ORIGINAL ARTICLE

Daclatasvir and asunaprevir improves health-related quality of life in Japanese patients infected with hepatitis C virus

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Abstract

Aims: Interferon-free direct-acting antiviral agent (DAA) regimens for chronic hepatitis C virus (HCV) patients have improved their health-related quality of life (HRQOL). Currently, there are no published data assessing the impact of DAAs regimens without sofosbuvir on HRQOL. The aim of this study was to investigate the improvement of HRQOL in Japanese HCV patients treated with a protease inhibitor and a nonstructural protein 5A inhibitor.

Methods and Results: A total of 123 Japanese genotype 1b HCV patients receiving daclatasvir (DCV) and asunaprevir (ASV) for 24 weeks were enrolled. HRQOL was assessed using the Japanese version of the Chronic Liver Disease Questionnaire (CLDQ) at baseline; weeks 4, 12, and 24; and post-24 weeks. Changes in CLDQ scores were calculated by subtracting the CLDQ score at each time point from the baseline value. Improvement in the mean change of the Japanese version of the CLDQ score became statistically significant as early as week 4 after the initiation of treatment (+9.3%; $P < 0.0001$) and was sustained during and after DCV/ASV treatment. The changes of CLDQ at posttreatment week 24 in patients with sustained virological responses (SVR) were significantly higher than those in patients without SVR (0.4% and −4.1%, respectively; $P < 0.05$).

Conclusions: This study of DCV/ASV treatment for Japanese HCV patients in a clinical setting demonstrated that HRQOL can improve as early as at the initiation of treatment and can continue during and after treatment, regardless of the classes of DAAs regimens and race. Moreover, SVR are needed to continue HRQOL improvement.

Introduction

The development of direct-acting antiviral agents (DAAs) has drastically changed the treatment of hepatitis C virus (HCV) infection and made it highly safe, as well as efficacious, compared to the era of interferon (IFN)-based treatment.[1,2] However, the high costs of DAAs have increased the economic burden; therefore, it is important to assess whether this huge economic burden is cost-effective in terms of the improvement of social welfare.[3,4] Currently, it is necessary to assess not only the traditional clinical end-points, such as the disappearance of HCV RNA, improvement of hepatic fibrosis, and a reduced risk of developing hepatocellular carcinoma, but also aspects of the patients' experiences, assessed by patient-reported outcomes (PROs), such as the

health-related quality of life (HRQOL), when evaluating HCV treatment.[5]

Tools have been developed to measure the HRQOL and are classified as generic tools and disease-specific tools. In general, generic tools, such as Short form-36 and the Euro-QOL of Life 5 Dimension, are available regardless of differences in disease and the general population.[6,7] On the other hand, disease-specific tools provide more responsive and sensitive information of HRQOL for a particular illness. For chronic hepatitis, the Chronic Liver Disease Questionnaire (CLDQ) developed by Younossi is widely used to assess the HRQOL.[8]

Various evaluations of HRQOL in patients with HCV infection have been obtained through numerous studies over the last 10 years, mainly using CLDQ. Previous assessments revealed the following landmark insights: the HRQOL in HCV

patients is lower than the general population;[9] worsening of disease severity is associated with lower HRQOL;[10–12] HCV elimination by antiviral treatment improves the HRQOL in HCV patients; and the HRQOL in HCV patients receiving the IFN- and ribavirin (RBV)-free DAA regimen improves during the treatment, in contrast to a decrease of the HRQOL during the treatment of HCV patients undergoing regimens including IFN and/or RBV.[13–17]

However, some issues pertaining to the HRQOL regarding treatment by IFN-free DAA regimens remain to be resolved. First, knowledge concerning IFN-free DAA regimens is restricted to nonstructural protein 5B (NS5B) inhibitor sofosbuvir (SOF)-based regimens only. Hence, it is not clear whether other DAA regimens, without SOF, achieve similar results. Secondly, because most of the results based on IFN-free DAA regimes are from 12 weeks of treatment, whether longer durations of the DAA regimens can achieve the same effect is unclear. Thirdly, the studies based on SOF-based regimes comprise data from clinical trials. Therefore, these effects require further validation using data from real-world clinical practice.

In 2014, a combination regimen of the NS3 protease inhibitor (PI) asunaprevir (ASV) and the NS5A inhibitor daclatasvir (DCV), in a treatment period of 24 weeks, was approved in Japan as the first IFN- and RBV-free DAAs combination regimen against genotype 1b HCV.[18] DCV/ASV treatment is affected, to a large degree, by resistance-associated substitutions (RAS) in the NS5A region, and the sustained virological response (SVR) rate is only 43% in patients with NS5A-RAS, compared to 91% in those without NS5A-RAS.

Thus, the aim of this study was to investigate the impact of DCV/ASV, which is an IFN-free, RBV-free DAA regimen without SOF, and of a treatment duration of 24 weeks on the HRQOL using the CLDQ in Japanese HCV patients. Furthermore, we also examined the impact of SVR induced by IFN-free DAA regimes on the improvement of HRQOL.

Materials and methods

The study cohort. Between December 2014 and December 2015, 123 chronic HCV genotype 1b patients whose HRQOL values were assessed longitudinally, during and after treatment with DCV/ASV, were enrolled in this study. The exclusion criteria included decompensated cirrhosis, coinfection with hepatitis B virus, coinfection with human immunodeficiency virus, currently active liver cancer, and other chronic liver diseases, such as autoimmune hepatitis, primary biliary cirrhosis, and alcoholic liver disease.

All patients were administered 60 mg DCV (Daklinza®; Bristol-Myers KK, Tokyo, Japan) once daily and 100 mg ASV (Sunvepra®; Bristol-Myers KK, Tokyo, Japan) twice daily for 24 weeks.[18] Virological responses were determined at 24 weeks after completion of treatment. SVR was defined as undetectable serum HCV RNA at 24 weeks after the completion of treatment.

This study was conducted with the approval of the ethics committee of St. Marianna University School of Medicine in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki and its later amendments, and written informed consent was obtained from all patients (Approval No. 2959).

The *IL28B* rs8099917 single-nucleotide polymorphism (SNP) genotype was determined using the TaqMan Pre-Designed SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA), as described previously.[19] We calculated the FIB-4 index using each patient's information and laboratory data at the start of treatment to estimate liver fibrosis noninvasively.[20] In this study, we determined that FIB-4 indexes of ≥3.5 reflected advanced fibrosis.

The Japanese version of the CLDQ. The CLDQ is widely used as a validated disease-specific HRQOL instrument developed specifically for patients with chronic liver disease.[8] The Japanese version of the CLDQ has been reported to be reliable and valid for the assessment of the HRQOL of Japanese patients with chronic viral hepatitis.[12] The Japanese version of the CLDQ questionnaire was self-administered by patients treated with DCV/ASV in this hospital and was administered at baseline; weeks 4, 12, and 24; and post-24 weeks. To eliminate a possible effect on perceived quality of life, both patients and site staff were blinded to each patient's HCV RNA level, measured at the time of each visit. The Japanese version of the CLDQ consists of 29 items and includes six HRQOL domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function, and worry, all ranging 1 to 7, with the higher values representing better HRQOL. An overall CLDQ score is calculated by considering the mean of the scores for each item. Similarly, the CLDQ scores of individual domains are calculated as the mean of the scores of those domains. Overall and individual domains of CLDQ scores are transformed to a uniform 0–100% scale.

Measurement of serum monocyte chemotactic protein 1/chemokine (C-C motif) ligand 2 (MCP-1/CCL2). Serum MCP-1/CCL2 concentrations were measured to determine the impact of serum host immune responses on the HRQOL.[21] Frozen serum samples from baseline and 24 weeks posttreatment were used to determine the circulating MCP-1/CCL2 concentrations, using an enzyme-linked immunosorbent assay (eBioscience, CA, USA) according to the manufacturer's instructions.

Statistical analysis. Continuous variables are summarized as mean $\pm$ SD. Analyses of continuous variables between two groups were carried out using paired or nonpaired *t*-tests. Analyses of continuous variables between three or more groups were carried out using one-way ANOVA, and multiple comparisons are based on the Tukey test. Categorical variables were analyzed using the Chi-squared test. All *P* values <0.05 are considered statistically significant. All statistical analyses were performed using Prism 5 for Windows (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Baseline characteristics of the study cohort. A total of 123 Japanese HCV patients were enrolled in this study (Table 1). Their mean age was 68 years, and patients aged 70 or older comprised 57%. Generally, the mean age of patients in clinical trials for HCV is around 50 years in Western countries and 60 years in Japan;[22–26] the patients in this study cohort were

Table 1 Characteristics of Japanese patients infected with genotype 1b HCV

Characteristic	n = 123
Age, years[†]	68 ± 12
Male gender, n (%)	50 (40.7)
Hemoglobin, g/dL[†]	12.9 ± 1.5
Platelets, × 10^{-4}/μL[†]	14.6 ± 5.4
ALT, U/L[†]	43 ± 26
HCV RNA, log IU/mL[†]	6.0 ± 0.7
FIB-4 index[†]	4.1 ± 2.4
IL28B SNP (rs8099917) TT, n (%)	75 (61.0)
Previous history of HCC, n (%)	9 (7.3)
Treatment-naïve, n (%)	86 (69.9)
SVR rate	
Overall, n/N (%)	107/123 (87.0)
with RAS (L31, Y93) in NS5A, n/N (%)	7/15 (46.7)
without RAS (L31, Y93) in NS5A, n/N (%)	100/108 (92.6)

[†]Mean ± standard deviation.
ALT, alanine aminotransferase; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; *IL28B*, *interleukin 28b*; RAS, resistance-associated substitution; SNP, single-nucleotide polymorphism; SVR, sustained virological response.

significantly older. The mean value of FIB-4 was 4.1, and 50% had advanced fibrosis (FIB-4 ≥3.5). Nine patients had a history of treatment for hepatocellular carcinoma. Seventy-five patients had the TT genotype of the *IL28B* gene, which is favorable for effective HCV treatment with IFN. In this study cohort, the overall SVR rate was 87.0%, and the SVR rates of patients with NS5A-RAS (Y93H and/or L31 M/V/I) and without NS5A-RAS were 46.7% and 92.6%, respectively. DCV/ASV therapy is greatly affected by the presence of NS5A-RAS, as pointed out in our previous report.[27]

Baseline HRQOL in Japanese HCV patients. Table 2 shows the HRQOL assessed using the Japanese version of the CLDQ in this study cohort.[12] At baseline, the mean overall CLDQ score was 5.43, and the mean CLDQ scores for the various individual domains were 5.83 for abdominal symptoms, 5.18 for fatigue, 5.32 for systemic symptoms, 5.83 for activity, 5.43 for emotional function, and 5.32 for worry. Among the individual domains, the lowest mean CLDQ score observed in our cohort was for the fatigue domain. Previous studies in Western

Table 2 Baseline of the Japanese version of CLDQ score in patients infected with genotype 1b HCV

Domain	Number of items	Score(mean ± SD)
Overall	29 items	5.43 ± 0.87
Abdominal symptoms	3 items	5.83 ± 1.05
Fatigue	5 items	5.18 ± 1.04
Systemic symptoms	5 items	5.32 ± 0.99
Activity	3 items	5.83 ± 1.09
Emotional function	8 items	5.43 ± 1.06
Worry	5 items	5.32 ± 1.20

CLDQ, Chronic Liver Disease Questionnaire; SD, standard deviation.

countries produced a similar result; the CLDQ score was the lowest for the fatigue domain.[8,28]

Sustained improvement in the HRQOL during the 24-week treatment with DCV/ASV. To find early changes of HRQOL values for Japanese HCV patients receiving antiviral treatment with DCV/ASV, we calculated the mean changes in CLDQ score transformed to a 0–100% scale from each patient's baseline value to that at treatment week 4. At week 4 of active treatment, the HRQOL values had already started to show significant improvement (Fig. 1). The improvement in the mean change of overall CLDQ score was statistically significant (+9.3%; $P < 0.0001$). Similarly, improvement in the mean change of each individual domain score was also statistically significant (+7.2% to +15.4%; all $P < 0.0001$). Among the individual domains, the maximum improvement in the mean change at week 4 was observed for the worry domain (+15.4%). When compared to previous reports of SOF-based DAAs regimens in Western countries, this tendency was similar despite the different race and different DAA combination regimens using PI and NS5A inhibitors.[13,16]

Figure 2 shows the trend of the mean change of overall and individual CLDQ scores during the 24 weeks of treatment. The mean changes of overall CLDQ score at weeks 4, 12, and 24 from baseline were + 9.3%, +8.9%, and + 8.6%, respectively. Similarly, the mean change of each individual CLDQ score showed sustained increases through the treatment period. Our results indicated that the improvement in the HRQOL during the 24 weeks is similar to the clinical trial data predominantly for 12-week treatment.[13,14,16] These results indicated that HCV treatment by DAAs, compared to IFN treatments, did not decrease the HRQOL during treatment, and the length of treatment with DAAs did not affect the improvement in the HRQOL.
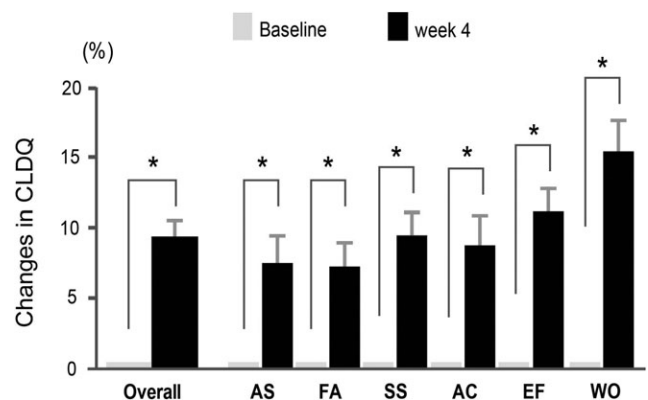

Figure 1 Early changes of the Japanese version of the CLDQ for HCV patients receiving antiviral treatment with DCV/ASV. We calculated the mean changes in the CLDQ transformed to a 0–100% scale from each patient's baseline value to treatment week 4. Comparing the CLDQ score at the onset of treatment and at week 4, overall CLDQ scores and all individual domains show significant improvement after the initiation of treatment. Asterisks show significant differences from the baseline ($P < 0.05$ by paired t-test). AS, abdominal symptoms; FA, fatigue; SS, systemic symptoms; AC, activity; EF, emotional function; WO, worry.
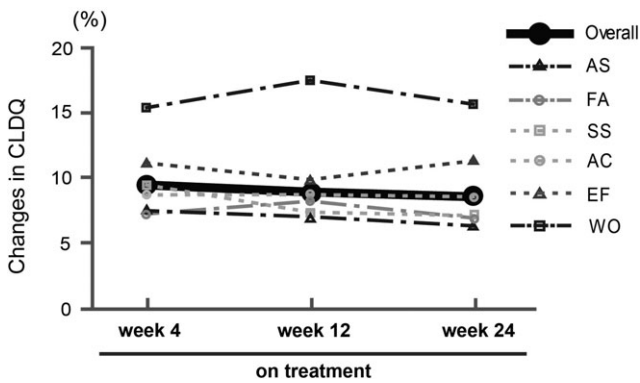
Figure 2 Course of the Japanese version of the CLDQ during 24 weeks of treatment with DCV/ASV. We calculated the mean changes in the CLDQ transformed to a 0–100% scale from each patient's baseline to treatment weeks 4, 12, and 24 (end of treatment). Improvements of overall CLDQ scores and all individual domains were sustained through treatment with DCV/ASV for 24 weeks. AS, abdominal symptoms; FA, fatigue; SS, systemic symptoms; AC, activity; EF, emotional function; WO, worry.

HRQOL after antiviral treatment. Figure 3a shows the mean changes in CLDQ transformed to a 0–100% score from each patient's baseline value to the end of treatment (treatment week 24) and posttreatment week 24. At posttreatment week 24, the improvements in overall CLDQ score (+6.8%; $P < 0.0001$) and in each individual CLDQ domain (+4.6% to +17.1%; all $P < 0.01$) were significantly sustained. However, a decrease in the mean change of overall CLDQ was observed at posttreatment week 24, rather than at the end of treatment (treatment week 24), but without significant difference. Among the individual CLDQ domains, the decrease of the mean changes of fatigue, systemic symptoms, activity, and emotional function domains were also detected at posttreatment week 24, rather than at the end of treatment, without significant difference.

Previous reports suggested that a virological response is associated with improvements in physical health and fatigue symptoms.[29] To reveal the impact of virus elimination on the HRQOL after treatment, we calculated the mean changes in CLDQ transformed to a 0–100% scale from each patient's end-of-treatment (treatment week 24) value to posttreatment week 24 and compared patients with SVR and without SVR (Fig. 3b). The mean changes of overall CLDQ at posttreatment week
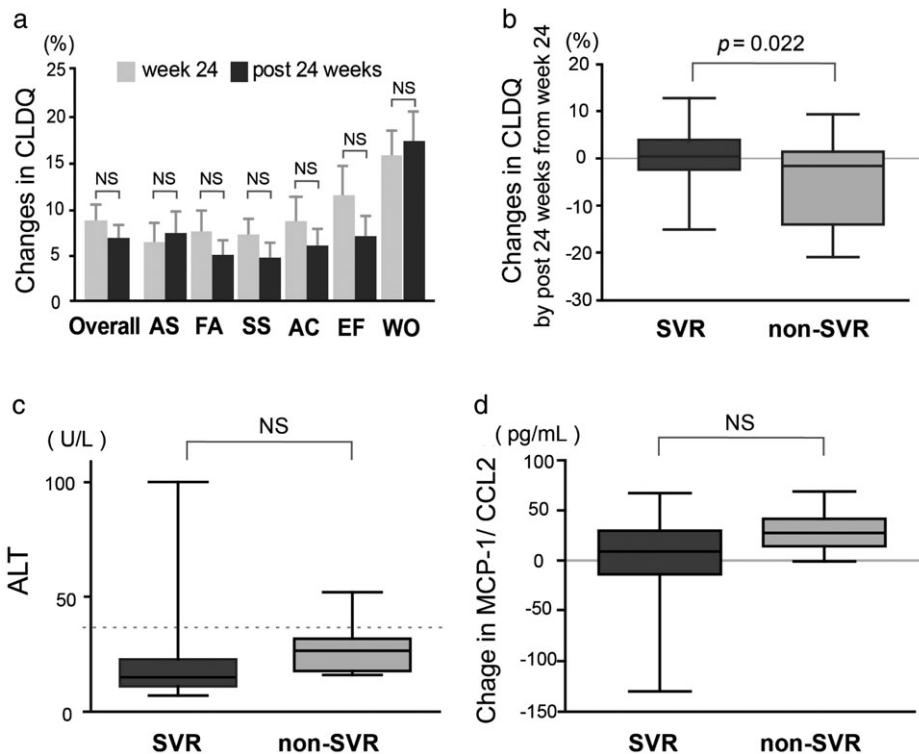

Figure 3 Influence of the virological response on the changes in the Japanese version of the CLDQ following treatment. We calculated the mean changes in the CLDQ transformed to a 0–100% scare from each patient's baseline to the end of treatment (treatment week 24) and posttreatment week 24. Comparing the CLDQ scores at the end of treatment with those at posttreatment week 24, there is no significant difference in the overall CLDQ score or the individual domains. However, there was a tendency for decreases of CLDQ scores in the FA, SS, AC, and EF domains (a). We calculated the mean changes in the CLDQ transformed 0–100% scale from each patient's end-of-treatment score to posttreatment week 24. Comparing the virological responses, the changes of the CLDQ scores from treatment week 24 to posttreatment week 24 differed significantly between SVR and non-SVR patients (b). The mean ALT level at posttreatment week 24 and the change in MCP-1/CCL2 levels from each patient's baseline value to posttreatment week 24 did not differ significantly between SVR and non-SVR patients (c, d). AS, abdominal symptoms; FA, fatigue; SS, systemic symptoms; AC, activity; EF, emotional function; WO, worry; MCP-1/CCL2, monocyte chemotactic protein 1/chemokine (C-C motif) ligand 2.

24 from the end of treatment in patients with SVR and those without SVR were 0.4% and −4.1%, respectively ($P < 0.05$), indicating that virus elimination is strongly associated with improvements in the HRQOL after HCV treatment by DAAs.

Biological parameters in virological response after antiviral treatment. To determine what the mechanism that causes the decrease of the HRQOL following viral relapse after treatment, we measured serum alanine transaminase (ALT) and MCP-1/CCL2 levels at baseline and posttreatment week 24 as biological parameters because the change in serum MCP-1/CCL2 level might be associated with persistent fatigue after treatment.[21] Comparing the serum ALT level at posttreatment week 24 in patients with SVR to those with non-SVR, the serum ALT level showed no significant difference between the two groups and remained within the normal range for both groups (Fig. 3c). Similarly, the change in serum MCP-1/CCL2 level from each patient's baseline value to posttreatment week 24 showed no significant difference between SVR and non-SVR patients (Fig. 3d).

Discussion

Our study found that the HRQOL values of Japanese HCV patients receiving DCV/ASV improve as early as 4 weeks after the initiation of treatment and continue to improve during and after treatment. Although this result is similar to previous reports of the changes of the HRQOL with IFN-free, RBV-free DAA regimens,[13,16] our study has some important outcomes that resolve the remaining issues. First, all previous reports relating to the HRQOL of HCV patients receiving IFN-free, RBV-free regimens comprise data obtained from HCV patients receiving SOF-base regimens,[13,14,16] and our study is the first of HCV patients receiving DAA regimens without SOF. Hence, we concluded that the HRQOL improvement is not limited to SOF-based DAA regimens but is likely a universal consequence of IFN-free, RBV-free DAA regimens. Secondly, although the treatment duration of previous DAA regimens was mainly 12 weeks, our data obtained from HCV patients receiving 24 weeks of DCV/ASV indicate that the improvement of the HRQOL is not affected by prolonging DAA regimens. Thirdly, our study population in a clinical setting was more elderly than in the previous reports of clinical trials in Western countries and Japan.[22–25] Therefore, our data demonstrated that DAA regimens can improve HRQOL in real-world clinical practice, and improvement in the HRQOL is not influenced by age. In addition, our data reinforce the notion that improvements of the HRQOL occur in IFN-free, RBV-free DAA regimens regardless of race.

Our study also found that the HRQOL of non-SVR patients decreased after treatment, despite the continuous HRQOL improvement of SVR patients after treatment. Regarding DAA regimens, there is no previous report to clarify the difference in the HRQOL between SVR and non-SVR patients after treatment because of the small number of non-SVR patients treated by DAA regimens. Our results indicate that improvement in the HRQOL is not only attributable to HCV therapy using IFN- and RBV-free DAA but also to sustained virus elimination. In addition, when comparing the change of CLDQ at treatment week 24 and the change of CLDQ at posttreatment week 24, a tendency for CLDQ decreases in physical components, such as fatigue, systemic symptoms, activity, and emotional function domains, was observed, in contrast to the continuous CLDQ improvement in the worry domain. These results suggest that the HRQOL improvement due to HCV elimination is not merely mental but also physical. Therefore, we tried to elucidate the factors for the physical components of decreases in CLDQ.

The mechanisms by which HCV infection lead to a decrease of the HRQOL are less well understood. Some reports suggest the possibility that HCV infection in the brain and central nervous system impacts HRQOL impairment, and other reports suggest the possibility that the production of cytokines due to HCV infection impacts HRQOL impairment.[21,30] In this study, we analyzed serum ALT levels at posttreatment week 24 and change in levels of MCP-1/CCL2 following treatment to investigate the factors associated with the HRQOL impairment. MCP-1/CCL2 is one of the chemokines that has been reported to be associated with persistent fatigue after treatment.[21] However, our results from the biological parameters failed to find an obvious association between the HRQOL impairment and viral relapse.

There are several limitations to this study. First, there was a relatively small number of study subjects. Second, there were some failures of HRQOL administration, mainly for patients with treatment discontinuation. Despite these limitations, we could demonstrate significant HRQOL improvement soon after treatment and significant decreases in the HRQOL of non-SVR patients after treatment. Third, we assessed only the CLDQ score as PROs data. Working productivity is also important information among PROs. Hence, further studies are needed to assess the working productivity of Japanese HCV patients.

In conclusion, this study of 24 weeks of treatment with DCV/ASV for Japanese HCV patients in a clinical setting demonstrated that the HRQOL can improve as early as 4 weeks after initiation of treatment and continue during and after treatment, regardless of the classes of DAA regimens, treatment duration, race, and age. Moreover, SVR are needed to continue the HRQOL improvement by DAA regimens, as well as IFN-based regimens.

Acknowledgments

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