LETTER TO THE EDITOR

Severe acute pancreatitis related to the use of adefovir in a liver transplant recipient

Pancréatite aiguë sévère induite par l’adéfovir chez un transplanté hépatique

Adefovir dipivoxil is a nucleotide analogue of adenosine monophosphate, which provides strong inhibition of the hepatitis B virus (HBV) polymerase. The most common side effects are renal toxicity and hypophosphoremia [1]. In a recent multicenter trial of adefovir dipivoxil in HBV-infected patients undergoing liver transplantation and HBV-infected liver transplant recipients, adefovir dipivoxil was reported to have a good safety profile [2], and unlike with nucleoside analogues, no mitochondrial toxicity or pancreatitis was reported with this drug. We report the first case of acute pancreatitis related to the use of adefovir dipivoxil in a HBV-infected liver transplant recipient. The withdrawal of adefovir dipivoxil resulted in HBV reactivation causing fatal liver failure.

Case report

A 71-year-old man was admitted on 2003 September 17th for asthenia, anorexia and liver tests abnormalities. He had been followed since 1996 for an HBe Antigen (Ag) negative (precore mutant) HBV-related chronic hepatitis. Despite interferon therapy (from 1993 to 1995), then famciclovir therapy, chronic hepatitis B progressed to end-stage liver disease. The patient was transplanted in November 2000. He received passive immunoprophylaxis against Hepatitis B virus recurrence with anti-HBs immune globulins (10,000 IU given intravenously) to obtain more than 500 IU/L of residual HBs Antibodies (Abs). On October 2002, liver biopsy showed recurrent chronic hepatitis B with moderate activity and septal fibrosis (A2F2 according to the METAVIR scoring system). Lamivudine therapy was subsequently started. On July 2003, an increase in serum alanine aminotransferase (three times the upper limit of normal range (ULN)) and in serum HBV-DNA levels (652 pg/mL) were observed. The YMDD mutation was concomitantly detected by sequence analysis of the HBV polymerase gene suggesting the involvement of lamivudine resistant HBV.

At admission, serum ALT was 2.7 ULN, prothrombin time was 44 s, serum HBV-DNA levels were 3030 pg/mL. The patient weighed 58 kg. Three days after admission, a 10 mg/day course of adefovir dipivoxil therapy was started. On September 22th, serum creatinine increased up to 131 μM. The adefovir regimen was reduced to 10 mg every two days, and lamivudine therapy was maintained. On September 27th, HBV DNA was below (1310 pg/mL), but the patient had abdominal pain and vomiting. Serum amylase and lipase were increased to 3.4 ULN and 2.8 ULN, respectively. Severe acute pancreatitis was suggested by additional biochemical abnormalities: white blood cell count 33700/mm³, LDH at 1.5 ULN, urea 14.1 mmol/L (first evaluation of the Ranson score: 3/5). Computed Tomography-scan showed an increase in pancreatic volume and two areas of extra-pancreatic necrosis were noted (stage E according to the Balthazar scoring system). Neither Computed Tomography-scan nor cholangio-magnetic resonance imaging showed gallstones in the biliary tract. Anti-CMV IgM, antiVCA IgM, anti HAV IgM, anti-coxsackie, - adenovirus, -paramyxovirus, antibodies were not detected. Serum triglycerides levels were 1.2 mmol/L, and calcemia was 2.05 mmol/L. No alcohol intake was self-reported or detected (alcohol detection was negative in blood and urine). Drug-induced pancreatitis was thus suspected. Adefovir dipivoxil was stopped. Amylase and lipase levels decreased and returned to the normal range on October 2nd. Because of an increase in serum ALT, ganciclovir therapy was started on October 5th, but did not control HBV replication: on October 12th, HBV DNA level was 2501 pg/mL. This HBV reactivation was associated with jaundice, ascites, and encephalopathy on October 18th. On October 22th, the patient died from liver failure (Fig. 1). Postmortem liver biopsy showed the presence of active cirrhosis with high levels of HB-core antigen. No macrovacuolar or microvesicular steatosis was found.

Discussion

This patient developed severe acute pancreatitis after changing anti-HBV therapy. The hypothesis of drug-induced pancreatitis is likely since adequate alcoholic, viral, and metabolic pancreatitis were ruled out with tests. A biliary-related pancreatitis, which is uncommon in the setting of liver transplantation because of the systematic cholecys-
tectomy performed during the surgical procedure, was also carefully ruled out. Although it has been described [3], HBV was probably not involved in the present case of acute pancreatitis. Indeed, acute pancreatitis occurred together with a decrease in HBV-DNA levels and did not recur when HBV reactivated. In the present case, adefovir dipivoxil is probably the cause. The immunosuppressive regimen had not changed for two years before admission and lamivudine therapy had been administered for one year. Moreover, maintaining these drugs did not prevent recovery from acute pancreatitis. Conversely, adefovir dipivoxil was started five days before the onset of acute pancreatitis and its withdrawal was associated with a decrease in pancreatic enzymes.

To our knowledge, this is the first case of acute pancreatitis that is probably associated with the use of adefovir dipivoxil. Other antiviral agents, mostly antiretroviral drugs, have been associated with numerous cases of acute pancreatitis [4]. The mechanism involved has been reported as mitochondrial toxicity. In anti-HBV drugs, several cases were described with lamivudine [5]. Similarly, recent cases of pancreatitis were reported with the use of tenofovir concomitantly with didanosine [6]. In these cases, factors such as low CD4 cell count or body weight below 60 kg may have increased the risk of pancreatotoxicity. The mechanism involved in the present case of adefovir-related pancreatitis is unknown. The low body weight of our patient (58 kg) as well as impaired renal and liver functions may have favored a dose-related pancreatic toxicity of adefovir dipivoxil. Moreover, immune mediated pancreatitis is unlikely in the setting of liver transplantation and the immunosuppressive drugs may have mimicked a depletion in CD4 lymphocytes. A depletion of mitochondrial DNA is uncommon in animals receiving adefovir dipivoxil but has recently been reported in the renal toxicity of this drug [7]. Hence, we can hypothesize that depletion of mitochondrial DNA may have contributed to the pancreatic damage in our patient, in addition to that reported for nucleoside analogues. However, no extrapancreatic manifestations of mitochondrial toxicity were observed such as lactic acidosis or microvesicular steatosis in our patient. Another unresolved question is the role of lamivudine as a cofactor of adefovir pancreatotoxicity.

Although the present case of adefovir-induced pancreatitis was severe based on the common classifications for the prognosis of acute pancreatitis, the patient recovered rapidly. Unfortunately, withdrawal of adefovir was followed by HBV reactivation despite the maintenance of lamivudine. Unlike previously described results [8], ganciclovir therapy did not control replication of lamivudine-resistant HBV strains. Other antiviral drugs such as tenofovir or entecavir were not available and interferon therapy is contra-indicated in decompensated HBV cirrhosis.

This case suggests a new potential toxicity of adefovir dipivoxil. Both maintenance and withdrawal of adefovir were a problem due to the severity of pancreatitis on one hand and the control of HBV replication on the other. We hope that new antiviral agents effective against HBV replication will help the management of serious adverse events related to the use of adefovir dipivoxil such as pancreatitis. The absence of pancreatic side effects in these new drugs, however must be demonstrated.

References


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Available online 8 April 2008