EDUCATION PRACTICE

Chronic Hepatitis C in the Human Immunodeficiency Virus–Infected Patient: Management Strategies

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Clinical Scenario

A 45-year-old man with chronic hepatitis C and human immunodeficiency virus (HIV) infection is referred for treatment of hepatitis C. He is concerned about the effects of HIV therapy on his liver disease and hesitant about initiating treatment for hepatitis C virus (HCV) infection. His anti-HIV medications include stavudine (d4T), didanosine (ddI), and efavirenz, and he reports complete adherence to his treatment regimen. He is asymptomatic. Physical examination reveals a total liver span of 8 cm. There are no spider angiomas, splenomegaly, ascites, or peripheral edema. His HIV helper cell (CD4) count is 300 cells/mm^3, and HIV viral load is <50 copies/mL. His hemoglobin level is 14.2 g/dL, white cell count 3.4 × 10^9/L, platelet count 140 × 10^9/L, and international normalized ratio for prothrombin time 1.0. Serum bilirubin is 1.2 mg/dL, serum albumin 3.6 g/dL, AST 56 U/L, and ALT 75 U/L. His serum HCV RNA level is 1,600,000 IU/mL, and HCV genotype is 1a. Ultrasound examination of the abdomen reveals a coarse echotexture of the liver and no splenomegaly.

How should you counsel this patient with HIV/HCV coinfection regarding progression of chronic hepatitis C and the effect of HIV therapy on his liver? Should he be treated for chronic hepatitis C, and, if so, how should he be followed on therapy?

The Problem

HIV and HCV (HIV/HCV) coinfection is a common problem in the United States and Europe, with coinfection present in 15%–30% of all patients infected with HIV and 5%–10% of patients infected with HCV. The prevalence of HCV coinfection in HIV-infected patients varies according to risk factor for HIV infection, with injection drug use being associated with the highest rate (~75%) of coinfection.

Effect of Human Immunodeficiency Virus on Progression of Chronic Hepatitis C

HIV infection accelerates the progression rate of chronic hepatitis C, along with other factors including older age, high body weight, male gender, heavy use of alcohol, and coinfection with hepatitis B virus (HBV). HIV/HCV coinfection is characterized by a decreased rate of spontaneous clearance of HCV, as well as an accelerated progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. With the advent of highly active antiretroviral therapy (HAART), end-stage liver disease has become the leading cause of morbidity and mortality in HIV/HCV coinfection, and chronic hepatitis C is considered a major opportunistic infection in HIV-infected patients.

Hepatotoxicity During Highly Active Antiretroviral Therapy in Patients With Human Immunodeficiency Virus/Hepatitis C Virus Coinfection

Severe hepatotoxicity occurs in 6%–16% of patients receiving HAART, and the incidence of hepatotoxicity is increased in those with HCV coinfection. Although all classes of antiretroviral drugs (nucleoside reverse transcriptase inhibitors, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors) have been associated with hepatotoxicity in HIV/HCV-coinfected patients, the majority of treated patients do not

Abbreviations used in this paper: ACTG, Acquired Immunodeficiency Syndrome Clinical Trials Group; APRICOT, Acquired Immunodeficiency Syndrome Pegasys Ribavirin International Coinfection Trials; AZT, zidovudine; CD4, human immunodeficiency virus helper cell count; ddI, didanosine; d4T, stavudine; EASL, European Association for the Study of the Liver; EVR, early virologic response; FDA, Food and Drug Administration; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response

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experience severe hepatotoxicity. Evidence suggests that antiretroviral therapy can be administered safely in patients coinfected with HIV/HCV, although careful monitoring of laboratory tests and symptoms is mandatory. The mechanisms of HAART-induced hepatotoxicity are not well understood, but potential factors include impaired drug metabolism, immune reconstitution syndrome, and increased susceptibility to mitochondrial dysfunction. Certain drugs in the nucleoside reverse transcriptase inhibitor class, including zalcitabine (ddC), ddI, and d4T primarily, have been associated with lactic acidosis, which is diagnosed on the basis of an elevated anion gap and plasma lactate above 4 mEq/L. Patients might have asymptomatic hyperlactemia, severe lactic acidosis alone, or a constellation of clinical findings ranging from hepatic steatosis to hepatic failure.

Management Strategies and Supporting Evidence

Screening for Hepatitis C Virus Coinfection

All HIV-infected patients should be screened for HCV infection. Patients with a positive HCV antibody test (anti-HCV) should undergo further testing, including serum HCV RNA by a sensitive polymerase chain reaction assay. In HIV-infected patients with low CD4 counts (especially <100 cells/mm^3), anti-HCV titers might fall below the detection limits of standard antibody assays, necessitating testing for serum HCV RNA to confirm the presence of chronic HCV infection.

Coinfected patients should also be tested for total antibody to HAV (anti-HAV total) and for infection or immunity to HBV with HBsAG, total antibody to hepatitis B core (anti-HBc total), and antibody to HBsAg (anti-HBs). If there is no immunity to hepatitis A or B, patients should be vaccinated. These recommendations are based on the potential increased risk of more severe or fulminant hepatitis A or B in patients with chronic hepatitis C, as well as the fact that HIV-infected patients are at an increased risk for acquiring HAV and HBV infection. The immunogenicity of hepatitis A and B vaccine in patients with HIV infection and/or chronic liver disease is somewhat reduced, but the great majority of patients will respond and be protected.

Evaluation of the Patient Coinfected With Human Immunodeficiency Virus/Hepatitis C Virus

Evaluation of the HIV/HCV-coinfected patient should include a careful history and physical examination, complete blood count, comprehensive metabolic panel, α-fetoprotein, quantitative serum HCV RNA, HCV genotyping, and serologic testing for HAV and HBV. Liver biopsy is generally recommended, because it provides information regarding the grade of inflammation and stage of fibrosis, which are useful to determine the relative urgency of therapy. However, given the expense and potential risks associated with liver biopsy, some clinicians chose to offer therapy to all eligible coinfected patients without histologic confirmation of the grade and stage of disease.

Hepatitis C Virus Therapy in Persons Coinfected With Human Immunodeficiency Virus and Hepatitis C Virus

Current consensus guidelines from the National Institutes of Health, Department of Veterans Affairs, and European Association for the Study of the Liver (EASL) recommend that all coinfected patients be considered potential candidates for HCV antiviral therapy. The only treatment approved by the Food and Drug Administration (FDA) for treatment of HIV/HCV coinfection is peginterferon alfa-2a (Pegasys; Roche Laboratories, Nutley, NJ) plus ribavirin (Copegus; Roche Laboratories). Regardless of HCV genotype, the recommended duration of therapy is 48 weeks. The benefits of treatment of HCV include potential eradication of virus and reduction in the progression of liver disease, as well as regression in the stage of fibrosis.

Three large multicenter trials have examined the treatment of HCV in HIV-infected patients: the Acquired Immunodeficiency Syndrome (AIDS) Pegasys Ribavirin International Coinfection Trials (APRICOT), AIDS Clinical Trials Group (ACTG) A5071 Study, and the French RIBAVICtrial. Because peginterferon alfa-2a with ribavirin is the only FDA-approved treatment of HIV/HCV coinfection, the APRICOT trial, the largest study to date that studied peginterferon alfa-2a, will be discussed in detail. In this study, 860 patients received peginterferon alfa-2a (180 μg subcutaneous weekly) plus ribavirin (400 mg orally twice daily), standard interferon alfa-2a and ribavirin, or peginterferon alfa-2a alone for 48 weeks. Early virologic response (EVR), defined as a >2 $\log_{10}$ decrease or undetectable serum HCV RNA level at week 12 of therapy, was determined. Serum HCV RNA was also assessed at week 24, end of treatment (week 48), and end of observation (week 72). A sustained virologic response (SVR) was defined as undetectable HCV RNA at week 72. The overall SVR was 40%, with SVR rates of 29% in patients with genotype 1 and 62% in those with genotypes 2 and 3. Baseline viral load was also an important factor in predicting SVR in this study, with a higher viral load ($>$800,000 IU/mL vs $\leq$800,000 IU/mL) associated with lower SVR rates (33% vs 61%).