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Efficacy and tolerability of interferon-free regimen for patients with genotype-1 HCV infection

KOSUKE TAKEDA[1], RYUICHI NOGUCHI[1], TADASHI NAMISAKI[1], KEI MORIYA[1], TAKEMI AKAHANE[1], MITSUTERU KITADE[1], HIDETO KAWARATANI[1], NAOTAKA SHIMOZATO[1], KOSUKE KAJI[1], HIROAKI TAKAYA[1], YASUHIKO SAWADA[1], KENICHIRO SEKI[1], YUKIHISA FUJINAGA[1], YUKI TSUJI[1], TAKUYA KUBO[1], SHINYA SATO[1], SOICHIRO SAIKAWA[1], KEISUKE NAKANISHI[1], MASANORI FURUKAWA[1], KOH KITAGAWA[1], TAKAHIRO OZUTSUMI[1], DAISUKE KAYA[1], AKIRA MITORO[1], TSUYOSHI MASHITANI[1], YASUSHI OKURA[2], JUNICHI YAMAO[2] and HITOSHI YOSHIJI[1]

[1]Third Department of Internal Medicine and [2]Department of Endoscopy, Nara Medical University, Kashihara, Nara 634-8522, Japan

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Abstract. Depression is a major reason for interferon (IFN) therapy cessation. IFN-free direct-acting antiviral (DAA) therapy for depression is not well-documented. Thus, four different IFN-free regimens were assessed in genotype-1 hepatitis C virus (HCV) patients with depression. Overall, 287 HCV genotype-1 patients who received combination therapies with IFN-free DAAs of daclatasvir/asunaprevir (DCV/ASV) (n=84), sofosbuvir/ledipasvir (SOF/LDV) (n=95), ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) (n=74), and elbasvir/grazoprevir (EBR/GZR) (n=34) were included. Treatment-induced depression as a complication of HCV therapy in IFN-free DAA regimens was assessed. The severity of depression was evaluated using the Beck Depression Inventory-II (BDI-II) questionnaire. It was demonstrated that all four DAA regimens achieved similar high efficacy in Japanese patients with HCV genotype-1 infection. Moreover, in seven patients with depression who received the 24-week DCV/ASV treatment regimen, the BDI-II scores significantly increased at week 4 as compared with pretreatment values; furthermore, they decreased below baseline at week 12 despite the rapid decline of serum HCV levels after the initiation of DCV/ASV therapy. The BDI-II scores gradually decreased during therapy in the remaining 77 DCV/ASV-treated patients without depression. The BDI-II scores showed a significant decrease from baseline to the end of treatment with 12-week regimens, including SOF/LDV and EBR/GZR. The 12-week DAA regimen of SOF/LDV and EBR/GZR can be safely used with high efficacy in patients with genotype-1 HCV infection, including those with depression.

Correspondence to: Dr Tadashi Namisaki, Third Department of Internal Medicine, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
E-mail: tadashin@naramed-u.ac.jp

Abbreviations: HCV, hepatitis C virus; HCC, hepatocellular carcinoma; IFN, interferon; DAAs, direct-acting antivirals; DCV/ASV, daclatasvir/asunaprevir; SOF/LDV, sofosbuvir/ledipasvir; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; EBR/GZR, elbasvir/grazoprevir; BDI-II, Beck Depression Inventory-II; RBV, ribavirin, RVR, rapid virological response; ETR, end of treatment; SVR, sustained virologic response

Key words: HCV genotype 1, direct-acting antiviral agents, BDI-II, depression, sustained virological response

Introduction

Chronic hepatitis C virus (HCV) infection is a common cause of liver cirrhosis and hepatocellular carcinoma (HCC) (1,2). HCC is the third leading cause of cancer-related death in Japan, and the annual risk of developing HCC among HCV-infected patients with compensated cirrhosis is reportedly 1.8-8.3% (3). The goal of anti-HCV therapy is to successfully eradicate HCV to resolve liver disease. Currently, interferon (IFN)-based therapies, usually in combination with ribavirin (RBV), are commonly used to eradicate HCV infection, but this combination therapy causes severe adverse effects, such as hematological toxicity and depression (4-7); therefore, direct-acting antiviral (DAA) agents are increasingly used for the treatment of HCV infection (8). To date, the effects of IFN-free DAA therapy on depressive symptoms has not been well-documented. Therefore, the aims of the present study were to evaluate the efficacy and tolerability of various IFN-free treatment regimens in Japanese patients with HCV genotype-1 infection and to evaluate the severity of depression symptoms using the Beck Depression Inventory-II (BDI-II) questionnaire (9,10).

Materials and methods

Patients. The study cohort consisted of 287 consecutive patients with HCV genotype-1 infection who were

Table I. Baseline characteristics of patients treated with IFN-free DAA therapies (n=287).

Parameters	Value
Mean age, years (SD)	66.3 (23.2)
Sex (%)	
Male	112 (39.0)
Female	175 (61.0)
Liver disease (%)	
Chronic hepatitis	234 (81.5)
Liver cirrhosis	53 (18.5)
Genotype (%)	
Ia	5 (1.7)
Ib	282 (98.3)
Previous IFN therapy (%)	110 (38.3)
Y93/L31 resistance-associated variants (%)	53 (18.4)
Mean serum HCV-RNA level, $\log_{10}$ IU/ml (SD)	5.6 (2.1)
Mean aspartate transaminase, IU/l (SD)	40 (17)
Mean alanine aminotransferase, IU/l (SD)	47 (24)
Mean platelet count, $10^3/\mu$l (SD)	16 (6.2)
Mean albumin, g/dl (SD)	4.1 (1.7)
Mean total bilirubin, mg/dl (SD)	0.5 (0.1)
SSRI use (before DAA therapy) (%)	4 (1.4)
Antipsychotic use (before DAA therapy) (%)	10 (3.5)
Benzodiazepine use (before DAA therapy) (%)	2 (0.7)
Tricyclic or Tetracyclic antidepressants (before DAA therapy) (%)	5 (1.7)
No medication (before DAA therapy) (%)	273 (95.1)
SSRI use (after DAA therapy) (%)	4 (1.4)
Antipsychotic use (after DAA therapy) (%)	10 (3.5)
Benzodiazepine use (after DAA therapy) (%)	2 (0.7)
Tricyclic or Tetracyclic antidepressants (after DAA therapy) (%)	5 (1.7)
No medication (after DAA therapy) (%)	273 (95.1)

Data are summarized as the count (percentage) for categorical variables and the mean ± standard deviation for numerical variables. SSRI, selective serotonin reuptake inhibitors; DAA, direct acting antiviral; IFN, interferon; HCV, hepatitis C virus.

treated at Nara Medical University Hospital (Kashihara, Japan) from November 2013 to July 2015. The remaining 287 patients included 84 who were treated for 24 weeks with daclatasvir/asunaprevir (DCV/ASV; Bristol-Myers Squibb, Princeton, NJ, USA), 95 treated for 12 weeks with sofosbuvir/ledipasvir (SOF/LDV; Gilead Sciences, Inc., Foster City, CA, USA), 74 treated for 12 weeks with ombitasvir/paritaprevir/ritonavir (OBV/PTV/r; AbbVie Inc., North Chicago, IL, USA), and 34 treated for 12 weeks with elbasvir/grazoprevir (EBV/GZR; MSD, Tokyo, Japan) (Fig. 1). The presence of NS5A resistance-associated substitutions (RASs), which decrease the sustained the sustained virological response (SVR) rate (11,12), was assessed in all patients receiving DAAs prior to the start of therapy by direct sequencing (13). Exclusion criteria were coinfection with another virus, pregnancy, history of clinical hepatic decompensation, or the use of immunosuppressants. The study protocol was approved by the Ethics Committee of Nara Medical University Hospital and conducted in accordance with the tenets of the Tokyo revision of the Declaration of Helsinki (1975).

BDI-II questionnaire. All patients enrolled in the study also completed the BDI-II, which is a 21-question, self-reported, screening instrument used to assess characteristic attitudes and symptoms of depression. Each item is assigned a score of 0-3, with 3 indicating the most severe symptoms. A cumulative score is determined by adding the scores of the individual items. BDI-II scores were determined using the guidelines set forth in the BDI-II manual (14,15). In general, a score of <9 indicates no or minimal depression, that of 10-18 indicates mild-to-moderate depression, that of 19-29 indicates moderate-to-severe depression, and that of >30 indicates severe depression. The clustering of depressive symptoms was further examined using specific, somatic, and cognitive-affective symptom dimensions described by Beck *et al* (16).

Statistical analysis. BDI-II subscale scores were evaluated using one-way analysis of variance followed by the Bonferroni multiple-comparison test. Bivariate analyses of nominal parameters were performed using the chi-squared test. A paired t-test was used to evaluate changes in body mass index (BMI).

Table II. Baseline characteristics of depressive patients with DCV/ASV therapy (n=7).

Parameters	Value
Mean age, years (SD)	59.1 (23.2)
Sex (%)	
Male	1 (14.3)
Female	6 (85.7)
Liver disease (%)	
Chronic hepatitis	6 (85.7)
Liver cirrhosis	1 (14.3)
Genotype (%)	
Ib	6 (85.7)
I	1 (14.3)
Previous IFN therapy (%)	3 (42.9)
Y93/L31 resistance-associated variants (%)	0 (0)
Mean serum HCV-RNA level, $\log_{10}$ IU/ml (SD)	5.7 (0.6)
Mean aspartate transaminase, IU/l (SD)	38.0 (21.0)
Mean alanine aminotransferase, IU/l (SD)	32.6 (29.2)
Mean platelet count, $10^3/\mu$l (SD)	19.2 (5.1)
Mean albumin, g/dl (SD)	4.0 (1.8)
Mean total bilirubin, mg/dl (SD)	0.3 (0.2)
SSRI use (%)	1 (14.3)
Antipsychotic use (%)	5 (71.4)
Benzodiazepine use (%)	1 (14.3)
Tricyclic or Tetracyclic antidepressants (%)	2 (28.6)
No medication (%)	2 (28.6)

Data are summarized as the count (percentage) for categorical variables and the mean ± standard deviation for numerical variables. SSRI, selective serotonin reuptake inhibitors; DAA, direct acting antiviral; DCV/ASV, daclatasvir plus asunaprevir; HCV, hepatitis C virus.

Statistical analyses were performed using GraphPad Prism version 6.04 software (GraphPad Software, Inc., La Jolla, CA, USA). All tests were two-tailed and a probability P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics of patients treated with IFN-free DAAs. Overall, 287 patients were enrolled in this study (Table I). The study cohort comprised 61.0% female patients, 81.5% patients with chronic hepatitis, 98.3% with HCV genotype 1b, and 38.3% who received previous IFN therapy, and the mean age was 66.3±23.2 years. NS5A RASs were identified in 18.4% patients.

The baseline characteristics of seven patients with depression who received the 24-week DCV/ASV treatment regimen are summarized in Table II. Among the seven patients, six (85.7%) had chronic hepatitis, six (85.7%) had HCV genotype 1b, none had RASs, and six (85.7%) were female.

Baseline characteristics of patients treated with IFN-free DAAs. Eighty four Japanese patients received 24 weeks of DCV/ASV (SVR, 97%), 95 received 12 weeks of SOF/LDV, 74 received 12 weeks of OBT/PTV/r, and 34 received 12 weeks of EBV/GZR (Table III). Patients aged ≥65 years were more often treated with EBV/GZR (85.2%, 29/34) than DCV/ASV (52.4%, 44/84), SOF/LDV (69.5%, 66/95), or OBT/PTV/r (62.2%, 46/74) (P<0.01). Patients with cirrhosis were more commonly treated with DCV/ASV [29.8% (25/84)] than SOF/LDV (18.9%. 18/95), OBT/PTV/r (10.8%, 7/74), or EBV/GZR (8.8%, 3/34) (P<0.01). The NS5A resistance-associated variant Y93H was not detected at baseline in any patient treated with OBV/PTV/r. Patients with NS5A resistance were more commonly treated with DCV/ASV (3.5%, 3/84) than *SOF/LDV (40.0%, 38/95) or EBV/GZR (35.3%, 12/34)* (P<0.01). Patients who received IFN-based therapy were more commonly treated with *DCV/ASV (*61.9%, 52/84) than SOF/LDV (40.0%, 38/95), OBT/PTV/r (27.2%, 20/74), or EBV/GZR (35.3%, 12/34) (P<0.01). Among the four treatment groups, the percentage of non-responders to IFN was greatest among patients treated with ASV/DCV (P<0.01). Patients with impaired renal function were more commonly treated with EBV/GZR (23.5%, 8/34) than OBT/PTV/r (11%, 9/74), SOF/LDV (0%, 0), or DCV/ASV (0%, 0) (P<0.01). There were no statistical differences between the depression rates between the four groups.

Viral suppression after initiation of IFN-free therapy, end of treatment response, and SVR. Fig. 2 shows the percentages of patients in the four groups who achieved viral suppression based on the duration after the start of therapy, while treatment

Table III. Baseline demographics and disease characteristics of the patients with HCV infection.

Characteristic	DCV/ASV (n=84)	SOF/LDV (n=95)	OBT/PTV/r (n=74)	EBV/GZR (n=34)	P-value
Age (years)	64±15.3	68±10.5	67±24.9	71±8.6	n.s
Age ≥65 years	44 (52.4)	66 (69.5)	46 (62.2)	29 (85.2)	P<0.01
Male	42 (50.0)	35 (36.8)	21 (32.3)	14 (41.2)	P<0.05
Cirrhosis	25 (29.8)	18 (18.9)	7 (10.8)	3 (8.8)	P<0.01
Genotype 1b	79 (94.0)	85 (89.5)	63 (96.9)	30 (88.2)	n.s
HCV-RNA (log_{10} IU/ml)	5.6±0.9	5.9±0.7	5.9±0.6	5.2±0.5	n.s
Resistance-associated variants	3 (3.5)	38 (40.0)	0 (0.0)	12 (35.3)	P<0.01
Prior IFN-based therapy	52 (61.9)	38 (40.0)	20 (27.2)	12 (35.3)	P<0.01
Intolerable	5 (9.6)	8 (21.1)	4 (20.0)	4 (33.3)	n.s
Breakthrough/relapse	12 (23.1)	18 (47.3)	8 (40.0)	4 (33.3)	n.s
Non-response	35 (67.3)	12 (31.6)	8 (40.0)	6 (50.0)	P<0.01
eGFR >30 ml/min/1.73 m^2 or hemodialysis	0	0	9 (11.0)	8 (23.5)	P<0.01
Depression	7 (8.3)	5 (5.2)	5 (6.8)	2 (5.9)	n.s

Data are summarized as the count (percentage) for categorical variables and the mean ± standard deviation for numerical variables. IFN, interferon; DCV/ASV, daclatasvir/asunaprevir; SOF/LDV, sofosbuvir/ledipasvir; OBT/PTV/r, ombitasvir/paritaprevir/ritonavir; EBV/GZR, elbasvir/grazoprevir; eGFR, estimate glomerular filtration rate; HCV, hepatitis C virus.

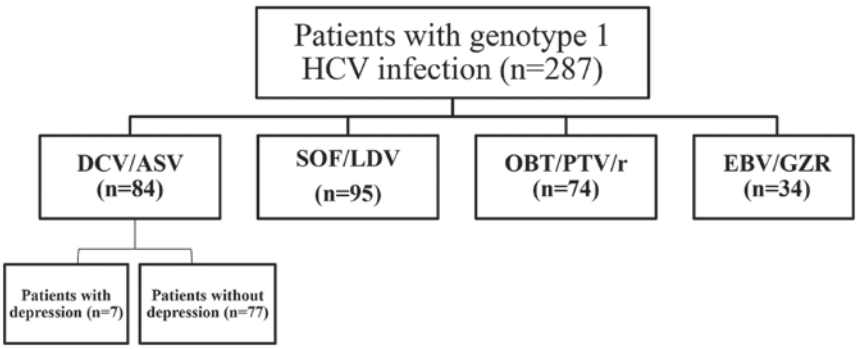

Figure 1. A flow chart of the study design**.** The medical records of 287 patients with HCV genotype 1 infection were retrospectively reviewed. Treatment regimens include DCV/ASV (n=84), SOF/LDV (n=95), OBV/PTV/r (n=74), and EBV/GZR (n=34). DCV/ASV-treated group included seven HCV patients with depression and 77 without. DCV/ASV, daclatasvir/asunaprevir; SOF/LDV, sofosbuvir/ledipasvir; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; EBR/GZR, elbasvir/grazoprevir; BDI-II, Beck Depression Inventory; HCV, hepatitis C virus.

was still ongoing, at week 4 (rapid virological response, RVR), at week 12 (end of treatment, ETR), and at 4 and 12 weeks after the end of treatment (SVR4 and SVR12). The RVR, ETR, SVR4, and SVR12 rates were 76% (64/84), 92% (54/55), 93% (78/84), and 92% (77/84), respectively, in patients treated with DCV/ASV; 85% (81/95), 99% (94/95), 97% (92/95), and 98% (93/95) for those treated with SOF/LDV; 88% (65/74), 100% (72/72), 99% (67/68), and 98% (65/66) for those treated with OBV/PTV/r; and 85% (29/34), 100% (25/25), 100% (22/22), and 100% (20/20) for those treated with EBV/GZR. No significant differences were observed in the RVR, ETR, SVR4, and, SVR12 rates among the four groups.

Change in depressive symptoms in patients treated with IFN-free DAA therapies. In seven patients with depression who received a 24-week DCV/ASV treatment regimen, the BDI-II scores had increased at week 4, as compared to baseline and at week 12 (Fig. 3) in spite of the rapid decline of serum HCV levels after intiation of DCV/ASV therapy (Fig. 4). The patients treated with DCV/ASV, OBT/PTV/r, SOF/LDV, and EBR/GZR were divided according to their median BDI-II scores at baseline into BDI-II relatively high group and BDI-II relatively low group to examine the effects of DAA therapies on BDI-II scores (Fig. 5). The BDI-II scores had decreased, but not significantly, at weeks 4 and 12, as compared to pretreatment values among patients treated with DCV/ASV in both BDI-II relatively high and low groups (Fig. 5A and B). BDI-II scores declined significantly from baseline to week 12 among patients treated with SOF/LDV and EBR/GZR in both BDI-II relatively high and low groups and OBT/PTV/r in BDI-II relatively high group (Fig. 5C-G). However, BDI-II scores had decreased significantly from baseline to week 4, but not week 12, in BDI-II relatively low group (Fig. 5H).

Change in psychotropic medication use in patients treated with IFN-free DAAs. Among the seven patients with depression

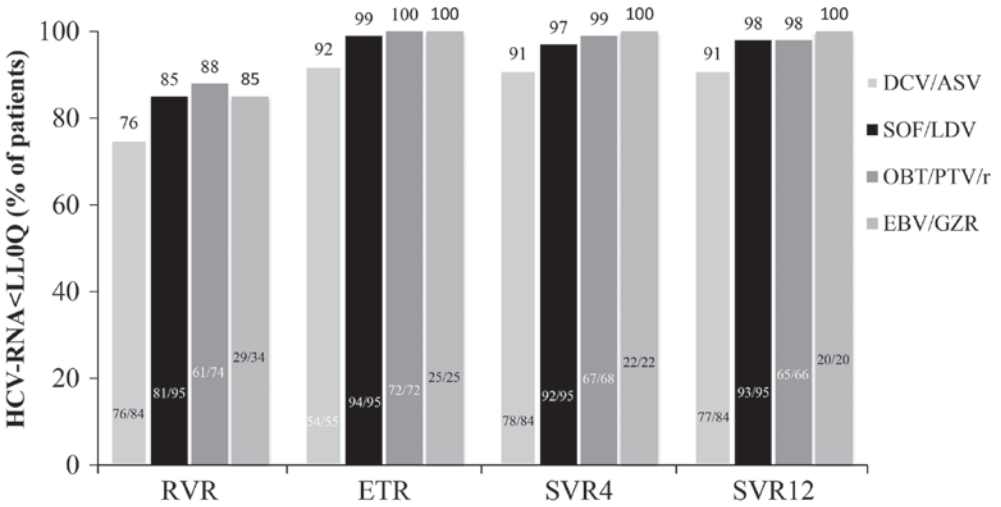

Figure 2. The proportion of HCV-infected patients exhibiting viral suppression in response to DAA treatment. Therapies consisted of DCV/ASV, SOF/LDV, OBV/PTV/r, and EBV/GZR. The cumulative proportions of patients in the four different groups who achieved viral suppression at 4 weeks after the start of treatment, during treatment ongoing, at the ETR, and at 4 and 12 weeks after the end of treatment (SVR4 and SVR12) were shown. Patient numbers are also shown in the bar graph. No significant differences were observed in the RVR, ETR, SVR4, and SVR12 rates among the four groups. ETR, end of treatment; HCV, hepatitis C virus; DCV/ASV, daclatasvir/asunaprevir; SOF/LDV, sofosbuvir/ledipasvir; OBT/PTV/r, ombitasvir/paritaprevir/ritonavir; EBV/GZR, elbasvir/grazoprevir; RVR, rapid virological response; SVR, sustained virological response.

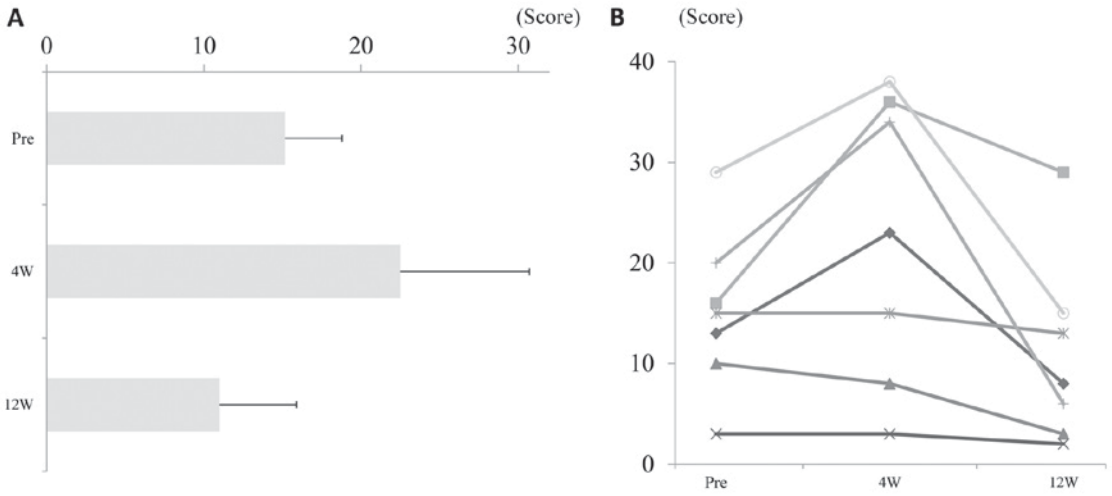

Figure 3. Change in BDI-II scores during daclatasvir/asunaprevir therapy in patients with depression. (A) Bar charts and (B) scatter plots showing that the BDI-II scores had increased at week 4 and decreased to below baseline values at week 12 in patients with depression who received the 24-week DCV/ASV treatment regimen. BDI, Beck Depression Inventory; DCV/ASV, daclatasvir/asunaprevir; W, week.

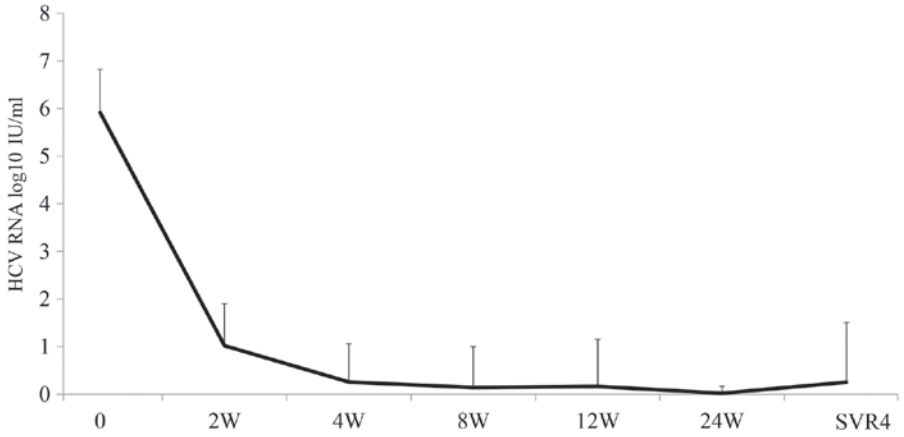

Figure 4. Change in serum HCV RNA levels after the start of DCV/ASV therapy. Serum HCV RNA levels decreased rapidly after initiation of DCV/ASV therapy. DCV/ASV, daclatasvir/asunaprevir; HCV, hepatitis C virus; W, week.

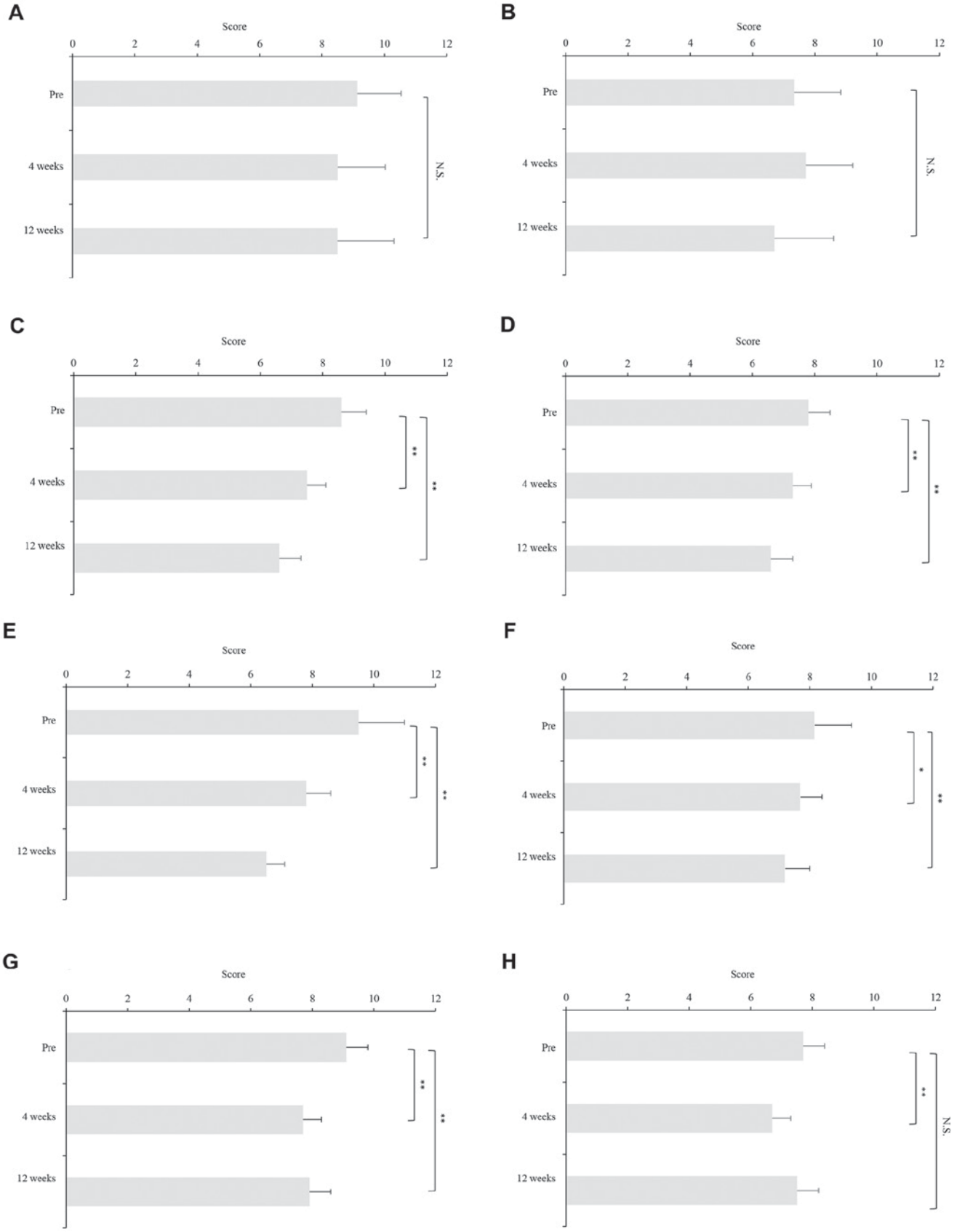

Figure 5. Change in BDI-II scores during DAA therapies. The patients treated with DCV/ASV, OBT/PTV/r, SOF/LDV, and EBR/GZR were divided according to their median BDI-II scores at baseline into BDI-II relatively high group and BDI-II relatively low group to examine the effects of DAA therapies on BDI-II scores. The BDI-II scores had decreased, but not significantly, at weeks 4 and 12 as compared to pretreatment values among patients treated with DCV/ASV in both BDI-II relatively (A) high and (B) low groups. BDI-II scores declined significantly from baseline to week 12 among patients treated with SOF/LDV in both BDI-II relatively (C) high and (D) low groups, EBR/GZR in BDI-II (E) high and (F) groups, and (G) OBT/PTV/r in BDI-II relatively high group. (H) However, BDI-II scores had decreased significantly from baseline to week 4, but not week 12, in BDI-II relatively low group. Asterisks indicate statistically significant differences between indicated experimental groups. (*P<0.05, **P<0.01) N.S, not significant; DAA, direct acting antiviral; DCV/ASV, daclatasvir/asunaprevir; SOF/LDV, sofosbuvir/ledipasvir; OBT/PTV/r, ombitasvir/paritaprevir/ritonavir; EBV/GZR, elbasvir/grazoprevir; BDI, Beck Depression Inventory.

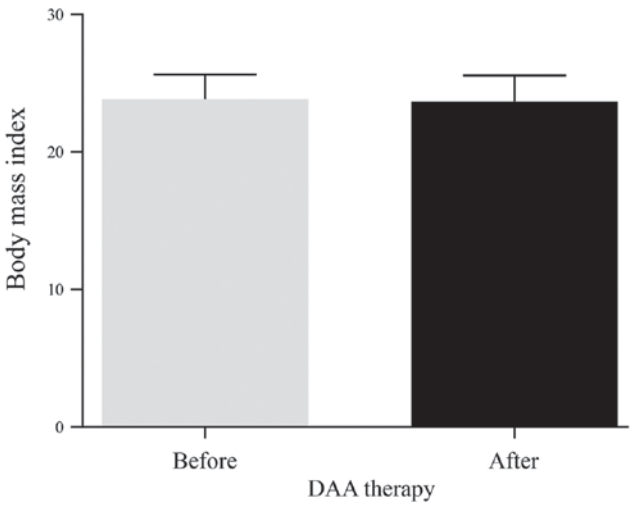

Figure 6. Change in body mass index during DAA therapies. There was no significant change in the body mass index in patients after DAA therapy. DAA, direct acting antiviral.

treated with DCV/ASV, one (14.3%) received selective serotonin reuptake inhibitors (SSRI), five (71.4%) received antipsychotic medication, one (14.3%) received benzodiazepine, two (28.6%) received tricyclic or tetracyclic antidepressants, and two (28.6%) received no treatment (Table II). There was no difference in psychotropic medication use before and after DAA therapy (Table I).

Change in BMI in patients treated with IFN-free DAAs. There was no significant change in the BMI in patients after DAA therapy (Fig. 6).

Discussion

The results of the present study clearly show that various 12-week IFN-free treatment regimens were highly effective and tolerable in patients with HCV genotype-1 infection. The percentages of patients aged ≥65 years with cirrhosis who received IFN-based therapy and non-responders to IFN-based therapy were highest in those who received 24 weeks of DCV/ASV, probably because DCV/ASV is the first IFN-free regimen for the treatment of HCV infection. Chronic HCV infection has a profound negative impact on mental health disorders, including depression (17-20). To the best of our knowledge, this study is the first to evaluate the effects of different IFN-free DAA regimens on the psychometric properties of the BDI-II in Japanese patients with HCV genotype-1 infection. In the present study, the BDI-II scores decreased from baseline to the end of the 12-week DAA therapies. Younossi *et al* (5,7,21-23) have reported that 12 weeks of SOF/LDV therapy improve the health-related quality of life during treatment. Consistent with the findings of the present study, the use of SOF/LDV regimen has been reportedly associated with improved BDI-II scores both during and after treatment (24). In contrast, in the present study, patients with depression treated with DCV/ASV for 24 weeks had higher BDI-II scores at week 4, but lower scores at week 12 than at pretreatment in spite of the rapid decline of serum HCV levels. Ichikawa *et al* (25) demonstrated that 24-week DAA treatment eliminated HCV-RNA and improved psychologic distress. Furthermore, the results of a recent study demonstrated that 24-week DAA treatment with DCV plus ASV did not affect mental component scores at either 12 or 24 weeks after treatment initiation (26). The discrepancy in tolerability of 24-week DAA treatment may be explained in part by the fact that clinical profiles of patients differ between studies. The 24-week DAA treatment would have temporary negative effects by leading to the development of anxiety over a long term therapy but would have also provided positive effects in the long term by yielding clinical benefits following HCV eradication. These findings reinforce the notion that the 12-week regimen was effective and safe for patients with HCV genotype-1 infection, including those with depression. Nevertheless, there were several limitations to this study, including the small number of depressed patients with HCV infection and the relatively short follow-up period, which prevented evaluation of the effect on post treatment BDI-II scores.

Collectively, all four DAA regimens achieved similar high efficacy in Japanese patients with HCV genotype-1 infection. The 24-week DAA treatment had temporary negative impact on the mental health in patients with HCV infection. The BDI-II scores had significantly decreased following a 12-week regimen of SOF/LDV or EBR/GZR. Meanwhile, the tolerability was superior with the 12-week DAA regimes and allowed more patients to reach SVR sooner and with fewer side effects.

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Availability of data and materials

Raw data were generated at Nara Medical University Hospital. Derived data supporting the findings of the present study are available from the corresponding author on request.

Authors' contributions

KT, RN, KM, TA, MK, HK, NS, KKa, HT, YS, KS, YF, YT, SSat, SSai, KN, MF, KKi, TK, TO, DK, AM, TM, YO and JY performed data analysis. All statistical analyses in this current study were supervised by TM. HY and TN made substantial contributions to conception and design and analysis and interpretation of data.

Ethics approval and consent to participate

Written informed consent for the use of resected tissue was obtained from all patients and the study protocol was approved by the Ethics Committee of Nara Medical University.

Patient consent for publication

All study participants or their legal guardians provided written informed consent prior to study enrollment.

Competing interests

The authors declare that they have no conflicts of interest.

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