Original Article

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Health-Related Quality of Life after Direct Acting Antiviral Treatment for Chronic Hepatitis C in a community Led Program

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Abstract

Background: Introduction: HCV infection causes significant impairment of health-related quality of life (HRQoL) and other patient-reported outcomes. Interferon-based treatment was strongly associated with a decreased HRQoL. Clinical trials showed that an interferon-free treatment also leads to a mild impairment of HRQoL during treatment that improves after end of treatment. Our aim was to assess the impact of Direct Acting Antiviral (DAA) treatment on HRQoL in a prospectively followed real-life cohort in the context of community-led program. **Methods:** HRQoL was assessed in 601 HCV-infected patients using the Short-Form 36 before the start of DAA treatment and was repeated after about 12 weeks of end of treatment when SVR was assessed. The patients were classified into two groups according to treatment regimen: Group I patients received 400 mg of sofosbuvir daily with weight-based ribavirin for 24 weeks, while Group II patients received daily oral sofosbuvir 400 mg and daclatasvir 60 mg for 12 weeks. **Results:** HRQoL domains (with the exception of role physical domain) showed improvement, regardless whether ribavirin was part of the treatment regimen or not. Both the physical and the mental component summary score increased significantly in each group, with no significant difference between the two treatment arms. **Conclusion:** The current real-world study confirms results from clinical trials that the majority of patients report an increased HRQoL after finishing HCV treatment.

Introduction

Hepatitis C virus infection is a major global health problem, with an estimated 71 million with chronic hepatitis C infection [1], with the highest prevalence in Egypt, where over 90% of the infections have been reported to be HCV genotype 4 [2]. HCV infection causes significant impairment of health-related quality of life (HRQoL) and other patient-reported outcomes (PRO) such as work productivity, fatigue, and various aspects of daily functioning and well-being [3-5].

Interferon-based treatment was strongly associated with a decreased HRQoL [6]. Treatment of HCV has been revolutionized so that the new interferon (IFN)-free regimens with the new direct-acting antiviral agents (DAAs) have led to substantial efficacy exceeding 90% accompanied by excellent tolerability in most populations, with minimal serious side effects [7]. However, it has been shown that an interferon-free treatment with sofosbuvir and ribavirin also leads to a mild impairment of HRQoL during treatment [8] and that removing interferon and ribavirin has led to substantial improvement of health-related quality of life during treatment [6]. In contrast, RBV-free treatment leads to an improved HRQoL during the treatment period [6].

Given the rarity of previously published real-life data about the impact of the new DAA-based regimens on patients' HRQoL, we aim in this study to assess the impact of DAAs on the HRQoL in a prospectively followed Egyptian real-life cohort in the context of community-led program.

Patients and methods

Study design: This is a prospective longitudinal study conducted among patients with HCV who received either 24 weeks of combination therapy using sofosbuvir (SOF) and ribavirin (RBV) or 12 weeks of combination of SOF and daclatasvir (DCV) between June 2015 and November 2016 that showed sustained viral response (SVR) after 12 weeks from end of treatment.

Study site: This study was conducted by the Egyptian Liver Research Institute and Hospital (ELRIAH), Sherbin, El Mansoura, Egypt, in the context of the hepatitis virus elimination program conducted by ELRIAH [9]. The program was implemented in 73 communities in Egypt [10] and randomly selected sample of patients from 8 of these communities (Al-Othmanya, Elibrahimia Elkebliah, Elibrahimia Elbahariah, Elsadiah Elkebliah, Elkordy, Elrodah, Elghawabeen and Elsegaiah) were included in the current study.

Patient selection: This study included 601 HCV patients randomly selected in 8 communities from those who are willing to participate. Eligible patients were aged ≥ 18 years old with the diagnosis of chronic HCV. Exclusion criteria were: failure of previous treatment for chronic HCV infection, liver cirrhosis, co-infection with other hepatitis viruses or/and human immunodeficiency viruses;

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coexistence of other forms of hepatic disease; a recent episode of decompensation of the liver disease (ascites, variceal hemorrhage, hepatic encephalopathy, or spontaneous bacterial peritonitis in the previous 6 months); extremely low literacy level or cognitive status precluding reliable participation.

The patients were classified into two groups according to treatment regimen received. Group I patients received 400 mg of SOF daily with weight-based RBV for 24 weeks; and Group II patients received daily oral SOF 400 mg and DCV 60 mg for 12 weeks. Group I regimen was implemented in patients included in the study early, and Group II regimen was implemented in patients enrolled late, because this was the standard of care in Egypt at the time of enrollment.

The study included only patients that showed SVR, as indicated by absence of HCV virus 12 weeks after the end of treatment (SVR12).

Health related quality of life (HRQoL) assessment: For these HCV patients SF-36 questionnaire for quality of life was implemented. The instrument is extensively validated and has been widely used for assessment of HRQoL in various settings including clinical trials [11]. The questionnaire was provided in Arabic and this was done in the patient's villages. The questionnaire was implemented before start of treatment and was repeated after about 12 weeks of end of treatment (12.75±4.99 weeks) when SVR was assessed.

The SF-36 includes 36 questions about patients' perception of wellbeing, health status and daily functioning, which are used to calculate 8 HRQoL domain scores, each ranging from 0 to 100 with higher scores indicating better health: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH). Two summary scores, namely, Physical Component Summary Score (PCS) and Mental Component Summary Scores (MCS) were calculated as weighted averages of the domain scores linearly transformed. SF-36 score were also calculated as weighted average of the two scores.

Ethics: The study was conducted in accordance to the Declaration of Helsinki and International Conference on Harmonization guidelines. All patients gave written informed consent prior to inclusion in the study. ELRIAH Institutional Research Board (OHRP IRB #8819) gave approval for the study and for the use of patients' data for this publication.

Statistical analysis: Demographic parameters, baseline, and post-treatment HRQoL scores of the study participants were summarized and compared between the SOF+RBV and SOF+DCV treatment arms using chi-square test or Mann Whitney U nonparametric test. Comparison of scores between baseline and post-treatment were done using related samples Wilcoxon signed rank test. Changes (decrements or improvements) in HRQoL scores from patients' own baseline levels were calculated and compared between the two arms of study using Mann Whitney U test. P-values of 0.05 or less were considered statistically significant.

Results

The baseline characteristics of 601 patients with chronic HCV infection were summarized in Table 1. The mean age was 52.6±10.9 years and 46.4% of the subjects were males **(Table 1)**. The differences between the two arms of the study as regards age and sex were not significant.

Twelve weeks after HCV treatment, all dimensions for HRQoL (with the exception of role physical domain) showed improvement, regardless whether RBV was part of the treatment regimen or not **(Table 2 and Figure 1)**. Both cohorts reported this increase. In addition, patients who received RBV-containing treatment reported a significantly stronger improvement compared to RBV-free group for social functioning, bodily pain and general health. Patients treated with RBV-free regimen reported a significantly strong increase in vitality domain only compared to RBV-containing treatment. Both the physical and the mental component summary score increased significantly in each group, with no significant difference between the two treatment arms **(Figure 2).**

Table 1. Baseline characteristics of studied patients.

	Group I SOF+RBV 24 weeks	Group II SOF+DCV 12 weeks	Total	P value
Number	388	213	601	
Age	52.8±10.3	52.3±12.0	52.6±10.9	0.797
Sex - **Male** - **Female**	 173 (44.6%) 215 (55.4%)	 106 (49.8%) 107 (50.2%)	 279 (46.4%) 107 (50.2%)	0.223

Table 2: Changes in HRQoL for subjects stratified by type of treatment.

		Group I SOF+RBV 24 weeks	Group II SOF+DCV 12 weeks	Total	P value
PF	**Baseline**	58.47±25.24	61.13±23.13	59.42±24.53	0.222
	Post-treatment	66.49±29.98	72.79±28.71	68.73±29.67	0.018
	P value	<0.001	<0.001	<0.001	
	Change	8.02±38.51	11.67±36.40	9.31±37.79	0.154
RP	**Baseline**	77.19±35.61	71.01±39.92	75.00±37.28	0.083
	Post-treatment	68.49±45.59	68.43±44.88	68.47±45.30	0.861
	P value	0.001	0.469	0.003	
	Change	-8.70±57.06	-2.58±62.42	-6.53±69.04	0.229
RE	**Baseline**	56.01±29.66	59.94±35.19	57.40±31.76	0.089
	Post-treatment	75.95±42.19	74.96±42.70	75.60±42.34	0.800
	P value	<0.001	<0.001	<0.001	
	Change	19.93±50.07	15.02±58.22	18.19±53.11	0.403
VT	**Baseline**	49.81±13.77	49.58±20.10	49.73±16.28	0.641
	Post-treatment	63.38±23.06	71.03±20.18	66.09±22.37	<0.001
	P value	<0.001	<0.001	<0.001	
	Change	13.57±27.57	21.46±28.62	16.36±28.18	0.001
MH	**Baseline**	53.64±9.41	59.68±13.84	55.78±11.54	<0.001
	Post-treatment	69.99±19.19	76.81±17.56	72.41±18.90	<0.001
	P value	<0.001	<0.001	<0.001	
	Change	16.35±20.64	17.13±21.92	16.63±21.08	0.396
SF	**Baseline**	45.22±19.70	60.30±22.28	50.56±21.86	<0.001
	Post-treatment	76.16±16.50	75.59±18.52	75.96±17.23	0.878
	P value	<0.001	<0.001	<0.001	
	Change	30.94±24.46	15.29±30.57	25.39±27.79	<0.001
BP	**Baseline**	50.72±20.69	59.98±23.98	54.00±23.34	<0.001
	Post-treatment	75.79±31.17	77.07±26.68	76.24±29.64	0.562
	P value	<0.001	<0.001	<0.001	
	Change	25.06±35.60	17.09±37.39	22.24±36.42	0.011
GH	**Baseline**	47.95±14.20	55.38±14.89	50.58±14.87	<0.001
	Post-treatment	64.20±18.92	64.88±19.10	64.44±18.97	0.0753
	P value	<0.001	<0.001	<0.001	
	Change	16.25±23.13	9.51±24.91	13.86±23.97	0.002
PCS	**Baseline**	58.59±15.94	61.87±17.69	59.75±16.64	0.004
	Post-treatment	68.74±22.49	70.79±21.57	69.47±22.18	0.359
	P value	<0.001	<0.001	<0.001	
	Change	10.16±26.60	8.92±29.46	9.72±27.63	0.649
MCS	**Baseline**	51.17±10.36	57.37±17.15	53.37±13.49	0.002
	Post-treatment	71.36±19.03	74.60±19.63	72.51±19.29	0.007
	P value	<0.001	<0.001	<0.001	
	Change	20.23±21.10	17.22±26.90	19.16±23.34	0.360
SF-36	**Baseline**	54.88±11.97	59.62±16.02	56.56±13.72	0.001
	Post-treatment	70.11±19.51	72.70±19.22	71.03±19.43	0.082
	P value	<0.001	<0.001	<0.001	
	Change	15.26±22.10	13.07±26.17	14.48±23.63	0.342

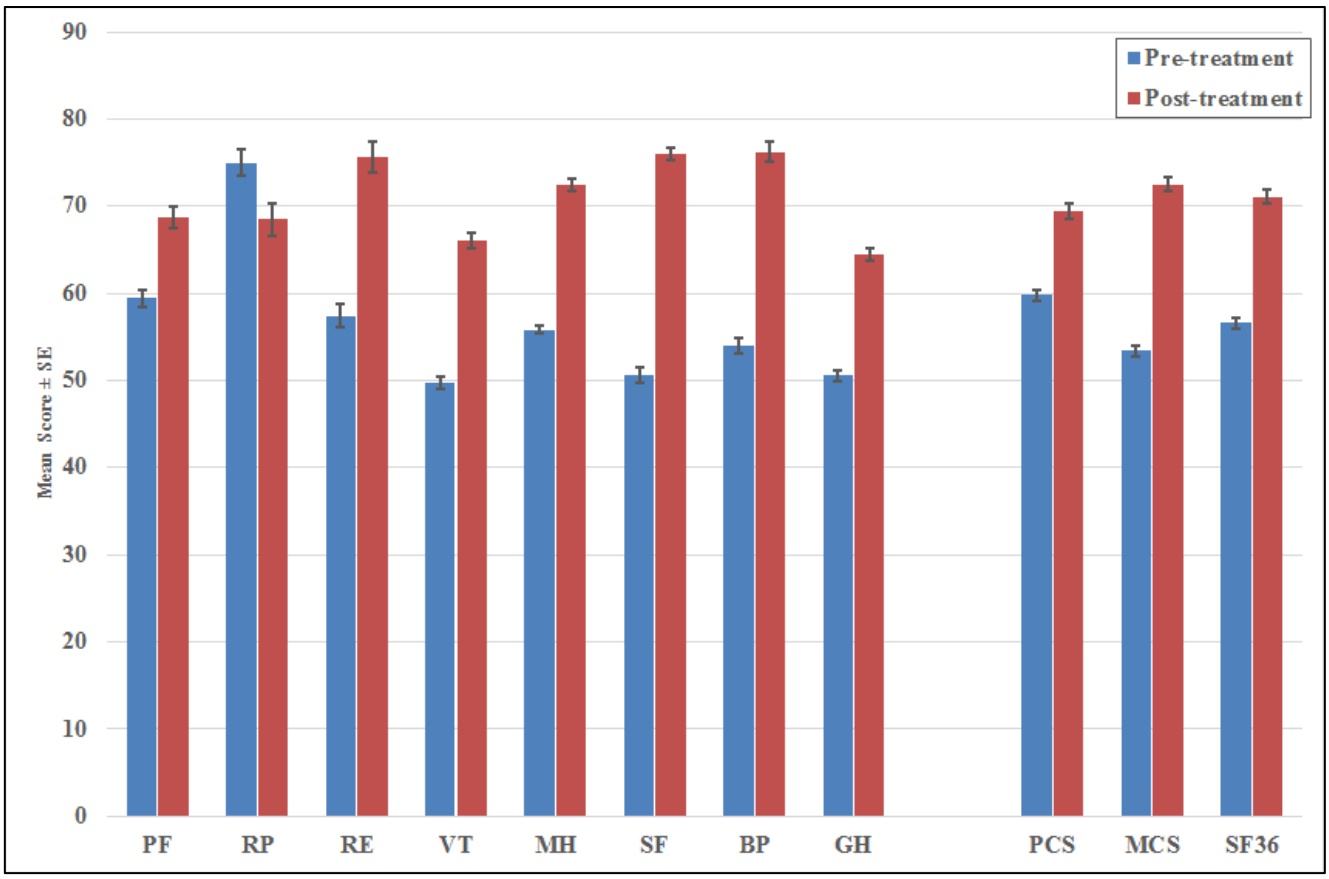

Figure 1: Changes in HRQoL for subjects stratified by type of treatment.

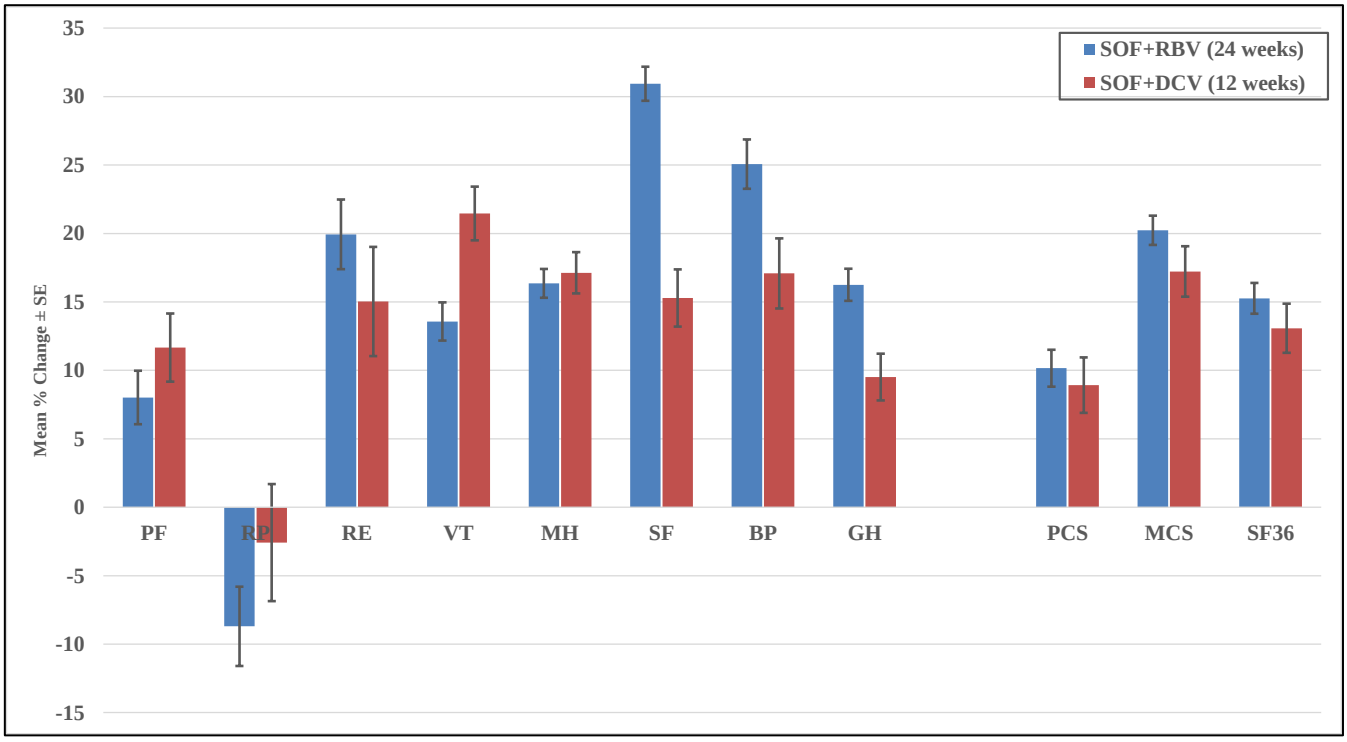

Figure 2: Percent Changes in HRQoL for subjects stratified by type of treatment.

Discussion

Our results showed that successful treatment of chronic HCV led to significant improvement of all aspects of HRQoL (except for RP). This improvement occurred in both arms of the study (SOF+RBV for 24 weeks and SOF+DCV for 12 weeks). To our knowledge, this have been rarely reported as part of treatment programs outside of clinical trials.

These improvements in HRQoL domain scores were more noticeable after treatment with the SOF+RBV in most of the domain scores. Both the physical and the mental component summary score increased significantly in each group, with no significant difference between the two treatment arms. This is concordant to what was reported by Siederdissen et al. in 2018 [12] which found that after treatment of 174 German patients, all dimensions for HRQoL showed improvement across the study cohort, regardless whether RBV was part of the treatment regimen or not. They reported that during HCV treatment, RBV-free treatment led to an increase in all measured dimensions of quality of life, whereas RBV treatment led to a decrease in the emotional and physical functioning. Our findings is also concordant with Ikeda et al. in 2017 [13] that studied 123 Japanese patients receiving daclatasvir and asunaprevir for 24 weeks in a clinical setting and demonstrated that HRQoL can improve as early as at the initiation of treatment and can continue during and after treatment. The changes of HRQoL at post treatment week 24 in patients with sustained virological responses were significantly higher than those in patients without SVR. Goñi Esarte et al. (2019) [14] studied long term changes in HRQoL in 199 Spanish patients (29% had cirrhosis and 32% had HIV co-infection) using EQ-5D, and found improvement in all subgroups of patients, both in post-12 weeks and post-48 weeks after the end of DAAs treatment.

Our findings is not in concordance of what reported by Ichikawa et al. in 2018 [15]. They studied 107 Japanese patients and reported that HRQoL had not recovered one year after beginning DAA treatment, although patient-reported outcomes measured by cirrhosis-related symptom score, presence of restless legs syndrome, Pittsburg sleep quality index, and Kessler 6 score improved significantly. They concluded that DAA treatment cleared HCV-RNA in patients, but HRQoL did not fully recover. In a recent study by Juanbeltz et al. in 2019 [16], they studied 206 Spanish HCV patients that attained SVR using the EQ-5D-5L questionnaire and compared them to general population of the same sex and age. Before treatment, patients had more problems than the general population in every domain of EQ-5D-5L, except in self-care dimension. HRQoL of chronic hepatitis C patients remained lower than that of the general population despite viral clearance, with primary problems in usual activities and anxiety/depression.

Different Egyptian studies reported affection of HRQoL due to chronic HCV infection [17-19]. Recently, Youssef et al. in 2017 [20] studied 62 Egyptian patients receiving SOF-based treatment with and without IFN and they reported that by the end of treatment, a substantial deterioration was observed in most of the HRQoL domains including role physical and role emotional of SF-36 regardless of type of therapy (with and without INF). At follow-up, all HRQoL domains returned to their baseline levels or moderately improved as early as post-treatment week 4.

Younossi et al. in 2018 [21] assessed HRQoL in 686 East Asian HCV patients treated with pegylated-IFN+SOF+RBV for 12 weeks or SOF+RBV for 12-24 weeks. By end of treatment, IFN-treated group experienced significant declines in most HRQoL scores (on average, by up to -13.3 points on a 0-100 scale from the baseline level, $p<0.02$) while subjects on SOF+RBV had milder impairments (up to -5.4 points). Achieving SVR-12 was associated with HRQoL improvement regardless of regimen (up to +2.9 points, $p<0.05$).

This study has some limitations due to its open-label design caused by its real-world nature. A direct comparison between the RBV and the RBV-free cohort is difficult because the cohorts are not matched and show different baseline characteristics, which may confound results after treatment. This is an important limitation, which cannot be ruled out in the real-world studies.

Conclusion

In summary, the current real-world study confirms results from clinical trials that the majority of patients report an increased HRQoL after finishing HCV treatment with DAAs.

Funding sources

None to declare.

Conflict of interest

The authors declare no conflicts of interest.

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