

Evaluation of the health-related quality of life using the 36-item short form health survey in patients with chronic hepatitis C receiving pegylated interferon/ribavirin/telaprevir triple treatment

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Abstract. The rate of sustained virologic response (SVR) has increased in patients with chronic hepatitis C (CHC; genotype 1) since triple treatment with pegylated interferon (PEG-IFN), ribavirin (RBV) and telaprevir (TVR) was included in Japanese health insurance. However, side effects such as high-grade anemia and skin disorders means it is important to investigate the extent to which quality of life (QOL) is maintained during treatment. The impact on health-related (HR) QOL, as a result of TVR-based triple treatment was investigated long-term (48 weeks) in 34 patients (18 men, 16 women) following TVR-based triple treatment, using the 36-item short form health survey (SF-36). While scores for physical health were significantly lower during treatment, an improvement was seen in patients who showed complete response to treatment from 12 weeks following treatment ($P < 0.05$). HRQOL improved significantly following completion of TVR-based triple treatment in these complete-responders, with higher scores compared with those prior to treatment. Anemia and skin symptoms appeared frequently during treatment and scores for physical health dropped. Particular care needs to be taken in regards to the management of side effects during TVR treatment. Further evaluations using the SF-36 may help in controlling doses to achieve SVR.

Introduction

Pegylated IFN (PEG-IFN) and ribavirin (RBV) treatment for chronic hepatitis C (CHC) infection in 2005 has improved treatment outcomes (1). Furthermore, the approval of a new PEG-IFN/RBV/telaprevir (TVR) triple treatment for CHC in 2011 improved the rate of achieving a sustained virologic response (SVR) and shortened the length of treatment (1-3).

Qualitative and quantitative methods have identified that IFN-based CHC treatment has a negative impact on the health-related quality of life (HRQOL) of patients (4-6). To the best of our knowledge, there are no previous reports on the impact of TVR-based treatment on the QOL of patients with CHC infection. In TVR-based triple treatment, the possibility of side effects, such as high-grade anemia, skin disorders and renal insufficiency, has made understanding its impact on patient QOL important. Therefore, the present study aimed to investigate the HRQOL of patients with CHC treated with TVR-based triple therapy using the 36-item short form health survey (SF-36) (7).

Materials and methods

Study participants and treatment. The present study examined 34 patients with CHC (18 men and 16 women; mean age, 62.8 ± 10.1 for men and 63.6 ± 10.4 years for women), who could be followed up long term, following triple treatment with PEG-IFN/RBV/TVR at Saiseikai Niigata Daini Hospital (Niigata, Japan) between November 2011 and March 2014. Written informed consent was obtained from all patients, and the Ethical Committee of Saiseikai Niigata Daini Hospital (Niigata, Japan) approved this study, which was conducted in accordance with the Declaration of Helsinki.

All patients received TVR (Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) in combination with PEG-IFN $\alpha 2b$ and RBV (both MSD, Tokyo, Japan) for 12 weeks. This was followed by an additional 12 weeks of PEG-IFN $\alpha 2b$ and RBV alone. TVR (750 mg) was orally administered every 8 h,

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Table I. Clinical characteristics of patients with chronic hepatitis C during TVR-based triple treatment according to gender.

Characteristic	Gender		P-value
	Male (n=18)	Female (n=16)	
Age (years)	62.8±10.1	63.6±10.4	ns ^a
Height (cm)	165.2±5.8	155±5.1	P<0.01 ^a
Weight (kg)	66.5±9.3	52.7±5.8	P<0.01 ^a
BMI (kg/m ²)	24.3±2.6	22.0±2.6	P<0.05 ^a
Treatment history (no. naïve/relapse/null)	8/9/1	6/10/0	ns ^b
Serum PEG-IFN concentration (μg/kg)	1.55±0.2	1.76±0.3	ns ^a
Serum RBV concentration (mg/kg)	10.6±2.1	12.6±2.1	P<0.05 ^a
Serum TVR concentration (mg/kg)	30.6±5.6	39.8±7.7	P<0.01 ^a

^aStudent's t-test; ^bMann-Whitney U test. Ns, not significant; BMI, body mass index; PEG-IFN, pegylated interferon; RBV, ribavirin; TVR, telaprevir.

PEG-IFN $\alpha 2b$ (1.5 μg/kg) was injected subcutaneously weekly and oral RBV was given daily at a dose of between 600 and 800 mg based on the body weight of the patient.

Assessment of HRQOL. The association between the HRQOL of patients with CHC treated with TVR-based treatment and gender, age or treatment history was examined. The HRQOL of study participants was measured using a 36-item self-administered questionnaire, the SF-36. The SF-36 evaluates the following eight physical and mental health areas: 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) (7). Each of the 8 areas was scored on a scale of 0-100, where a higher score indicated better health subjectively. These scores were calculated from the questionnaires as described previously (8-10). Briefly, a Japanese-validated version of SF-36 was used and the results were compared to a Japanese normative sample score of the SF-36 in 2,966 individuals (10,11). Scores were calculated based on the standard value (100 points) for the Japanese population.

Evaluation of HRQOL using the SF-36 was performed prior to treatment (0W), 2 weeks following the start of treatment (2W), 3 months following the start of treatment (12W), 6 months following the start of treatment (24W) and 1 year following the start of treatment (48W). In examination on the basis of treatment history, patients were classified as naïve (no prior CHC treatment; n=14), relapsed (recurrence of virus following treatment for CHC; n=19) or null responders (no change in viral load following CHC treatment; n=1, excluded from analysis due to low number).

Statistical analysis. Intergroup HRQOL was compared using the Student's t-test, the chi-squared test and the Mann-Whitney U test, while scores prior to and following the start of treatment were compared using a paired t-test. P<0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed using StatView software (version 5.0; SAS Institute, Inc., Cary, NC, USA).

Results

Examination on the basis of gender. The clinical characteristics of patients were compared on the basis of gender (Table I). The men showed significantly higher values for height (P<0.01), weight (P<0.01), and body mass index (BMI; P<0.05), whereas the women exhibited a significantly higher serum concentration of RBV (12.6±2.1 mg/kg vs. 10.6±2.1 mg/kg; P<0.05) and TVR (39.8±7.7 mg/kg vs. 30.6±5.6 mg/kg; P<0.01). Hemoglobin (Hb) levels dropped in men and women during treatment as SF-36 scores fell (Fig. 1A). Mean Hb levels were 13.0±1.6 g/dl in men and 13.1±1.0 g/dl in women prior to starting treatment, but dropped significantly to 9.4±1.4 g/dl and 8.4±1.2 g/dl, respectively, by 12W (P<0.05; Fig. 1A). However, at 48W Hb values were 13.0±2.5 g/dl in men and 13.0±0.6 g/dl in women (Fig. 1A), indicating that baseline Hb levels had been recovered.

HRQOL improved markedly following completion of TVR-based triple treatment in complete-responders, with higher scores compared with those prior to treatment (data not shown). Interestingly, anemia (Hb <8 g/dl) and skin symptoms appeared frequently during treatment, corresponding to scores for physical functioning dropped (data not shown).

Comparison of PF scores revealed a downward trend for men (n=18) and women (n=16) following TVR-based triple treatment until 12W, with PF scores in men dropping significantly from 39.8±16.4 at 2W to 27.2±15.4 at 12W (P=0.037; Fig. 1B). In addition, PF improved from 12W, with a mean PF score in men of 53.9±3.0 at 48W, significantly higher than the pre-treatment score of 39.6±13.1 (P=0.0009; Fig. 2). In addition, scores for RP dropped significantly in women between 0W and 2W (P=0.0046; Fig. 2).

The score for MH in women was 42.5±10.8 prior to treatment (0W) and 35.5±9.8 at 12W (Fig. 3). Although a downward trend was seen, this difference was not significant. No significant differences in MH scores were seen between men and women, and no effects of TVR-based treatment on MH scores were observed (Fig. 3).

Examination on the basis of age. Patient characteristics were compared between patients ≥65 years old (elderly group, n=19)

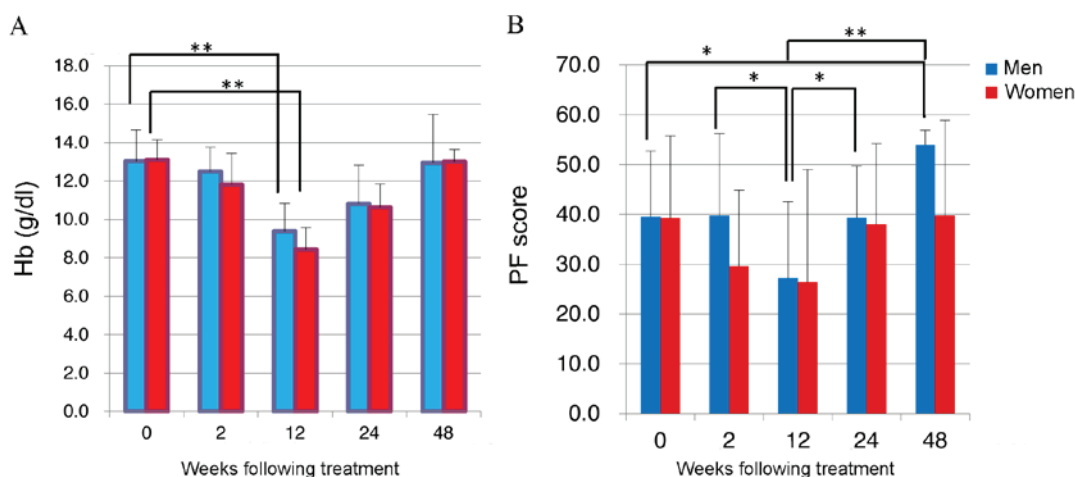


Figure 1. Comparison of (A) Hb levels and (B) PF scores in patients with chronic hepatitis C during telaprevir-based triple treatment according to gender. Scores are from the 36-item Short Form Health Survey. * $P<0.05$, ** $P<0.01$. Results are presented as the mean \pm SD. PF, physical functioning; Hb, hemoglobin; SD, standard deviation.

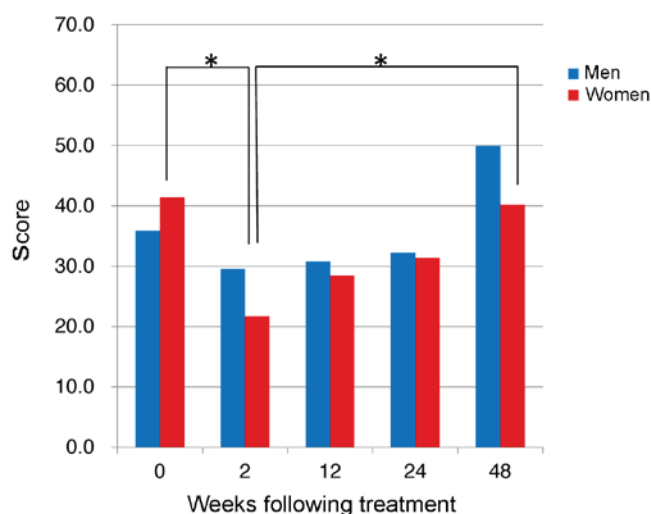


Figure 2. Comparison of physical role functioning scores in patients with chronic hepatitis C during telaprevir-based triple treatment according to gender. Scores are from the 36-item Short Form Health Survey. * $P<0.05$. Results are presented as the mean \pm the standard deviation.

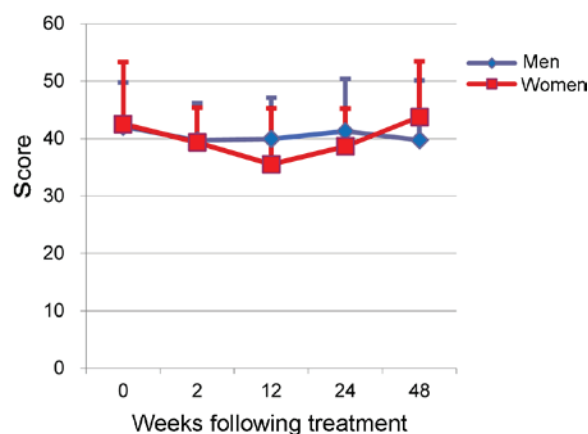


Figure 3. Comparison of mental health scores in patients with chronic hepatitis C during telaprevir-based triple treatment according to gender. Scores are from the 36-item Short Form Health Survey. Results are presented as the mean \pm the standard deviation.

and those <65 years old (non-elderly group, $n=15$). The results of this comparison are presented in Table II. While significant differences in height ($P<0.05$) and treatment history ($P<0.01$) were seen between the elderly and non-elderly groups, no significant differences were seen in PEG-IFN, RBV or TVR dosage.

The non-elderly group exhibited significantly higher scores in PF ($P<0.05$) and RP ($P<0.01$) prior to treatment, which are correlated with physical health (Fig. 4). However, a drop in scores was seen the non-elderly and elderly groups during TVR treatment (Fig. 4). A significant rise in RP score was seen in the non-elderly group at 48W, following completion of treatment ($P<0.01$; Fig. 4).

Examination on the basis of prior treatment history. A comparison of patient characteristics according to prior treatment history is presented in Table III. Patients were classified

as naïve ($n=14$), relapsed ($n=19$) or null responders ($n=1$). However, the null responders group was excluded from this analysis. A tendency towards low PF scores, correlated with poor physical health, was seen in the naïve and relapse groups during TVR-based treatment. In the naïve group, the mean PF score was 44.0 ± 13.7 prior to treatment and decreased significantly to 29.2 ± 17.6 between 0W and 12W ($P=0.02$; Fig. 5). In the relapse group the decrease was not significant (Fig. 5). MH tended to decrease during TVR-based treatment, however, no significant difference was seen between groups (Fig. 5).

Discussion

CHC infection may be associated with a considerable reduction in HRQOL, regardless of the disease stage (12-15). However, the precise mechanism of decreased HRQOL in patients with CHC has not been elucidated, although there are a number of reports indicating an association between the degree of fibrosis, gender and age (16,17).

Table II. Clinical characteristics of patients with chronic hepatitis C during TVR-based triple treatment according to age.

Characteristic	Age		P-value
	Non-elderly group (<65 years old; n=15)	Elderly group (≥65 years old; n=19)	
Age (years)	52.8±4.8	70.4±4.9	P<0.01 ^a
Gender (male/female)	8/7	10/9	ns ^b
BMI(kg/m ²)	22.9±2.6	23.5±3.1	ns ^a
Height (cm)	163.8±7.3	158.4±6.9	P<0.05 ^a
Weight (kg)	62.0±11.1	59.1±10.0	ns ^a
Treatment history (Naïve/Relapse/Null)	10/5/0	4/14/1	P<0.01 ^b
Serum PEG-IFN concentration (μg/kg)	1.65±0.2	1.64±0.3	ns ^a
Serum RBV concentration (mg/kg)	11.68±1.4	11.3±2.8	ns ^a
Serum TVR concentration (mg/kg)	36.3±7.2	33.6±8.6	ns ^a

^aStudent's t-test; ^bMann-Whitney U test. Ns, not significant; BMI, body mass index; PEG-IFN, pegylated interferon; RBV, ribavirin; TVR, telaprevir.

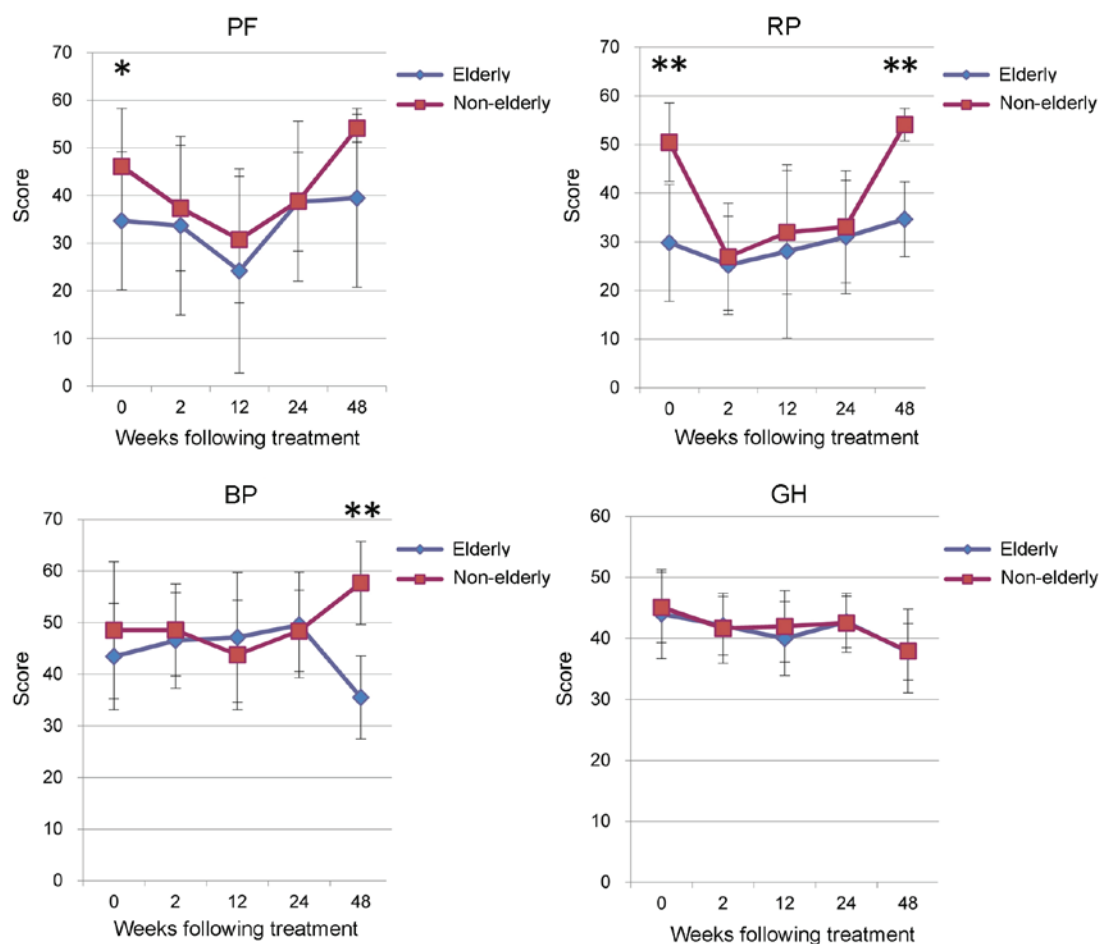


Figure 4. Comparison of PF, RP, BP and GH scores in patients with chronic hepatitis C during telaprevir-based triple treatment according to age. Scores are from the 36-item Short Form Health Survey. *P<0.05, **P<0.01 elderly group vs. non-elderly group. Results are presented as the mean ± SD. PF, physical functioning; RP, physical role functioning; BP, bodily pain; GH, general health; SD, standard deviation.

IFN treatment requires long-term outpatient treatment, making QOL evaluations essential. IFN-free hepatitis C treatment has now been approved (18) and is being actively

implemented. However, QOL evaluations prior to and following IFN treatment remain important, even in this era of IFN-free treatment.

Table III. Clinical characteristics of patients with chronic hepatitis C during TVR-based triple treatment according to prior treatment history.

Characteristic	Treatment history		P-value
	Naïve (n=14)	Relapse (n=19)	
Age (years)	58.8±10.9	66.3±8.7	ns ^a
Gender (male/female)	8/6	9/10	ns ^b
BMI (kg/m ²)	22.7±2.9	23.6±2.9	ns ^a
Height (cm)	163.4±7.25	158.5±7.4	ns ^a
Weight (kg)	60.7±9.8	59.7±11.4	ns ^a
Serum PEG-IFN concentration (μg/kg)	1.7±0.2	1.6±0.4	ns ^a
Serum RBV concentration (mg/kg)	11.0±1.7	11.8±2.7	ns ^a
Serum TVR concentration (mg/kg)	35.7±6.8	34.1±9.2	ns ^a

^aStudent's t-test; ^bMann-Whitney U test. Ns, not significant; BMI, body mass index; PEG-IFN, pegylated interferon; RBV, ribavirin; TVR, telaprevir.

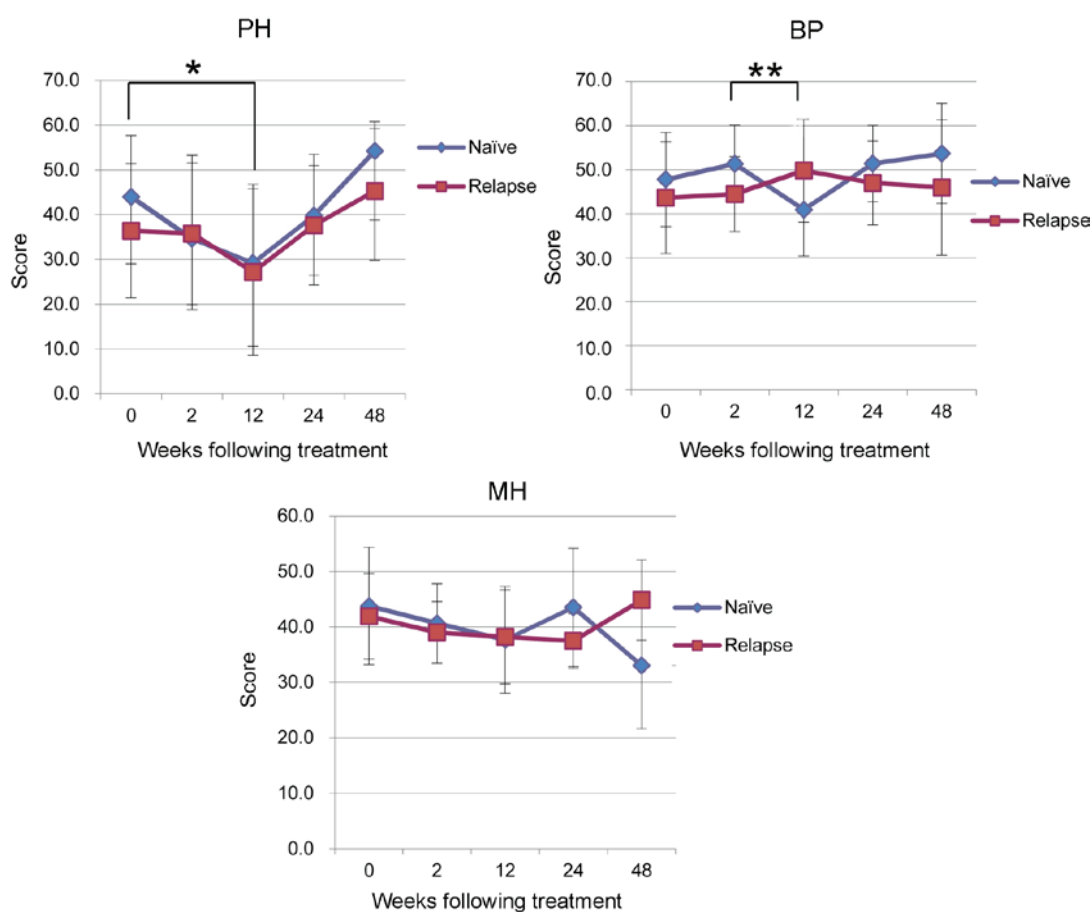


Figure 5. Comparison of PH, BP and MH scores in patients with chronic hepatitis C during telaprevir-based triple treatment according to treatment history. Scores are from the 36-item Short Form Health Survey. *P<0.05 naïve 0W vs. naïve 12W; **P<0.05 naïve 2W vs. relapse 12W. Results are presented as the mean ± SD. PH, physical functioning; BP, bodily pain; MH, mental health; SD, standard deviation.

HRQOL evaluations include comprehensive health-related and disease-specific assessments. Comprehensive HRQOL evaluations include the SF-36, developed in the United States and used worldwide. A Japanese version, developed

by Fukuhara *et al* (10), is used in various fields in Japan and reports of its usefulness have emerged (10,11). The SF-36 allows patients to quantitatively self-evaluate their physical and emotional QOL with relative ease. The SF-36 is a multidimen-

sional, comprehensive QOL measure comprising of 36 items covering 8 areas, which are related to physical or emotional health. Each of the 8 areas contains 2-5 levels of questions that are scored on an ordinal scale, allowing the patient to understand their health from multiple aspects and evaluate their QOL. Each of the 8 areas was scored on a scale of 0-100, where a higher score indicated better health subjectively.

A systematic review by Spiegel *et al* (19) found 15 studies that compared the HRQOL of patients with hepatitis C virus (seropositive) with healthy controls, which identified a decrease in weighted mean SF-36 scores including PF and RP. Previous studies have reported a decreased HRQOL in 6 SF-36 areas in patients with CHC compared with patients without CHC, particularly in VT, GH and RP (20,21). In the current study, patients with CHC undergoing TVR-based treatment exhibited significantly lower SF-36 scores in 5 areas (PF, RP, BP, GH and MH), indicating a decrease in their HRQOL. The results of the current study are in agreement with previous studies comparing the HRQOL of patients with CHC patients prior to and following antiviral treatment (IFN or IFN/RBV) (22,23).

In the current study, SF-36 scores dropped in conjunction with the progression of anemia and were lowest at 12W. It is important to assess subjective symptoms with the SF-36 early and to adjust dosages accordingly, in order to minimize the number of patients who drop out of treatment, improve therapeutic efficacy and maintain patient QOL. Furthermore, the findings of the current study suggest that anemia is an important factor in maintaining QOL, highlighting the importance of controlling drug dosage during treatment.

A number of improvements have been made to IFN treatment in recent years, enhancing its therapeutic effects and increasing the patient response rate. In the present study, the negative effects of TVR-based triple treatment on HRQOL were stronger in regards to physical health compared with emotional health. This is because PF scores decreased until 12W, but then followed an upward trend, which may be the result of the side effects of TVR decreasing. Conversely, PF scores, which correlate strongly with physical health, tended to exceed scores from prior to treatment (0W) by 48W, regardless of gender, age or treatment history. This suggests that TVR-based triple treatment improves physical HRQOL, which is likely associated with a SVR. In further studies, the HRQOL in patients with IFN vs. IFN-free treatment will be investigated.

In conclusion, the present study evaluated HRQOL, using the SF-36, in patients with CHC during TVR-based triple treatment. Surveys using the SF-36 offer a useful indicator of patient QOL, which may be used to reduce the number of patients who discontinue treatment and to improve IFN treatment in the future.

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