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Case Report

Treatment of Hepatitis B Virus Reactivation in a Cadaveric Renal Transplant Recipient with Entecavir

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Abstract

Introduction: Risk of reactivation of Hepatitis B virus (HBV) infection and other liver related complications continues to be a major cause of concern in HBV carriers undergoing cadaveric renal transplantation. Antiviral medications have been recommended post renal transplantation in patients who are chronic HBV carriers.

Case Report: Here we present the case of a 15-year-old girl known to have kidney failure and chronic active HBV infection indicated by positivity of both HBsAg and HBeAg. She was treated with interferon alpha for six months resulting in clearance of HBeAg and reduction of HBV-DNA titer to 32.15 copies/ml. She underwent successful cadaveric renal transplantation and was maintained on cyclosporine, azathioprine and prednisolone. Two years post transplant, the patient developed elevated liver enzymes, positive HBeAg and high HBV-DNA titers. She was treated with lamivudin resulting in normalization of liver function tests. Lamivudine was discontinued after nine months due to poor compliance resulting from psychological problems. Three years post transplant, the patient was started on Entecavir 0.5 mg oral, daily. At follow up clinic visits till present time, the patient is tolerating Entecavir treatment with no reported side effects. Liver enzymes remained stable, but the effect on viral load and viral markers was unremarkable.

Conclusion: The role of various antiviral agents in treating HBV infection among kidney transplant recipients requires further evaluation.

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Introduction

Hepatitis B virus (HBV) infection, either in its acute or chronic form, continues to be a major cause of concern globally; with an excess of 300 million people worldwide suffering from chronic HBV infection [1]. In the transplant population and among those receiving immunosuppressive therapy, infection with the HBV is associated with significant morbidity and mortality by accelerated liver pathology that may culminate in cirrhosis or hepatocellular carcinoma [2].

Although safety protocols have decreased the prevalence of primary HBV infection in hemodialysis and transplant units, chronic immunosuppression would theoretically increase the risk of HBV reactivation in individuals with a quiescent HBV status. This re-activation is defined as (1) the reappearance of hepatitis B surface antigen (HBsAg) in people with previous evidence of resolved infection [HBsAg negative and hepatitis B surface antibody (HBsAb) positive], (2) the reappearance of the serum envelope 'e' antigen (HBeAg) in patients already serologically positive for HBsAg, (3) a change from low infectivity to high infectivity or (4) a change from chronic inactive hepatitis to chronic active hepatitis. We herein present a case of HBV reactivation in a patient after renal transplantation and describe her management.

Case Report

We herein present the case of a 15 year-old Caucasian female known to have chronic renal impairment due to recurrent pyelonephritis. She was also known to be a chronic carrier of HBV. She underwent bilateral

nephrectomy due to recurrent pyelonephritis with *Pseudomonas aeruginosa* sepsis.

Initial testing at our institution revealed a chronic active HBV carrier state indicated by serum positivity of both HBsAg and HBeAg. This prompted treatment with interferon alpha (3 million IU, 3 times per week for 6 months). Pre-transplant laboratory testing revealed seroconversion to a chronic inactive carrier status as the HBeAg became negative and HBV-DNA titer was 32.15 copies/ml (range 31-145 copies/ml). Pre-transplant liver function tests revealed elevated alkaline phosphatase (ALP) at 210 IU/L (range 30-120 IU/L) but otherwise normal liver parameters with serum bilirubin 0.5 mg/dl (range 0.1-1.0 mg/dl), alanine aminotransferase (ALT) 28 IU/L (range 7-56 IU/L) and serum albumin 4.5 g/dL (range 3.5-4.8 g/dL). Percutaneous liver biopsy was performed and demonstrated mild fibrosis with no evidence of active hepatitis or malignancy.

She underwent successful cadaveric renal transplantation with no complications. Patient's HLA mismatch was 1-2-1, panel reactive antibody (PRA) was 10%, donor Cytomegalovirus (CMV) was positive, recipient CMV was negative and warm ischemia time was 40 minutes. The patient required dialysis on post-operative day-1 due to delayed graft function but graft function improved by post-operative day-3. Initial immunosuppressant consisted of anti-thymocyte globulin (ATG) 5 mg/kg intravenously (IV) over 4 hours once every 24 hours for 2 doses, followed by a dose of 2.5 mg/kg IV once every 24 hours for 6 dose, azathioprine 2.5 mg/kg/day IV, cyclosporine 5 mg/kg/12 hourly IV and then adjusted to maintain 12-hourly trough levels at 200 ± 250 mg/L and prednisolone 500 mg IV 12 hours following transplantation. Prednisolone dosage was tapered to 250mg IV twice daily for two days and reduced to a daily morning dose of 250 mg IV for another two days. Following this, the patient was switched to a daily dose of 20 mg oral prednisolone. Patient recovered without any complications and was discharged in stable condition on post-operative day-12. Discharge post transplant medications included daily oral dose of cyclosporin 475 mg, prednisolone 20 mg, acyclovir 400 mg, and frusemide 20 mg.

Two years post transplant, the patient had persistent elevated liver enzymes over 3-6 months period which prompted referral to the hepatology service. Liver function tests were as follows: serum bilirubin 1.0 mg/dl, ALT 84 IU/L and ALP 262 IU/L. lamivudin treatment was then started at a dose of 100 mg orally daily. Subsequent serology revealed seroconversion to an active carrier state once again with positive HBsAg and HBeAg markers. Follow-up over the following year revealed normalization of the liver enzymes with no clinical stigmata of chronic liver disease. However, active replication of HBV continued, with persistence of HBeAg positivity on serology tests. Polymerase Chain Reaction (PCR) for HBV-DNA showed high viral loads on three consecutive tests. After a period of nine months, lamivudin was discontinued due to poor patient compliance resulting from severe psychological problems. Computerized Tomography (CT) of the liver showed no active liver lesions. Percutaneous liver biopsy was performed and histology demonstrated mild portal fibrosis and mild hepatitis with no evidence of malignancy. Three years post-transplant, the patient was started on antiviral treatment consisting of entecavir 0.5 mg oral daily. At follow up clinic visits till present time, the patient is tolerating entecavir treatment with no reported side effects. Liver enzymes remained stable, but the effect on viral load and viral markers was unremarkable. She was also enrolled in a hepatocellular cancer (HCC) screening programme with annual liver ultrasound scans and serum alpha fetoprotein measurements to screen for any early HCC formation.

Discussion

HBV is a hepadna (hepatotrophic DNA) virus that uses reverse transcriptase for replication. Chronic HBV infection is associated with multiple hepatic complications including recurrent acute hepatitis, cirrhosis and hepatocellular carcinoma (HCC) and reactivation of HBV may result in fulminant liver failure [2, 3]. In the setting of renal transplantation, HBV infection has also been associated with decreased renal allograft survival [4]. Epidemiologically, it is estimated that the incidence of acute HBV infection is 1.5/100,000 population in the United States alone [5]. In the Irish setting, the health protection service center of Ireland reported an incidence of 1.9/100,000 population of acute HBV infection [6, 7].

In North America and Europe, the prevalence of HBV infection is 1% among hemodialysis and renal transplant recipients' patients [8]. Numerous studies examined renal transplantation with previous HBV exposure. A low rate of HBV reactivation (<1%) following renal transplantation was previously reported [9, 10]. However, in a study by Savas *et al*, they examined transplantation in inactive chronic carriers (HBsAg positive, HBV-DNA negative) and found a very high rate of reactivation of 14/20 patients (70%) at 16 months post-transplantation [11].

Complications related to chronic HBV infection should be appropriately managed whenever immunosuppressants are used in patients undergoing renal transplantation. Various antiviral medications have been used post-renal transplantation in patients who are chronic HBV carriers

including lamivudine, adefovir and entecavir and all were shown to provide better graft survival in both renal and liver transplants [12-15, 18]. Rostaing *et al* studied lamivudine therapy of HBV in cadaveric renal transplant recipients and subsequently promoted the concept of continuing therapy indefinitely [16]. However, Chan *et al* [17] reported only 21% seroconversion of HBeAg positivity on lamivudine therapy. Additionally, with the emergence of lamivudine-resistant HBV strains, the search for alternative therapies has been strongly advocated in the management of HBV infection in renal transplantation. In a study by Ridruejo *et al*, the efficacy and safety of entecavir in patient with chronic HBV infection undergoing renal transplantation was studied. Three kidney transplant recipients were followed over two-year period. Ridruejo's study has shown that entecavir therapy was associated with a significant decrease in HBV DNA viral load [6.84 ± 1.45 log10 UI/mL (range 5.21–9.04) at baseline, dropping at the time of evaluation to 1.73 ± 2.11 log10 UI/mL (range <0.78–4.72)] and concluded that entecavir therapy is safe and efficient in HBV-positive patients with varying degrees of renal dysfunction, particularly in the kidney transplant recipient [18].

Conclusion

In conclusion, HBV infection is an important consideration in patients undergoing renal transplantation given the risk of reactivation and the possibility of subsequent complications. More studies to further evaluate the various antiviral agents and the timing of administration of these agents in the setting of renal transplantation would be useful.

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