fig. 1. Mean baseline HRQL and work productivity in patients with and without advanced fibrosis (normalized to the 0–1 scale). (A) End of treatment with LDV/SOF+RBV; (B) End of treatment with LDV/SOF; (C) SVR-12 after LDV/SOF+RBV; (D) SVR-12 after LDV/SOF.

LDV/SOF+RBV are summarized in Table 3 (Supplementary Table 2A by Metavir stages, Supplementary Fig. 1 by treatment week).

At week four of active treatment, a decline in some HRQL scales was observed in patients with none-to-mild-fibrosis, including physical and social functioning, role physical and emotional, and vitality of SF-36, physical and functional well-being and fatigue scale of FACIT-F, and activity/energy domain of CLDQ-HCV (all p <0.05). Of similar declines in patients with advanced fibrosis (all p >0.05 when compared to declines in none-to-mild fibrosis), only a decline in role emotional of SF-36 was statistically significant (p = 0.0089).

By the end of treatment, a more substantial decline was observed in most of the HRQL domains regardless of patients' fibrosis status (Table 3, Fig. 2A). In particular, the decrements in role physical and role emotional of SF-36 were statistically significant in both fibrosis cohorts, while physical and social functioning, vitality, and MCS of SF-36, physical and functional well-being and fatigue scale of FACIT-F, activity/energy of CLDQ-HCV, work productivity and SF-6D health utility declined significantly in patients with none-to-mild fibrosis only (all decline p <0.05). Furthermore, at the end of treatment, GH of SF-36, emotional well-being of FACIT-F, and worry domain of CLDQ-HCV significantly improved in both fibrosis cohorts (all improvement p <0.01), and neither individual or summary HRQL or work

productivity metric experienced a more substantial decrement in patients with advanced fibrosis compared to those with none-to-mild fibrosis at any time point during the course of treatment with LDV/SOF+RBV (all p >0.05) (Table 3).

At follow-up, in patients with both advanced and none-to-mild fibrosis, all HRQL domains and work productivity returned to their baseline levels or moderately improved as early as post-treatment week 4 (Table 3). These changes were similar in all patients regardless of their fibrosis stage (all p >0.05).

At SVR-12 follow-up (n = 407, Fig. 2C), most HRQL domains notably improved from the baseline in both fibrosis cohorts (Table 3). However, work productivity and health utility improved in patients with none-to-mild fibrosis only. Again, these improvements were not different between patients with different stages of fibrosis (all p >0.05). However, the absolute values of some HRQL domains were still lower in patients with advanced fibrosis, including physical functioning, role physical, general health and PCS of SF-36, and activity of WPAI.

Furthermore, among the individual HRQL domains, at least some improvement from baseline was observed in up to 74.7% of patients who achieved SVR. The only clinico-demographic factor associated with the absence this improvement in multivariate logistic regression was being treatment-naïve (odds ratio (95% confidence interval) = 0.56 (0.35–0.87). At the same time, improvement in no or only one HRQL domain was observed in only 4.8% of patients while 95.2% of patients had improvements in at least two different HRQL domains. On the other hand, the smallest proportion of patients had an improvement in the absenteeism domain of WPAI:SHP (7.9%).

HRQL, work productivity and health utilities in patients with different stages of hepatic fibrosis during and after treatment with LDV/SOF without RBV

Of the study cohort, 582 patients received an RBV-free regimen: 156 for 8 weeks, 343 for 12 weeks and 83 for 24 weeks. After

Table 3. The HRQL, work productivity and health utilities changes (mean ± SD) during treatment in patients with and without advanced fibrosis (mean ± SD) in RBV-containing and RBV-free regimens.

	LDV/SOF + RBV			LDV/SOF		
Instrument: domain	Advanced fibrosis	None-to-mild fibrosis	p value	Advanced fibrosis	None-to-mild fibrosis	p value
N	137	286		162	420	
SF-36: physical component summary						
Baseline	49.50 ± 9.36	51.35 ± 8.30	0.08	47.46 ± 9.62	51.03 ± 9.33	<0.0001
Change by:						
Week 4 *	-0.32 ± 6.93	-0.35 ± 5.82	0.84	0.55 ± 5.90[&]	0.36 ± 4.66	0.27
End of treatment	0.05 ± 7.38	0.16 ± 6.46	0.67	1.80 ± 6.37[&]	1.51 ± 5.80[&]	0.45
4 weeks post-treatment	1.47 ± 7.14[&]	1.22 ± 5.91[&]	0.77	1.73 ± 6.61[&]	1.76 ± 5.70[&]	0.33
SVR-12	1.86 ± 7.58[&]	1.92 ± 6.17[&]	0.72	2.08 ± 6.93[&]	1.70 ± 5.85[&]	0.95
SF-36: mental component summary						
Baseline	51.62 ± 10.15	50.96 ± 8.95	0.19	49.16 ± 11.01	50.94 ± 10.33	0.06
Change by:						
Week 4 *	-0.72 ± 8.10	-0.70 ± 7.39	0.69	1.23 ± 6.58[&]	0.76 ± 7.09[&]	0.59
End of treatment	-2.12 ± 9.97	-1.91 ± 9.36[&]	0.75	1.53 ± 8.69[&]	2.23 ± 8.33[&]	0.90
4 weeks post-treatment	0.01 ± 9.43	0.83 ± 7.83	0.55	2.04 ± 7.57[&]	2.19 ± 8.26[&]	0.87
SVR-12	0.43 ± 8.59	2.18 ± 8.09[&]	0.05	1.94 ± 8.57[&]	2.51 ± 7.95[&]	0.80
FACIT-F: fatigue						
Baseline	39.16 ± 12.07	40.11 ± 10.88	0.63	36.63 ± 12.65	39.72 ± 12.59	0.0007
Change by:						
Week 4 *	-0.60 ± 9.43	-1.04 ± 8.94[&]	0.38	1.48 ± 8.24	1.59 ± 8.03[&]	0.87
End of treatment	-1.38 ± 12.61	-1.51 ± 11.10[&]	0.98	2.49 ± 9.41[&]	3.07 ± 9.13[&]	0.99
4 weeks post-treatment	3.01 ± 10.30[&]	2.60 ± 9.40[&]	0.94	3.52 ± 9.77[&]	3.84 ± 9.38[&]	0.76
SVR-12	3.68 ± 11.30[&]	4.34 ± 9.21[&]	0.20	3.59 ± 9.55[&]	4.18 ± 8.90[&]	0.99
FACIT-F: total						
Baseline	122.55 ± 27.49	125.44 ± 24.61	0.43	115.50 ± 30.33	125.51 ± 28.52	0.0001
Change by:						
Week 4 *	0.91 ± 19.27	-0.71 ± 18.43	0.26	4.85 ± 16.06[&]	4.66 ± 16.47[&]	0.46
End of treatment	-0.30 ± 25.34	-1.19 ± 24.30	0.81	6.97 ± 19.69[&]	8.31 ± 18.97[&]	0.98
4 weeks post-treatment	8.05 ± 22.07[&]	6.92 ± 20.43[&]	0.56	9.11 ± 20.37[&]	9.99 ± 19.55[&]	0.59
SVR-12	9.16 ± 23.22[&]	10.75 ± 20.02[&]	0.44	8.23 ± 21.02[&]	10.27 ± 19.57[&]	0.71

(*continued on next page*)

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Table 3. (continued)

	LDV/SOF + RBV			LDV/SOF		
Instrument: domain	Advanced fibrosis	None-to-mild fibrosis	*p* value	Advanced fibrosis	None-to-mild fibrosis	*p* value
CLDQ-HCV: total						
Baseline	5.31 ± 1.21	5.47 ± 1.04	0.34	5.07 ± 1.18	5.41 ± 1.20	0.0003
Change by:						
Week 4 *	0.17 ± 0.78[&]	0.12 ± 0.70[&]	0.48	0.30 ± 0.64[&]	0.32 ± 0.68[&]	0.76
End of treatment	0.21 ± 0.92[&]	0.12 ± 0.91[&]	0.45	0.41 ± 0.86[&]	0.51 ± 0.81[&]	0.45
4 weeks post-treatment	0.45 ± 0.91[&]	0.42 ± 0.86[&]	0.90	0.48 ± 0.79[&]	0.57 ± 0.86[&]	0.65
SVR-12	0.50 ± 0.95[&]	0.50 ± 0.85[&]	0.69	0.48 ± 0.88[&]	0.61 ± 0.88[&]	0.43
WPAI:SHP: work productivity impairment						
Baseline	0.154 ± 0.248	0.123 ± 0.221	0.29	0.132 ± 0.224	0.089 ± 0.188	0.0427
Change by:						
Week 4 *	0.023 ± 0.216	0.035 ± 0.251	0.95	0.010 ± 0.227	-0.004 ± 0.165	0.28
End of treatment	0.040 ± 0.239	0.053 ± 0.243[&]	0.56	0.018 ± 0.251	-0.045 ± 0.188[&]	0.48
4 weeks post-treatment	-0.071 ± 0.195[&]	-0.049 ± 0.223[&]	0.40	-0.008 ± 0.231	-0.035 ± 0.196[&]	0.70
SVR-12	-0.060 ± 0.248	-0.076 ± 0.238[&]	0.89	-0.046 ± 0.190	-0.032 ± 0.210[&]	0.31
WPAI:SHP: activity impairment						
Baseline	0.197 ± 0.265	0.152 ± 0.241	0.05	0.216 ± 0.287	0.161 ± 0.260	0.0151
Change by:						
Week 4 *	0.009 ± 0.242	0.019 ± 0.228	0.61	-0.028 ± 0.210	-0.018 ± 0.208[&]	0.57
End of treatment	0.002 ± 0.280	0.026 ± 0.276	0.21	-0.061 ± 0.251[&]	-0.059 ± 0.227[&]	0.76
4 weeks post-treatment	-0.089 ± 0.217[&]	-0.059 ± 0.218[&]	0.29	-0.082 ± 0.259[&]	-0.070 ± 0.233[&]	0.69
SVR-12	-0.090 ± 0.272[&]	-0.093 ± 0.230[&]	0.97	-0.095 ± 0.236[&]	-0.082 ± 0.240[&]	0.48
SF-6D health utility						
Baseline	0.706 ± 0.146	0.719 ± 0.135	0.72	0.676 ± 0.147	0.728 ± 0.155	0.0007
Change by:						
Week 4 *	-0.012 ± 0.119	-0.011 ± 0.098	0.89	0.018 ± 0.098[&]	0.018 ± 0.102[&]	0.97
End of treatment	-0.007 ± 0.133	-0.019 ± 0.126[&]	0.37	0.034 ± 0.113	0.041 ± 0.119[&]	0.94
4 weeks post-treatment	0.018 ± 0.124	0.028 ± 0.129[&]	0.50	0.038 ± 0.111	0.042 ± 0.121[&]	0.88
SVR-12	0.020 ± 0.127	0.042 ± 0.124[&]	0.05	0.040 ± 0.118[&]	0.052 ± 0.130[&]	0.47

[&]Significant difference from patients' own baseline (p <0.05 by a paired non-parametric test).
*Positive change indicates improvement (except for WPAI:SHP domains).

treatment, 563 patients achieved SVR-12. Changes in HRQL, work productivity and health utilities during and post-treatment in patients receiving LDV/SOF are summarized in Table 3 (Supplementary Table 2B by Metavir stages, Supplementary Fig. 1 by treatment week).

In patients receiving LDV/SOF without RBV, moderate improvements in HRQL were observed soon after the start of treatment, including improvements in BP, GH, vitality, mental health and both summary scales of SF-36, all domains except for SWB of FACIT-F, all domains of CLDQ-HCV, activity impairment of WPAI:SHP and health utility (all p <0.05 in both fibrosis cohorts). These HRQL improvements increased further by the end of treatment (Fig. 2B, Supplementary Table 2B, Supplementary Fig. 1). Similarly to the RBV-containing regimen reported above, neither of these improvements at any time point were different between patients with advanced and none-to-mild fibrosis receiving an RBV-free regimen (all p >0.05).

Improvements by the end of treatment were again greatest in the CLDQ-HCV score: 76.4% had at least some improvement in CLDQ-HCV score (no clinico-demographic predictors were identified in multivariate regression analysis). No or only one HRQL domain improved in only 3.85% of the patients.

In follow-up, the improvements in HRQL became more prominent as early as week 4 post-treatment for all HRQL domains mentioned above, as well as for work productivity (in F0–2 only) and its presenteeism component (Table 3, Supplementary Table 2B). No difference between patients with different stages of fibrosis were observed at this time point (all p >0.05).

At week-12 of follow-up, HRQL and work productivity improvements became the most notable (Supplementary Fig. 1). All improvements were again similar between the two fibrosis cohorts (all p >0.05) (Table 3, Supplementary Table 2B, Fig. 2D). Despite this, similarly to those at baseline, in patients with advanced fibrosis, lower absolute values were observed for all studied HRQL domains of SF-36, FACIT-F, and CLDQ-HCV, health utility and activity impairment of WPAI:SHP (all p <0.05).

Furthermore, in patients who achieved SVR, CLDQ-HCV was improved in 79.2% of patients, while no or at most one HRQL domain improved in only 2.5% of patients. The smallest

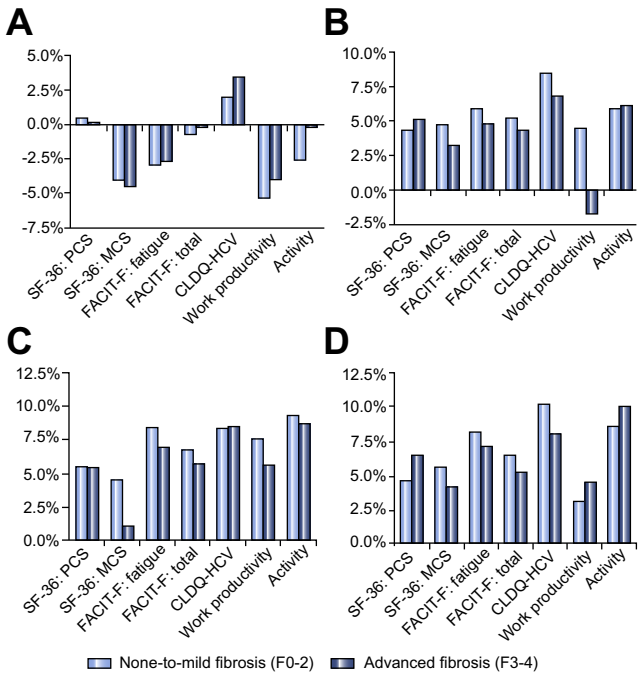

Fig. 2. Mean changes in HRQL and work productivity at the end of treatment and post-SVR-12 in patients with and without advanced fibrosis (all p >0.05). Note: The mean changes in HRQL and work productivity are transformed to the 0–100% scale. PCS – physical component summary of SF-36; MCS – mental component summary of SF-36.

proportion of post-SVR improvement was again observed for the absenteeism domain of work productivity impairment (5.1%).

Independent predictors of HRQL, work productivity and health utilities

In multivariate analysis (Supplementary Table 3), predictors of HRQL, work productivity and health utilities at baseline, end of treatment and SVR-12 follow-up included baseline clinico-demographic variables such as being enrolled in the U.S., female gender, older age, baseline depression, anxiety, insomnia, fatigue and type 2 diabetes, as well as treatment regimen (RBV-containing *vs.* RBV-free). After adjustment for those confounders, having advanced fibrosis was associated with more impairment in PCS (betas = −1.97 to −1.69 at different time points, p = 0.0011 to 0.0027), fatigue (betas = −1.74 to −1.65, p = 0.0070 to 0.0277), total FACIT-F (betas = −6.18 to −4.20, p = 0.0001 to 0.0167), CLDQ-HCV (betas = −0.23 to −0.16, p = 0.0006 to 0.0282), and SF-6D health utility (betas = −0.029 to −0.024, p = 0.0065 to 0.0144). Furthermore, advanced fibrosis was also associated with more work productivity impairment (at the last day of treatment only, beta = 0.044, p = 0.0391) and activity impairment (SVR-12 follow-up only, beta = 0.043, p = 0.0007). In fact, the only summary HRQL metric that was not found to be affected in patients with advanced fibrosis was MCS of SF-36 (all p >0.05).

At the same time, no HRQL, work productivity or health utility decrement or improvement from baseline during treatment or in follow-up was found to be independently associated with more advanced fibrosis (all p >0.05).

Discussion

This study involved over 1000 patients with CH-C and available liver biopsies who were treated with LDV/SOF. Our study provides several new and important lines of evidence about outcomes important to patients related to the stage of hepatic fibrosis and treatment with LDV/SOF.

First, our study clearly documented the superiority of interferon- and RBV-free regimen in relation to HRQL and work productivity regardless of the stage of liver disease. Historic HRQL data from one of our previous studies of an interferon-based sofosbuvir-containing regimen could be used for comparison [28]. In particular, in this study, we have showed that interferon- and RBV-free regimen is associated with significant gains in most aspects of HRQL during treatment for patients with early stage liver disease (up to +13.8% for the worry domain of CLDQ-HCV transformed to a 0–100% normalized scale). In contrast, patients without cirrhosis who received SOF+RBV+interferon had substantial treatment-emergent impairments in the same HRQL domains (up to −25.5% for role physical of SF-36) [28]. On the other hand, an interferon-free RBV-containing regimen was also associated with moderate HRQL and work productivity impairment regardless of the stage of fibrosis (up to −5.4% for role physical of SF-36 in early fibrosis and up to −8.3% for role emotional of SF-36 in advanced fibrosis), but this impairment was again substantially lower when compared to the interferon-containing regimen. Furthermore, since no difference between the stages of fibrosis were observed in relation to HRQL changes during treatment, we believe that it is the side effects of RBV, rather than the stage of liver disease, that primarily determines on-treatment impact on quality of life in LDV/SOF-based treatment [32,38–42].

It is also important to note that improvement in HRQL during interferon-free RBV-free treatment occurs early during treatment, suggesting the effect of viral clearance rather than the change of fibrosis stage. Thus, it is possible that with longer post-treatment follow-up, more improvement in HRQL, work productivity and health utilities can be observed after partial reversal of fibrosis and resolution of some extrahepatic manifestations of HCV.

As expected, CH-C patients with advanced fibrosis had more HRQL impairment compared to those with early liver disease. In fact, the gradual worsening of HRQL scores, especially those related to activity and physical functioning, correlated with increasing Metavir stage of fibrosis. However, improvement of HRQL occurred after SVR-12 regardless of the stage of liver disease. In particular, despite minimal baseline impairment in HRQL and work productivity, patients with early fibrosis experienced post-SVR improvement in all HRQL domains as well as in work productivity (driven by its presenteeism component) and health utilities. Furthermore, improvements of HRQL, work productivity and health utilities during treatment or post-SVR regardless of the regimen were not associated with the stage of liver disease and were solely determined by the treatment regimen and the previously reported predictors of HRQL impairment such as history of prior anti-HCV treatment, psychiatric disorders and type 2 diabetes [32,38–42].

The study has certain limitations aside from those typical for the use of questionnaires for assessment of health status and for derivation of continuous metrics from ordinal entries. In particular, no patients with decompensated disease were included, so no

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conclusion about HRQL and work productivity (if any) could be made for patients with decompensated cirrhosis. Although patients were blinded to their interim outcomes such as HCV RNA, they were not blinded to their fibrosis stage, and this could potentially result in some bias. Finally, our ability to assess the impact of SVR was limited due to the lack of comparison to non-SVR population with early and advanced fibrosis.

In summary, we have shown that LDV/SOF-based treatment improves HRQL and other PROs in HCV patients regardless of the stage of liver disease, and that the most significant decrements in HRQL observed in our study were associated with the use of RBV. We believe that expanding the access to the highly effective cure for this systemic disease to all HCV-infected patients regardless of their histologic fibrosis stage will not only potentially improve the clinical outcomes but also patient-reported outcomes such as HRQL and work productivity, resulting in comprehensive benefit to patients and the society.

Financial support

The study was supported by funding from Gilead Sciences. The authors had full access to the data and complete autonomy for analysis design data analysis, data interpretation, manuscript writing, and submissions.

Conflict of interest

ZMY, NA, KK, SZ, PM have received research grants and/or are advisors for Gilead Sciences. MS, LH, and SH have no conflict of interest with respect to this manuscript.

Authors' contributions

ZMY: Study design, data analysis plan, data interpretation and manuscript writing; guarantor of the article. MS: Data analysis, data interpretation and manuscript writing.

NA: Study design, data interpretation and manuscript review and editing. KK: Study design, data interpretation and manuscript review and editing. SZ: Study design, data interpretation and manuscript review and editing. LH: Study design, data management, data interpretation and manuscript writing and editing. SH: Study design, data management, data interpretation and manuscript review and editing. PM: Study design, data interpretation and manuscript review and editing.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2015.03.014.

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