Liver Fibrosis and Antiretroviral Therapy

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(See the article by Verma et al. on pages 262–70)

It is estimated that 30% of HIV-infected patients are coinfectcd with hepatitis C virus (HCV). Since the introduction of combined HAART regimens, liver disease has emerged as an important cause of death among people living with HIV infection, especially among HIV-HCV–coinfected patients [1]. Complications of HCV-related liver disease are the leading cause of hospitalization and death among people living with HIV infection [2]. Indeed, as was previously reported in Clinical Infectious Diseases, the progression of liver fibrosis is accelerated in HIV-HCV–coinfected patients, compared with HCV-monoinfected patients [3]. Therefore, management of chronic HCV infection is a major public health issue in the HIV-infected population.

The impact of antiretroviral drugs on the progression of HCV-related liver fibrosis is far from clear, and studies aimed to assess this issue are difficult to conduct. The prospect of sequential liver biopsies is not easily accepted by patients, and the fibrosis progression rate is often used to assess the speed of fibrosis development, but this parameter is not always relevant, because of a lack of linear progression of fibrosis and uncertainty regarding the date that HCV infection was acquired [4]. In addition, because antiretroviral drugs are prescribed in combinations, it is difficult to determine which drug is responsible for hepatic harm [4]. The few available studies have provided conflicting results [5–9].

In this issue of the journal, Verma et al. [10] have addressed the impact of type and duration of antiretroviral therapy on liver fibrosis in HIV-HCV–coinfected patients. HIV-HCV–coinfected patients were retrospectively recruited by reviewing charts for the period 1994–2004. To be eligible, patients had to have a positive HCV PCR result, to have undergone a liver biopsy, and to have complete clinical data available. Fibrosis was evaluated with the Ishak modified histological activity index, a validated score that dissociates necroinflammatory score and fibrosis stage. Patients were classified according to type of antiretroviral therapy, as follows: patients in group 2 had received no treatment or only nucleoside reverse-transcriptase inhibitors (NRTIs), those in group 3 had received a modified histological activity index, a validated score that dissociates necroinflammatory score and fibrosis stage. Patients were classified according to type of antiretroviral therapy, as follows: patients in group 2 had received no treatment or only nucleoside reverse-transcriptase inhibitors (NRTIs), those in group 3 had received a diagnosis after 1996 and thus received combined HAART, and those in group 4 had initially received mono- or dual-drug therapy, which was then switched to combined HAART after 1996; group 1 included HCV-monoinfected patients. The main finding was that patients in group 3 had similar necroinflammatory scores, fibrosis stages, rates of fibrosis progression, and prevalences of and mean times to cirrhosis development, compared with the HCV-monoinfected population. Verma et al. [10] explained the absence of a similar benefit among patients in group 4 because of the delay between the diagnosis of HCV infection and the initiation of combined HAART. In this study, use of nevirapine was not associated with life-threatening or long-term adverse consequences. The authors concluded that it is not just the presence or duration of HAART, but also the short delay between diagnosis of HIV infection and the initiation of HAART that positively influences liver fibrosis in HIV-HCV–coinfected patients. This observation would provide support for early initiation of HAART in HIV-infected patients who are coinfectcd with HCV.

However, one must not forget that HCV cannot be eradicated with current available antiretroviral drugs and that prolonged use of these drugs is associated with toxicity. Although HAART-induced immune restoration may attenuate the increased risk of cirrhosis associated with HIV-HCV coinfection, it may also cause liver damage [11]. In addition, HIV-HCV–coinfected patients are more prone to develop hepatotoxicity caused by HAART than are HIV-monoinfected subjects [12].

Some drugs, such as stavudine [13] and nevirapine [9], have been associated with a harmful impact on the liver, which may subsequently enhance the progression of liver fibrosis. Data on the effect of protease inhibitors are scant and contradictory. Therefore, because the major goal for persons treating HIV-HCV–
coinfected patients is to slow or interrupt liver fibrosis, the best way to achieve this goal is to treat HCV infection with pegylated IFN and ribavirin. Indeed, recently published, large, randomized studies have shown that this combination was potent, yielding sustained virological response in 29% and 62% of patients coinfected with HCV genotype 1 and genotype 2/3, respectively [14]. Nonetheless, few HIV-HCV–coinfected patients are treated, especially because of the overlapping and additive toxicities of HAART and antiviral HCV drugs.

Current guidelines for the treatment of people living with HIV infection recommend that HAART not be initiated until the CD4 cell count is <350 cells/mm³. HIV-HCV–coinfected patients with a CD4 cell count of >350 cells/mm³ should first be assigned to receive anti-HCV treatment, because tolerance of this treatment would be optimal in the absence of HAART. For HIV-HCV–coinfected patients who require HAART, the availability of new fixed NRTI combinations, such as abacavir and lamivudine or tenofovir and emtricitabine, may prove to be helpful for reducing the additive toxicities (especially mitochondrial and hematological toxicities) of HAART and ribavirin. Patients who are not willing to receive pegylated IFN and ribavirin or who have contraindications may benefit from early HAART.

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References