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Significant rate of hepatitis B reactivation following kidney transplantation in patients with resolved infection

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ABSTRACT

Background: Limited data is available on the risk of hepatitis B virus (HBV) reactivation in patients with resolved infection undergoing kidney transplantation. It is generally thought that this risk is negligible.
Objectives: To evaluate the incidence of HBV reactivation in such patients, and the potential risk factors for reactivation.
Study design: Retrospective cohort study including 93 patients transplanted with a kidney between 1995 and 2007 who had evidence of resolved HBV infection (HBsAg negative, anti-HBc positive, anti-HBs positive or negative, and normal liver enzymes). HBV reactivation was defined as HBsAg reversion with HBV DNA > 2000 IU/mL.
Results: Six patients experienced HBsAg reversion followed by HBV reactivation, 3 within the first post-transplant year. Immunosuppression regimen was similar in patients with and without reactivation. Among patients with reactivation only one was positive for anti-HBs antibodies at time of transplantation; these were progressively lost before reactivation. The odds ratio for reactivation in patients without anti-HBs antibodies at transplantation compared to those with anti-HBs antibodies was 26 (95% CI [2.8–240.5], $p = 0.0012$). In patients with anti-HBs antibody titer above 100 IU/L, no reactivation was observed.
Conclusions: Reactivation rate of resolved hepatitis B is not negligible in patients without anti-HBs antibodies at transplantation. We suggest monitoring of liver tests and HBV serology including HBsAg and anti-HBs antibodies after transplantation as well as vaccination pre- and post-transplantation in all patients, including those with resolved hepatitis B, aiming at maintaining anti-HBs antibody level above 100 IU/L.

1. Background

Hepatitis B virus (HBV) infection entails a significant rate of morbidity and mortality in kidney transplant recipients (KTRs).[1,2] After successful renal transplantation, the rate of spontaneous hepatitis B surface antigen (HBsAg) clearance is decreased compared to the general population.[3] Indeed, immunosuppression affects the T- and B-cell functions that are essential in the control of HBV infection, and steroids stimulate HBV replication by a direct effect on a glucocorticoid responsive element present in the HBV genome.[4–6] This results in persisting viral replication. HBV is not directly cytopathic; liver injury is determined by the host immune response.[7] Chronic hepatitis results in progressive liver fibrosis and increased mortality related to cirrhosis and hepatocellular carcinoma.[3,8] HBV reactivation is well described in recipients of bone marrow, liver or kidney transplantation with positive HBsAg and undetectable HBV DNA at time of transplantation.[3,9] By contrast, previous studies have suggested that the risk of reactivation is low in patients undergoing kidney transplantation with a previously resolved HBV infection characterized by negative HBsAg and positive antibodies against HBcAg (anti-HBc), with or without antibodies to HBsAg (anti-HBs). These studies have also suggested that, when reactivation occurs, its consequences are benign.[10–12]

Abbreviations: HBV, hepatitis B virus; KT, kidney transplantation; KTR, kidney transplant recipient; HBsAg, hepatitis B surface antigen; anti-HBs, antibodies against HBsAg; anti-HBc, antibodies against HBcAg; ALT, alanine aminotransferase; AST, alanine aspartate transferase.

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2. Objectives

The aims of our study were to evaluate the incidence of post-transplant HBV reactivation in patients who had previously cleared HBsAg and to identify potential risk factors for reactivation.

3. Study design

3.1. Study population

Retrospective cohort study included patients with previously resolved hepatitis B infection transplanted with a kidney at the Cliniques Universitaires Saint-Luc (Brussels, Belgium) between January 1995 and December 2007. Diagnostic criteria for resolved HBV infection at transplantation were: HBsAg negative, anti-HBc positive, anti-HBs positive or negative, and normal liver enzymes. HBsAg reversion was defined as the reappearance of HBsAg during follow-up. HBV reactivation was defined as HBsAg reversion with a serum HBV DNA > 2000 IU/mL.[13] Acute rejection was defined as an increase in creatinine with biopsy proven rejection that required treatment with glucocorticoids alone or associated to antithymocyte globulin.

3.2. Procedures and assays

All patients had a pre-transplant HBV serology up-to-date at time of transplantation. Post-transplant serological follow-up, including HBsAg, anti-HBs, anti-HBc was done at 3, 6, 12 months, and then annually, according to protocol. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were checked at every visit, and recorded at transplantation, 12 months, and end of follow-up. HBV DNA was measured in case of elevated aminotransferases and/or HBsAg reversion. In patients with HBV reactivation, ALT and AST were followed and recorded every 3 months. HBsAg, anti-HBs and anti-HBc antibodies were detected using the Abbott's immunodiagnostic system, previously the Abbott radioimmunoassay and presently the Abbott Architect assay. HBV DNA was tested using the Abbott HBV RealTime assay (Abbott Laboratories, North Chicago, IL, USA) with a dynamic range of 15 IU/mL to 1,000,000,000 IU/mL. In patients with HBV reactivation, HBV DNA was tested on pre-transplant serum samples that were collected immediately before transplantation, centrifuged, aliquoted and stored at −25 °C until analysis. HBV genotyping was performed using an in-house sequencing assay of the overlap S/P genes (703 bp fragment)[14] followed by querying against NCBI's sequence databases using the BLAST (blastn) web-based analysis tool (http://blast.ncbi.nlm.nih.gov/Blast.cgi), allowing simultaneous genotyping and detection of drug resistance mutations.

3.3. Statistics

Results are presented as median [percentile 25–percentile 75] or *n* and % as appropriate. Patient and graft survival rates were calculated using the Kaplan–Meier estimator. Univariate analyses were performed using Fisher's exact test, *t*-test, Mann–Whitney's *U*-test or odds ratios (ORs) as appropriate. Statistical analyses were performed using PASW 18.0 software. All tests were two-tailed and a *p*-value of <0.05 was considered as significant.

4. Results

4.1. Patient characteristics

The files of 764 KTRs were reviewed. Ninety-three patients (12%) were included (Table 1). All patients received 20 mg of prednisolone daily following transplantation, rapidly tapered to 5 mg/day at week 6.

Table 1
Characteristics of 93 patients with resolved HBV infection at the time of transplantation.

Age (years) median [P25–P75]	56[46–61]
Gender, *n* (%)	
Male	57 (61)
female	36 (39)
Geographical distribution, *n* (%)	
Northern Europe	45 (48)
Mediterranean area	33 (36)
Sub Saharan Africa	14 (15)
Other	1 (1)
Original disease, *n* (%)	
Glomerulonephritis	32 (34)
Diabetes	13 (14)
Interstitial nephropathy	10 (11)
Nephroangiosclerosis	5 (5)
Polycystic kidney disease	18 (19)
Other	15 16)
Previous transplantation, *n* (%)	3(3)
Combined transplantation, *n* (%)	5 (5)
Pancreas	4 (4)
Liver	1 (1)
Donors, *n* (%)	
Deceased	85 (91)
Living	8 (9)
Time on dialysis (years)	2.6 [1.1–4.1]
Type of dialysis, *n* (%)	
HD	76 (82)
PD	13 (14)

Prophylaxis against cytomegalovirus was administered for a period of 3 months in seronegative patient receiving a seropositive graft. Patients did not receive prophylaxis against Pneumocystis.

4.2. Patient and graft survival

Patients were followed after transplantation for a median time of 73 [44–114] months. Five and 10-year patient survival was 94.6% and 82.6% respectively. Ten patients died (4 from septic shock, 1 from cardiac and septic complications, 2 from cardiac causes, 2 from cancer, and one of unknown cause), 19–123 months after transplantation. Ten patients were treated for acute rejection episodes. Five and 10-year graft survival rates were 94.5% and 79.8% respectively. Two patients lost their graft from acute rejection and 4 from chronic allograft nephropathy.

4.3. HBsAg reversion and HBV reactivation (Table 2)

HBsAg reversion occurred in 6 patients (2 males and 4 females), followed by reactivation. All had received a graft negative for HBsAg. In 5 patients, HBV DNA was negative on pre-transplant serum, and the donor anti-HBc antibodies were negative. HBV genotype was D in 4 patients and A in one. The information was not available in one patient.

The viral load was high when reactivation was detected. HBeAg was positive in all patients at time of reactivation. In 5 patients (# 2–6), repeated HBV DNA testing after reactivation confirmed a sustained viremia. The median time between transplantation and HBsAg reversion was 2 [0.41–3.53] years.

4.4. Impact of reactivation (Table 2)

One patient with HBV reactivation died during follow-up from septic chock. Graft survival was not affected by HBV reactivation. ALT and AST serum levels were increased at reactivation (median ALT 29 [18–194] IU/L, AST 25 [18–102] IU/L), compared to their baseline levels (median ALT 12 [10–19] IU/L, AST 16 [13–21] IU/L),