Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0091-17
Intern Med 57: 1959-1966, 2018
http://internmed.jp

【 ORIGINAL ARTICLE 】

Chronic Hepatitis C Treatment with Daclatasvir Plus Asunaprevir Does Not Lead to a Decreased Quality of Life

Megumi Kawakubo[1], Yuichiro Eguchi[2], Michiaki Okada[2], Shinji Iwane[2], Satoshi Oeda[2], Taiga Otsuka[3], Syunya Nakashita[3], Norimasa Araki[3] and Akemi Koga[1]

Abstract:

Objective The aim of this study was to determine if direct-acting antiviral (DAA) treatment with daclatasvir (DCV) plus asunaprevir (ASV) for 24 weeks influenced the health-related quality of life (HRQOL) at 12 and 24 weeks after treatment initiation [end of treatment (EOT)].

Methods This was a prospective, longitudinal study comparing the HRQOL of patients receiving DAA treatment at 12 weeks after treatment initiation and EOT with the HRQOL at baseline. We used a Japanese-validated version of the 8-item Short Form Health Survey (SF-8) to assess the HRQOL of patients. This score can be compared to the Japanese normative sample scores of SF-8. Wilcoxon signed-rank tests were used to compare the HRQOL before treatment, 12 weeks after treatment initiation, and at EOT.

Patients We enrolled patients who received 24-week combination therapy using DCV and ASV for HCV at Saga University Hospital between November 2014 and July 2015. Those who discontinued treatment due to relapse or adverse reactions during the treatment period were excluded from the study.

Results There were no significant changes in any of the SF-8 subscales, Physical component scores (PCS) or mental component scores (MCS) during the treatment period for both males and females.

Conclusion Our study makes a significant contribution to the literature because 24-week DAA treatment with DCV plus ASV did not decrease the HRQOL at 12 or 24 weeks after treatment initiation.

Key words: hepatitis C virus, direct acting antiviral treatment, health related quality of life, daclatasvir plus asunaprevir

(Intern Med 57: 1959-1966, 2018)
(DOI: 10.2169/internalmedicine.0091-17)

Introduction

The hepatitis C virus (HCV) is prevalent globally; annually, it affects 71 million people worldwide (1). HCV is a major cause of cirrhosis and hepatic cancer. The number of deaths as a result of these complications is on the rise, with 350,000 deaths annually due to diseases associated with HCV infection (2).

Interferon (IFN) was previously the most common treatment of HCV. However, serious adverse reactions and a long treatment duration remain issues affecting its applicability for the treatment of HCV (3, 4). Direct-acting antiviral (DAA) treatment, which was introduced in 2014 does not use IFN and is associated with high sustained viral response (SVR) rates, few adverse symptoms, and a reduced treatment duration. DAAs also have high virus clearance rates. The introduction of DAA treatment has advanced HCV treatment, as it enables the treatment of patients that did not fit the treatment indications for IFN in the past (5). Indeed, SVR rates have reached 80-90% in recent years because of DAA treatment (6). As of 2015, it was reported that 50 million people have undergone HCV treatment with DAAs worldwide (1).

The health-related quality of life (HRQOL) is a patient-centered outcome used internationally for patients with various diseases, such as diabetes and cardiovascular and renal diseases (7-9). HCV infection is known to lead to a de-

[1]Department of Nursing, Saga Medical School, Japan, [2]Liver Center, Saga Medical School, Japan and [3]Department of Internal Medicine, Saga University Hospital, Japan
Received: August 20, 2017; Accepted: December 21, 2017; Advance Publication by J-STAGE: March 9, 2018
Correspondence to Dr. Megumi Kawakubo, sh2335@edu.cc.saga-u.ac.jp

creased HRQOL (10, 11). Conventional IFN treatment has a considerable influence on patients' daily lives, leading to a decrease in the HRQOL due to the high incidence of adverse reactions with diverse symptoms (12-14). In another study conducted among patients with chronic HCV, it was reported that the HRQOL decreased on the vitality (VT) subscale (15). Previous studies have reported that there was a significant decrease on subscales such as Role physical (RP) and VT in the physical domain (6, 12). A decrease in the patient HRQOL is believed to be largely due to the diverse range of adverse symptoms and the patient's inability to live their everyday life in the same manner as they did prior to the adverse events.

DAA treatment is associated with fewer adverse reactions than IFN treatment and has little physical and/or psychological burden on patients, as the treatment duration is relatively short (16). In addition, as a result of the high SVR rates associated with DAA treatment, access to treatment can be expanded to those previously considered unsuitable for such treatment. However, the influence of DAA treatment on the patients' HRQOL has yet to be determined.

The aim of this study was to determine whether or not DAA treatment with daclatasvir (DCV) plus asunaprevir (ASV) for 24 weeks influenced the HRQOL at 12 and 24 weeks of treatment [end of treatment (EOT)].

Materials and Methods

Study design

This was a prospective longitudinal study conducted among patients with HCV who received at least 24 weeks of combination therapy using DCV and ASV between November 2014 and July 2015.

Patient selection

We enrolled patients who received 24 weeks of combination therapy using DCV and ASV for HCV at Saga University School of Medicine Hospital between November 2014 and July 2015. Those who discontinued treatment due to relapse or adverse reactions during the treatment period were excluded from the study.

Laboratory assessments

All venous blood samples were taken after a 12-h overnight fast. The serum HCV-RNA levels were identified using two different quantitative polymerase chain reaction (PCR) assays: one was the Amplicore HCV Monitor version 2.0, and the other was the COBAS TaqMan HCV Monitor Test (both Roche Diagnostics, Tokyo, Japan). A high viral load was defined as ≥100 kIU/mL using the Amplicore method and ≥5.0 log IU/mL using the TaqMan method. The HCV genotype was determined based on the sequence of the core region (17).

Assessment of the HRQOL

We used a Japanese-validated version of the 8-item Short Form Health Survey (SF-8) to assess HRQOL of patients. This score can be compared to the Japanese normative sample scores of the SF-8 (18, 19).

The SF-8 is an eight-item questionnaire that calculates eight physical and mental health domains: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH) (18). The physical component score (PCS) and mental component score (MCS) were calculated from the sum of the scores of the corresponding subscales: PF, RP, BP, and GH for PCS, and VT, SF, RE, and MH for MCS. Each of the eight items was calculated using the questionnaires as previously described. Physical and mental summary scores were calculated according to the manual (18); if any of the eight items was unanswered, the summary score was not calculated. Scores from the completed SF-8 were converted to a scale; higher scores indicated better health subjectively. They were calculated so that the national standard value of Japanese citizens as a whole was 50 points, and its standard deviation was 10 points.

Level of physical activity

It has been shown that there is a strong association between the exercise intensity and physical activity intensity (METs) measured using the Life Coder (19). The level of physical activity was therefore measured using the Life Coder EX® (Suzuken, Nagoya, Japan) for all of the included subjects. The number of steps, exercise intensity, and activity time were measured and stratified by activity level: light intensity, <3 METs; moderate intensity, 3 to 6 METs; vigorous intensity, >6 METs. The physical activity intensity was calculated using the following formula:

Physical activity intensity (METs)

=exercise volume (kcal)/{1.05×body weight (kg)}

The subjects were asked to wear the Life Coder for 10 days, and data from 5 consecutive days (excluding the first and last days and the days when the number of steps was 50 steps or less) were used for the analysis. Subjects missing data for days with ≥50 steps were excluded from the analysis of Life Coder data.

Physical symptoms

Subjects were asked about the incidence of 16 physical symptoms (a fever, joint pain, malaise, palpitation, shortness of breath, headache, wobble, loss of appetite, abdominal pain, nausea, vomiting, diarrhea, dysgeusia, rash, itching sensation, and insomnia) using a Likert scale (always, sometimes, rarely, and never). The subject responses were allocated scores as follows: four points for "always," three points for "sometimes," two points for "rarely," and one point for "never."

Data collection methods

The survey was conducted at three time points: pre-treatment, and at 12 and 24 weeks following HCV treatment initiation. We asked subjects to participate in the survey after an outpatient consultation a month or two prior to HCV treatment initiation. If subjects agreed to participate, they were given the questionnaire and the Life Coder. The questionnaires and Life Coders were collected by having them mailed back. All subsequent questionnaires were distributed in the mail.

Statistical analyses

The SPSS software program, Version 22 (IBM Japan, Tokyo, Japan) was used for all statistical analyses of Lifelyzer 05 coach® (version 2.12) data, and a behavior change support software program developed by Suzuken, was used to process the Life Coder data. Mann-Whitney U tests were used to compare gender differences in the study participants' clinical and demographic characteristics. Wilcoxon signed-rank tests were used to compare the HRQOL, number of steps, and physical activity intensity before treatment and at 12 weeks following treatment initiation and at EOT. p values less than 0.05 were considered statistically significant.

Ethical considerations

The study protocol was in compliance with the Declaration of Helsinki and was approved by the Human and Animal Ethics committee of Saga University. Written informed consent was obtained from all of the patients.

Results

Subjects analyzed

Of the 107 subjects identified for enrollment, 24 were excluded due to the following reasons: they did not respond to the questionnaires or they refused to participate (n=16), they discontinued treatment (n=3), they were unable to continue with the questionnaires as they were hospitalized for treatment (n=4), or the subject passed away (n=1). Of the 83 patients enrolled in the study, an additional 31 subjects were excluded because they had incomplete data. Therefore, 52 subjects were included in the study, of which 32 (64%) were females.

Patients' characteristics

The average age of subjects was 69.8±9.3 years, with no significant difference in the average age based on sex. The height and body weight were significantly higher in males than in females, while there were no significant differences in the body mass index (BMI) based on sex. Hemoglobin levels were significantly lower in females than in males (p= 0.03). There were 24 subjects (46.2%) with platelet levels below the normal value of $13.0\times10^4/\mu L$; this did not significantly differ based on sex. There were 24 subjects (46.2%) with albumin levels below the normal value of 3.8 g/dL, 27 subjects (51.9%) with aspartate aminotransferase (AST) levels that were not within the normal range (12-33 U/L), and 19 subjects (36.5%) with alanine aminotransferase (ALT) levels that were not within the normal range (5-35 U/L). There were no significant differences between sexes for any of the blood parameters investigated. Thirty-one (59.6%) subjects had never received HCV treatment before, while 21 (40.4%) had a history of HCV treatment. In addition, 6 (11.5%) subjects had a history of liver cancer treatment (1 male, 5 females). Nine (17.3%) subjects had cirrhosis (2 males, 7 females) (Table 1).

Changes in biochemical test values

In males, the AST and ALT values did not significantly differ at 12 weeks after treatment initiation; however, they were significantly decreased at EOT. In females, both the AST and ALT values were significantly decreased at 12 weeks after treatment initiation and at EOT. In addition, AFP was significantly decreased at 12 weeks after treatment initiation as well as at EOT. HCV-RNA was not detected in any of the subjects at 12 weeks after treatment initiation or at EOT (Table 2).

Changes in the HRQOL

The average SF-8 score before HCV treatment was 1.7-5.3 points lower than the Japanese national standard value for 70- to 79-year-olds for PF, RP, GH, SF, and MCS in males, while it was 2.0 points lower for SF in females. There were no significant changes in any of the SF-8 subscales, PCS, or MCS during the treatment period for both either males or females (Table 3).

Changes in the incidence of physical symptoms

There were no marked changes in the incidence of any of the physical symptoms at baseline, 12 weeks after treatment initiation, or EOT (Figure).

Changes in physical activity levels

Although the physical activity levels of all 52 subjects were measured using the Life Coder, we were unable to obtain data from some subjects for the following reasons: rejected investigation with the Life Coder (n=16), device failure (n=2), forgot to wear the device during the measurement period (n=3), and retired (n=1). In total, we analyzed Life Coder data from 30 subjects. In females, the METs at the time of EOT were significantly lower than those before treatment. With respect to activity time by activity level, the activity time for light-intensity activity was significantly lower in females than in males (Table 4).

Discussion

Previous studies have reported that the HRQOL in patients with HCV infection is impaired (20). However, in the present study, the HRQOL in subjects before HCV treatment

Table 1. Clinical and Demographic Characteristics of Enrolled Subjects Stratified by Gender (n=52).

	All (n=52)		Male (n=20)		Female (n=32)		p value
	n (%) or Mean±SD	range	n or Mean±SD	range	n or Mean±SD	range	
Age (years)	69.8±9.3	47-86	68.2±9.6	47-86	70.8±9.1	49-81	0.13
Body height (cm)	156.4±9.8	135.5-183.0	164.0±10.6	135.5-183.0	151.6±5.4	138.0-163.0	<0.001
Body weight (kg)	55.4±11.3	34.0-86.0	61.9±12.1	38.4-86.0	51.3±8.7	34.0-73.0	<0.001
BMI (kg/m^2)	22.3±3.8	15.5-32.0	22.9±3.6	17.4-31.1	22.3±3.7	15.5-32.0	0.40
WBC (/μL)	4.9±1.6	2.5-10.6	5.5±1.9	3.6-10.6	4.5±1.2	2.5-8.1	0.06
Hemoglobin (g/dL)	13.4±1.4	9.8-16.5	14.0±1.5	12.0-16.5	13.1±1.3	9.8-15.6	0.03*
Platelets (×10^4/μL)	13.2±5.2	1.4-28.6	14.2±6.0	1.4-23.2	12.7±4.6	5.2-28.6	0.11
Albumin(g/dL)	3.8±0.4	2.5-4.6	3.9±0.4	3.1-4.4	3.8±0.5	2.5-4.6	0.29
AST (U/L)	46.3±25.2	20-116	38.6±19.8	20-84	51.1±27.2	20-116	0.12
ALT (U/L)	39.9±28.6	11-143	39.7±32.5	14-143	40.0±26.4	11-128	0.65
AFP (ng/mL)	11.7±20.5	1-97	5.0±3.7	1-14	15.0±24.3	2-97	0.22
HCV-RNA (Log IU/mL)	5.9±0.7	3.5-6.9	5.8±0.8	3.5-6.7	6.0±0.7	4.4-6.9	0.23
HCV genotype (1b/1a)	52/0						
Treatment history for HCV (+)	21 (40.4%)		5 (25.0%)		16 (50.0%)		
Treatment history for HCC (+)	6 (11.5%)		1 (5.0%)		5 (15.6%)		
LC (+)	9 (17.3%)		2 (10.0%)		7 (21.9%)		

Mann-Whitney U tests were used to determine differences between the study variables based on gender.

SD: standard deviation, BMI: body mass index, WBC: white blood cells, AST: aspartate transaminase, ALT: alanine transaminase, AFP: alpha-fetoprotein, HCV: hepatitis C virus, HCV-RNA: hepatitis C virus- ribonucleic acid, HCC: hepatocellular carcinoma, LC: liver cirrhosis

Table 2. Changes in Biochemical Test Values for Enrolled Subjects Stratified by Gender (n=52).

	Baseline Mean±SD (Median)	12-weeks after treatment initiation Mean±SD (Median)	p value	24-weeks after treatment initiation (EOT) Mean±SD (Median)	p value
WBC (/μL)	4.9±1.6 (4.5)	5.2±1.7 (4.7)	0.043	5.2±1.5 (4.9)	0.040
Male	5.5±1.9 (4.9)	5.8±2.1 (5.0)	0.556	5.9±1.9 (5.7)	0.148
Female	4.5±1.2 (4.4)	4.8±1.3 (4.4)	0.029	4.7±1.0 (4.6)	0.182
Hemoglobin (g/dL)	13.4±1.4 (13.4)	13.1±1.5 (13.3)	0<0.001	13.2±1.5 (13.3)	0.054
Male	14.0±1.5 (14.2)	13.5±1.7 (13.8)	0.007	13.8±1.6 (13.8)	0.308
Female	13.1±1.3 (13.3)	12.8±1.3 (13.2)	0.007	12.8±1.3 (13.1)	0.076
Platelets (×10^4/μL)	13.2±5.2 (13.6)	13.9±5.5 (13.9)	0.320	14.1±6.1 (12.3)	0.141
Male	14.2±6.0 (16.0)	14.2±5.7 (14.7)	0.968	15.1±6.7 (15.9)	0.068
Female	12.7±4.6 (12.6)	13.7±5.4 (12.7)	0.214	13.5±5.7 (11.8)	0.707
Albumin (g/dL)	3.8±0.4 (3.8)	3.8±0.4 (3.9)	0.890	3.9±0.4 (4.0)	0.070
Male	3.9±0.4 (3.9)	4.0±0.2 (3.9)	0.446	4.0±18.8 (4.0)	0.341
Female	3.8±0.5 (3.7)	3.8±0.4 (3.9)	0.896	3.9±0.4 (3.8)	0.155
AST (U/L)	46.3±25.2 (35.0)	35.7±28.6 (29.0)	0.004	25.9±8.5 (24.0)	0<0.001
Male	38.6±19.8 (30.5)	30.6±16.5 (26.0)	0.227	23.8±8.3 (21.0)	0.010
Female	51.1±27.2 (53.5)	39.0±34.3 (29.0)	0.009	27.1±8.5 (25.0)	<0.001
ALT (U/L)	39.9±28.6 (31.0)	31.9±32.5 (21.0)	0.017	20.6±13.1 (19.0)	0<0.001
Male	39.7±32.5 (29.0)	30.5±29.1 (18.0)	0.251	22.9±18.8 (17.0)	0.013
Female	40.0±26.4 (31.0)	32.8±35.0 (24.0)	0.031	19.2±8.0 (19.0)	<0.001
AFP (ng/mL)	11.7±20.5 (5.0)	4.3±4.6 (3.0)	0.001	4.9±8.6 (3.0)	0.002
Male	5.0±3.7 (5.0)	2.4±1.3 (2.5)	0.059	2.9±1.3 (3.0)	0.068
Female	15.0±24.3 (5.0)	5.2±5.4 (3.0)	0.007	5.9±10.4 (3.3)	0.011
HCV-RNA (Log IU/mL)	5.9±0.7 (6.2)	N.D		N.D	
Male	5.8±0.8 (6.2)	N.D		N.D	
Female	6.0±0.7 (6.3)	N.D		N.D	

Wilcoxon signed-rank tests were used to compare biochemical test values at 12-weeks and 24-weeks (end of treatment) following treatment initiation, with the baseline values.

EOT: end of treatment, N.D: not detected, WBC: white blood cells, AST: aspartate transaminase, ALT: alanine transaminase, AFP: alpha-fetoprotein, HCV-RNA: hepatitis C virus- ribonucleic acid

Table 3. Changes in Health Related Quality of Life for Enrolled Subjects Stratified by Gender (n=52).

	Baseline Mean±SD (Median)	12-weeks after treatment initiation Mean±SD (Median)	p value	24-weeks after treatment initiation (EOT) Mean±SD (Median)	p value
PF	45.4±8.6 (47.8)	45.0±7.2 (47.8)	0.642	45.0±7.2 (47.8)	0.891
Male	46.3±8.6 (47.8)	44.6±8.5 (47.8)	0.437	44.3±8.3 (47.8)	0.432
Female	44.9±8.7 (47.8)	45.2±6.4 (47.8)	0.985	45.4±6.6 (47.8)	0.793
RP	46.0±8.5 (47.4)	46.2±8.2 (47.4)	0.993	46.1±8.5 (47.4)	0.709
Male	45.8±8.2 (47.4)	45.1±8.6 (47.4)	0.673	45.2±9.5 (47.4)	0.798
Female	46.2±8.8 (47.4)	46.8±8.1 (47.4)	0.792	46.6±8.0 (47.4)	0.705
BP	49.5±9.1 (49.3)	49.3±8.0 (49.3)	0.712	50.2±8.7 (52.5)	0.694
Male	53.0±7.0 (52.5)	50.4±8.3 (52.5)	0.068	50.4±9.7 (52.5)	0.154
Female	47.3±9.7 (46.1)	48.6±7.8 (46.1)	0.257	50.0±8.2 (52.5)	0.104
GH	48.1±5.5 (50.3)	49.6±6.0 (50.3)	0.125	48.6±6.5 (50.3)	0.699
Male	48.7±4.6 (50.3)	49.8±7.3 (50.3)	0.665	48.1±7.4 (50.3)	0.532
Female	47.8±6.0 (50.3)	49.5±5.2 (50.3)	0.071	48.9±5.9 (50.3)	0.218
VT	50.4±5.2 (53.7)	50.3±6.1 (53.7)	0.710	50.7±6.4 (53.7)	0.408
Male	51.7±4.5 (53.7)	49.4±6.1 (49.1)	0.392	50.2±7.9 (53.7)	0.944
Female	49.6±5.6 (53.7)	50.9±6.1 (53.7)	0.157	51.1±5.5 (53.7)	0.174
SF	47.0±9.0 (45.6)	47.7±7.2 (45.6)	0.690	47.1±8.2 (45.6)	0.992
Male	46.5±9.5 (45.6)	49.1±6.1 (45.6)	0.168	46.1±9.4 (45.6)	0.844
Female	47.3±8.8 (45.6)	46.9±7.8 (45.6)	0.465	47.8±7.6 (45.6)	0.965
RE	49.5±5.0 (48.0)	48.3±6.5 (48.3)	0.400	48.0±6.7 (48.6)	0.243
Male	49.6±4.7 (48.0)	48.2±7.0 (48.0)	0.776	46.8±7.8 (48.0)	0.220
Female	49.5±5.3 (48.0)	48.4±6.3 (48.0)	0.498	48.8±5.8 (48.0)	0.601
MH	51.1±5.5 (50.7)	50.8±6.9 (50.7)	0.437	51.6±7.0 (53.8)	0.536
Male	49.1±6.0 (50.7)	49.8±8.4 (50.7)	0.776	50.3±8.5 (50.7)	0.477
Female	52.4±4.8 (51.0)	51.4±5.9 (50.7)	0.125	52.4±6.0 (56.9)	0.962
PCS	44.7±9.0 (45.7)	45.0±7.5 (46.0)	0.996	44.9±7.4 (45.6)	0.491
Male	46.9±8.2 (48.0)	45.1±8.4 (45.9)	0.205	44.8±8.1 (47.0)	0.550
Female	43.3±9.3 (45.3)	45.0±7.1 (46.0)	0.342	44.9±7.0 (45.4)	0.147
MCS	50.7±5.8 (51.9)	50.3±6.0 (51.1)	0.937	50.4±6.5 (52.1)	0.873
Male	49.0±6.6 (50.2)	49.9±5.7 (51.1)	0.573	49.0±7.8 (51.2)	0.240
Female	51.8±5.0 (52.3)	50.5±6.3 (51.1)	0.484	51.2±5.5 (52.1)	0.544

Items are subscales of SF-8, the physical component summary, and the mental component summary.

Wilcoxon signed-rank tests were used to compare health related quality of life at 12-weeks and 24-weeks (end of treatment) following treatment initiation, with the baseline measures.

IR: interquartile ranges, EOT: end of treatment, 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

was not impaired, nor did it change following treatment initiation.

A study conducted in the United States that investigated the HRQOL after the initiation of treatment with DAA (combination treatment for 12 weeks with ledipasvir and sofosbuvir) found an improved QOL 4 weeks after treatment initiation and at EOT when compared to baseline (21). Based on these results, we hypothesized that the HRQOL would be increased following treatment initiation when compared to baseline. However, we did not detect an increase in the HRQOL. We believe this may be because the study conducted in the United States used different DAA drugs for treatment and for a shorter treatment duration in younger subjects (average 50 years of age) than our study.

Because recent studies have reported that antiviral treatment by DAAs influences glucose metabolism (22), this issue should be examined in detail. However, we did not collect detailed data on glucose metabolism in this study. Further studies will be needed to clarify the relationship between the HRQOL and improvement in the glucose metabolism by viral treatment by DAA.

In previous studies, a decreased HRQOL as well as an increased fatigue was reported as a result of IFN treatment and ribavirin combination therapy (23, 24). We hypothesized that physical activity levels would not decrease, as a previous study found that the incidence of fatigue because of DAA treatment was low and the HRQOL did not decrease (21). However, in the present study, we found that both the number of steps and METs significantly decreased during treatment compared to before treatment. Although we

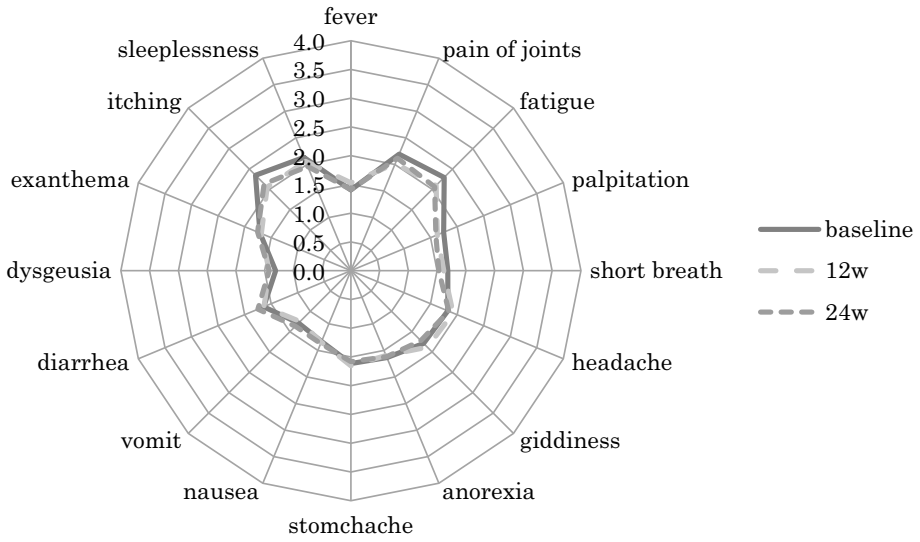

Figure. **Changes in the incidence of physical symptoms for enrolled subjects (n=52). Average scores for the incidence of 16 physical symptoms at baseline and 12 and 24 weeks (end of treatment) following treatment initiation.**

Table 4. **Changes in Physical Activity Levels for Subjects Stratified by Gender (n=30).**

	Baseline Mean±SD (Median)	12-weeks following treatment initiation Mean±SD (Median)	p value	24-weeks following treatment initiation (EOT) Mean±SD (Median)	p value
Number of steps/day	5,888.8±2,170.7 (6,087.5)	6,312.2±2,754.7 (6,346.0)	0.558	4,719.8±2,509.2 (5,119.7)	0.015
Male	6,224.6±2,116.4 (6,105.6)	6,397.2±3,047.1 (6,208.0)	0.929	4,444.4±3,057.4 (4,122.2)	0.110
Female	5,694.4±2,234.9 (4,962.0)	6,263.1±26,572 (6,363.6)	0.376	4,879.3±2,208.6 (5,571.8)	0.053
METs/day	2.2±0.9 (2.2)	2.4±1.2 (2.3)	0.765	1.7±1.0 (1.8)	0.009
Male	2.4±1.3 (2.2)	2.4±1.3 (2.2)	0.656	1.7±1.2 (1.4)	0.110
Female	2.1±0.9 (1.8)	2.3±1.1 (2.3)	0.532	1.8±0.9 (2.0)	0.036
Activity time/day (min)					
Light intensity (less than 3 METs)	51.0±21.4 (46.7)	54.1±22.7 (53.0)	0.289	38.4±22.5 (38.7)	0.006
Male	54.9±23.0 (58.6)	56.7±24.7 (52.2)	0.594	32.4±25.5 (38.7)	0.062
Female	48.7±20.8 (44.5)	52.6±22.0 (53.7)	0.314	41.9±20.4 (38.7)	0.036
Moderate intensity (3-6 METs)	11.7±8.4 (10.0)	13.3±11.4 (11.1)	0.681	8.3±7.5 (6.0)	0.045
Male	11.4±8.5 (11.0)	11.6±11.6 (10.6)	0.563	6.8±7.2 (4.5)	0.182
Female	11.8±8.5 (10.0)	14.2±11.4 (11.7)	0.355	9.1±7.8 (6.9)	0.091
Vigorous intensity (at least 6 METs)	0.8±1.3 (0.3)	1.0±2.4 (0.2)	0.166	0.3±0.5 (0.1)	0.077
Male	1.1±2.0 (0.2)	1.9±3.7 (0.2)	0.918	0.1±0.1 (0.04)	0.284
Female	0.6±0.8 (0.4)	0.4±0.7 (0.2)	0.129	0.5±0.6 (0.2)	0.287

The Wilcoxon signed-rank tests were used to compare changes in physical activity at 12-weeks and 24-weeks (end of treatment) following treatment with the baseline activity.

EOT: end of treatment, METs: physical activity intensity

did not conduct a questionnaire directly on fatigue, the "physical function" and "vitality" subscales of the SF-8 did not significantly decrease. Therefore, despite assessing various factors, such as the age, liver function, nutritional status, and BMI, we were unable to verify the cause of the decreased physical activity levels in the present study. However, we were able to determine the actual physical activity levels of elderly subjects receiving DAA treatment. Decreased physical activity levels lead to health problems, such as obesity. It has been shown that obesity in chronic HCV patients increases the risk of liver fibrosis progression, hepatocellular carcinoma, and diabetes (25-29). We must continue to monitor the liver function, liver fibrosis, and tumor markers as well as encourage exercise and body weight control after the completion of treatment using DAAs.

In the present study, we only conducted questionnaires up

to EOT; therefore, we were unable to evaluate the long-term HRQOL of the subjects. Future studies should evaluate the HRQOL one to two years after EOT.

Several limitations associated with the present study warrant mention. The subjects enrolled were elderly, with an average age of 70 years; therefore, wearing a physical activity meter for 2 weeks may have been stressful for them. Since the device was not waterproof, we asked subjects to remove it when bathing, swimming, or performing tasks that might cause the device to become wet. Therefore, it is possible that the activity levels for the subjects were underreported. Finally, as previously indicated we did not examine the HRQOL after the completion of treatment; therefore, we are unable to report the long-term HRQOL for DAA treatment for HCV.

In the present study, we found that 24 weeks of oral DAA treatment, including DCV/ASV, did not decrease the HRQOL at 12 or 24 weeks after the treatment initiation. Further studies are needed to determine the HRQOL of patients receiving DAA treatment for HCV, including different drugs.

The authors state that they have no Conflict of Interest (COI).

Financial Supports

This work was supported by JSPS KAKENHI Grant Number 15K20703.

Acknowledgement

We thank all of the patients and their families for their participation in the study. The authors would like to thank Ms. Natsumi Izumi, Ms. Hiromi Kaneko, and Ms. Asami Kawakubo for their assistance with the investigation. We would also like to thank all of the staff at Saga Medical School Hospital for their kind advice.

References

1. World Health Organization. Global Hepatitis Report 2017 [Internet]. [cited 2017 May 16]. Available from: http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1
2. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol **45**: 529-538, 2006.
3. Kanda T, Imazeki F, Yokosuka O. New antiviral therapies for chronic hepatitis C. Hepatol Int **4**: 548-561, 2010.
4. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med **364**: 2405-2416, 2011.
5. Chayama K, Takahashi S, Toyota J, et al. Dual therapy with the nonstructural protein 5A inhibitor, daclatasvir, and the nonstructural protein 3 protease inhibitor, asunaprevir, in hepatitis C virus genotype 1b-infected null responders. Hepatology **55**: 742-748, 2012.
6. Kumada H, Suzuki Y, Ikeda K, et al. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. Hepatology **59**: 2083-2091, 2014.
7. Lloyd A, Sawyer W, Hopkinson P. Impact of long-term complications on quality of life in patients with type 2 diabetes not using insulin. Value Health **4**: 392-400, 2001.
8. Zambroski CH, Moser DK, Bhat G, Ziegler C. Impact of symptom prevalence and symptom burden on quality of life in patients with heart failure. Eur J Cardiovasc Nurs **4**: 198-206, 2005.
9. Rebollo P, Ortega F, Baltar JM, et al. Health-related quality of life (HRQOL) in end stage renal disease (ESRD) patients over 65 years. Geriatr Nephrol Urol **8**: 85-94, 1998.
10. 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 **41**: 790-800, 2005.
11. Younossi ZM, Stepanova M, Henry L, et al. Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. Clin Gastroenterol Hepatol **12**: 1349-1359.e13, 2014.
12. Suzuki M, Ishikawa T, Sakuma A, et al. Evaluation of the health-related quality of life using the 36-item short form health survey in patients with chronic hepatitis C receiving pegylated interferon/ribavirin/telaprevir triple treatment. Exp Ther Med **12**: 3353-3358, 2016.
13. Perrillo R, Rothstein KD, Rubin R, et al. Comparison of quality of life, work productivity and medical resource utilization of peginterferon alpha 2a vs the combination of interferon alpha 2b plus ribavirin as initial treatment in patients with chronic hepatitis C. J Viral Hepat **11**: 157-165, 2004.
14. Matsushita H, Ikeda F, Iwasaki Y, et al. Assessment of health-related quality of life and how it predicts the outcome of pegylated interferon and ribavirin therapy for chronic hepatitis C. J Gastroenterol Hepatol **29**: 337-343, 2014.
15. Kuwashiro T, Mizuta T, Kawaquchi Y, et al. Impairment of health-related quality of life in patients with chronic hepatitis C is associated with insulin resistance. J Gastroenterol **49**: 317-323, 2014.
16. Younossi ZM, Stepanova M, Pol S, Bronowicki JP, Carrieri MP, Bourlière M. The impact of ledipasvir/sofosbuvir on patient-reported outcomes in cirrhotic patients with chronic hepatitis C: the SIRIUS study. Liver Int **36**: 42-48, 2016.
17. Ohno O, Mizokami M, Wu RR, et al. New hepatitis C virus (HCV) genotyping system that allows for identification of HCV genotypes 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a, and 6a. J Clin Microbiol **35**: 201-207, 1997.
18. Fukuhara S, Suzukamo Y. Manual of the SF-8 Japanese Version. Institute for Health Outcomes & Process Evaluation Research. Kyoto, 2004 (in Japanese).
19. Kumahara H, Schutz Y, Ayabe M, et al. The use of uniaxial accelerometry for the assessment of physical-activity-related energy expenditure: a validation study against whole-body indirect calorimetry. Br J Nutr **91**: 235-243, 2004.
20. Kallman J, O'Neil MM, Larive B, Boparai N, Calabrese L, Younossi ZM. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. Dig Dis Sci **52**: 2531-2539, 2007.
21. Younossi ZM, Stepanova M, Afdhal N, et al. 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. J Hepatol **63.2**: 337-345, 2015.
22. Hum J, Jou JH, Green PK, et al. Improvement in glycemic control of type 2 diabetes after successful treatment of hepatitis C virus. Diabetes Care **40**: 1173-1180, 2017.
23. Younossi ZM, Stepanova M, Zeuzem S, et al. Patient-reported outcomes assessment in chronic hepatitis C treated with sofosbuvir and ribavirin: the VALENCE study. J Hepatol **61**: 228-234, 2014.
24. Hassanein T, Cooksley G, Sulkowski M, et al. The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. J Hepatol **40**: 675-681, 2004.
25. Hu KQ, Kyulo NL, Esrailian E, et al. Overweight and obesity, he-

patic steatosis, and progression of chronic hepatitis C: a retrospective study on a large cohort of patients in the United States. J Hepatol **40**: 147-154, 2004.

26. Bertuccio P, Turati F, Carioli G, et al. Global trends and predictions in hepatocellular carcinoma mortality. J Hepatol **67**: 302-309, 2017.

27. McMahon BJ, Bruden D, Townshend-Bulson L, et al. Infection with hepatitis C virus genotype 3 is an independent risk factor for end-stage liver disease, hepatocellular carcinoma, and liver-related death. Clin Gastroenterol Hepatol **15**: 431-437, 2017.

28. Hickman IJ, Jonsson JR, Prins JB, et al. Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. Gut **53**: 413-419, 2004.

29. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology **27**: 209-212, 1998.