Editorial

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Hepatitis C treatment and quality of life – You can't always get what you want, but you might get what you need

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See Article, pages 337–345

Chronic hepatitis C causes progressive hepatic fibrosis, and, in a proportion of infected patients, leads to cirrhosis and hepatocellular carcinoma. Severe extrahepatic manifestations are well recognised, including mixed type 2 cryoglobulinemia, non-Hodgkins lymphoma, porphyria cutanea tarda, and possibly type 2 diabetes. In addition to the major extrahepatic syndromes associated with chronic hepatitis C, several studies have pointed to a decrement in health-related quality of life (HRQL) in hepatitis C, in comparison to the general population [1–3]. HRQL is defined as a person's subjective assessment of a range of conditions that can affect that person's perception of their state of health [3]. The most common symptoms cited by patients with hepatitis C and that impact upon their quality of life are fatigue, depression, anxiety, cognitive impairment and painful muscle and joint symptoms. The biological mechanisms and pathogenesis of these symptoms remain uncertain. Some symptoms may be due to the release of inflammatory cytokines, or the direct presence of HCV in the central nervous system. Those with greater histological hepatic inflammatory activity may have worse fatigue, but symptoms tend to be present irrespective of the degree of hepatic fibrosis.

New DAA's have resulted in striking SVR rates, even in patients with advanced fibrosis due to hepatitis C [4]. What then are the effects of interferon-free treatments on HRQL? Younossi and co-authors have examined quality of life in patients with chronic hepatitis C in prospective trials of sofosbuvir and ledipasvir, to assess alterations in HRQL before, during and after treatment [5]. Their data provides an important opportunity to assess patient-reported outcomes (PROMs) during treatment and following an SVR, without the confounding effects of interferon that markedly reduced 'on-treatment' quality of life indices in previous studies [6–9].

The authors' provide a detailed and comprehensive analysis of HRQL and work productivity in patients with different stages of hepatic fibrosis treated with sofosbuvir and ledipasvir, or sofosbuvir and ledipasvir plus ribavirin (RBV). Four questionnaires [Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), Short Form-36 (SF-36) (encompassing eight domains), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Work Productivity and Activity Index: Specific Health Problem (WPAI:SHP)] were administered to patients at baseline, during, and after treatment with sofosbuvir and ledipasvir, with or without ribavirin, in the ION-1, 2, and 3 clinical trials. Just over 1000 patients with available liver biopsies were included, and 42.1% of patients in the cohort were treated with a RBV-containing regimen for 8–24 weeks.

What are the major findings of the study? At baseline, patients with more advanced fibrosis had greater HRQL impairments, predominantly related to physical functioning. However HRQL domains related to emotional well-being and mental health were similar regardless of the severity of fibrosis. Treatment-related anemia was observed more frequently in patients with cirrhosis (48.0% in patients with cirrhosis *vs.* 32.4% in those with METAVIR stage F0-3). At week four of active treatment, a decline in some HRQL scales was observed in patients with mild fibrosis. By the end of treatment, a more substantial decline was observed in most HRQL domains. However at the end of treatment, general health measured by SF-36, emotional well-being by FACIT-F, and worry domain by CLDQ-HCV significantly improved in both fibrosis cohorts. By the SVR-12 follow-up visit most HRQL domains notably improved from baseline in both fibrosis cohorts, but work productivity and health utility improved in patients with mild fibrosis only.

The on-treatment improvements rather than decrements in HRQL observed in this study have not been previously reported. Concomitant ribavirin administration in the regimen appeared to be a factor in determining HRQL; in patients receiving sofosbuvir and ledipasvir moderate improvements in HRQL were observed shortly after the start of treatment, but an opposite effect was noted in patients receiving ribavirin. By multivariate analysis, advanced fibrosis was independently associated with the degree of HRQL impairment and loss of work productivity, but improvement of HRQL and work productivity after viral clearance was not related to the stage of fibrosis. Thus, the data suggest that this interferon-free regimen is associated with

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significant 'on-treatment' improvement in most aspects of HRQL for patients with early stage liver disease. Moreover, although advanced hepatic fibrosis is associated with HRQL impairment, viral eradication with sofosbuvir and ledipasvir leads to HRQL improvements irrespective of fibrosis stage.

These improvements in PROMs are an encouraging accompaniment of an SVR. However, some decrements observed during treatment with ribavirin-containing regimens will need to be considered. The on-treatment impacts on HRQL are probably attributable to the side effects of ribavirin, rather than the stage of liver disease. In order to meet expectations, patients should be informed that some decrement of HRQL might be observed during treatment with DAA regimens, particularly those containing ribavirin.

HRQL studies are difficult to conduct rigorously and may have a risk of bias. Frequent weaknesses with HRQL studies include the absence of appropriate placebo control groups, and consequent problems with accounting for the effects of frequent clinical visits, timing of clinical assessments, and other trial-related confounders. In many hepatitis C HRQL studies, there is frequently insufficient information on the mode of acquisition of hepatitis C, the severity of liver disease, concomitant intravenous drug and alcohol use, or prior treatment status. Nevertheless the current study provides convincing and clinically significant evidence of a decrement in HRQL affecting both mental health and physical health domains that can be improved by successful antiviral treatment.

The study emphasizes some inherent difficulties. The cohort includes a control group with ribavirin but did not contain a control group treated with interferon, thus making it difficult to gauge the size of the HRQL effect in the ribavirin recipients in this study compared to interferon. The authors do make a comparison to interferon-based HRQL data, but in a different population. Ideally for HRQL studies the comparison and control groups should be unaware of their diagnosis so that their perceptions of health can be compared – clearly such a comparison is impossible in therapeutic clinical trials for hepatitis C. However, patients can be blinded to their own on-treatment results, to avoid an influence on PROMs. No patients with decompensated disease were included. Additionally, as noted above, there is no mention of factors that may impact perception of HRQL, such as the frequency of visits, and timing of clinical assessments. The changes in HRQL scores are also small in magnitude despite statistical significance, and the ability of these instruments to capture symptoms specific to hepatitis C in the population being studied requires ongoing evaluation. A further question regarding the inferences drawn from the data relates to improvements in symptoms and PROMs following SVR in patients with advanced fibrosis. These improvements occurred during a period when fibrosis stage would have changed only marginally, suggesting that the benefit is derived from a reduction in viremia. However, these changes were noted relatively early during treatment and could reflect an accompanying reduction in ALT and inflammatory change in the liver and perhaps other sites.

Current treatment of hepatitis C is largely aimed at preventing progression of liver disease; these data suggest that successful treatment will also alleviate symptoms. Successful treatment will improve quality of life, in addition to reducing the stigma of hepatitis C and preventing the transmission and thus decreasing the burden of chronic hepatitis C. Because of the costs of current therapies, treatment is largely being directed to patients with advanced fibrosis to slow progression of their liver disease, to improve liver function and prevent decompensation.

The results should be seen in context. The symptoms of chronic hepatitis C add another dimension to the disease, since the impaired physical and mental health, and social impact, of chronic hepatitis C is considerable [10,11]. However, as a subjective perception, symptoms of hepatitis C are often regarded as less important, and not given the same weight as discernible advanced fibrosis or end-stage liver disease. Nonetheless as ongoing viral replication has an effect on these symptoms, the effect of treatment and a SVR are important to ascertain. Moreover, health economic outcomes are fundamentally influenced by HRQL data, which are now considered critical secondary endpoints of clinical trials of medical and surgical interventions for chronic diseases.

As shown in this study, symptoms are in fact associated with the presence of the virus, and a treatment effect and effect of cure on HRQL is evident. Will curing hepatitis C, and the symptomatic improvements observed in these trials, translate into improved work productivity and economic gain with these high cost regimens? Presently payers seek improvements in "hard" measurable outcomes such as hospitalisation for hepatic decompensation, transplantation rates, a reduction in hepatocellular carcinoma, and deaths attributable to hepatitis C. Whether these discernible improvements, in quality of life and productivity, will persuade payers to fund treatment for those with minimal fibrosis remains to be seen. The situation is akin to the words of a famous rock band of the 1960s, '*You can't always get what you want, but if you try sometimes, you just might get what you need...*'.

Conflict of interest

Gautam Mehta: None. G Dusheiko has acted as an advisor to Gilead Sciences, AbbVie, Janssen, Bristol Myers Squibb, and Merck.

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Editorial

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