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

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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

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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-
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:

\[
\text{Physical activity intensity (METs)} = \frac{\text{exercise volume (kcal)}}{1.05 \times \text{body weight (kg)}}
\]

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: pretreatment, 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 males, 7 females. Nine (17.3%) subjects had cirrhosis (2 males, 7 females) (Table 1).

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 13.0×10⁵/μL; 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, 2.0 points lower for SF in females. There were no marked changes in the incidence of any of the physical symptoms at baseline, 12 weeks after treatment initiation, or EOT (Figure).

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 |
|--------------------|------------|-------------|---------------|---------|
| Age (years)        | 69.8±9.3   | 68.2±9.6    | 70.8±9.1      | 0.13    |
| Body height (cm)   | 156.4±9.8  | 154.0±10.6  | 151.6±5.4     | <0.001  |
| Body weight (kg)   | 55.4±11.3  | 61.9±12.1   | 51.3±8.7      | <0.001  |
| BMI (kg/m²)        | 22.3±3.8   | 22.9±3.6    | 22.3±3.7      | 0.40    |
| WBC (/μL)          | 4.9±1.6    | 5.5±1.9     | 4.5±1.2       | 0.06    |
| Hemoglobin (g/dL)  | 13.4±1.4   | 14.0±1.5    | 13.1±1.3      | 0.03*   |
| Platelets (x10^9/μL) | 13.2±5.2  | 14.2±6.0    | 12.7±4.6      | 0.11    |
| Albumin (g/dL)     | 3.8±0.4    | 3.9±0.4     | 3.8±0.5       | 0.29    |
| AST (U/L)          | 46.3±25.2  | 38.6±19.8   | 51.1±27.2     | 0.12    |
| ALT (U/L)          | 39.9±28.6  | 39.7±32.5   | 40.0±26.4     | 0.65    |
| AFP (ng/mL)        | 11.7±20.5  | 5.0±3.7     | 15.0±24.3     | 0.22    |
| HCV-RNA (Log IU/mL)| 5.9±0.7    | 5.8±0.8     | 6.0±0.7       | 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)                                     | 0.001   | 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 (x10^9/μL) | 13.2±5.2  | 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±1.8 (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)                                         | <0.001  |
| 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)                                        | <0.001  |
| Male               | 39.7±32.5 (29.3)         | 30.5±29.1 (18.0)                                    | 0.251   | 22.9±8.8 (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     | N.D                                                      |         |
| Male               | 5.8±0.8 (6.2)            | N.D                                                 | N.D     | N.D                                                      |         |
| Female             | 6.0±0.7 (6.3)            | N.D                                                 | 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
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

| Subject | 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±7.6 (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±3.8 (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 range; 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.
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).

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