Fulminant hepatic failure after the start of an efavirenz-based HAART regimen in a treatment-naive female AIDS patient without hepatitis virus co-infection


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Sir,
The life expectancy of HIV-positive subjects has dramatically improved with the use of triple drug combinations. However, adverse effects have now become a limiting cause of benefit in a substantial proportion of patients. In particular, hepatotoxicity has been reported by many centres in the developed world and is now recognized as a major cause of morbidity and mortality in patients receiving antiretroviral treatment.

We report the case of an AIDS patient who developed acute, ultimately fatal, toxic liver failure, only 2 weeks after beginning a triple combination regimen that included two nucleoside reverse transcriptase inhibitors (NRTIs), stavudine and lamivudine, and efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI).1

A 30-year-old female patient, the sexual partner of an HIV-infected drug addict, was admitted to our Infectious Diseases Department because of fever, dyspnoea and oral candidiasis. Blood screening revealed moderately raised levels of alanine aminotransferase (ALT), γ-glutamyl transferase (γGT) and lactate dehydrogenase (LDH), respectively 0.5, 2 and 1.9 times the maximum normal value (MNV), moderate leucopenia and anaemia. Cholinesterase (CHE) and total bilirubin values were normal. Serology for hepatitis B, D and C viruses was negative; IgG antibodies to hepatitis A virus, Epstein–Barr virus, cytomegalovirus and herpes simplex virus were present. HIV-1 viral load in plasma was 5.7 log10 copies/mL, and the CD4 count was 26 cells/mm3. Echotomography of the abdomen showed mild hepatosteatosis and an asymptomatic cholelithiasis. No previous alcohol abuse was reported. Chest high-resolution CT scan and blood gases (PaO2 50 mmHg) were consistent with a diagnosis of Pneumocystis carinii pneumonia (PCP). Treatment with co-trimoxazole, corticosteroids and fluconazole was initiated, which led to a gradual improvement and the resolution of dyspnoea and fever. During the cycle of induction-treatment for PCP with co-trimoxazole, the patient experienced a progressive rise in ALT values up to >5-fold the MNV, together with severe leucopenia and neutropenia. Nevertheless, she completed the treatment. Liver enzymes slowly returned to the pre-treatment values over several days once the co-trimoxazole dosage was reduced as secondary prophylaxis. Eight days later, normal liver function having been restored, she started a highly active antiretroviral therapy (HAART) regimen, with stavudine, selected for its lower bone marrow toxicity than zidovudine, lamivudine and efavirenz, which was preferred to nevirapine because of its reported low hepatotoxicity.1 Seven days after the start of HAART, the patient developed an efavirenz-related skin rash that resolved within 4 days, without the need for drug discontinuation. Three days later (14 days after the start of HAART), jaundice appeared. Laboratory results revealed a severe ALT increase (>6-fold MNV) and hyperbilirubinaemia (total bilirubin 12.6 mg/dL, direct bilirubin 9.16 mg/dL); the plasma lactate level was 2.3 mmol/L. Serum concentrations of γGT and LDH increased by 20- and 4-fold, respectively, and the CHE value decreased to 3344 U/L. Hypoalbuminaemia (1.7 g/dL) and anaemia (Hb: 9.2 g/dL) were documented. Prothrombin time (PTT), activated PTT and fibrinogen values were initially normal. Serology for hepatitis B, D and C viruses was persistently negative. Antiretroviral therapy was promptly stopped and riboflavin and acetyl-L-carnitine were started to treat the plasma lactate increase. The condition of the patient rapidly worsened: total bilirubin (up to 17 mg/dL) and ALT (>8-fold MNV) values rapidly increased and 1 week later she died because of a liver failure syndrome and disseminated intravascular coagulation. Autopsy was turned down by the family.

Transaminitis and liver disease are now a major cause of morbidity and mortality in patients being treated for HIV infection, particularly in individuals co-infected with hepatitis C or B virus.2–4 Nevertheless, severe hepatitis remains very uncommon in patients receiving any HAART regimen. In patients co-infected with hepatitis C virus, it can be the result of an immune reconstitution syndrome.5 In this case, the...
brief treatment and the very low CD4 baseline levels were not sufficient to support immune reconstitution. As the patient had no viral hepatitis, the hepatotoxicity is most likely to have been drug related.

Hepatotoxicity has been investigated in a recent retrospective analysis of >9000 patients from 21 adult AIDS Clinical Trials Group studies receiving a variety of antiretroviral regimens. Reisler and colleagues demonstrated severe hepatotoxicity (defined as grade 3 or 4 elevations of ALT or total bilirubin) in ∼10% of all patients in treatment regimens, and 23% of these permanently discontinued treatment. The overall and the hepatitis-related death rates were 15% and 0.3%, respectively.6 Italian data from the ICONA (Italian Cohort Naive Antiretrovirals) study also showed a low rate of severe hepatotoxicity in 7.9% of 1255 patients treated over a 24 month period.7

Taking the HAART regimen given to our patient into consideration, there appear to be several lines of evidence indicating the role of NRTIs in the induction of lactic acidosis and hepatitis. However, the plasma lactate levels found in our patient were too low to cause a fulminant hepatitis. NNRTI-based regimens can also lead to severe liver toxicity resulting in a high rate of treatment discontinuation. Nevertheless, presumed drug-related hepatotoxicity deaths in the NNRTI regimens are very rare (<1%).8 Reports of NNRTI hepatotoxicity led to a Food and Drug Administration (FDA) alert for nevirapine use, with the recommendation that liver function should be carefully monitored during the first 2 months of HAART that includes this drug.9

Efavirenz, the other NNRTI available in Italy, has been associated with lower hepatotoxicity than nevirapine; in the main efavirenz studies, laboratory abnormalities of grade 3 to 4 occur at a similar frequency to control arms, with elevated hepatic transaminases in 2–3% of treated individuals.1 However, there is an increasing awareness of efavirenz-induced liver toxicity in HIV-positive patients, especially where coinfection with hepatitis viruses is present. Rarely, this toxicity develops from the start of HAART and it is usually reversible upon discontinuation of treatment. Moreover, there are no reports of efavirenz-related fulminant and fatal hepatic failure in HIV-positive individuals without hepatitis virus co-infection. Hepatitis virus co-infection is considered to be the most important risk factor for hepatotoxicity in HAART regimens. However, the coexistence of other risk factors for hepatotoxicity, such as female gender, hepatosteatosis, abnormal baseline ALT levels, transaminitis during a previous non-antiretroviral treatment, recent idiosyncratic reaction to efavirenz and pregnancy, can significantly increase the possibility of a severe outcome for efavirenz-related liver toxicity.2–6,8–10

We believe that close monitoring of liver enzymes is essential during the first 3 weeks of treatment, especially in individuals with many coexisting recognized risk factors for hepatotoxicity. Finally, an increased emphasis on identifying and evaluating every baseline factor that can predict hepatotoxic events is strongly warranted to lead to safe and durable antiretroviral treatments.

References
