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Original Articles

Rituximab and hepatitis B reactivation in HBsAg-negative/anti-HBc-positive kidney transplant recipients

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ABSTRACT

Background. Hepatitis B virus (HBV) reactivation is a well-known complication of immunosuppressive therapy. Although rituximab is increasingly used for desensitization of ABO-incompatible or positive crossmatch kidney transplantation, the risk of HBV reactivation in hepatitis B surface antigen (HBsAg)-negative/hepatitis B core antibody (anti-HBc)-positive kidney transplant patients receiving rituximab desensitization remains undetermined.

Methods. We analysed 172 resolved HBV patients who underwent living donor kidney transplantation between 2008 and 2014. Patients were divided into rituximab (n = 49) or control (n = 123) groups. All patients were observed for HBV reactivation, which was defined as the reappearance of hepatitis B surface antigen or HBV DNA.

Results. During the follow-up period (median, 58 months; range, 4–95 months), five patients (10.2%) in the rituximab group and two patients (1.6%) in the control group experienced HBV reactivation (P = 0.003). In the rituximab group, two patients experienced HBV-related severe hepatitis, and one patient died due to hepatic failure. The median time from rituximab desensitization to HBV reactivation was 11 months (range, 5–22 months). By contrast, no patients in the control group experienced severe hepatitis. The status of hepatitis B surface antibody was similar between groups. Rituximab desensitization [hazard ratio (HR), 9.18; 95% confidence interval (CI), 1.74–48.86; P = 0.009] and hepatitis B surface antibody status (HR, 4.74; 95% CI, 1.05–21.23, P = 0.04) were significant risk factors for HBV reactivation.

Conclusions. Rituximab desensitization for incompatible kidney transplantation significantly increased the risk of HBV reactivation in HBsAg-negative/anti-HBc-positive patients. Therefore, close monitoring of HBV DNA is required in these patients.

Keywords: hepatitis B virus, immunosuppression, kidney transplantation, reactivation, rituximab

INTRODUCTION

One-third of the world's population shows serological evidence of hepatitis B virus (HBV) infection, and more than 350 million people are chronic HBV carriers [1]. Despite the availability of effective antiviral agents, reactivation of HBV infection is a significant problem for chronic HBV patients who undergo immunosuppressive therapies [2].

In particular, although rituximab has greatly improved the prognosis of patients with haematologic malignancy, it is also associated with HBV reactivation [3, 4]. Furthermore, previous studies show that rituximab is associated with a high rate of HBV reactivation in so-called 'resolved HBV infection' [hepatitis B surface antigen (HBsAg)-negative, hepatitis B core antibody (anti-HBc)-positive] patients [5, 6]. Therefore, in September 2013, the US Food and Drug Administration released a new boxed warning that rituximab can lead to HBV reactivation [7].

Recently, B-cell depletion with rituximab has become an important component of desensitization for ABO-incompatible or positive crossmatch kidney transplantation [8]. However, despite the increasing use of rituximab, there is a lack of information regarding HBV reactivation in kidney transplant patients receiving rituximab [9].

With a high seroprevalence of anti-HBc worldwide and increasing use of rituximab in kidney transplantation, there is an urgent need to identify the risk of HBV reactivation in these populations. Therefore, we examined a cohort of kidney transplant patients from an HBV-endemic area to determine the frequency of and risk factors for HBV reactivation in HBsAg-negative/anti-HBc-positive patients who did or did not undergo rituximab desensitization.

MATERIALS AND METHODS

Patients and study design

A total of 599 adult patients who underwent living donor kidney transplantation under tacrolimus-based immunosuppression between January 2008 and September 2014 at Severance Hospital in Seoul, Korea were screened. HBsAg-negative, anti-HBc-positive and hepatitis B surface antibody (anti-HBs)-positive or -negative patients were selected. Exclusion criteria were co-infection with hepatitis C virus (HCV), a history of liver transplantation, use of mammalian target of rapamycin (mTOR) inhibitor, lack of data or a loss to follow-up. Included patients were divided into rituximab or control groups based on their treatment history. In the control group, patients receiving rituximab for antibody-mediated rejection (AMR) treatment were excluded.

Definitions of resolved HBV, HBV reactivation and severe hepatitis

We defined resolved HBV infection as HBsAg-negative/anti-HBc-positive patients without HBV DNA at the time of transplantation [2, 5, 10]. HBV reactivation was defined as the reappearance of HBsAg (HBsAg seroreversion) or HBV DNA after transplantation [11]. Severe hepatitis was defined as more than a 10-fold increase of serum alanine aminotransferase (ALT) above the upper limit of normal (ULN) or more than a 2-fold increase of bilirubin above the ULN. HBV-related severe hepatitis was defined as severe hepatitis with HBV reactivation, in the absence of laboratory features of acute infection with hepatitis A virus, HCV or cytomegalovirus.

Monitoring and treatment of HBV reactivation

Routine biochemical tests, including assessment of ALT, were performed every month for the first post-transplant year and every 3 months thereafter. All patients were screened for HBV (HBsAg, anti-HBs, anti-HBc and HBV DNA) and HCV before transplantation, and HBV markers (HBsAg and anti-HBs) were checked annually after kidney transplantation. HBsAg was also checked for patients with elevated serum ALT ($\geq$100 IU/L) during the follow-up. Additional assessment of HBV DNA was performed in cases of HBsAg seroreversion and/or ALT elevation.

Serum HBsAg, anti-HBc and anti-HBs were evaluated using commercially available enzyme immunoassays (Abbott Diagnostics, Abbott Park, IL, USA). Titers of serum anti-HBs $<$10 IU/L were considered negative. Serum HBV DNA was measured using real-time polymerase chain reaction assay on a Cobas TaqMan 48 Analyzer (Roche Molecular Systems, Branchburg, NJ, USA), with 20 IU/mL as the lower limit of detection.

No patients received prophylactic antiviral agents. Entecavir was started for patients who experienced HBV reactivation.

Immunosuppressive regimen

Rituximab was administered at a single dose (375 mg/m^2 or 200 mg) within 7 days before transplantation in cases of ABO-incompatible or positive crossmatch kidney transplantation. Patients with high panel reactive antibodies (PRA; having a PRA $>$50%) also received a single dose (375 mg/m^2 or 200 mg) of rituximab prior to transplantation. Rituximab dosage was reduced to 200 mg based on immunologic risk in August 2013 [i.e. for patients with high PRA, baseline antidonor isoagglutinin titer (anti-A and/or anti-B) $<$1:256, or flow cytometric positive crossmatch] [12].

Most patients received basiliximab for induction therapy. From 2013, we used anti-thymocyte globulin (ATG) for induction in positive crossmatch patients. The maintenance immunosuppressive regimen mostly consisted of tacrolimus and prednisolone with or without mycophenolate mofetil (MMF). Initial tacrolimus was administered orally at 0.1 mg/kg twice daily. Subsequent doses were adjusted to maintain a target trough concentration between 5 and 8 ng/mL. The initial dose of methylprednisolone (500–1000 mg) was tapered to oral prednisolone (5–10 mg/day) during the first 3 weeks after transplantation. The initial dose of MMF was 1.5 g/day, and this dose was adjusted to minimize adverse events, such as gastrointestinal trouble or leucopoenia. No patients received augmented immunosuppression.

Acute cellular rejection (ACR) was treated by methylprednisolone pulse therapy (500 mg/day, three to four times). Steroid-resistant ACR patients received ATG. AMR was treated with a combination of plasmapheresis and intravenous immunoglobulin with or without rituximab.

Statistical analysis

Demographic information was summarized using frequency (percentage), or mean $\pm$ standard deviation depending on data type. Chi-square or Fisher's exact tests were used as appropriate to compare categorical variables. Continuous variables were compared using Student's *t*-tests. Cumulative rates of HBV reactivation were estimated by the Kaplan–Meier method and statistically compared using log-rank tests. Univariate and multivariate analyses were performed using Cox proportional hazard regression models to determine risk factors for HBV reactivation. Statistical analysis was performed using SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered statistically significant.

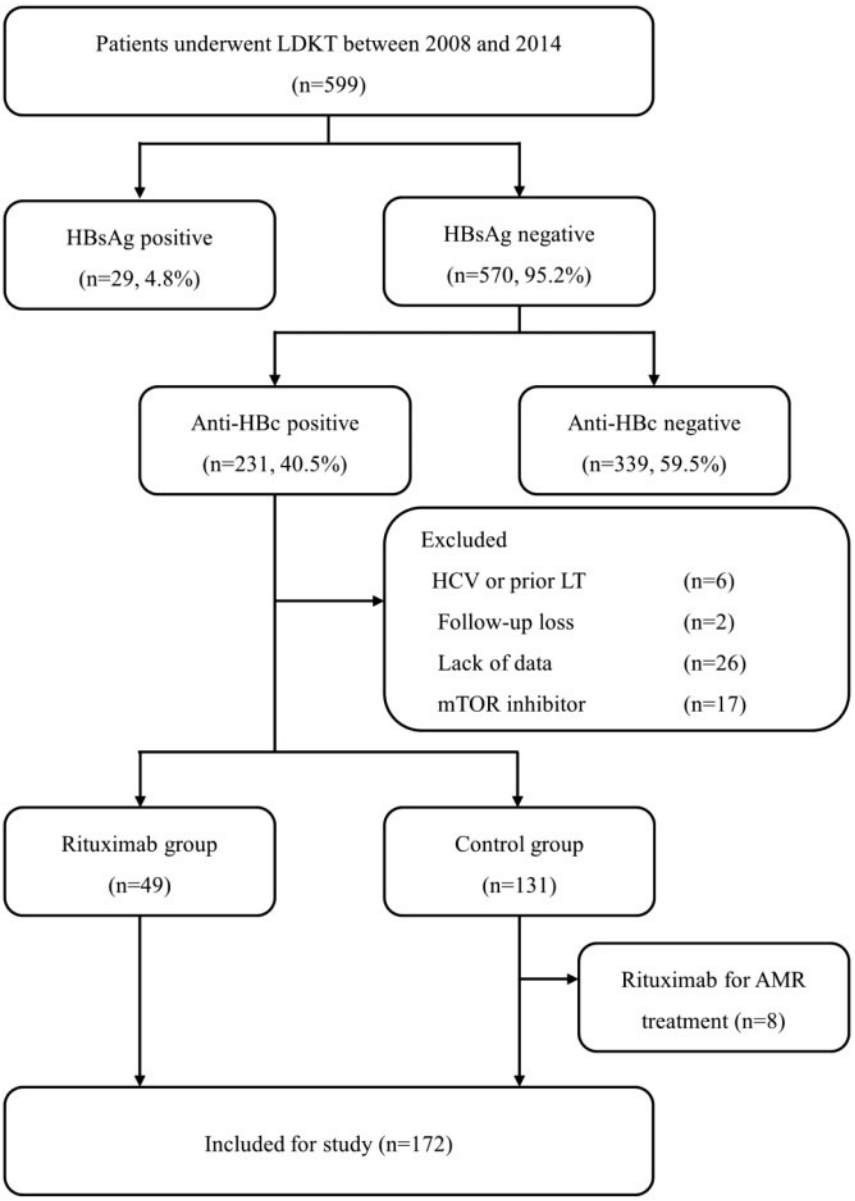

FIGURE 1: Study design. LDKT, living donor kidney transplantation; LT, liver transplantation.

Ethics statement

The study procedures were in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Severance Hospital (4-2015-0883).

RESULTS

Patient characteristics

A total of 172 patients were included in the analysis (Figure 1). Of these patients, 49 received rituximab for desensitization (31 patients with ABO-incompatible kidney transplantation, 12 patients with positive crossmatch kidney transplantation and 6 patients with high PRA). In all, 11 patients received a reduced dose of rituximab. Of these, three patients received rituximab twice, with the first dose for desensitization and the second dose for AMR treatment. The time intervals between the two doses of rituximab were 6, 31 and 39 months, respectively. The use of rituximab for desensitization increased rapidly across the study period (Figure 2).

Baseline characteristics of patients are presented in Table 1. There were no significant differences between the rituximab and control groups in age, dialysis method and dialysis duration. However, the proportion of female patients and the mean number of human leukocyte antigen mismatches were significantly higher in the rituximab group than in the control group. The proportions of anti-HBs-positive patients and donor anti-HBc-positive were similar between groups. Use of basiliximab was similar between groups, but the use of ATG was significantly more common for patients in the rituximab group than for patients in the control group. A total of 18 patients received ATG treatment during the study period. In the rituximab group, six patients (12.2%) received ATG for induction at the

time of transplantation. Further, seven patients (14.3%) of the rituximab group and five patients (4.1%) of the control group received ATG for anti-rejection treatment (P = 0.04). Furthermore, the follow-up duration for patients in the control group was significantly longer than that for patients in the rituximab group.

HBV reactivation and HBV-related severe hepatitis

HBV reactivation occurred in seven patients. A total of five instances of HBV reactivation occurred in the rituximab group (10.2%), and two instances occurred in the control group (1.6%, P = 0.003). In the rituximab group, there was no significant difference in rates of HBV reactivation between ABO-incompatible (3/31, 9.7%) and other sensitized patients (2/18, 11.1%). There was no HBV reactivation in patients who received a reduced dose of rituximab. However, differences in the incidence of HBV reactivation with different rituximab doses were not statistically significant (P = 0.57). The median time from rituximab desensitization to HBV reactivation among patients in the rituximab group was 11 months (range, 5–22 months). HBV reactivation in the two control patients occurred 24 and 48 months after transplantation, respectively. A couple of patients in the rituximab group experienced HBV-related severe hepatitis, whereas no HBV-related severe hepatitis occurred among control patients.

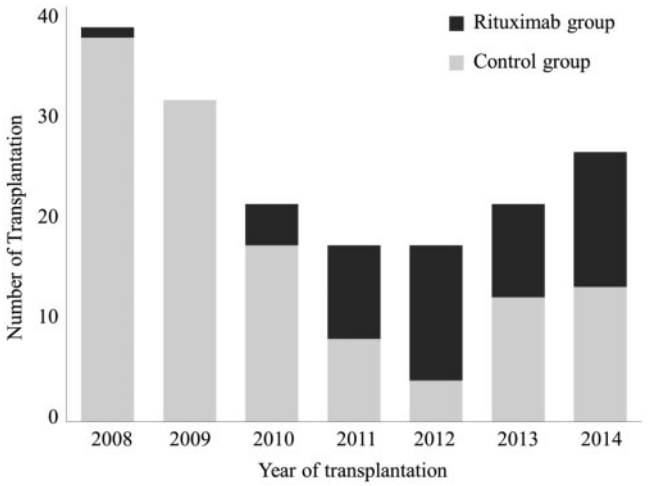

FIGURE 2: Increasing use of rituximab in patients undergoing kidney transplantation.

Clinical outcomes

Clinical features of the seven patients with HBV reactivation are shown in Table 2. Five patients received a single dose of rituximab 2–7 days before kidney transplantation. At the time of HBV reactivation, all patients were maintained on a triple immunosuppressant regimen consisting of tacrolimus, prednisone and MMF. Two patients (C and E) were treated for acute rejection prior to HBV reactivation. ACR was treated with methylprednisolone pulse therapy (500 mg/day, 4 days), and AMR was treated with a combination of plasmapheresis and intravenous immunoglobulin (200 mg/kg). Entecavir was initiated for patients who experienced HBV reactivation. Despite active antiviral treatment, one patient (B) died from hepatic failure 10 weeks after HBV reactivation. Another patient (D) died due to unknown cause 20 months after HBV reactivation.

Patterns of HBV reactivation for the five patients in the rituximab group are shown in Figure 3. The four patients (A, B, D and E) who experienced HBV reactivation during the first year after transplantation exhibited a hepatitis flare (i.e. serum ALT >100 IU/L) at the time of HBV reactivation. For the fifth patient (C), HBV reactivation was diagnosed 2 years after transplantation without a hepatitis flare.

Risk factor analysis for HBV reactivation

The induction agent and maintenance immunosuppressive regimens were similar between the rituximab and control groups. Mean serum tacrolimus trough levels were also similar between the groups (P > 0.05, Figure 4). Of the 18 patients who received ATG treatment, one patient (D) experienced HBV

Table 1. Baseline characteristics of patients

Variables	Rituximab group ($n = 49$)	Control group ($n = 123$)	P-value
Age (years)	50.7 ± 8.2	49.2 ± 10.3	0.36
Female, *n* (%)	21 (42.9)	33 (26.8)	0.04
Pre-emptive/HD/PD	14/31/4	42/58/23	0.10
Dialysis duration (months)	25.8 ± 45.2	18.6 ± 31.9	0.29
HLA mismatches	3.6 ± 1.6	3.0 ± 1.5	0.01
Retransplantation, *n* (%)	6 (12.2)	7 (5.7)	0.20
Anti-HBs positive (≥10 IU/L), *n* (%)	43 (87.8)	104 (84.6)	0.64
10–100	16	49	
100–1000	17	37	
≥1000	10	18	
Donor anti-HBc positive, *n* (%)	14 (28.6)	46 (37.4)	0.27
Induction			0.77
Basiliximab, *n* (%)	43 (87.8)	114 (92.7)	
ATG, *n* (%)	6 (12.2)	0	
No induction, *n* (%)	0	9 (7.3)	
ATG for anti-rejection treatment, *n* (%)	7 (14.3)	5 (4.1)	0.04
Follow-up duration (months)	37.5 ± 17.3	64.2 ± 25.2	<0.001

HLA, human leukocyte antigen; HD, haemodialysis; PD, peritoneal dialysis.

Table 2. Clinical features of seven patients with HBV reactivation

Patient	Age (years)	Sex	Baseline anti-HBs, (IU/L)	Rituximab	Rejection prior to HBV reactivation (months ago)	Time to reactivation (months)[a]	ATG use	HBV DNA (IU/mL) at diagnosis of HBV reactivation	Peak ALT (U/L)	Outcomes
A	48	M	265.65	375 mg/m^2 (ABOi)		11		$>1.7 \times 10^8$	641	Alive with functioning graft
B	59	M	13.56	375 mg/m^2 (ABOi)		5		$>1.7 \times 10^8$	340	Death due to liver failure
C	48	M	52.08	375 mg/m^2 (XM +)	ACR (21 months)	22		1.23×10^7	39	Alive with functioning graft
D	61	M	Negative (3.99)	375 mg/m^2 (ABOi)		5	Anti-rejection[b]	$>1.7 \times 10^8$	524	Death due to unknown cause
E	51	M	Negative (0.63)	375 mg/m^2 (XM +)	AMR (8 months)	12		4.94×10^7	237	Alive with functioning graft
F	61	M	Negative (1.22)	No		24		$>1.7 \times 10^8$	213	Alive with functioning graft
G	60	M	10.91	No		48		5.22×10^7	52	Alive with functioning graft

ABOi, ABO incompatible; M, male; XM, crossmatch.
[a]Starting from kidney transplantation.
[b]HBV reactivation occurred 2 months prior to ATG treatment.

reactivation. However, his HBV reactivation occurred 2 months prior to ATG treatment.

Factors associated with HBV reactivation were analysed using a Cox regression model. As shown in Table 3, negative anti-HBs at the time of transplantation and use of rituximab were significant independent risk factors for HBV reactivation. The cumulative rates of HBV reactivation, depending on rituximab desensitization and anti-HBs status, are shown in Figure 5.

DISCUSSION

A growing number of studies suggest that using rituximab to treat haematologic malignancies markedly increases the risk of HBV reactivation in HBsAg-negative/anti-HBc-positive patients [6, 10, 13]. At the same time, the off-label use of rituximab in kidney transplantation for desensitization and AMR treatment has increased [8]. Although rituximab-induced HBV reactivation can occur in both haematologic malignancy and kidney transplantation patients, there are some important differences between the two populations. Patients with haematologic malignancy receive multiple cycles of rituximab with or without other chemotherapy drugs, and HBV reactivation has been reported to occur after a median of six doses of rituximab [4]. By contrast, except for management of post-transplant lymphoproliferative disorder, rituximab is generally given as a single dose to patients undergoing kidney transplantation. Although a single dose of rituximab might be safe for immunocompetent individuals [14], it could be problematic in kidney transplant patients who receive concomitant T-cell immunosuppressive agents [11]. Previous studies demonstrate that even a low dose of rituximab can achieve B-cell depletion lasting more than 12 months in kidney transplant patients [15]. Therefore, for kidney transplantation patients, even a single dose of rituximab for desensitization could contribute to HBV reactivation [12].

To our knowledge, this is the first study to investigate HBV reactivation in kidney transplant patients who received rituximab for desensitization. Our findings indicate that HBsAg-negative/anti-HBc-positive patients are at risk for HBV reactivation after kidney transplantation. In addition, the use of rituximab desensitization and negative anti-HBs at the time of transplantation are important risk factors for HBV reactivation.

Immunosuppression enhances viral replication, leading to progressive liver failure [16]. Before the introduction of antiviral prophylaxis, the rates of HBV reactivation in HBsAg-positive patients after kidney transplantation ranged from 50 to 94% [2]. Thus, chronic HBV infection is considered a relative contraindication to kidney transplantation. However, the introduction of effective antiviral agents has improved transplant outcomes in chronic HBV patients [17, 18]. Recent guidelines recommend antiviral prophylaxis in HBsAg-positive patients, whereas little attention has been paid to patients with resolved HBV [19–22]. However, HBV reactivation after kidney transplantation in HBsAg-negative/anti-HBc-positive patients, particularly among those receiving rituximab [21, 23, 24], has not been well characterized [25–27]. Considering the economic burden of HBV and its lifelong treatment, universal prophylaxis in these patients should be carefully considered.

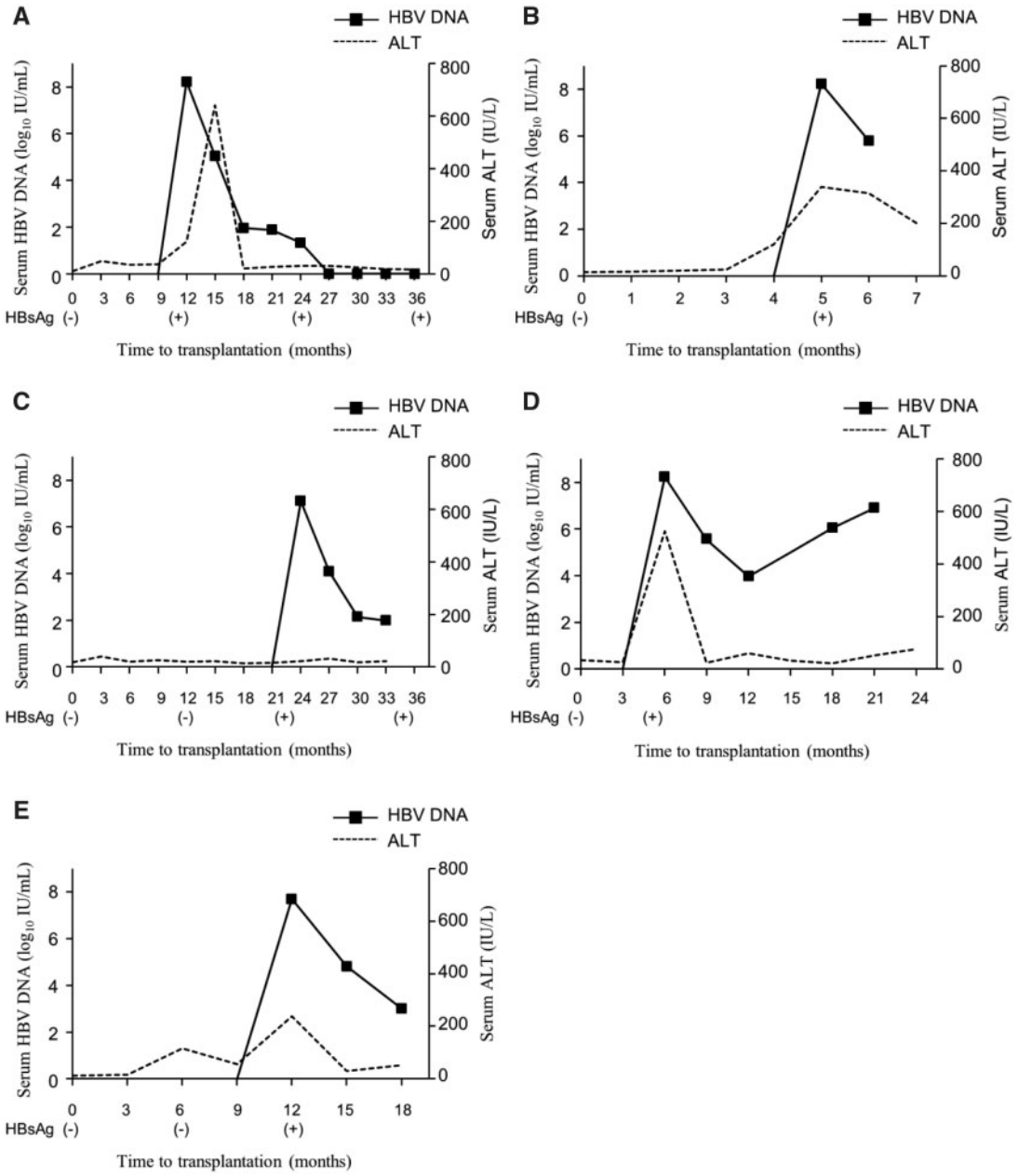

FIGURE 3: (**A**–**E**) Patterns of HBV reactivation for the five patients in the rituximab group.

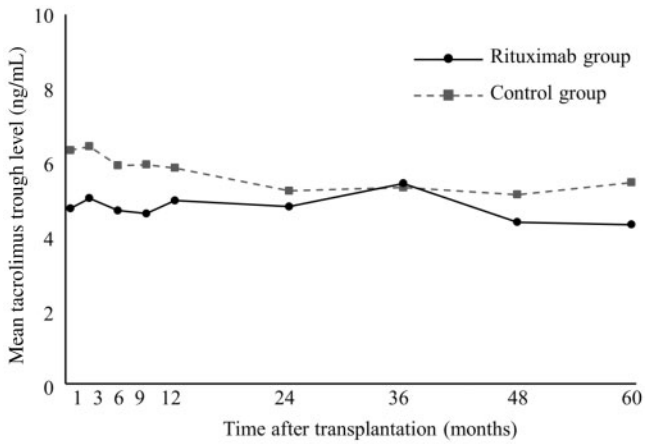

FIGURE 4: Mean trough level of tacrolimus.

Table 3. Risk factors for HBV reactivation

Factors	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Rejection	2.51 (0.54, 11.70)	0.24		
Use of ATG[a]	1.45 (0.17, 12.78)	0.74		
Use of rituximab	6.88 (1.29, 36.73)	0.02	9.18 (1.74, 48.46)	0.009
Negative anti-HBs	4.88 (1.02, 23.26)	0.05	4.738 (1.05, 21.23)	0.04
Donor anti-HBc positive	1.36 (0.26, 7.20)	0.72		

HR, hazard ratio; CI, confidence interval.
[a]ATG for both purposes of induction and anti-rejection treatment were included.

Rituximab is a chimeric anti-CD20 antibody that has mainly been used to treat non-Hodgkin's lymphoma, leukaemia and autoimmune disease. Although a relatively safe and well-tolerated drug, rituximab can lead to HBV reactivation in both

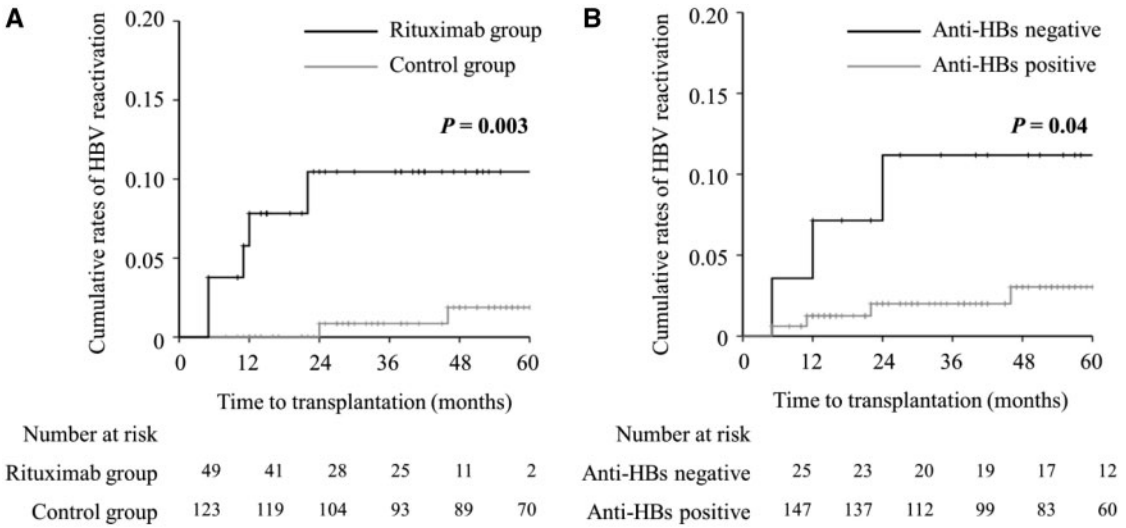

FIGURE 5: Cumulative rates of HBV reactivation depending on rituximab desensitization and anti-HBs status. (**A**) Rituximab group versus control group; (**B**) anti-HBs positive versus anti-HBs negative. Anti-HBs negativity was defined as <10 IU/L at the time of transplantation.

HBsAg-positive patients and HBsAg-negative/anti-HBc-positive HBV patients. Recent prospective studies show that the rate of HBV reactivation in HBsAg-negative/anti-HBc-positive patients undergoing rituximab-containing chemotherapy varies between 11.3 and 41.5% [5, 10, 13]. Furthermore, patients with autoimmune diseases who receive rituximab are also at risk of HBV reactivation [28, 29].

We found that the risk of HBV reactivation was significantly increased in patients who were anti-HBs negative at the time of transplantation. This finding is consistent with those from previous studies of kidney transplant recipients [25, 27] and rituximab-treated lymphoma patients [6, 10]. Anti-HBs prevents the entry of HBV into hepatocytes and is thought to protect against HBV reactivation [30]. However, although previous reports indicate that patients with pre-transplant anti-HBs antibody titres >100 IU/L are relatively safe, HBV reactivation has been observed in a patient with a high titer of anti-HBs (265.65 IU/L at transplant) [26, 27]. Therefore, in the rituximab era, patients with high titres of anti-HBs at the time of transplantation may still be at risk for HBV reactivation.

Our results suggest that regular HBV DNA monitoring is required for the detection of HBV reactivation and the start of early antiviral treatment in kidney transplant patients, even those receiving a single dose of rituximab. In fact, HBsAg seroreversion with or without ALT elevation occurs late in the clinical course of HBV replication [3, 31]. Despite the close monitoring of ALT levels in patients for the first year after transplantation, we observed multiple occurrences of HBV reactivation with a high viral load. Furthermore, one patient died from hepatic failure despite antiviral treatment, possibly because of a delay in antiviral administration [3]. In the event of HBV reactivation in patients receiving rituximab, it is recommended to immediately discontinue the drug and start appropriate treatment for HBV [7]. However, discontinuation of immunosuppression in patients with solid organ transplants is almost impossible, as this may lead to suboptimal therapeutic efficacy and can even jeopardize patients' lives. Thus, to prevent HBV-associated morbidity and mortality, resolved HBV patients should be closely monitored for HBV DNA after rituximab desensitization [6, 10].

The present study has some limitations. First, it was performed retrospectively at a single institution; however, this made it possible to maintain universal HBV screening and follow-up. Secondly, there was an imbalance between groups in immunological risk factors, as rituximab is more commonly used in highly sensitized patients who are at higher risk of rejection. This heterogeneity was inevitable, regardless of similar maintenance immunosuppressive regimen. Therefore, multivariate analyses were performed to adjust confounding factors.

In conclusion, the use of rituximab for desensitization significantly increased the risk of HBV reactivation in HBsAg-negative/anti-HBc-positive patients after kidney transplantation. Therefore, close monitoring of HBV DNA is required to prevent HBV-related morbidity and mortality. With the increasing use of rituximab desensitization in kidney transplantation, further prospective studies are warranted to confirm our findings and to develop appropriate prophylactic strategies.

CONFLICT OF INTEREST STATEMENT

None declared.

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