

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Racial Differences in Hepatitis C Virus Progression Following Orthotopic Liver Transplantation

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G&H Are there racial differences seen with hepatitis C virus outside of the context of liver transplantation?

JL Yes, there are many such differences. For example, blacks have a higher prevalence of the disease. A study published in 1999 in the *New England Journal of Medicine* by Alter and colleagues found that among the 1.8% (3.9 million) of people in the United States who tested positive for the hepatitis C virus (HCV) antibody, the rate of occurrence was 2-fold higher in blacks versus whites (3.4% vs 1.5%).

With regard to treatment for HCV, several studies have found that black patients respond less favorably to interferon-based therapy compared with white patients. By contrast, a slower progression of disease is seen among black patients compared with white patients. Studies have found lower levels of transaminases, which are markers of liver inflammation, and a slower course of fibrosis progression among black patients. This outcome is opposite to what is seen following liver transplantation.

G&H What are the differences seen after liver transplantation?

JL Several studies have shown that overall survival and graft survival is worse among black HCV patients compared with other racial groups. This outcome was observed in the years before we used the Mayo End-Stage Liver Disease (MELD) scoring system, and it has also been seen in the MELD era.

G&H Are there any explanations for these differences?

JL No clear explanations have emerged yet. These differences in the natural history of the disease, treatment response rates, and survival rates after liver transplantation have been elucidated in just the last 5–10 years; thus, extensive studies to understand the reasons for the differences are still under way.

Recent studies have suggested that there may be immunologic or genetic differences that could, at least partially, account for some of the differences. In the Vira-Hep cohort, Rosen and colleagues found differences in the HCV-specific immunity between blacks and whites that correlated with treatment response.

Investigators at Duke University recently reported in *Nature* a genetic polymorphism associated with better treatment response. The group found that this mutation, a variation in IL28B, is less prevalent among African-American patients compared with those of European ancestry.

These findings are very recent, and work is ongoing to better understand the association between these differences and differences in outcome.

G&H Could you describe the study you conducted to understand these post-transplantation differences, which was presented at the 2009 annual meeting of the AASLD?

JL Having seen the slower progression among black HCV patients in the absence of liver transplantation, yet worse survival after liver transplantation, we wanted to understand why black patients tend to fare worse after transplantation.

We conducted a retrospective, multicenter study to compare the progression of HCV histologic disease following orthotopic liver transplantation between racial groups. Pooling data from 5 sites enabled us to look at more patients, and the reason we chose to first conduct a retrospective analysis was to provide a foundation for a future prospective study.

G&H What data were collected for this study?

JL Data were collected on donor and recipient demographics, transplant type, pretransplantation diagnosis, use of antilymphocytic products, retransplantation, post-transplantation treatment for HCV or rejection, and survival.

G&H What was the primary measure for determining outcome?

JL Allograft biopsy fibrosis stage and inflammation grade were compared at 6 months, 1 year, and 2 years after liver transplantation.

G&H The data pooled for your study came from 551 white patients, 141 black patients, and 81 Hispanic patients who had undergone liver transplantation between 1999 and 2008. The proportions are different from those of the population at large. Are the findings still broadly applicable?

JL It is important to note that although there were many more white patients in our study population than there are, proportionately, in the HCV population at large, the demographics of this study were better than the nationwide distribution. With regard to demographics, we wanted to achieve a greater racial diversity than what is seen nationwide. Among HCV patients who undergo transplantation, approximately 10% are black. Although the prevalence of HCV is higher among this racial group, black patients tend to be underrepresented when it comes to liver transplantation.

G&H Among the 530 patients who had had at least 1 informative liver biopsy during the first 2 years after liver transplantation, did black patients have significantly higher mean fibrosis scores compared with Hispanic and non-Hispanic white patients at the 3 predetermined time points (6 months, 1 year, and 2 years)?

JL Yes. This difference was the primary finding of our study.

G&H What is the significance of the higher fibrosis score being seen among black HCV patients following liver transplantation?

JL A higher fibrosis score indicates more scarring and damage to the liver. When an individual undergoes liver transplantation for HCV-associated cirrhosis, the HCV universally recurs—the virus is always present in the blood following transplantation. For some patients, HCV can be present without causing damage to the new liver for a long time. Other patients experience rapid disease progression, indicated by a high fibrosis score.

G&H Inflammation grade scores were also higher among black patients compared with white patients. Was this difference significant?

JL This score was significantly different at 6 months, but not at 1 or 2 years.

G&H Were there other statistically significant differences?

JL Among a subset of patients for whom more detailed biopsy information was available, the time to fibrosis stage 3 or 4 was significantly shorter among black patients compared with white patients.

G&H Did the outcomes of Hispanic and white liver transplant recipients also differ?

JL Hispanic and white liver transplant recipients had similar grade and stage scores at each measured time point.

G&H Were there other differences among the racial groups?

JL There was no difference in age, type of transplant, or pretransplant comorbidities of alcohol or hepatoma seen among these groups. Black recipients had a higher rate of re-transplantation, were more often female, and had more often received an antilymphocyte agent. In the subset of patients for whom donor information was known, black patients had more often received a donor race-mismatched liver compared to white patients.

G&H In your analysis, did you try to eliminate age or other factors as a possible explanation for the difference seen in fibrosis score?

JL This study was retrospective, so we could not completely control for all factors other than race. It is well known that donor age is associated with worse outcomes.

Steroid treatment for transplant rejection also affects the rate of fibrosis progression. Our analysis did control for these factors, as well as numerous other variables.

G&H Did all black patients included in your analysis fare worse?

JL This is an important point. Not all black patients fared worse, just as not all non-Hispanic white patients did better. Variations do exist within each group. What is important now is to try to understand why we are seeing these differences overall.

G&H What is the next step in understanding, and possibly improving, these outcomes?

JL The next step is a prospective study with standardized liver biopsies, so that we can more clearly examine the extent of the differences in progression. This study would also look at all factors that could be impacting outcomes following transplantation, so that it could be determined what exactly is different about black patients who do as well as white and Hispanic patients compared to those black patients who do not do as well. It may be possible to define early predictors of outcome and, ultimately, to try to develop treatments or interventions to slow progression of fibrosis.

G&H Are there other treatment options for patients who tend to progress rapidly following liver transplantation?

JL As mentioned earlier, black patients with HCV do not respond as well to interferon therapy, but this treatment may be a better option for patients who are

likely to experience rapid disease progression following liver transplant. Also, knowing the likelihood of rapid progression could influence treatment decisions following transplant. For example, treating for rejection with steroids is associated with more rapid fibrosis progression, so it would be important to keep this in mind before administering a high dose of steroids to a patient already likely to experience rapid progression following transplantation.

G&H Would a prospective study collect data on potential genetic markers?

JL Yes, it would be important to look at genetic polymorphisms, but also sociologic factors, compliance, and other potential factors in progression. Most likely, the cause of rapid progression is multifactorial, so a prospective study should be designed to look at numerous factors.

We are currently in the process of developing a prospective study to further examine this important issue.

Suggested Reading

Layden JE, Brown K, Lucey MR, et al. Hepatitis C virus (HCV) progresses more rapidly after orthotopic liver transplantation (OLT) in African Americans (AA) compared to whites (W). Presented at the 60th Meeting of the American Association for the Study of Liver Diseases. Boston, MA. October 30–November 3, 2009.

Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med.* 1999;341:556-562.

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Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature.* 2009;461:399-401.