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Chapter 13

Health-Related Quality of Life in Antiviral-Treated Chronic Hepatitis C Patients

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Additional information is available at the end of the chapter

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Abstract

Chronic hepatitis C has a profound negative impact on both physical and mental well-being, thus decreasing health-related quality of life (HRQL). The most common complaints include symptoms such as fatigue, depression, and neurocognitive deficits. The burden of chronic HCV infections is multiplied by emotional and psychological issues that affect patients' functional health and work ability. Treatment of chronic HCV infection may at the beginning cause worse HRQL rates, as a result of common adverse effects like fatigue, muscle aches, and depression. However, the relationship between sustained virologic response (SVR) and improvement in HRQL is well known. Treatment-related adverse effects may discourage patients from starting therapy and reduce their adherence to treatment. Novel agents, with improved adverse effect profiles and SVR rates, allow more patients the opportunity to achieve improvements in HRQL during and after treatment.

Keywords: chronic hepatitis C, HCV treatment, adverse effects, health-related quality of life

1. Introduction

Life expectancy and causes of death have been used as key indicators of population health. Although these indicators provide information about the health status of populations, they do not offer any evidence about the quality of the physical, mental, or social functioning. To date, health is systematically included as a significant aspect of quality of life. Health-related quality of life (HRQL) measures have been developed to evaluate numerous aspects of an individual's subjective experience that cover health, disease, and different disabilities [1]. Despite the huge interest in quality of life, agreement is lacking on the definition and

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measurement of quality of life. Therefore, quality of life is used as a generic designation to describe a range of different physical and psychosocial variables [2].

2. Health-related quality of life (HRQL)

At the beginning of the 1990s, the World Health Organization (WHO) accepted the importance of evaluating and improving people's quality of life and developed a project in order to create a cross-cultural instrument of quality of life assessment: the World Health Organization Quality of Life (WHOQOL) [3]. WHO started its own project for several reasons. One of the reasons was to develop an international quality of life evaluation. Also, it was important to include a consideration of patients' quality of life in treatment decisions, approval of new pharmaceuticals, and policy research. Hence, having an international quality of life assessment as WHOQOL makes it possible to follow up quality of life research in different cultural settings and to directly compare results obtained in these different placements [4].

Likewise, clinicians and public health professionals have used health-related quality of life (HRQL) to evaluate the effects of the chronic diseases, treatments, and different disabilities. Institutes at the National Institutes of Health (NIH): for instance, the National Cancer Institute (NCI) and centers within the Centers for Disease Control and Prevention (CDC) have involved the evaluation and improvement of HRQL as a public health preference [5].

There are two potential explanations for the increasing interest in the assessment of quality of life in health care. The first explanation is an increased life expectancy as a result of improved medical care. Diagnostic and therapeutic treatments have increasingly advanced prognoses and management of many diseases, also increasing the life expectancy of individuals affected by these diseases. Consequently, many more patients are diagnosed with chronic, clinically manageable diseases than terminal diseases [2]. This evolution has led to the conclusion that health care interventions can no longer be evaluated solely on the basis of mortality or morbidity. Indeed, the impact of a disorder on a patient's life must also be observed [6]. The second explanation is referred to as the proliferation of improved medical and surgical technologies. Quality of life is included in the evaluation of the benefits of different treatment options.

HRQL aims at measuring disabilities related to specific diseases and also on effectiveness of treatment. Studies on HRQL focus on quality of life components that can be impacted by specific diseases. For example, measures of well-being typically evaluate the positive aspects of a person's life such as positive emotions. Therefore, numerous studies evaluate the quality and outcome of provided health care [2, 5].

It is important to emphasize that in HRQL, the experience of patients is most important. However, not only patient's estimation of their level of functioning is significant, for instance, cognitive process, but also the level of satisfaction in the different scopes, for instance, emotional process [7]. Investigators focused on HRQL may overestimate the impact of health-related factors. In addition, they could seriously underestimate the importance of nonmedical

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phenomena [8]. Some analyses of quality of life that have been undertaken have recognized this idea. Therefore, the majority of analyses have demonstrated that quality of life is most properly defined in patient satisfaction [9]. Finally, health should be observed as significant indicator as well as an important contributor to better quality of life.

3. HRQL measurements

Assessment of HRQL is related to functioning and well being in physical, mental, and social parts of life. Moreover, it shows importance in screening for disability and in improving communication between patients and clinicians [10, 11].

Common HRQL profile measures use multiple points to evaluate each of multiple parts of health and to decrease response burden. For that purpose, short-form HRQL measures, such as short-form 36 (SF-36), are widely used. Their briefness makes short-form measures practical for use as only 7 to 10 minutes are required to complete the form [12]. To provide the briefest possible measure of HRQL, the Dartmouth Cooperative Functional Assessment Charts (COOP) were designed. They consist of global items representing every single domain of health. These items are managed using five response choices: *Excellent*, *Very good*, *Good*, *Fair*, *Poor*, and COOP charts are original examples of global health items to evaluate multiple HRQL domains [13]. The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) assesses global physical, mental, and social HRQL. It also designs, develops, validates, and standardizes item banks to measure patient-reported outcomes (PROs) relevant across common medical conditions. PRO is a 10-question measure which was developed through PROMIS, a NIH Roadmap electronic system designed to collect self-reported HRQL data from different populations with different types of chronic diseases [14]. The PROMIS global measure includes questions that evaluate self-rated health, physical HRQL, mental HRQL and evaluate for fatigue, pain, emotional distress, and their effects on different types of social activities. Recent investigations showed that psychometric evaluation of the PROMIS global health questions identified global physical and mental health summary scales but also separate scoring for global health, social activities, and numerous roles. Since it has been demonstrated, individual questions can be used to assess physical and mental HRQL, and social questions are included to assess social HRQL [14]. The PROMIS global health measure is scheduled to be managed on the National Health Interview Survey (NHIS) every 5 years. Analysis of summary scores and individual questions are expected to provide useful results and information. Their results are also expected to be reported every 5 years.

Well-being measures evaluate the positive aspects of people's lives. These measures have an association with their health and satisfaction, the quality of their relationships, positive emotions, their resiliency, and also with the realization of their potential. Well-being indicators measure when people feel very healthy and satisfied with life. Therefore, these characteristics representing well-being are associated with different benefits related to health, work, family, and economics. For instance, positive emotions are associated with decreased risk of disease and injury, as well as better immune functioning, which includes faster recovery time and

increased longevity [15]. Measures of well-being can helpful for the public because they track results, such as meaningful work, relationships, satisfaction, and happiness. These outcomes are personally significant, easily understood, and can motivate change or modification [15, 16].

Participation measures reflect individual's assessments of the impact of their health on their social involvement within their environment. Participation includes education, employment, civic, social, and leisure activities. The principle behind participation measures is that an individual with a functional limitation can live a long and productive life and enjoy a good quality of life [17]. Hence, this approach of the measurement of participation is a significant supplement to the evaluation of quality of life. Participation is measured in the context of a person's health state and within his current social and physical ambiences [18].

Three scales are often used to measure HRQL among patients living with HCV: the SF-36 questionnaire, a generic instrument used to assess HRQL, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, and Chronic Liver Disease Questionnaire–Hepatitis C Virus (CLDQ-HCV) instrument [19].

FACIT-F is a generic core questionnaire which involves 27 items that are divided into four parts: functional well-being, physical, social, or family and emotional [20]. The above items, as well as a fatigue subscale, range from 0 (worst) to 160 (best) [21]. No information regarding the validity of FACIT-F or its minimal clinically important difference (MCID) in hepatitis C patients were found.

SF-36 is a generic health instrument that has been used for assessment of HRQL and also in clinical trials to study the impact of chronic disease on HRQL. SF-36 uses eight scales: physical functioning, pain, vitality, social functioning, role emotional, role physical, general health perceptions (GH), and mental health. SF-36 also predicts two constituent summaries: the first one is physical component summary (SF-36 PCS), and the second is mental component summary (SF-36 MCS) [20]. The SF-36 PCS, SF-36 MCS, and other eight scales are measured on a scale of 0 to 100 [21].

The CLDQ is a HRQL assessment for patients with chronic liver disease and involves 29 items divided into six different parts: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function, and worry. For each item, the patient allocates a score of 1 (all the time) to 7 (none of the time). Finally, the domain score is divided by the number of items in the domain; therefore, scores are represented on a 1 to 7 scale. Consequently, it is important to emphasize that higher numbers indicate the best potential function [22].

4. Socioeconomic burden of HCV infection and HRQL

Chronic liver disease is a major medical and public health problem worldwide. Reports from the European Center for Disease Prevention and Control indicate that the prevalence of chronic hepatitis B virus (HBV) infection in the general population ranges from 0.2% to over 7% in the different European countries, while the prevalence of hepatitis C virus (HCV) varies from 0.4% to over 3% in Mediterranean countries [23].

Hepatitis C virus is a blood-borne disease that infects approximately 160 million people worldwide [24]. The infection has been transmitted through blood transfusions, contaminated injections during medical treatments, and through needle-sharing by injection drug users [25]. Combined efforts to educate the injection drug use population and anticipate different methods by which they can acquire sterile needles are indispensable and relatively economical, especially in countries where prevention and support programs for substance abusers are developed [26, 27]. Testing populations at high risk for HCV infection reduce economic burden by identifying patients with HCV infection and anticipating early therapy, hence potentially preventing progression to more serious and costly complications.

Nevertheless, HCV is asymptomatic, and nowadays, most new cases go undiscovered and approximately 75% become chronic conditions [23] which increases risk for cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [28]. Economic burden is multiplied by the impact of HCV on HRQL resulting from complications of some liver diseases such as encephalopathy, variceal hemorrhage, ascites, and need for liver transplantation [29].

The recognition that the burden of HCV expands beyond its economic impact corresponds with recommendations by the NIH to conduct studies that measure not only traditional biological results in HCV, such as HCV RNA, liver enzyme levels, liver histology, but also patient-oriented results [30]. However, clinicians often do not use HRQL in HCV, and patient-oriented results may fail to resonate with clinicians in the same way as long-established practice. In light of the disconnect between the growing significance of measuring HRQL in the HCV population and the incompetence of clinicians to interpret HRQL differences, it is crucial to establish the clinical importance of HRQL score differences by anchoring them to changes in clinically familiar results [31]. In conclusion, public health officials, physicians, and patients should also discuss the impact of HCV infection on HRQL when considering treatment strategies [32].

5. HCV infection impact on HRQL

Patients with chronic hepatitis C have a decreased HRQL compared to the general population. The impact of HCV infection on physical well-being is comparable to other chronic diseases or some stressful life events [33]. Many symptoms of chronic HCV infection negatively affect patients' functional health, psychological well-being, and self-perceived health (**Figure 1**). HCV patients commonly experience physical and psychiatric symptoms as a direct consequence of chronic infection and its sequelae.

HCV causes both hepatic and extrahepatic manifestations. The clinical outcomes of the hepatic manifestations include hepatocellular carcinoma and cirrhosis, which are the primary indications for liver transplantation. HCV infection is also associated with a range of extrahepatic manifestations including mixed cryoglobulinemia, vasculitis, arthritis, thyroid disease, and type 2 diabetes [34]. Somatic symptoms of chronic HCV infection include fatigue, nausea, anorexia, headache, irritability, abdominal discomfort, and muscle aches [35, 38]. Fatigue is among the most frequent and disabling complaints of chronic

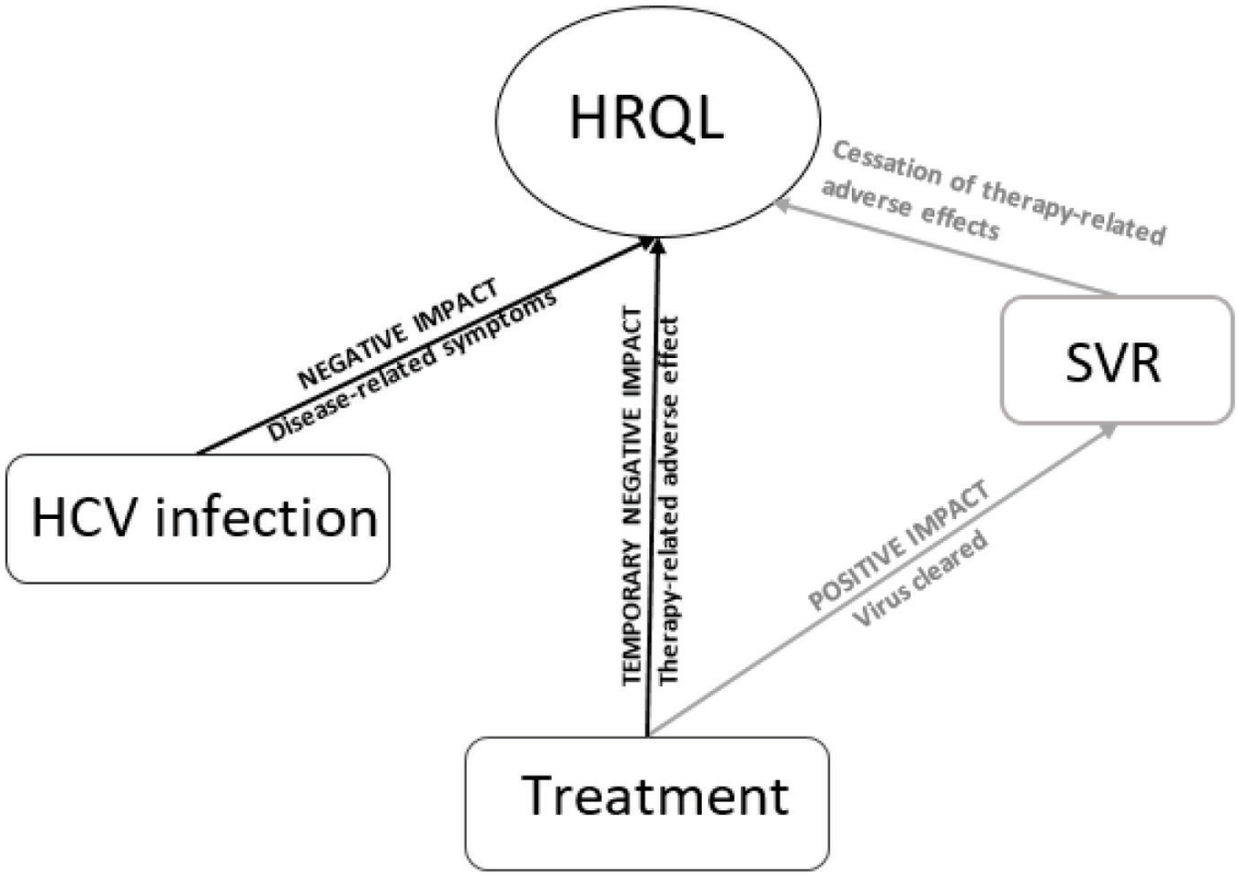


Figure 1. Chronic infection with hepatitis C compromises HRQL due to disease-related symptoms. Antiviral therapy affects HRQL negatively through side effects, but successful treatment of CHC improves HRQL because of cessation of treatment-related adverse effects and also due to disease eradication and virus clearance.

hepatitis C, and it serves as an independent predictor of low HRQL. Neuropsychological symptoms and hepatic encephalopathy can be found among patients with chronic hepatitis C, as well as mild cognitive deficits. Those symptoms may be the result of released inflammatory cytokines and altered neurotransmission [35]. Depression is another common feature of chronic hepatitis C which has been shown to be associated with lower work and social adjustment, lower acceptance of illness, and higher rates of subjective physical symptoms [36]. It is possible that mood-related aspects of HRQL are mediated by HCV colonization of brain microglia.

Poor baseline HRQL is partly psychosocial in origin, relating to the psychiatric comorbidity associated with acquisition of HCV, stigma of illness, and history of illicit drug use [37]. Patients with HCV infection are stigmatized in society which affects their HRQL but may also be a barrier to treatment, resulting in decreased social support [36]. Chronic hepatitis C as a disease with uncertain outcome raises serious concerns about future health status and presents significant emotional and psychological burden. Patients with chronic HCV infection aware of their diagnosis had worse HRQL scores as compared with unaware seropositive patients, suggesting the psychological impact of diagnosis awareness.

HCV patients who experience greater physical and psychiatric symptoms and have poorer HRQL are more likely to discontinue treatment prematurely. These issues highlight the importance of investigating the physical and psychosocial experiences and HRQL of patients chronically infected with HCV [38].

6. HCV treatment impact on HRQL

Patient-reported outcome (PRO) measures are important to evaluate the impact of chronic infection, willingness for treatment and assessment of HRQL during and post treatment. These measures ensure that patient preferences are taken into consideration when deciding between treatment options. While antiviral treatment can eradicate the virus and prevent liver-related death, associated toxicity can have effect on HRQL by decreasing physical, social, and emotional functioning [39].

In recent years, treatment options for HCV infection have moved from the use of interferon with low efficacy and significant toxicity to first-generation direct antiviral agents (DAAs) which were more efficient but still toxic to interferon-free regimens with high efficacy and minimal toxicity [40].

Besides HRQL burden of HCV infection, the previous anti-HCV treatment with interferon and ribavirin had further negative impact on patients' HRQL due to substantial side effects. Well documented side effects of interferon include fever, myalgias, and headache, often described as influenza-like illness. IFN-mediated myelosuppression may lead to decreases in erythrocyte, leukocyte, and platelet counts. Neuropsychiatric side effects include irritability, depression, anxiety, and fatigue. Fatigue is the most commonly reported adverse effect which occurs as a part of neurovegetative symptoms during the first 3 months of treatment [41]. Anorexia, nausea, vomiting, and diarrhea are gastrointestinal adverse effect [36]. Adding RBV to interferon improves SVR, but it substantially impairs physical functioning, which may be the result of hemolytic anemia, occasional rash, and additional fatigue [42]. The use of peg-IFN and RBV is associated with less fatigue and bodily pain than standard IFN and RBV, but it is also characterized by considerable toxicity, neuropsychiatric side-effects, lethargy, and influenza-like symptoms [43]. The side effects of HCV therapy increase the likelihood that patients will discontinue treatment, and because of that, adjunctive therapy must be considered to treat those side effects. Fatigue, depression, and anemia are more difficult to control so addressing those symptoms is of major importance for patients' adherence to therapy [36].

However, successful clearance of the virus after treatment results in certain HRQL improvement in patients who respond well to therapy. Patient-reported outcomes, including HRQL, fatigue, and work productivity improved in patients after achieving sustained virologic response (SVR) with interferon and ribavirin-containing regimens [44]. Therefore, reaching SVR is crucial in achieving long-term HRQL in patients with chronic HCV infection.

The first-generation direct antiviral agents (DAA) shifted the treatment focus to protease inhibitors (PI). A triple combination therapy (PEG-IFN + ribavirin + a protease inhibitor) increased SVR rates but decreased HRQL. Along with the pegylated interferon and RBV side effects, PIs carried plenty of additional side effects. Telaprevir treatment causes nausea, rectal burning, diarrhea, and recently, it has been connected to decrease renal function. Lower glomerular filtration rate led to decreased renal elimination of RBV. Boceprevir has been associated with nausea, headache, and anemia. Furthermore, these regimens had significant drug–drug interactions (DDIs) [41]. However, symptom alleviation after successful treatment can improve HRQL, having economic and social benefits and resulting in removal of social stigma [39].

The next generation of DAAs focused on different targets: HCV viral replication in the cytoplasm. These new drugs, given without concomitant interferon, can result in SVR in over 90% of cases. Additionally, toxicity is reduced in comparison with second generation triple combinations, although response is influenced by genotype, stage of hepatic fibrosis, and drug-resistant mutations [39]. Shortly after initiation of treatment, there is an improvement in PRO scores which correlates with viral suppression. Furthermore, therapy with the new generation of DAAs maximizes PRO rates during treatment as well as after achieving SVR [40]. Most of the data about HRQL come from sofosbuvir (SOF)-based treatment options. Analysis showed that the PRO profile of interferon-free regimens (SOF/RBV) was significantly better compared to peg-IFN/RBV regimens. However, RBV-containing regimens still carry important HRQL impairment, possibly due to hemolytic anemia and mental health side effects of RBV. When both RBV and interferon are removed from the regimen, improvements in HRQL, work productivity, and other PROs were noted 2 weeks after starting treatment (**Figure 1**) [41].

7. The road to success: future directions to improve HCV HRQL

Regardless of the regimen, there are significant improvements in PRO scores after achieving SVR. Still, these improvements are more noticeable in patients who achieve SVR with DAAs. It is shown in multivariate analysis that receiving a regimen that contained IFN and RBV was the strongest negative predictor of HRQL during treatment [45]. On the other hand, IFN- and RBV-free was the only regimen independently associated with improved HRQL during treatment. Moreover, DAAs remained the only independent predictor of HRQL improvement after achieving SVR [46]. However, there are still unanswered questions in terms of DAA safety, and we require data from real-world settings. For example, postauthorization studies would be useful to identify and characterize safety profiles of the new DAAs [47].

8. Conclusions

Chronic HCV infection causes a decline in HRQL measures through a broad spectrum of clinical complaints. The impact on HRQL affects physical, social, and mental health domains. SVR is associated with improvement in HRQL, thereby indicating that treatment of HCV may

improve PRO rates in patients who respond well to therapy. Considering low efficacy and significant toxicity of IFN/RBV regimens, treatment options are shifting to the new DAAs which offer improved SVR rates with less toxicity, leading to improvements in HRQL in patients with chronic hepatitis C.

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