Hepatitis C Virus Infection Is Systemic: Meeting Additional Goals

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(See the major article by Younossi et al on pages 367–77.)

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Chronic hepatitis C virus (HCV) infection is a major public health concern in the United States. HCV infection is the leading cause of cirrhosis and is the most common indication for liver transplantation [1]. There is growing appreciation that HCV infection is a systemic infection and does not only cause liver disease. For instance, health-related quality of life (HRQL) may be notably diminished, even in the absence of overt complications of liver dysfunction. Patient-reported outcomes (PROs) represent a systematic attempt to quantify the subjective experience of illness. Self-perceptions of health predict mortality and morbidity, as well as enhance the patient-provider relationship [2,3].

Research involving patients coinfected with HCV and human immunodeficiency virus (HIV) represents a major unmet healthcare need in the United States. Approximately 30% of patients with HIV infection are coinfected with HCV, and their sustained virologic response (SVR) rates of HCV have until recently trailed behind HCV-monoinfected patients [4–6].

Hepatitis C causes progressive liver disease at a faster rate in HIV/HCV-coinfected patients, compared with HCV-monoinfected patients [7]. Equally important, there have been few major studies assessing the impact of HCV on PROs in HIV infected patients.

In this issue of The Journal of Infectious Diseases, Younossi et al elegantly address the relationship between HCV and HIV infection and PROs [8]. Subjects used in the analysis were obtained from studies using interferon-free regimens consisting of sofosbuvir and weight-based ribavirin. The HIV/HCV-coinfected patients were drawn from 2 large studies, PHOTON-1 and PHOTON-2 [9,10]. In these studies, HIV-infected patients were either untreated and had a CD4+ T-cell count of >500 cells/µL or received antiretroviral therapy and had a CD4+ T-cell count of >200 cells/µL and an HCV RNA load of <50 copies/mL [9,10]. All patients were naive to treatment for HCV infection. In contrast, the studies of HCV-monoinfected patients (FUSION and VALENCE) included treatment-experienced patients, and the distribution of HCV genotypes among them was restricted to genotypes 2 and 3 [11,12].

HIV/HCV-coinfected individuals were matched with HCV-monoinfected controls according to HCV treatment history, age, sex, body mass index, presence of cirrhosis, baseline HCV load, anxiety, depression, insomnia, clinically overt fatigue, and the presence of type 2 diabetes.

Four PRO questionnaires were administered before, during, and after treatment: the Short-Form 36 (SF-36) questionnaire, the Functional Assessment of Chronic Illness Therapy-Fatigue questionnaire, the Chronic Liver Disease Questionnaire–Hepatitis C Virus questionnaire, and the Work Productivity and Activity–Specific Health Problem questionnaire.

The results of this study are important. Baseline PROs were lower in coinfected patients, compared with monoinfected patients, and this trend continued throughout treatment. The authors found that most PROs improved for coinfected patients who achieved a SVR. In contrast, no improvement was seen in coinfected patients who did not achieve an SVR. The results of their multivariate analysis indicate that HIV/HCV coinfection was an independent predictor of PRO scores at baseline (P < .02) but not during or after treatment (P > .05 for both). The presence of cirrhosis was associated with lower PRO scores at baseline. However, all changes that emerged during treatment and in patients with a SVR for 12 weeks after treatment cessation were similar in HIV/HCV-coinfected patients with cirrhosis, compared with patients without cirrhosis (P > .05), with the exception of the General Health domain of SF-36 (P = .0002).

Equally important, PROs can help predict the likelihood of achieving a SVR. Patients who were cured had less fatigue, fewer...
physical or somatic complaints, improved psychosocial affect, and lower work-productivity impairments than those who were not cured. HIV/HCV-coinfected patients had lower absolute baseline and peri-treatment values for these domains, even after achieving SVR. However, their treatment-emergent changes were similar to those for HCV-monoinfected patients, suggesting that they also can respond to sofosbuvir-based regimens.

There are important limitations that highlight the need for further study and restrict the generalizability of these results to all HIV/HCV-coinfected patients. The most salient limitations are the patient demographic characteristics. Most patients in the study population were male, white, naive to HCV treatment, and non-cirrhotic. Do these findings suggest a selection bias unique to this study? In addition, patients were followed for a comparatively short period—only 12 weeks after treatment cessation—and further study is needed to confirm the long-term durability of improved PROs after SVR. In contrast to the results obtained by Younossi et al, Fleming et al found similar baseline HRQL for coinfected patients, compared with HCV or HIV monoinfection [13]. Of note, their analysis also used the SF-36 instrument. These differences cannot be easily explained but may be related to patient selection criteria and study design. The differences emphasize the need to further investigate PROs in the HIV/HCV-coinfected population.

Younossi et al should be commended for not relying on a single instrument to measure PROs. They used an appropriate mix of both generic health instruments and disease-specific instruments, along with a metric for work productivity. However, in a recent systematic review of PROs used for patients with chronic hepatitis C, only one of the reviewed metrics—the HQLQ—showed evidence of content validity in the population with chronic hepatitis C [14]. Further, PRO instruments will need to be developed and validated for patients with chronic viremia.

Many questions remain unanswered. Will the PRO-associated benefits of achieving a SVR be extended to all of the newer direct-acting antiviral agents, including the recently approved combinations of sofosbuvir-ledipasvir and of ombitasvir-paritaprevir-ritonavir plus dasabuvir? Given the excellent safety and tolerability profiles of each regimen, there is no reason to believe they would not be equally effective.

Controversy exists over indications for HCV-associated antiviral therapy. One of the most salient findings of the current study by Younossi et al is the improvement in PRO. Currently, the highest priority for HCV-associated antiviral therapy is for liver transplant recipients, patients with advanced liver disease, and patients with severe extra-hepatic manifestations [15]. High priority can be extended to patients with disabling fatigue. Can the results of this study be used to justify extending therapy to additional patients? Clearly, curing HCV infection improves PROs and HRQL with current therapies that are safe, effective, and tolerable. Physiologic correlates are now being described for HCV infection and HRQL [16].

An evidence-based, pragmatic approach to treatment with the new direct-acting antiviral agents is a difficult and evolving endeavor, given the considerable costs of these regimens. It is clear that PROs can assist in this manner. The development of effective therapies for hepatitis C represents a medical triumph, but fully understanding how these therapies affect the daily physical, social, and emotional functioning of patients with HCV infection is still a battle to be won.

Note

Potential conflict of interest. S. S. is a consultant for the company Gilead that manufactures the medication used in the study. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


