Health-related quality of life on the clinical course of patients with chronic hepatitis C receiving daclatasvir/asunaprevir therapy: A prospective observational study comparing younger (<70) and elderly (≥70) patients

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Abstract. Interferon-free direct acting antiviral agent regimens for chronic hepatitis C (CHC) have been developed. These regimens have shown a high rate of sustained virologic response (SVR), and a reduction in side effects during treatment is also anticipated. However, the impact of the regimens on health-related quality of life (HRQOL) and side effects during treatment is not fully understood. The purpose of the present study was to evaluate HRQOL in the clinical course of patients with CHC receiving daclatasvir/asunaprevir (DCV/ASV) therapy using the Short Form-36 (SF-36) method. Twenty-eight patients with CHC receiving DCV/ASV therapy were analyzed in the present study, and HRQOL was measured by SF-36. Patients were asked to fill out the SF-36 prior to therapy (baseline), following 12 weeks of therapy, at the end of treatment and at SVR week 24 (SVR24) to evaluate HRQOL. Laboratory data were also investigated during the same period, and associations between these results and SF-36 were investigated. Aspartate aminotransferase, alanine aminotransferase, serum albumin, α-fetoprotein, platelet counts and Fibrosis (Fib)-4 index were all significantly improved at each time point when compared with baseline. With regard to alterations in HRQOL during therapy, the ≥70-year-old group displayed a significantly greater improvement in physical functioning during the period between baseline and 12 weeks when compared with the <70-year-old group. In the analysis of the SF-36 differences within each group, general health improved significantly in the ≥70-year-old group, as well as albumin levels. In addition, Fib-4-index significantly improved at all time points (12 and 24 weeks, and SVR24) when compared with baseline in the ≥70-year-old group. Therefore, DCV/ASV therapy may improve HRQOL and hepatic functional reserve, particularly in elderly patients.

Introduction

Hepatitis C virus (HCV) was discovered by Choo *et al* in the United States in 1989 (1). It revealed that over 90% of cases diagnosed previously as non-A non-B hepatitis is caused by HCV. There are an estimated 170 million HCV-infected patients worldwide (2-4). It is estimated that 15-30% of such patients will develop serious complications, including liver cirrhosis, end-stage liver disease and hepatocellular carcinoma (5). HCV-infected patients have mortality rate of 5.0 deaths/100,000 population in 2013 (6).

Recently, direct acting antiviral agents (DAAs) were developed and advanced interferon (IFN)-free treatment. As a result, a high rate of sustained virologic response (SVR) has shown, and a reduction of side effects during treatment is also anticipated. DAAs selectively inhibit HCV proteins such as nonstructural protein NS 3/4A protease, NS5A, NS5B polymerase (7,8). New DAA combination therapies such as sofosbuvir plus ledipasvir and ombitasvir/paritaprevir/ritonavir have also recently been approved in Japan (9-11). Previous studies have shown that HCV-infected patients treated with IFN-containing DAAs experience a significant health-related quality of life (HRQOL) impairment. IFN-containing DAAs often cause side-effects, such as flu-like-symptoms and fatigue, gastrointestinal disorders. Thereby reducing HRQOL during treatment (12,13). On the other hand, IFN-free DAAs have been reported to have little impact on HRQOL and side effects during treatment (14-17). However, very few studies

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have examined HRQOL during daclatasvir/asunaprevir therapy (DCV/ASV therapy).

The purpose of this study was to evaluate HRQOL on the clinical course of patients with chronic hepatitis C (CHC) receiving DCV/ASV therapy using the Short Form-36 (SF-36) and comparison between younger (<70) and elderly (≥70) patients.

Subjects and methods

A prospective observational design was used to conduct this study. A total 30 CHC and cirrhotic patients underwent DCV/ASV therapy were invited to participate in the study from September 2014 to February 2017 at Saiseikai Niigata Daini Hospital (Niigata, Japan). Written informed consent was obtained from all patients, and the Ethics Committee of Saiseikai Niigata Daini Hospital (Niigata, Japan) approved this study, which was conducted in accordance with the Declaration of Helsinki.

All patients received fixed dose of DCV (60 mg once daily) and ASV (100 mg twice daily) for 24 weeks. Two of these 30 patients were excluded from analysis because they required treatments for hepatocellular cancer and other malignant tumors during therapy. As a result, 28 patients were analyzed. HCV-RNA were measured using the RealTime HCV assay (Abbott Laboratories, Abott Park, IL, USA) with a lower limit of qualification of 12 IU/ml at baseline, every 2 weeks during treatment and every 2 weeks until 24 weeks after completion or cession of the dual oral therapy. SVR was defined as negative for serum HCV RNA at 24 weeks after end of treatment (EOT). HRQOL was measured by the SF-36. The SF-36 comprised 36 questions, with 8 subscales related to physical and mental health: Physical functioning (PF), physical role functioning (RP), bodily pain (BP), general health (GH), vitality (VT), social role functioning (SF), emotional role functioning (RE), and mental health (MH). Each subscale is scored from 0 to 100, and higher scores indicate greater HRQOL. In this study, patients were asked to fill out the SF-36 before DCV/ASV therapy (baseline), after 12 weeks of DCV/ASV therapy (12 weeks), at the EOT, and at SVR week 24 (SVR24) to evaluate HRQOL. Blood biochemistry was also investigated during the same period, and associations between these results and SF-36 were investigated.

Statistical analysis. Patient characteristics were summarized with means and standard deviations. SF-36 scores were summarized as proportions with median and interquartile range. Continuous variables were compared by Student's t-test or Mann-Whitney U test. Categorical variables were compared by Fisher's exact test. The changes in SF-36 and blood biochemistry measurements from baseline were compared using Student's t-test. The Friedman test was used for comparison of repeated measures over time, and Bonferroni's multiple comparison correction was used for post hoc analysis. $P<0.05$ was considered to indicate a statistically significant difference.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics (18).

Table I. Baseline characteristics of the patients recruited to the present study (n=28).

Characteristic	Mean ± standard deviation, or number
Age (years)	70.46±12.00
Gender (male/female)	12/16
AST (IU/l)	41.43±19.40
ALT (IU/l)	36.14±20.48
Hb (g/dl)	12.54±2.18
PLT ($x10^4$)	15.26±8.55
Fib-4	5.28±5.19
ALB (mg/dl)	3.80±0.42
AFP (ng/ml)	4.90 (3.08, 8.93)
eGFR (ml/m/1.73 m^2)	70.54±23.95
Hepatocellular carcinoma (yes/no)	6/22

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, hemoglobin; PLT, platelet count; Fib-4, fibrosis-4 score; ALB, serum albumin; AFP, α-fetoprotein; eGFR, estimate glomerular filtration rate.

Table II. Baseline Short Form-36 survey score of participants.

SF-36 subscale	Median (interquartile range)
Physical functioning	82.50 (73.75, 90.00)
Physical role functioning	84.38 (54.69, 100.00)
Bodily pain	67.00 (58.00, 100.00)
General health	52.00 (31.50, 52.00)
Vitality	62.50 (37.50, 70.31)
Social role functioning	100.00 (62.50, 100.00)
Emotional role functioning	87.50 (75.00, 100.00)
Mental health	75.00 (58.75, 82.19)

SF-36, Short Form-36.

Results

Twenty-eight patients who underwent DCV/ASV therapy and SVR assessment between September 2014 and February 2017 were analyzed. Subjects comprised 12 men and 16 women, with a mean age of 70.46 years. Among 28 patients, SVR24 was achieved by 26 (93%). Gender, mean age, and blood biochemistry measurements before therapy are shown in Table I, and SF-36 scores at baseline are shown in Table II. GH was low in patients undergoing this therapy (Table II). No significant changes in the courses of any SF-36 subscale were identified during therapy (Fig. 1). For blood biochemistry measurements, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin (ALB), α-fetoprotein (AFP), Platelets

Table III. Differences in blood biochemistry during and following daclatasvir/asunaprevir therapy.

Factor	Baseline	12 weeks	EOT	SVR24	P-value
AST (IU/l)	41.43±19.40	26.14±9.48[a]	24.46±7.71[a]	22.57±7.05[a]	<0.01
ALT (IU/l)	36.14±20.48	20.07±11.69[a]	17.61±7.41[a]	15.32±7.30[a]	<0.01
Hb (g/dl)	12.54±2.18	12.56±2.21	12.53±2.38	12.39±2.67	0.72
PLT (x10^4/μl)	15.26±8.55	15.47±7.70	15.49±7.67	17.14±9.25[a]	<0.01
Fib-4	5.28±5.19	3.79±2.77[a]	3.63±2.62[a]	3.40±2.33[a]	<0.01
ALB (mg/dl)	3.80±0.42	3.87±0.40	3.92±0.30	3.99±0.41[a]	<0.01
AFP (ng/ml)	4.90 (3.08, 8.93)	2.80 (2.38, 5.92)[a]	2.85 (2.30, 5.43)[a]	3.05 (2.40, 5.45)[a]	<0.01
eGFR (ml/m/1.73 m^2)	70.54±23.95	66.12±22.22	66.35±21.98	66.43±21.77	<0.05

Data are expressed as the mean ± standard deviation, or median (interquartile range). [a]P<0.05 vs. baseline. Data analyses were performed using the Friedman-test and Bonferroni's multiple comparison correction. DCV/ASV, daclatasvir/asunaprevir; 12 weeks, following 12 weeks of DCV/ASV therapy; EOT, the end of treatment; SVR24, sustained virologic response week 24; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, hemoglobin; PLT, platelet count; Fib-4, fibrosis-4 score; ALB, serum albumin; AFP, α-fetoprotein; eGFR, estimate glomerular filtration rate.

Table IV. Baseline characteristics of participants and treatment outcome according to age.

Baseline	Age <70	Age ≥70	P-value
Age (years)	58.09±7.84	78.47±5.58	<0.01
Gender (male/female)	7/4	5/12	0.12
AST (IU/l)	36.82±15.20	44.41±21.60	0.32
ALT (IU/l)	37.09±19.05	35.53±21.91	0.84
Hb (g/dl)	13.86±1.83	11.68±1.99	<0.01
PLT (x10^4/dl)	18.49±10.27	13.18±6.77	0.11
Fib-4	3.46±3.85	6.45±5.70	0.14
ALB (mg/dl)	3.97±0.33	3.69±0.44	0.08
AFP (ng/ml)	4.70 (2.90, 10.05)	5.00 (4.30, 6.50)	0.69
eGFR (ml/m/1.73 m^2)	75.65±29.89	67.23±19.50	0.37
Hepatocellular carcinoma (yes/no)	0/11	6/11	0.06
Treatment outcome			
Sustained virologic response week 24 (yes/no)	11/0	15/2	0.51

Data are presented as the mean ± standard deviation, or the median (interquartile range), or as the n number of participants. Data analyses were performed using the Fisher's exact test or Student's t test. AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, hemoglobin; PLT, platelet count; Fib-4, fibrosis-4 score; ALB, serum albumin; AFP, α-fetoprotein; eGFR, estimate glomerular filtration rate.

count (PLT), and FIB-4 index were all significantly improved at each time point compared to baseline (Table III).

The healthy life expectancy of the Japanese is 70.66 years for males and 75.55 years for females (19). We assumed that about 70 years old is a branch point of HRQOL and divided it into two groups of under 70 and over 70 years, and blood biochemistry measurements (Table IV) and SF-36 scores (Table V) at baseline were compared between groups. Regarding changes in HRQOL during therapy, the ≥70-year-old group displayed a significantly greater improvement in PF during the period between baseline and 12 weeks compared to the <70-year-old group (Table VI). No significant differences in changes to blood biochemistry measurements were seen between groups.

In the analysis of SF-36 changes within each group, GH changed significantly in the ≥70-year-old group. Many of the blood biochemistry measurements improved in both groups, but ALB improved only in the ≥70-year-old group. In addition, Fib4-index significantly improved at all time points (12 weeks, EOT, and 48 weeks) compared to baseline in the ≥70-year-old group (Table VII).

Discussion

HCV patients have previously been reported to experience chronically decreased HRQOL due to fatigue, influenza-like symptoms, itchiness, and depression compared to non-infected

Table V. Comparison of baseline Short Form-36 score according to age.

Measure	Age <70	Age ≥70	P-value
PF	85.00 (80.00, 95.00)	75.00 (60.00, 88.89)	0.05
RP	100.00 (78.12, 100.00)	75.00 (50.00, 100.00)	0.26
BP	62.00 (57.00, 84.00)	72.00 (60.00, 100.00)	0.83
GH	52.00 (25.00, 64.50)	52.00 (37.50, 52.00)	0.55
VT	62.50 (18.75, 68.75)	62.50 (43.75, 75.00)	0.37
SF	100.00 (56.25, 100.00)	87.50 (62.50, 100.00)	0.89
RE	91.67 (70.83, 100.00)	83.33 (75.00, 100.00)	0.74
MH	80.00 (57.50, 87.50)	75.00 (40.00, 95.00)	0.60

Data are expressed as the median (interquartile range). Data analyses were performed using the Mann Whitney U test. PF, physical functioning; RP, physical role functioning; BP, bodily pain; GH, general health; VT, vitality; SF, social role functioning; RE, emotional role functioning; MH, mental health.

Table VI. Comparison of differences in Short Form-36 scores during and folowing daclatasvir/asunaprevir therapy according to age.

Group	Measure	Age <70	Age ≥70	P-value
Baseline-12 weeks	PF	-5.00±17.75	8.79±15.22	<0.05
	RP	-5.00±39.06	3.31±15.80	0.44
	BP	-3.09±31.45	3.64±23.31	0.58
	GH	-1.00±15.97	7.66±12.90	0.14
	VT	0.57±23.79	1.59±12.00	0.88
	SF	-4.55±32.73	-5.15±22.56	0.95
	RE	-5.83±39.49	-1.47±13.89	0.68
	MH	-5.57±25.90	4.49±9.75	0.16
Baseline-EOT	PF	-6.82±23.16	1.27±21.42	0.35
	RP	-11.93±43.79	2.94±16.55	0.21
	BP	-14.27±37.50	4.06±21.79	0.11
	GH	-1.09±12.80	9.44±13.47	0.05
	VT	7.95±23.06	1.56±15.73	0.40
	SF	-5.68±33.71	-1.47±21.14	0.69
	RE	-3.03±39.66	1.96±9.56	0.62
	MH	-0.11±24.22	2.89±12.13	0.67
Baseline-SVR24	PF	-9.00±29.61	-4.05±24.39	0.64
	RP	-10.62±36.09	-1.84±21.74	0.44
	BP	1.00±29.58	-8.65±21.84	0.33
	GH	-0.73±12.15	9.91±16.93	0.08
	VT	6.82±25.69	0.74±14.13	0.43
	SF	-4.55±28.65	-12.50±18.75	0.38
	RE	2.27±40.84	-2.45±21.60	0.69
	MH	-3.30±20.87	-2.21±17.67	0.88

Data are expressed as the mean ± standard deviation. Data analyses were performed using the Student's t-test. DCV/ASV, daclatasvir/asunaprevir; 12 weeks, following 12 weeks of DCV/ASV therapy; EOT, the end of treatment; SVR24, sustained virologic response week 24; PF, physical functioning; RP, physical role functioning; BP, bodily pain; GH, general health; VT, vitality; SF, social role functioning; RE, emotional role functioning; MH, mental health.

individuals (20,21). In recent years, treatment of HCV has been revolution with the development of highly effective all-oral direct-acting antiviral agents. These regimens such as ledipasvir/sofosbuvir and ombitasvir/paritaprevir/ritonavir with high efficacy as well as shorter and safer, with little side effects (9-11,22,23). In the future, the significant factors in

Table VII. Differences in the blood chemistry during and following daclatasvir/asunaprevir therapy according to age.

Measure	Baseline	12 weeks	EOT	SVR24	P-value
Age <70					
AST (IU/l)	36.82±15.20	21.00±6.78	21.18±6.42[a]	20.55±6.31[a]	<0.01
ALT (IU/l)	37.09±19.05	19.00±13.28	16.91±6.74[a]	16.18±8.02[a]	<0.01
Hb (g/dl)	13.86±1.83	13.93±1.64	14.14±1.69	14.16±1.77	0.74
PLT (x$10^4/\mu$l)	18.49±10.27	17.84±8.35	18.46±8.96	20.35±10.16	0.01
Fib-4	3.46±3.85	2.30±1.81	2.30±1.78	2.16±1.74	0.01
ALB (mg/dl)	3.97±0.33	3.97±0.38	4.03±0.25	4.05±0.39	0.71
AFP (ng/ml)	4.70 (2.90, 10.05)	2.80 (2.10, 5.95)[a]	3.40 (2.25, 5.50)	3.20 (2.40, 5.90)	<0.05
eGFR (ml/m/1.73 m^2)	75.65±29.89	71.70±27.12	72.68±28.93	70.43±29.03	0.14
Age ≥70					
AST (IU/l)	44.41±21.60	29.47±9.64	26.59±7.91[a]	23.88±7.37[a]	<0.01
ALT (IU/l)	35.53±21.91	20.76±10.92	18.06±7.97[a]	14.76±7.00[a]	<0.01
Hb (g/dl)	11.68±1.99	11.68±2.12	11.48±2.19	11.24±2.54	0.38
PLT (x$10^4/\mu$l)	13.18±6.77	13.95±7.07	13.57±6.26	15.06±8.25	<0.05
Fib-4	6.45±5.70	4.75±2.90[a]	4.49±2.75[a]	4.21±2.35[a]	<0.01
ALB (mg/dl)	3.69±0.44	3.81±0.40	3.85±0.32	3.95±0.43[a]	<0.01
AFP (ng/ml)	5.00 (4.30, 6.50)	2.80 (2.40, 5.60)[a]	2.70 (2.30, 5.40)	2.90 (2.40, 5.10)	<0.05
eGFR (ml/m/1.73 m^2)	67.23±19.50	62.51±18.39	62.25±15.71	63.84±15.97	0.07

Data are presented as the mean ± standard deviation or the median (interquartile range). Data analyses were performed using the Friedman-test and Bonferroni's multiple comparison. [a]P<0.05 vs. Baseline. 12 weeks, following 12 weeks of daclatasvir/asunaprevir therapy; EOT, the end of treatment; SVR24, sustained virologic response week 24; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hb, hemoglobin; PLT, platelet count; Fib-4, fibrosis-4 score; ALB, serum albumin; AFP, α-fetoprotein; GFR, estimate glomerular filtration rate.

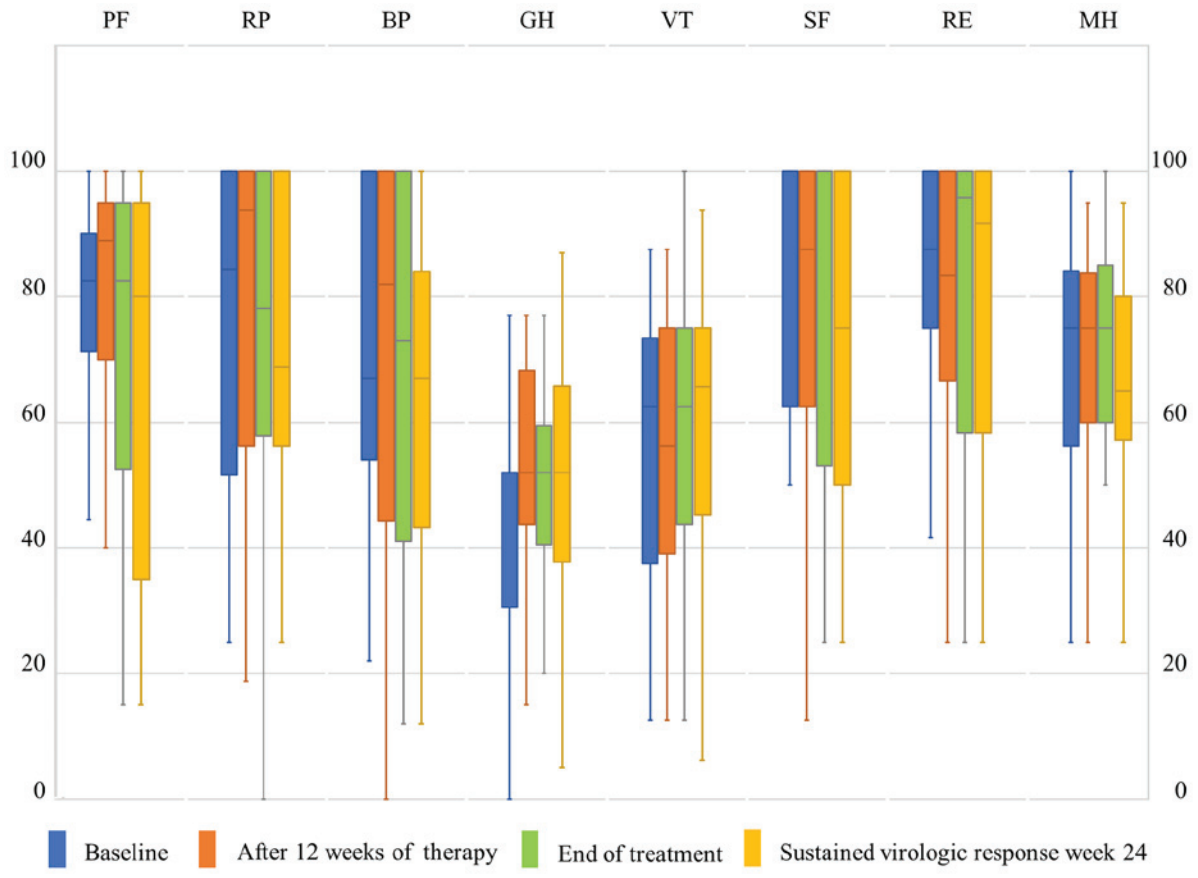

Figure 1. Differences in SF-36 scores during and following DCV/ASV therapy. PF, physical functioning; RP, Physical role functioning; BP, bodily pain; GH, general health; VT, vitality; SF, social role functioning; RE, emotional role functioning; MH, mental health.

selecting treatment will include not only the efficacy of treatments that target a viremia or amelioration of Fibrosis, but also the improvement of patient QOL during and after treatment.

In Japan, IFN-free, ribavirin-free all-oral therapy with DCV and ASV for 24 weeks is approved as well tolerated and can achieve a high rate of SVR in patients with HCV genotype 1b who were ineligible, intolerant, or had not responded to prior IFN-based therapy (24).

In the present study, GH and ALB were improved in the ≥70-year-old group. In older patients, it may have led to an amelioration of liver function as well as improvements in nutritional status such as ALB. As a result, GH scores in the SF-36 improved. Previous reports on DAA treatment containing IFN have indicated decreased HRQOL during treatment as well as an association between hemoglobin and HRQOL (13). On the other hand, because side effects such as loss of appetite and nausea are less likely to occur during DCV/ASV therapy, patients were unaffected by such side effects even during therapy (24). This may have led to the amelioration of HRQOL and ALB through improved liver function. Previous studies have also reported an association between ALB and HRQOL in patients with hemodialysis patients or liver cirrhosis (25,26). Similar results were shown in this study. ALB was postulated to have remained unimproved in the <70-year-old group because, while no significant difference was seen at baseline compared to the ≥70-year-old group (3.97 vs. 3.69, respectively; P=0.08), most patients in the <70-year-old group did not have hypoalbuminemia and had limited room for improvement.

Regarding changes in liver Fibrosis, Fib4-index, a liver Fibrosis marker, (27) improved over time in the ≥70-year-old group with indices of 6.45±5.70 at Baseline, 4.75±2.9 at 12 weeks, 4.49±2.75 at EOT, and 4.21±2.35 at SVR24. These results suggested that Fibrosis improved with hepatitis C treatment in older individuals. Furthermore, liver Fibrosis is a significant carcinogenic factor of hepatocellular carcinoma (28), and the ultimate improvement in liver Fibrosis through DCV/ASV therapy may lead to the suppression of carcinogenesis in elderly individuals.

DCV/ASV therapy improves HRQOL, hepatic functional reserve, nutritional status, and liver Fibrosis during therapy, and could therefore prompt long-term improvements in HRQOL in especially older HCV-infected patients. Recently, DAA with treatment period of 12 weeks has appeared (9-11). For example, ledipasvir/sofosbuvir are one of the most common treatments in Japan, the achievement rate of SVR 12 is reported as 98.8%. The discontinuation of treatment due to serious side effects is 0.6% (29). In addition, the achievement rate of SVR 12 of ombitasvir/paritaprevir/ritonavir has been reported 93.5-100% in Japan (30). In the future, further studies are needed in order to understand the influence of DAAs with treatment period of 12 weeks on HRQOL.

The limitations of this study were that the sample size was small, at only 28 patients, and that the data were representative of only a single institution covering a limited region. Future directions include expanding the study by increasing the number of patients from other institutions and regions.

In conclusion, improvements in hepatic functional reserve and nutritional status can be anticipated even during DCV/ASV therapy. Furthermore, this therapy improves HRQOL, especially in elderly patients.

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