HIV and Hepatitis C Virus: Special Concerns for Patients With Cirrhosis

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Since the advent of highly active antiretroviral therapy, liver disease has been a major cause of morbidity and mortality in patients with human immunodeficiency virus (HIV) infection. Chronic viral hepatitis accounts for >80% of liver-related mortality. Liver-related morbidity is due to acceleration of hepatitis C virus (HCV) disease, drug-induced hepatotoxicity, and, possibly, direct damage from HIV infection itself. As a consequence of this complex interaction, end-stage liver disease and hepatocellular carcinoma are frequent complications in patients with HIV infection. Infectious diseases physicians who care for HIV-infected patients with advanced HCV-related liver disease need to know how to assess for advanced fibrosis, to know when to refer a patient for endoscopic screening for varices, and to enroll patients in a screening program for hepatocellular carcinoma.

Keywords. co-infection; HIV–HCV; cirrhosis

DISEASE PROGRESSION

Early cohort studies assessing the progression of liver disease demonstrated a more rapid progression of liver disease in co-infected patients [2]. Benhamou et al were the first to study HIV/HCV-coinfected patients with respect to fibrosis progression rates. In their study of 122 patients with HIV/HCV coinfection and a control group of 122 HCV-monoinfected patients, the fibrosis progression rate was determined by the liver biopsy–determined stage of fibrosis and, on the basis of first exposure to blood products or injection drug use, by the estimated duration of infection. The prevalence estimates of advanced fibrosis (fibrosis stages 2–4) and moderate-to-severe necroinflammation were greater in the co-infected population. Fibrosis progression rate was significantly increased in the co-infected patients, compared with the HCV-monoinfected patients. HIV status, alcohol consumption >50 g/day, age at HCV infection, and CD4⁺ T-cell count were independent risk factors for progressive disease [3]. A more rapid progression of liver fibrosis has also been confirmed in studies involving paired biopsy specimens. Although the follow-up period in the 2 studies was short, at 2.9–3.3 years, these studies showed a progression in liver fibrosis of >2 histological stages in 16%–24% of patients [4, 5].

A meta-analysis of several cohort studies that examined the adjusted relative risk (RR) of decompensated liver disease or histological cirrhosis in patients with HIV/HCV coinfection, compared with patients with HCV infection alone, showed a RR of 2.07 for the development of histological cirrhosis and a RR of...
6.14 for development of decompensated cirrhosis [2]. Additionally, a recent large prospective study of >600 patients who had undergone liver biopsy as part of their liver disease assessment demonstrated that liver-related mortality is highly dependent on the stage of liver disease, with an increased risk of outcomes associated with a more advanced stage of liver fibrosis at initial assessment. Multivariate analysis showed that the presence of stage 2–4 fibrosis, as determined by the METAVIR scoring system, and anti-HCV therapy were independently associated with a composite end point of ESLD, hepatocellular carcinoma (HCC), and all-cause mortality. Treatment of HIV infection was associated with fewer clinical events, whereas treatment of HCV infection was only associated with fewer clinical events if the patient had achieved a sustained virological response (SVR) or if the patient relapsed following HCV treatment. Nonresponders did not achieve any protection from clinical events [6, 7]. Decompensation is seen in 26% of HIV/HCV-coinfected patients at 3 years after the diagnosis of cirrhosis and in 33% at 5 years [8]. Ascites is the most common decompensating event (observed in 50% of cases), followed by hepatic encephalopathy and gastrointestinal bleed (in 17% each) and jaundice and HCC (in 8% each). The median survival time after decompensation is 13 months. Highly active antiretroviral therapy (HAART) is significantly associated with survival (RR, 0.5 [95% confidence interval (CI), .3–.9]; P=.03). It is therefore extremely important to assess the degree of liver disease in patients with HIV/HCV coinfection so that risk stratification can be used to determine the need for initiation of anti-HCV therapy and screening for complications of liver cirrhosis.

**ASSESSMENT OF LIVER FIBROSIS**

The liver biopsy rate in HIV/HCV-coinfected patients is approximately 50%, and the absence of a liver biopsy has been mentioned in some studies as a limiting factor in initiating anti-HCV therapy. In a recent cohort study of a French HIV/HCV-coinfected population from 2004 to 2006, 44% of patients had undergone a noninvasive fibrosis assessment during their evaluation serum markers were measured in 67%, transient elastography was performed for 11%, and both assessments were performed for 22%. In this study, the absence of liver biopsy in the 2004 cohort was given as a reason for not providing anti-HCV treatment. In the 2006 cohort, more patients had received anti-HCV treatment, more of the treated patients had undergone liver biopsy, and noninvasive assessment of liver fibrosis was performed more often, compared with the 2004 cohort. The authors point out that assessment of liver damage should no longer be a barrier to anti-HCV treatment and that noninvasive assessment of liver fibrosis provides an accurate assessment of progression of liver disease in this population [9]. Furthermore, the European AIDS Clinical Society guidelines recommend that HIV/HCV-coinfected patients be assessed for liver fibrosis [10]. Several tests are now available for the assessment of liver fibrosis in patients with chronic liver disease. FIB-4 and Shasta have been developed for the assessment of liver fibrosis in patients with HIV infection, particularly those coinfected with HCV. There has been significant variation in the performance characteristics of some of these tests. A recent large study demonstrated that Hepascore, Fibrometer, and Fibrotest outperformed Shasta, APRI, FIB-4, and the FORNS index in assessing liver fibrosis in HIV/HCV-coinfected patients [11]. Tests that involve the markers hyaluronic acid and α-2 macroglobulin (Hepascore and Fibrometer) had a better predictive value, on the basis of area under the receiver operating curve (AUC) values, than tests that involve nonspecific biomarkers. An additional serum panel (the HICV test) that assesses liver fibrosis in HIV/HCV-coinfected patients on the basis of 3 independent variables (ie, aspartate transaminase level, α-2 macroglobulin level, and prothrombin index) had a significantly higher AUC than all of the other serum panels available for measuring fibrosis in this population [11].

The assessment of liver stiffness by transient elastography has been commonly used in Europe to assess liver fibrosis in a wide variety of liver diseases. In a recent meta-analysis of 35 studies that reported AUC data for severe fibrosis (defined as >stage 3 fibrosis), transient elastography was considered good at differentiating fibrosis stages 0–2 from stages 3–4, with an AUC of 0.89 (95% CI, .88–.91) and no significant difference seen between studies [12]. The assessment of liver stiffness by transient elastography has been added to the routine daily clinical care of patients with HIV and HCV in some countries in Europe, because transient elastography was shown in several studies to accurately predict the presence of liver fibrosis in patients with HIV-HCV coinfection. In a recent study of 239 HIV/HCV-coinfected patients, liver stiffness predicted the development of clinical complications in patients with compensated liver cirrhosis [13]. Only 8% of patients with a liver stiffness of <40 kPa developed decompensation or HCC as compared to 29% of patients with a liver stiffness of >40 kPa. Liver stiffness performed as well as the model for ESLD (MELD) score and better than the Child-Turcotte-Pugh classification in predicting outcome. In this same study, liver stiffness also predicted liver-related mortality. However, when the analysis was adjusted for other variables, the predictive association yielded a P value of .08 (hazard ratio, 1.03 [95% CI, 0.98–1.07]), which may have been related to the small number of clinical events (ie, only 10 liver related deaths and 1 liver transplantation) during the study period [13].

**DEVELOPMENT OF HCC**

The accelerated course of liver fibrosis, development of cirrhosis, and strong association with HCV infection results in
a higher incidence of HCC in patients with HIV/HCV coinfection, compared with HCV-monoinfected patients. Several studies from France have shown that up to a quarter of liver-related deaths in patients with HIV infection are related to HCC [14, 15]. This has been further borne out in a large study of 16 439 US veterans by Giordano et al. They showed a higher incidence rate of HCC in HIV/HCV-coinfected patients. These findings have been reproduced in another analysis of a US Veterans Affairs program for HIV-infected veterans, which showed a dramatic increase in the prevalence of HCC, from 0.07% to 1.6% between 1996 and 2009, predominantly related to HCV infection [16]. Although both studies are limited by their inclusion of a predominantly male population, a separate analysis in the US HIV/AIDS Cancer Match Study, which includes a more diverse group of individuals, has confirmed the finding of an increased risk of HCC among HIV-infected individuals [17]. In this population-based study, the risk of HCC has steadily increased in individuals with AIDS over the past 3 decades and is currently 4-fold higher than that in the general population. The increased incidence of HCC in patients with HIV infection was attributed to HCV, as the risk of HCC was 2-fold higher in patients with AIDS and a high likelihood of HCV, compared with those with a low likelihood of HCV infection. It is known that patients with HIV/HCV coinfection and HCC are younger than HCV-monoinfected controls and that the time from HCV infection to HCC is shorter in HIV/HCV-coinfected individuals, compared with HIV-negative patients [18]. The role of immunodeficiency in the generation of liver cancer has been investigated in a large French cohort. The risk of liver cancer is increased 2-fold at a CD4+ T-cell count of <500 cells/µL and plateaus at a CD4+ T-cell count of <200 cells/µL (RR, 7). The importance of immunodeficiency was seen even after adjustment for coinfection with hepatitis viruses [19].

The outcomes of HCC treatment in the HIV/HCV-coinfected population are difficult to interpret from the current literature. There are no prospective studies that address the outcome of HCC in this cohort. Maintenance of HIV suppression is important during treatment of HCC [18]. Results of liver transplantation for patients with HIV infection and HCC have shown comparable overall and disease-free survival rates, compared with rates for patients without HIV infection [20]. This supports the use of HCC screening for patients at risk, to ensure early and aggressive initiation of HCC treatment. No data are presently available to suggest a more aggressive screening strategy for HCC beyond that used for HIV-seronegative patients, and all patients with HIV/HCV coinfection and resultant cirrhosis should, every 6 months, undergo screening with ultrasonography and a test to measure alpha fetoprotein level.

**TREATMENT OF HIV-INFECTED PATIENTS WITH HCV-RELATED CIRRHOSIS**

Clinical trials of anti-HCV treatment in HIV/HCV-coinfected patients have traditionally not included significant numbers of patients with cirrhosis, with only 11%–16% of patients enrolled in the 2 pivotal trials of pegylated interferon alfa 2a plus ribavirin having cirrhosis or bridging fibrosis. The SVR rates seen in clinical practice are similar between patients with early stage liver fibrosis (stages 0–1) and those with moderate-to-advanced fibrosis (stages >2). Liver histologic analysis was not found to be a predictor of SVR in an AIDS Clinical Trials Group study [21]. However, in a subanalysis of patients in the AIDS Pegasys Ribavirin International Coinfection Trial who were receiving pegylated interferon alfa 2a, patients without cirrhosis had a 2-fold increase in SVR, compared with patients with cirrhosis ($P = .042$) [22, 23]. In the current clinical trials of anti-HCV treatment with combinations of pegylated interferon plus ribavirin and direct-acting antivirals in HIV/HCV-coinfected patients, there are few data available on patients with cirrhosis.

There is a significant benefit in delaying progression of liver fibrosis or preventing complications in patients who receive anti-HCV therapy, particularly in patients who achieve SVR. In one prospective study, no liver-related clinical events were noted in patients who achieved SVR or in those who initially responded to antiviral therapy but later relapsed, including some patients with advanced fibrosis prior to treatment [7].

**LIVER TRANSPLANTATION**

Liver transplantation is a widely accepted procedure for the management of complications of cirrhosis and ESLD. In addition, it is now used for the management of unresectable HCC in situations where the tumor burden is confined to the liver, lacks vascular invasion, and satisfies size limitations. In the United States, the United Network for Organ Sharing criteria for HCC are used for MELD exceptions. Patients with a single tumor of ≤5 cm and those with up to 3 tumors, the largest of which is ≤3 cm, receive additional priority on the transplant waiting list. In the past, solid organ transplantation was not considered for patients with HIV infection, because of concern about a heightened risk of opportunistic infection and malignancy. In recent times, several single-center and multicenter studies have demonstrated that liver transplantation can be performed in patients with HIV infection who satisfy commonly accepted eligibility criteria, including an undetectable plasma HIV RNA load, receipt of a stable HAART regimen or the ability to tolerate antiretroviral therapy after transplantation, a minimal CD4+ T-cell count of 100–200 cells/mm$^3$, and no opportunistic infections [20, 24]. These criteria vary by country, which makes it difficult to compare results from different countries. In the recent US multicenter Solid-Organ Transplantation in HIV study of liver
transplantation, the outcomes of liver transplantation for patients with HIV/HCV coinfection were inferior to those for patients with HCV infection alone [24]. Patient and graft survival rates were significantly lower at 3 years in HIV/HCV-coinfected patients, at 60% and 53%, respectively, compared with 79% and 74%, respectively, in HCV-monoinfected patients. HIV infection was the only baseline factor associated with the risk of early death (RR, 2.3) and graft loss (RR, 1.9). Factors associated with an increased risk of graft loss included combined receipt of a liver and kidney transplant; malnutrition, as defined by a body mass index (calculated as the weight in kilograms divided by height in meters squared) of <21; receipt of a liver from an HCV-positive donor; and older donor age. Recurrence of HCV infection and disease severity were similar between the HIV/HCV-coinfected cohort and controls, and HIV disease was not associated with an increased risk of graft loss due to HCV disease, which contrasts from the French series [20]. Acute cellular rejection was seen more frequently in the HIV/HCV-coinfected cohort and, similar to the transplantation findings among HCV-monoinfected individuals, treatment of acute cellular rejection was associated with increased severity of HCV disease after transplantation. Although these inferior results are of some concern, this study was able to identify risk factors that predict poor rates of patient and graft survival. Careful selection of candidates and donors, as well as improved management of immunosuppression, should lead to improved outcomes in this cohort.

Conclusion

HCV is the cause of significant morbidity and mortality in patients with HIV infection, with an accelerated progression to advanced fibrosis, decompensation, and HCC. Patients with HIV/HCV coinfection should be assessed at baseline for stage of liver fibrosis by either liver biopsy, noninvasive measurement of serum markers, measurement of liver stiffness, or a combination of these tests, and patients with advanced fibrosis should be offered treatment for HCV infection and enrollment in a screening program for complications of liver cirrhosis. Liver transplantation should be considered for patients with well-controlled HIV infection, and patients should be referred early, before the onset of malnutrition, debility, and renal failure.

Note

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