Liver Transplant in Patients with Viral Hepatitis and Human Immunodeficiency Virus Coinfection: The First 2 Cases in Turkey

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Abstract

Objectives: **The outcomes of liver transplant in human immunodeficiency virus-infected patients are improving with advances in antiretroviral treatment. Data about such cases are rare in Turkey. We present the first 2 living-donor liver transplants performed in Turkey in patients with viral hepatitis/human immunodeficiency virus coinfection.**

Case 1: **A 47-year-old man infected with human immunodeficiency virus with chronic hepatitis B and D and hepatocellular carcinoma within the Milan criteria had been taking antiretroviral medication before his liver transplant. An unrelated right lobe liver transplant was performed uneventfully in this patient, who was human immunodeficiency virus RNA-negative and had a CD4 T-cell count of 500/μL. Antiretroviral treatment continued in the early postoperative period, and a triple immunosuppressive regimen consisting of cyclosporine, mycophenolate mofetil, and steroids was initiated. *Burkholderia cepacia* pneumonia developed postoperatively, and was treated successfully. The patient was discharged on postoperative day 18, and is still alive 58 months after the operation.**

Case 2: **A 62-year-old man with human immunodeficiency virus and chronic hepatitis C virus infection was taking antiretroviral treatment before the liver transplant. The patient was hepatitis C virus RNA-positive, human immunodeficiency virus RNA-negative, and had a CD4 T-cell count of 620/μL. His son was the donor, and a right lobe liver transplant was performed uneventfully in antiretroviral treatment continued in the early postoperative period and a triple immunosuppressive regimen consisting tacrolimus, mycophenolate mofetil, and steroids was initiated. Broad-spectrum β-lactamase-positive *Escherichia coli* bacteremia and hospital-acquired pneumonia developed postoperatively and were treated successfully. The patient was discharged on postoperative day 19, and remains alive 13 months after the operation.**

Conclusions: **Living-donor liver transplant is a promising treatment choice for end-stage liver disease in human immunodeficiency virus-infected patients.**

Key words: *Human immunodeficiency virus, Liver transplant, Hepatitis B virus, Hepatitis C virus, Coinfection*

Introduction

Hepatitis virus and human immunodeficiency virus (HIV) coinfection are frequent due to their common routes of transmission. In patients infected with hepatitis B (HBV) and hepatitis C (HCV) viruses, HIV coinfection accelerates progression to cirrhosis causing intolerance and diminished responses to treatment.[1]

Liver transplant criteria in viral hepatitis/HIV-coinfected patients, according to European AIDS Clinical Society 2014 Guidelines and the American Society of Transplant Infectious Diseases Community of Practice 2013, study can be summarized as follows: Patients with viral hepatitis/HIV coinfection are

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indicated for liver transplant when advanced fibrosis, a history of decompensation, and hepatocellular carcinoma (HCC) develop. Liver transplant is recommended if the patient's HIV and HCV viral loads are undetectable in the blood, and the CD4 count is > 100 cells/μL. In the case of a positive history of AIDS-related opportunistic infections or malignancy, transplant is recommended if the CD4 count is > 200 cells/μL for 3 months before transplant. Liver transplant is not recommended when an active opportunistic infection or malignancy is present.[1,2]

This paper presents the first 2 cases of liver transplant performed for cirrhotic patients with viral hepatitis/HIV coinfection in Turkey.

Case 1

A 47-year-old man with cirrhosis, diagnosed with HBV and hepatitis D virus coinfection 13 years earlier, and diagnosed with HIV infection in 2013 was referred to our center for liver transplant. His alpha-fetoprotein level was elevated to 44.9 IU/mL (range, 0.5-5.5 IU/mL), and a 3-cm mass suggestive of HCC was detected in his left liver lobe. The patient's preoperative CD4 count was > 500 cells/μL and he was negative for HIV RNA. He was being treated with tenofovir disoproxil, emtricitabine, and efavirenz. His body mass index was 22 kg/m^2. His Child-Pugh score was B and his Model for End-Stage Liver Disease score was 12. Unrelated right lobe living-donor liver transplant was performed upon approval of the local ethics committee. The operative procedure was uneventful and a triple immunosuppressive regimen consisting of cyclosporine, MMF, and steroids was initiated. Pneumonia and parapneumonic effusion developed on the third postoperative day. *Burkholderia cepacia* was isolated from the thoracentesis fluid; it was sensitive to trimethoprim sulfamethoxazole, so this agent was added to the treatment protocol. After parenteral treatment for 14 days, peroral treatment was continued completing the whole treatment over 1 month. No further complications developed during the postoperative period, and the patient was discharged on postoperative day 13. Hepatitis B hyperimmune globulin and HBV-active antiretroviral treatments were given as prophylaxis against recurrent HBV. The patient is currently alive without HCC or HBV recurrence 58 months after the operation.

Case 2

Hepatitis C virus and HIV coinfection was recently diagnosed in a 62-year-old Nigerian man. Ribavirin and pegylated interferon were initiated, but treatment had to be withheld after the second administration because of intolerance. The patient was referred to our center for a liver transplant because of decompensation. At the time of referral, he had grade 1 to 2 encephalopathy, and was hospitalized in the intensive care unit. He was taking emtricitabine/tenofovir/efavirenz as antiretroviral therapy (ART). His body mass index was 22.8 kg/m^2, and his Child-Pugh score was B with a Model for End-Stage Liver Disease score of 19. He was negative for HIV RNA, his HCV RNA titre was 107 000 copies/mL and his CD4 count was 620 cells/μL. His son was the donor, and a right lobe living-donor liver transplant was performed.

Antiretroviral therapy was continued in the early postoperative period, and a triple immunosuppressive regimen consisting of tacrolimus, MMF, and steroids was initiated. The tacrolimus level (target blood level, 5 ng/mL) was maintained by peroral administration at a dosage of 2 mg/dL. Fever and cough developed on the sixth postoperative day. Thoracic computed tomography scanning revealed pneumonic infiltration, and broad-spectrum β-lactamase-positive *Escherichia coli* was isolated from a blood culture. Treatment with ertapenem, ciprofloxacin, and fluconazole was initiated. The patient recovered from the pneumonia and was discharged on postoperative day 19. Biliary anastomotic site stricture developed in the first postoperative month, and he was treated with endoscopic retrograde cholangiopancreatography and percutaneous intervention. The patient is alive and well in the 13th postoperative month. Antiretroviral therapy was continued in the preoperative and postoperative periods without stopping. The patient is continuing treatment and follow-up for HIV and HCV in Nigeria.

Discussion

Hepatitis B virus and HCV coinfection is seen in 6% to 14% and 33% of HIV/AIDS patients in Western Europe and the United States.[3,4] In comparison, a Turkish study reported that the HBV and HCV

coinfection rates in HIV/AIDS patients were 40% and 6%.[5] Liver transplant in patients with viral hepatitis/HIV coinfection has not been reported previously in Turkey; this report contains the first such cases in Turkey.

The indication for living-donor liver transplant in case 1 was the occurrence of cirrhosis due to HBV, hepatitis D virus, and subsequent HCC. The second patient had a recent diagnosis of HCV/HIV, and liver transplant was indicated when decompensation developed after treatment. Although the data suggest transplant when the viral load is negative, liver transplant was performed immediately because decompensation developed during treatment in the second patient. Conversely, cases of spontaneous HCV clearance after liver transplant have been reported.[6]

The leading factor affecting the outcomes of liver transplant in patients with viral hepatitis/HIV coinfection is the underlying disease. The outcomes are poorer in HIV/HCV coinfection because of HCV recurrence. Survival rates are better in patients with an undetectable HCV loads than in patients in whom HCV is detectable at the time of transplant. Conversely, the survival rates of patients with HBV/HIV coinfection are better than those of patients with HCV/HIV coinfection.[1]

In a multicentre study performed in Spain, the 5-year survival rates of liver transplant for patients with HCV infection and HCV/HIV coinfection were 71% and 54%. Human immunodeficiency virus infection was an independent predictor of mortality.[7]

The other major factor affecting the outcome is posttransplant rejection, with rejection rates being significantly higher by 2- to 3-fold in this group of patients.[1] Derangement of the immune system in HIV-infected patients and the pharmacokinetics interactions between ART drugs and immunosuppressive medications contribute to the higher rates of rejection. Therefore, the choice of immunosuppressive regimen becomes more of an issue in such cases. Cyclosporine may be preferred due to its antiviral activity against HIV. Conversely, high levels of tacrolimus are correlated with lower rejection rates compared with cyclosporine. Furthermore, taking the antiproliferative effectiveness of MMF into consideration, we preferred cyclosporine, MMF, and steroids in the first case, and tacrolimus, MMF; and steroids in the second case. Acute rejection requiring pulse steroid therapy did not develop in either case.

While protease inhibitors increase the blood levels of calcineurin inhibitors and mammalian target of rapamycin inhibitors by inhibiting the cytochrome enzyme system, nonnucleoside reverse transcriptase inhibitors such as efavirenz, etravirine, and nevirapine lower the blood levels of calcineurin inhibitors and mammalian target of rapamycin inhibitors by inducing CYP3A.[1] We did not encounter any problems between ART consisting of tenofovir, emtricitabines and efavirenzs and calcineurin inhibitors in obtaining sufficient immunosuppressive blood levels in either case. The maintenance dosage of tacrolimus in the second case was 2 mg/dL. The antiretroviral drugs taken by the patients in the preoperative period were continued in the postoperative period and no hepatotoxicity developed in either case.

Another factor affecting the outcome is infection. Bacterial infection and sepsis are the leading causes of mortality, with a rate of 50%.[8] Bacterial infections, which are typically seen in recipients without HIV infection, are reportedly more frequent in recipients with HIV infection.[1] Antibiotic prophylaxis consisted of ampicillin/sulbactam at a dose of 4 × 1 grams for 48 hours. Conversely, as the other patient was admitted to the intensive care unit with grade 1 to 2 encephalopathy, his antibiotic prophylax is consisted of piperacillin/tazobactam at a dosage of 4 × 4.5 grams for 48 hours, and fluconazole at a dosage of 1 × 400 mg for 14 days. However, despite antibiotic prophylaxis, *B. cepacia* pneumonia developed in the first patient and extended-spectrum beta-lactamases-positive *E. coli* bacteraemia and hospital-acquired pneumonia developed in the second patient. These infections were treated with appropriate antibiotics and the patients recovered without any morbidity.

Another possible complication is malignancy. The reported incidence of human papillomavirus-associated malignancies is increasing.[1] However, no malignancy developed in either of the patients in the posttransplant follow-up.

The presence of HIV/AIDS in patients with chronic liver disease or HCC because of chronic viral hepatitis is a significant cause of mortality and morbidity. Liver transplant, along with antiviral therapy, is the final choice of treatment in these patients. In addition, surgery in such patients is a source of anxiety among health care providers because of the high risk of percutaneous or mucosal exposure during surgery or the management of

HIV-positive patients. In addition to informative presentations to the health care workers, antiretroviral drugs were made available in the hospital for chemoprophylaxis considering the risks of accidental exposure. Standard infection control precautions such as safe injection practices, aseptic techniques, and individual infection control principles are followed with our HIV-positive patients as with other surgical cases. No additional precautions were taken in the operating room.

Conclusions

The first 2 cases of living-donor liver transplant in 2 HIV-infected patients in Turkey, 1 with HCV, and the other with HBV, hepatitis D virus, and HCC were performed successfully. The first patient is currently alive in the 58th postoperative month with no HBV or HCC recurrence, and the second is alive with no problems 13 months after surgery.

Liver transplant offers a promising treatment option for end-stage liver disease in HIV-infected patients. Antiretroviral therapy for HBV and HCV and managing ART are important during both the preoperative and postoperative periods. Surgery in such cases, may be performed successfully with standard infection control precautions.

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