Extrahepatic Manifestations of Hepatitis C Virus After Liver Transplantation

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KEYWORDS

• Diabetes mellitus • Lymphoproliferative disorders • Health-related quality of life
• Chronic kidney disease • Liver transplantation

KEY POINTS

- Extrahepatic manifestations of chronic hepatitis C virus (HCV) infection in the posttransplant setting are equally important than those seen in the absence of liver transplantation.
- Increased risks of metabolic abnormalities, especially diabetes mellitus, are compounded in the posttransplant setting.
- Although chronic HCV infection increases risk of lymphoproliferative disorders, these risks can be exacerbated by the increased risk of posttransplant Epstein–Barr virus–associated lymphoproliferative disorders.
- Understanding and addressing health-related quality of life impairments associated with chronic HCV is particularly important in the posttransplant setting.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection remains a leading cause of chronic liver disease and is one of the leading causes of cirrhosis and hepatocellular carcinoma

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requiring liver transplantation.[1–3] Although the emergence of highly effective antiviral therapies for the treatment of chronic HCV has revolutionized the treatment approach, leading to successful cure rates of greater than 90% to 95% associated with current available treatment regimens, there remains a large cohort of patients with HCV cirrhosis that will still progress to need for liver transplantation.[1,4] In addition, although highly effective therapies are available, barriers in access to these therapies will continue to contribute to HCV disease progression to cirrhosis and hepatocellular carcinoma.[5,6]

Several studies have reported on the beneficial effects of HCV cure, not only in terms of the benefits and improvements in hepatic disease, but improvements in extrahepatic and systemic manifestations of chronic HCV are also well-studied.[6,7] In particular, several recent studies have demonstrated significant improvements in patient-reported outcomes achieved with successful HCV treatment.[7–10] Despite these successes, disease progression to need for liver transplantation is not averted in all patients, and few studies have specifically evaluated extrahepatic manifestations of chronic HCV after liver transplantation. There is much debate on the optimal timing of HCV treatment among those awaiting liver transplantation. However, treatment of chronic HCV after liver transplantation is no longer a significant hurdle and the vast armamentarium of treatment options with short duration and high efficacy have made it much easier to achieve HCV cure in this population.[11–13]

The extrahepatic manifestations of chronic HCV in the posttransplant setting are similar to the manifestations exhibited in the pretransplant setting.[7,14–18] However, the overall milieu of the posttransplant state may interact with HCV such that certain extrahepatic manifestations become more relevant clinically and may impact the patient to a greater extent. As such, the current review focuses on the extrahepatic manifestations of chronic HCV that may be exacerbated in the posttransplant milieu (**Table 1**).

METABOLIC ABNORMALITIES

Significant metabolic abnormalities associated with chronic HCV infection are well-reported, with insulin resistance in the form of impaired glucose tolerance or diabetes mellitus having the greatest impact.[14,15,19–21] A recent metaanalysis evaluating the prevalence and burden of extrahepatic manifestations of chronic HCV included 31 studies evaluating the association of diabetes mellitus and chronic HCV.[15] Among these studies, which included 61,843 chronic HCV patients, the pooled prevalence of diabetes mellitus was 15% (95% confidence interval, 13–18) among chronic HCV patients compared with 10% (95% confidence interval, 6–15) among non-HCV controls. Furthermore, the authors calculated a pooled odds ratio of 1.58 (95% confidence interval, 1.30–1.86) for the association of DM in chronic HCV patients.[6] Despite being the second most common extrahepatic manifestation of chronic HCV, concurrent diabetes mellitus carries a much greater clinical burden given that it also increases risk of cardiovascular disease and chronic renal disease.[16,17,22,23] The prevalence of concurrent diabetes mellitus may also contribute to a higher risk of concurrent nonalcoholic fatty liver disease, which in the setting of chronic HCV contributes to more aggressive disease progression to cirrhosis and hepatocellular carcinoma. For example, 2 recent systematic reviews evaluated the impact of concurrent diabetes on the risk of disease progression and risk of hepatocellular carcinoma among chronic HCV patients.[24,25] Among a total of 20 observation studies included in the final analyses, the authors observed that concurrent obesity (odds ratio, 1.08–7.69), the presence of significant steatosis (odds ratio, 1.80–14.3), and concurrent diabetes mellitus (odds ratio,