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REVIEW

Quality of life considerations for patients with chronic hepatitis C

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SUMMARY. Chronic infection with the hepatitis C virus (HCV) has a profound effect on health-related quality of life (HRQoL) – with fatigue, depression and neurocognitive deficits among the most common complaints. Neuropsychiatric symptoms have prompted research to determine whether the HCV acts within the central nervous system. Replicating virus has been found in central nervous tissues, and changes in neurotransmitter levels in the frontal white matter of patients with chronic hepatitis C are correlated with impaired attention and concentration. Other symptoms of chronic hepatitis C that decrease HRQoL include associated sexual dysfunction and depression. Treatment of chronic HCV infection may temporarily worsen HRQoL, and common adverse effects of currently available agents include fatigue, muscle aches, depression and cognitive deficits. The relationship between sustained viral response and improvement in HRQoL is nonetheless well accepted. Although treatment-related adverse effects may dissuade people from starting therapy and reduce compliance with associated reductions in sustained viral response, for the majority of patients viral clearance produces improvements in both HRQoL and long-term prognosis. Novel agents, with improved adverse effect profiles, may afford more patients the opportunity to achieve a sustained viral response.

Keywords: central nervous system, cognitive deficits, health-related quality of life, hepatitis C virus, novel agents, sustained viral response.

Even in the absence of liver disease, chronic infection with the hepatitis C virus (HCV) compromises health-related quality of life (HRQoL), with profound negative impacts on both physical and mental well being, similar to other chronic conditions. In a classic study to define normative data for the Short Form 36 (SF-36), which is the most commonly used HRQoL assessment tool, 2489 of 9332 survey respondents reported a long-standing illness. Across all eight physical and mental health domains of the SF-36, scores for the chronic disease cohort were approximately 10–20 points lower than scores for individuals without long-standing illness, indicating consistently impaired well being as a consequence of chronic ill health [1]. Patients with chronic HCV infection had median decreases of 9–20 points (weighted mean decrease: 7–16 points) in a recent meta-analysis of 15 studies using the SF-36 to assess the HRQoL of patients with chronic hepatitis C *vs* healthy controls [2].

Hepatitis C-related detriments in physical well being are thus comparable to those of other chronic diseases. However, in an international comparison of the effects of various chronic conditions on HRQoL, physical and general health scores were significantly decreased by 7–12 points for arthritis, chronic lung disease, congestive heart failure, diabetes and ischemic heart disease, whereas mental health detriments were smaller, in the range of 2–5 points [3]. In contrast, HCV infection also significantly impacts mental health, with decrements of 10–12 points in median mental health scores (mean decrease: 7–13 points) [2]. The negative effects on HRQoL derive from various disease, host and treatment-related factors in chronic HCV infection. Understanding the scales used to measure quality of life, the physical and neurologic impairments due to chronic HCV infection, and the beneficial and adverse effects of available treatments is important for understanding patients' concerns. These topics will be addressed in this review.

Abbreviations: HCV, hepatitis C virus; HRQoL, health-related quality of life; MRS, magnetic resonance spectroscopy; SVR, sustained viral response.

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Measuring HRQoL in chronic hepatitis C

HRQoL, which comprises the physical, mental and social effects of a disease, is measured by assessing somatic

symptoms; psychological status; social interactions; physical, cognitive, and psychosocial functioning; sense of well being; and emotional status [4]. Various generic and disease-specific scales are available to measure HRQoL in patients with chronic hepatitis C. These include the SF-36, Hepatitis Quality of Life Questionnaire (HQLQ), Chronic Liver Disease Questionnaire (CLDQ), the Liver Disease Quality Of Life Questionnaire (LD QOL) and the Liver Disease Symptom Index 2.0 (LDSI 2.0). These instruments evaluate HRQoL from the patient's perspective. In addition, utility measures – such as the Health Utilities Index (HUI), Short Form-6D (SF-6D) and the EuroQol-5D (EQ-5D) – permit calculation of quality-adjusted life years (QALY) for cost effectiveness and medical decision-making analyses [4]. These instruments contain time-consuming questionnaires and are more widely used in research than in the clinical setting.

Of the patient-oriented scales, the SF-36 is the preferred tool for HRQoL assessment in a wide range of different diseases, including chronic HCV infection. This generic instrument, which permits comparison of HRQoL status with other conditions, includes 36 items divided into eight domain scales, which contribute to either a physical or a mental health summary measure (Fig. 1). Each scale is scored from 1 to 100, with higher scores indicating better HRQoL [1,5]. 'Normal' scores typically vary by scale; for example, vitality scores for the general population may be closer to 50 than 100, while a role-physical score for a healthy individual should be well above 80. Standard deviations within scales also vary widely. For these reasons, an updated SF-36 with norm-based scoring was issued in 2000. In the SF-36 version 2 (v2), each scale is scored to have the same average (50) and the same standard deviation of 10 points [5].

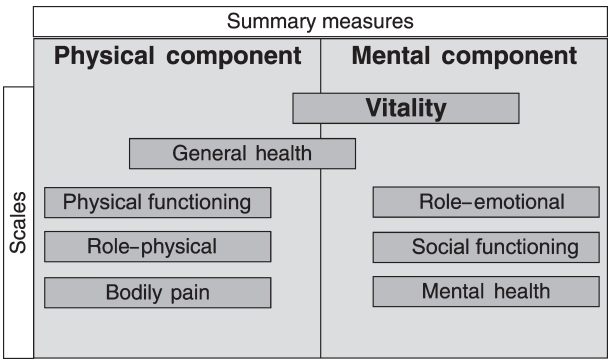

Fig. 1 SF-36 summary measures and scales. Vitality is listed as the first scale because it is the most sensitive predictor of HRQoL status in HCV infection [7]. Quantitatively, the general health score contributes to the physical health summary measure and vitality to the mental health summary measure. Overlap of general health and vitality into mental and physical component boxes, respectively, depicts qualitative contribution of each to the summary measure of the other scale. Adapted from Ware *et al.*, with permission [5].

In some HCV-specific assessments, such as the HQLQ, the SF-36 is supplemented with HCV-specific scales (e.g. HCV-associated distress and limitations) [6]. Such disease-specific questionnaires have the advantage of capturing data on disease-specific symptoms – but with the disadvantage that they cannot be used to compare the effects of different illnesses – whereas the SF-36 is a sensitive measure of HCV-associated reductions in HRQoL. The SF-36 vitality scale, which measures symptoms such as fatigue, energy level and lassitude, may be particularly relevant to patients with chronic hepatitis C [7]. A recent systematic review of 15 studies comparing HRQoL in HCV-infected patients *vs* healthy controls showed that HCV infection most profoundly impaired vitality, general health, physical function and social function. Of these, vitality was considered the most important scale to patients, and based on the results of the systematic review, the authors concluded that a change of 4.2 points on the SF-36 vitality scale has clinical significance [7].

Disease-related HRQoL issues

Numerous studies have demonstrated that HRQoL is reduced regardless of the severity of liver disease or psychiatric comorbidities [7–13]. Moreover, quality of life frequently improves after completion of antiviral treatment [1,14–19]. These observations suggest that HCV may exert a direct effect on HRQoL, although the mechanism is unknown. One possibility is that HCV may act within the central nervous system [20,21], since replicating virus has been found within nervous system tissues [22,23]. Moreover, fatigue, malaise, depression and cognitive impairment – all neuropsychiatric disorders – are among the most common complaints of patients with chronic hepatitis C and occur independently of liver disease or treatment status [8–11].

The strongest evidence for HCV action within the central nervous system comes from studies indicating that neurocognitive deficits occur in 15–30% of patients with chronic HCV infection [21,24,25]. These deficits are typically assessed using computer-directed, timed assessments of a variety of higher neurological functions, such as pattern recognition. These deficits were once attributed to cirrhosis-associated hepatic encephalopathy: in a study from 2003 that compared HRQoL and neuropsychological function in healthy control subjects and 120 patients divided according to severity of liver disease, neurologic abnormalities were found only in patients with decompensated cirrhosis [26]. However, studies using more sensitive tests of attention and concentration as well as brain imaging and evoked potential analyses have demonstrated that mild impairment of cognition and neural response does occur in patients with chronic HCV infection in the absence of liver disease [11,21,24].

Small but significant changes in P300 event-related potentials were demonstrated in a study of 100 untreated HCV-infected patients compared with healthy, matched controls. These changes were not related to viral activity, fatigue severity, or psychiatric comorbidities, nor were they more likely to occur in patients with cirrhosis *vs* those without [24]. In another study, which used a computer-based cognitive assessment battery to evaluate 27 HCV-positive patients and 16 patients with cleared HCV, concentration was impaired and working memory was slower in the infected patients irrespective of intravenous drug use, depression, fatigue or symptom severity [11]. A cerebral proton magnetic resonance spectroscopy (MRS) procedure conducted in 17 of the subjects showed that choline/creatine ratios in the basal ganglia and white matter were significantly higher than those of healthy controls ($P = 0.04$) [11]. Moreover, mean ratios in the basal ganglia were significantly higher in patients impaired on two or more tasks in the cognition battery than were ratios in patients without cognitive impairment ($P = 0.036$) or ratios in healthy controls ($P = 0.007$). A more recent imaging study has confirmed that HCV causes neurologic damage, possibly through immune activation of cerebral microglial cells, as occurs in HIV infection [21]. MRS was used to study 25 HCV-positive patients with histologically mild liver disease. Cognitive tests in 16 of these patients showed significant impairment in attention and working memory compared with healthy volunteers ($P < 0.005$) and with HCV-negative patients previously exposed to HCV ($P = 0.03$). Mean myo-inositol/creatine ratios in the frontal white matter were significantly higher in the HCV-positive patients than in healthy control subjects ($P = 0.02$). As shown in Fig. 2, these elevated ratios were significantly correlated with prolonged working memory reaction times ($R = 0.72$, $P = 0.002$) [21].

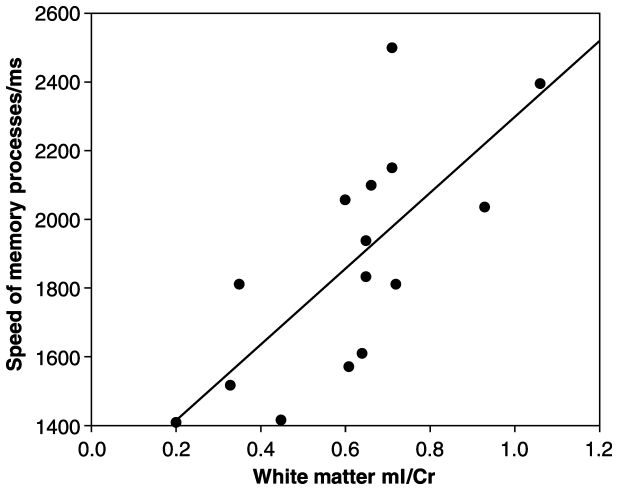

Fig. 2 Correlation of speed of memory score and frontal white matter myo-inositol-creatinine ratio (mI/Cr). $R = 0.72$, $P = 0.002$. From Forton *et al.*, 2008, with permission [21].

Whether neurocognitive deficits are reversible remains an open question. Studies of the cognitive effects of antiviral therapy have found that cognition typically worsens with interferon-α (IFN-α) treatment and subsequently improves to baseline levels upon completion or withdrawal of therapy [20,25]. However, no studies have examined whether cognition improves beyond baseline levels after patients with cognitive impairment have achieved viral clearance. Ongoing studies examining this important question are in progress.

Even as the body of evidence grows demonstrating that HCV affects the central nervous system, whether its negative impact on HRQoL derives from that effect remains a topic of debate. In the study evaluating patients with different degrees of liver disease, even patients with mild liver damage due to HCV had decrements in HRQoL compared with controls, confirming the negative effect of HCV on quality of life independently of liver disease. These authors concluded that neurocognitive dysfunction was not related to reduced HRQoL because physical summary scores on the SF-36 were not correlated with patients' cognition, although it is possible that the instruments used in this study were not sensitive enough to detect mild impairments in cognition, or too few patients were included in the study [26]. Moreover, the SF-36 does not include a cognitive function scale and thus cannot assess difficulties with memory, concentration and attention – all problems frequently reported by patients infected with HCV [11,27,28].

Other studies have also failed to find a link between cognitive deficits and reduced HRQoL. In a small study to determine whether the effects of HCV might contribute to learning difficulties in children, no significant differences were found in adaptive behavior, general intelligence, attention/concentration, expressive vocabulary or visual-spatial construction between HCV-positive and -negative patients aged 6–19 years [29]. In another study evaluating cognition with P300 event-related potentials, no association between subclinical cognitive brain dysfunction and reduced quality of life was found. Instead, fatigue severity and age were independent predictors of HRQoL impairments [13]. In this case, it is possible that the cognitive deficits were not severe enough to have a significant effect on quality of life. Taken together, these data suggest that patients with chronic HCV infection have small but significant effects on higher neurological functioning, but the impact of these changes on physical and mental well being is unclear and, presumably, relates to both the magnitude of the changes and the individuals personal 'coping' strategies that, in some patients, may mitigate the effects of infection.

Another extrahepatic manifestation of chronic HCV infection that reduces HRQoL is sexual dysfunction. More data are available for male than for female sexual dysfunction and HCV. In one small study that included women, 50%

of the 22 female patients in the study reported sexual dysfunction, compared with 43% in the general population [30,31]. The most frequently reported problems were lack of sexual drive (55%) and difficulties with arousal (50%) and orgasm (59%) [30]. The prevalence of male sexual dysfunction in patients with chronic HCV infection may range as high as 47%, with erectile dysfunction rates of up to 39% [30,32,33]. Antiviral treatment, depression and gamma glutamyl transpeptidase (GGT) levels may each contribute to male sexual dysfunction [30,34]. However, HCV itself appears to play a causative role [32,33].

In a study involving 205 HCV-infected men, testosterone levels were lower in HCV-positive patients than in age-matched controls, and the HCV patients with erectile dysfunction had significantly lower testosterone levels than those with normal sexual function ($P < 0.01$). Neither hepatic failure nor IFN-α therapy were related to erectile dysfunction in this study [32]. Another study involving 112 HCV-positive and 239 HCV-negative men found that HCV-related sexual dysfunction occurs independently of depression and significantly impairs HRQoL. Among the men in this study who did not have depression, 47% of HCV-positive men had low scores on sexual satisfaction scales, compared with only 11% of HCV-negative men ($P < 0.001$). In addition, HCV-positive men with sexual dysfunction scored significantly worse on six of the eight scales of the SF-36 than HCV-positive men with no sexual problems [33].

The association between psychiatric disturbances and chronic HCV infection is also strong. Between one quarter and more than half of patients who are infected with HCV show signs of clinical depression and/or anxiety, which dramatically affect HRQoL [35,36]. In a study involving 271 patients with HCV starting therapy with pegylated interferon (PEG-IFN), baseline depression scale scores were strongly correlated with HRQoL impairments. In fact, when history of depression and baseline depressive symptoms was added to an HRQoL regression analysis, the association between depression and HRQoL detriments was so strong that correlations between HRQoL and BMI, viral load and cirrhosis (previously analysed separately from depression) lost statistical significance. Not surprisingly, increasing degrees of depression, as indicated by higher scores on the Center for Epidemiologic Studies Depression Scale (CES-D), were associated with significantly greater detriments in HRQoL (Fig. 3) [37].

The cause-and-effect relationship between chronic HCV infection and neuropsychological symptoms may be impossible to decipher in a disease that so profoundly compromises quality of life: is the patient depressed because of viral activity within the central nervous system, or is depression secondary to functional impairments, social stigma or the inevitable concerns relating to long-term prognosis? By itself, the news of an HCV diagnosis can reduce patients' perceived quality of life [38–40], and host-related factors and supporting networks may play a crucial role. In a large, cross-sectional survey of unselected HCV-positive patients, low household income, diabetes and history of intravenous drug use was shown to be independent predictors of reduced HRQoL, while viral load, HCV RNA presence or absence, and history of treatment success or failure were not significantly correlated with reduced scores on the SF-36 or Hospital Anxiety Depression Scale (HADS) [12]. Ultimately, however, the relevant observation is that chronic HCV infection is strongly associated with both neuropsychiatric disturbances and reduced HRQoL, whatever the cause–effect relationship.

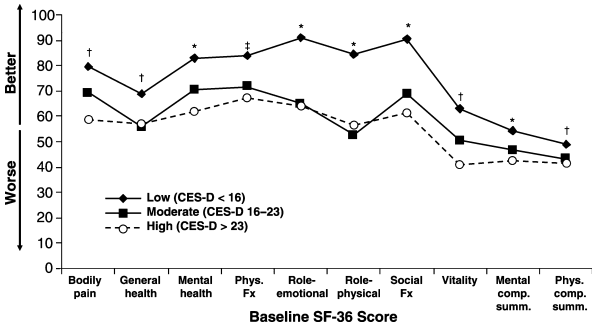

Fig. 3 Association between degrees of depression and HRQoL, stratified according to scores on the Center for Epidemiologic Studies Depression Scale (CES-D). Higher CES-D scores indicate more depressive symptoms. Between group differences: $^{*}P < 0.001$, $^{\dagger}P < 0.01$, $^{\ddagger}P < 0.05$. Fx, functioning. From Dan 2006, with permission [37].

Treatment-related HRQoL issues

The adverse event profiles of interferon-based treatments and ribavirin pose formidable barriers to achieving a sustained viral response (SVR) for many patients. Combination therapy with these agents is now the standard of care for patients with chronic HCV infection, but these agents carry a high incidence of fatigue, depression, insomnia, muscle aches and cognitive impairment. Inevitably these adverse effects are associated with decreased HRQoL [25,25,37,41,42]. As a result, rates of dose reduction or therapy discontinuation can be high. In a study that compared combination therapy with PEG-IFN-α2a and ribavirin with IFN-α2b plus ribavirin or with PEG-IFN-α2a alone, 34–42% of patients who discontinued combination therapy did so because of adverse events (insufficient response was the most frequently cited reason for discontinuations). Dose reductions were also common in this study; of patients receiving combination therapy, one out of 10 had the dose of interferon reduced and one out of five had the ribavirin dose reduced [43]. In a study of patient concerns, side effects and depression were cited by as many as 73% of antiviral therapy recipients as challenges to treatment adherence, and 15% of patients in this study had discontinued therapy [44]. A pooled analysis of 1441 patients randomized to either PEG-IFN-α-2a or IFN-α-2a showed that worsening fatigue ($P < 0.001$) and SF-36

physical ($P < 0.01$) and mental ($P < 0.05$) summary scores were significant predictors of treatment discontinuation, which occurred in 10% of the patients studied [41].

Patients often rate the impact of treatment side effects as worse than providers do. In a survey of 92 patients with chronic hepatitis C and 23 providers, patients' perceptions of future treatment side effects were worse than their perception of their current health – leading to an unwillingness to undergo therapy to stave off disease worsening later in life [45]. In another study of treated patients, 31% reported needing to scale back or quit employment, and another 20% reported deterioration of relationships with family and friends due to treatment-related adverse effects [46].

Does sustained viral response lead to improved HRQoL?

Various studies have shown that HRQoL improves after SVR has been achieved [14,15,17–19]. A recent study of HRQoL in 29 patients receiving PEG-IFN-α showed that the 13 patients who achieved SVR after 12 weeks of treatment had significantly improved mental health summary scores on the SF-36 [14]. A recent analysis of data from the Hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial showed that SVR significantly improved scores in the role physical, general health, vitality, and role emotional domains of the SF-36. All patients in this trial had been previous nonresponders to antiviral therapy. Of the 1144 who entered a 24-week lead-in phase involving PEG-IFN-α and ribavirin, 373 responded and underwent another 24 weeks of therapy (for a total of 48 weeks). HRQoL data were available for 258 patients who were surveyed at baseline and at week 72, 24 weeks after completing treatment. Of these, the 76 patients who relapsed had significantly worse HRQoL scores than those who achieved SVR [15].

Although the relationship between SVR and HRQoL improvement is well accepted, several issues must be considered. First, many studies are small in scale, so data may not be applicable to larger patient populations. Second, the majority of these studies are not prospective. Patients learned of their HCV status before taking the HRQoL questionnaire, which inevitably influences the results. It is reasonable to suppose that if a diagnosis of HCV reduces HRQoL by itself [38–40], learning of viral clearance may improve HRQoL scores. However, some evidence suggests this may not be the case. In one study designed so that patients learned of their viral status after taking the post-treatment HRQoL assessment, significant improvements in five of the eight SF-36 domains were observed in SVR patients compared with nonresponders [16]. Anecdotal evidence from the HALT-C trial also suggests that actual viral status has a stronger bearing on HRQoL than patient perception. Two patients in the HALT-C trial were late relapsers and believed themselves to be HCV-negative at the time they answered the 72-week SF-36 questionnaire. Consistent with their HCV-positive status, their HRQoL scores were low, similar to those of the other patients who did not achieve SVR in this study [15].

Occasionally, there are patients who have no detectable HCV RNA but who also do not have improved HRQoL. Some may be false-negative patients, like the two reported from the HALT-C study. Others may have residual chronic fatigue syndrome despite cleared virus, as occurs after eradication of hepatitis A and B viruses [47]. Another possibility is persistence of HCV in liver or other tissues, even when it is undetectable in serum. In a recent study demonstrating the durability of SVR, HCV RNA remained undetectable in serum or peripheral blood mononuclear cells (PBMCs) for a median of 3.3 years in patients who had no serum HCV RNA 6 months after treatment. Yet in 1.7% of the patients who had liver biopsies, HCV RNA was detected in hepatic tissues [48]. Other studies have documented persistent HCV infection in the liver and also in PBMCs long after SVR [49,50]. These provocative findings suggest that persistent virus may account for low HRQoL despite SVR in a small subset of patients.

CONCLUSIONS

Independently of liver disease, HCV infection reduces the HRQoL of most chronically infected patients. Fatigue, depression and cognitive impairment are among the most common complaints of patients, and all of these symptoms have the potential to impair patients' ability to function at work or in society. For the vast majority of patients, SVR improves not only long-term prognosis but also HRQoL. Yet SVR is frequently an elusive goal, often because of the adverse effects of currently available agents. Many patients also refuse to start treatment, probably due to concerns about adverse effects [45,51]. Without treatment, however, patients with chronic HCV infection will be unlikely to see any improvement in HRQoL. This calls for greater efforts to encourage patients to start and stay on antiviral treatment. Various novel agents, including telaprevir, boceprevir and longer-acting interferons such as albinterferon alfa-2b, appear to offer improved SVR rates and/or more convenient administration options compared with current therapies, potentially leading to improvements in HRQoL in patients with chronic hepatitis C.

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