Hepatitis C is a Systemic Infection: Meeting Additional Goals

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Chronic hepatitis C viral (HCV) infection is a major public health concern in the United States. Hepatitis C infection is the leading cause of cirrhosis, and 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 (HrQOL) may be notably diminished even in the absence of overt complications of liver dysfunction. Patient Reported Outcomes (PRO’s) 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 HCV/HIV co-infected patients represents a major unmet health care need in the United States. Approximately 30% of patients with HIV are co-infected with HCV, and their sustained HCV rates have until recently trailed behind HCV mono-infected patients [4 - 6]. Hepatitis C causes progressive liver disease at a faster rate in co-infected than HCV mono-infected patients [7]. Equally important, there have been few major studies assessing the impact of HCV on PRO’s 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 PRO’s [8]. Subjects used in the analysis were obtained from studies using interferon free regimens consisting of sofosbuvir and weight-based ribavarin. The HIV/HCV co-infected patients were drawn from two large studies named PHOTON-1 and PHOTON-2 [9,10]. In these studies, HIV-infected patients were either untreated with CD4 T-cell count > 500 cells/µL, or treated with ART with CD4 T-cell count >200 cells/µL and HCV RNA < 50 copies/mL [9,10]. All patients were HCV treatment naïve. In contrast, the mono-infected HCV
studies (FUSION, VALENCE) included treatment experienced patients and their genotype distribution was restricted to genotype 2 and 3 [11,12].

HIV/HCV co-infected individuals were matched with HCV mono-infected controls according to HCV treatment history, age, gender, body mass index, presence of cirrhosis, baseline HCV viral load, anxiety, depression, insomnia, clinically overt fatigue, and the presence of type 2 diabetes. Four PRO questionnaires were utilized at pre, during and post treatment intervals - SF-36, CLDQ-HCV, WPAI: SHP, FACIT-F.

The results of this study are important. Baseline PRO’s were lower in co-infected than mono-infected patients, and this trend continued throughout treatment. The authors found that most PRO’s improved for co-infected patients who achieved a SVR. In contrast, no improvement was seen in co-infected patients who did not achieve an SVR. The results of their multivariate analysis indicate that HIV/HCV co-infection was an independent predictor of PRO scores only at baseline (p<0.02), but not during or post treatment (all p>0.05). The presence of cirrhosis was associated with lower PRO scores at baseline. However, all treatment-emergent and post-SVR12 changes were similar in HIV/HCV co-infected patients with cirrhosis compared to patients without cirrhosis (p>0.05), with the exception of the General Health domain of SF-36 (p=0.0002).

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

There are important limitations that highlight the need for further study and restrict the generalizability of these results to all co-infected patients. The most salient limitations are the patient demographics. Most of the study population were male, Caucasian, HCV treatment naïve, 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 post treatment – and further study is needed to confirm the long term durability of improved PRO after SVR. In contrast to the results obtained by Younossi et al., Fleming et al. found similar baseline HrQOL for co-infected versus either HCV or HIV mono-infected patients [13]. Of note, their analysis also employed the SF-36 instrument. These differences cannot be easily explained, but may relate to patient selection criteria and study design. The differences emphasize the need to further investigate PRO’s in the HIV/HCV co-infected population.

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

Many questions remain unanswered. Will the benefits of achieving an SVR on PRO’s be extended to all the newer direct acting anti-viral agents (DAA), including the recently approved combinations of sofosbuvir and ledipasvir and ombitasvir, paritaprevir,
ritonavir with dasabuvir? Given the excellent safety and tolerability profiles of both of these drug regimens, there is no reason to believe they would not be equally effective.

Controversy exists over indications for HCV antiviral therapy. One of the most salient findings of the current study by Younossi et al. is the improvement in PRO. Currently, HCV antiviral therapy’s highest prioritization is for liver transplant recipients, patients with advanced liver disease, and those 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 improves PRO’s and HrQOL with current therapies that are safe, effective, and tolerable. Physiologic correlates are now being described for HCV and HrQOL [16].

An evidence based, but also pragmatic, approach to treatment with the new DAA’s is a difficult and evolving endeavor, given the considerable costs of these regimens. It is clear that PRO’s 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 our patients is still a battle to be won.
References:


