

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

## Gender Differences Among Hepatitis C Virus Patients Following Liver Transplantation

Jennifer Lai, MD  
University of California, San Francisco

**A discussion of:** *Lai JC, Verna EC, Brown RS, Forman LM, Duman J, Foster RG, Stravitz T, Terrault NA. Hepatitis C virus (HCV) infected females are at higher risk of graft loss after liver transplantation: a multicenter cohort. Presented at the 60th Annual Meeting of the American Association for the Study of Liver Diseases; October 30–November 3, 2009; Boston, MA.*

### **G&H** Are there gender-based differences among patients with hepatitis C virus outside the context of liver transplantation?

**JL** A substantial body of literature has long supported the fact that there are significant gender differences in the outcomes of patients infected with hepatitis C virus (HCV). In particular, natural history studies of HCV have shown that women experience higher rates of spontaneous clearance of HCV and lower rates of progression to advanced liver disease. Likely as a result of these and other favorable factors, women experience lower rates of hepatocellular carcinoma development and overall lower death rates from HCV-related liver disease.

### **G&H** Are there studies showing a difference in the transplant population?

**JL** Gender differences among patients who have undergone liver transplantation for HCV-related liver disease are not well established. In fact, there are very few studies directly addressing this issue in the post-transplant setting. Until now, prior studies evaluating the outcomes of HCV-infected liver transplant recipients have shown no

significant gender-based effect. However, these studies have either been small single-center cohort studies that were likely underpowered to detect a gender difference or, conversely, have been national cohort studies that have included patients who were not at risk for recurrent HCV disease.

### **G&H** Why is it important for a study to exclude data of patients not at risk for recurrent disease?

**JL** This issue is critically important for any study evaluating HCV-related outcomes, as patients who clear their virus prior to transplantation are not at risk for reinfection of the new graft. A proportion of patients listed for liver transplant for HCV-related liver disease undergo successful antiviral treatment and thus eradicate their virus prior to transplantation. In addition, misclassification of the etiology of liver disease can occur and is an issue of particular concern with large, national cohort studies. Given that women experience higher spontaneous clearance rates and more favorable response rates to antiviral treatment, inclusion of these patients in studies of HCV-related outcomes may falsely decrease the rates of recurrent HCV disease to a greater extent in women relative to men.

### **G&H** How did your study differ in this regard?

**JL** Our study was a multicenter cohort that included individual patient-level data, enabling us to exclude those who were HCV-uninfected after liver transplantation—in other words, those who had cleared HCV infection prior to undergoing transplantation.

### G&H Which centers were included in your study?

**JL** Our study included data from a consortium of 4 very well-established liver transplant centers: the University of California, San Francisco, New York-Presbyterian Hospital of Columbia University, the University of Colorado, Denver, and Virginia Commonwealth University. All of these centers have extensive experience with liver transplantation and with managing HCV-related complications and treatment in the post-transplant setting.

### G&H What are other key aspects of the methodology of your study?

**JL** One of the key aspects of our study is that our primary endpoints included the development of advanced HCV disease recurrence. Most studies evaluating outcomes in HCV-infected liver transplant recipients focus on patient and graft survival alone. Because this was one of our primary endpoints, we excluded patients who died within the peritransplant setting, which we defined as within 30 days of transplantation. In addition, we also included only adult patients undergoing primary transplantation because survival rates after retransplantation differ from those after a primary transplant.

### G&H Your study included 195 female and 655 male patients. Does this ratio represent the population at large?

**JL** Yes. Approximately one quarter of the patients included in our study were women, a proportion that is quite similar to the national transplant population as a whole.

### G&H Could you describe the findings of your study?

**JL** We looked at 4 primary endpoints: death, graft loss, development of advanced recurrent disease (defined as bridging fibrosis or cirrhosis on biopsy), and development of cholestatic hepatitis, an aggressive variant of recurrent HCV disease.

At a median follow-up of approximately 3 years, the overall rate of death was 22%, the rate of graft loss was 25%, the rate of advanced recurrent disease was 26%, and the rate of graft loss with advanced recurrent disease was 10%. The rates of mortality and graft loss are comparable to other studies evaluating outcomes of HCV-infected liver transplant recipients. However, the rate of advanced recurrent disease in our cohort was higher than that reported in prior studies, likely owing to the fact that

“advanced recurrent disease” was a combined endpoint that included both bridging fibrosis/cirrhosis and fibrosing cholestatic hepatitis.

In terms of our specific hypothesis regarding gender differences, in all 4 outcomes, an unadjusted analysis showed a distinct trend toward poorer outcomes among women than men for all 4 primary endpoints. At 3 years, the rate of patient survival was 76% for women and 81% for men ( $P=.06$ , unadjusted log rank), and the rate of graft survival was 73% for women and 78% for men ( $P=.1$ , unadjusted log rank). With respect to HCV-specific outcomes, the rate of advanced recurrent disease at 3 years was 35% for women and 29% for men ( $P=.14$ , unadjusted log rank), and the rate of graft loss from advanced recurrent disease was 14% for women and 9% for men ( $P=.04$ , unadjusted log rank).

### G&H Did you conduct adjusted analyses?

**JL** Yes. In these types of studies, it is essential to adjust for factors that we know influence disease progression among HCV-infected liver transplant recipients in order to determine the independent effect of gender on the outcomes of interest. The factors we adjusted for included recipient age, recipient race, donor age, donor race, cold ischemia time, post-transplant antiviral therapy, episodes of acute rejection, and cytomegalovirus infection.

In multivariate models adjusting for all of these potential confounders, female gender emerged as an independent predictor of each of the primary endpoints. Specifically, in our multivariate models, female gender was associated with a 46% increased risk of mortality, a 39% increased risk of graft loss, a 44% increased risk of advanced recurrent HCV disease, and an 84% increased risk of graft loss with advanced recurrent disease (compared to men). Although these results need to be confirmed in other large studies, these effects represent clinically relevant differences that warrant further investigation.

### G&H Did you have any indication beforehand that your study might reveal this stark difference?

**JL** Based upon the nontransplant HCV literature, we might have expected the reverse to be true—that HCV-infected women experienced more favorable post-transplant outcomes compared to HCV-infected men. However, our clinical experience in caring for women with HCV in the post-transplant setting suggested that women develop more rapid and advanced recurrent HCV disease than men, which is why our group embarked upon this study.

**G&H** Do you have any hypotheses to explain the findings of this study?

**JL** Our study was designed only to answer the question of whether there is a gender difference, and did not elucidate its etiology. However, we do have 3 major hypotheses about why this difference exists.

The first hypothesis is that there may be a differential effect of aging on women versus men in terms of HCV recurrence. An exploratory analysis of our data suggested that younger women (age <50 years) experienced increased rates of graft loss compared to older women. In addition, the gender difference found in our study was attenuated in a subgroup analysis restricted to patients over 50 years of age. It is thus possible that aging impacts disease-specific outcomes differently in men than in women, with younger women developing a more robust immune response to graft reinfection with HCV, leading to more rapid development of advanced disease and graft loss.

Our second hypothesis is that recipient-donor gender mismatch may contribute to graft outcomes, as we know that women have higher rates of gender mismatch compared to men. Although the findings are controversial, several prior studies have shown that gender mismatch is an important risk factor for poor outcomes among transplant recipients, but the precise mechanism underlying the effect of recipient-donor mismatch on graft survival is unknown.

Our third major hypothesis stems from the fact that decreased renal function at the time of transplant was more frequent among women versus men. This decreased

renal function at the time of transplant could lead to suboptimal immunosuppression post-transplantation, which would, in turn, result in increased rates of acute rejection, a well-recognized risk factor for advanced recurrent HCV disease and graft loss. In fact, women in our cohort experienced significantly higher rates of acute rejection than men, supporting this hypothesis.

**G&H** Could the findings of your study impact treatment decisions?

**JL** The identification of this gender difference raises the possibility of the need for gender-specific models in the post-transplant care of HCV-infected liver transplant recipients. For example, perhaps women should be monitored more closely for the development of advanced recurrent HCV disease or treated at an earlier stage than the current standard of care. Given the gender differences in renal function at the time of transplant, women may benefit from alternative immunosuppression regimens that are less nephrotoxic. In addition, we may need to develop gender-specific protocols for the treatment of acute rejection with more careful avoidance of steroid boluses in women experiencing acute rejection.

**Suggested Reading**

Belli LS, Burroughs AK, Burra P, Alberti AB, Samonakis D, et al. Liver transplantation for HCV cirrhosis: improved survival in recent years and increased severity of recurrent disease in female recipients: results of a long term retrospective study. *Liver Transpl.* 2007;13:733-740.

Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology.* 2002;122:889-896.