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Comparison of Clinical Outcomes in Hepatitis B Virus–Positive and –Negative Renal Transplant Recipients

Vural Taner Yilmaz[1], Ramazan Cetinkaya[1], Halide Akbas[2], Sebahat Ozdem[2], Burak Veli Ulger[3], Halil Erbis[4], Mehmet Bakirtas[5], İbrahim Aliosmanoglu[4], Gultekin Suleymanlar[1], Dilek Colak[6], Huseyin Kocak[1]

[1]*Division of Nephrology, Department of Internal Medicine, Akdeniz University Medical School, Antalya, Turkey*

[2]*Department of Biochemistry, Akdeniz University Medical School, Antalya, Turkey*

[3]*Department of General Surgery, Dicle University Medical School, Diyarbakir, Turkey*

[4]*Department of General Surgery, Akdeniz University Medical School, Antalya, Turkey*

[5]*Department of Internal Medicine, Akdeniz University Medical School, Antalya, Turkey*

[6]*Department of Microbiology, Akdeniz University Medical School, Antalya, Turkey*

Our aim was to compare the short- and long-term clinical outcomes of hepatitis B surface antigen–positive ($HbsAg^+$) renal transplant recipients with $HbsAg^-$ recipients. A total of 204 patients who underwent renal transplantation in our center between 2001 and 2014 were included in the study. The patients were divided into 2 groups. Group 1 was the $HbsAg^-$ group (n = 136), and group 2 was the $HbsAg^+$ group (n = 68). There was no significant difference between the groups in terms of lymphocyte crossmatches, numbers of mismatches, immunosuppressive treatment protocols, and induction treatments. In the $HbsAg^+$ group, 51 patients were hepatitis B virus DNA^+, 64 patients were $HbeAg^-$, and 4 patients were $HbeAg^+$. A total of 57 patients (83.8%) were treated with lamivudine, 4 patients (5.9%) with entecavir, and 7 patients (10.3%) with tenofovir for hepatitis B infection. Graft and patient survival rates, graft functions, acute

Corresponding author: Vural Taner Yilmaz, Division of Nephrology, Department of Internal Medicine, Akdeniz University Medical School, Antalya, Turkey.
Tel.: +90 242 2496122; Fax: +90 242 2224444; E-mail: vuraltaneryl@yahoo.com.tr

hepatitis rates, acute rejection rates, and other clinical outcomes of the groups were compared. Demographic data and immunologic risk profiles of the groups were similar. Acute rejection rates, graft survival rates, and patient survival rates were similar. Acute hepatitis rates, glomerular filtration rates on the last controls, and delayed graft function rates were higher in group 2, whereas chronic allograft dysfunction and new-onset diabetes mellitus after transplantation rates were similar between the groups. Our study revealed that graft and patient survival, and acute rejection rates were similar between $HbsAg^+$ and $HbsAg^-$ recipients, whereas acute hepatitis rate was higher in $HbsAg^+$ recipients.

Key words: Renal transplantation – Hepatitis B virus – Acute hepatitis – Acute rejection

Renal transplantation (Rtx) has many complications for patients with end-stage renal diseases whose hepatitis B surface antigen (HbsAg) is positive. Increased viral replication due to immunosuppressive treatment after Rtx can lead to viral reactivation, liver damage, liver cirrhosis, liver failure, hepatocellular carcinoma, superinfections, resistance to antiviral treatment, and increased risk for infections.[1–5] Additionally, hepatitis B virus (HBV)-related glomerulonephritis, *de novo* glomerulonephritis, graft dysfunction, and graft loss can develop.[6–8]

Many studies have been performed in order to determine the effects of HBV infection on graft or survival rates and liver complications after Rtx to HBV^+ patients.[1,9–17] Also, the effectiveness of antiviral treatment, interferon, or nucleoside analogues in HBV^+ patients have been demonstrated by some authors.[16–22]

In asymptomatic $HbsAg^+$ Rtx recipients, it has been shown that progression to cirrhosis has occurred and chronic active hepatitis rates have increased, whereas chronic persistent hepatitis rates have decreased. It was also shown that 36% of the mortalities occurred because of the liver diseases.[23–25]

In our study, we evaluated and compared the patient and graft survival rates, acute rejection rates, acute viral hepatitis rates, and other liver complications of the Rtx recipients who were $HbsAg^+$ and those who were $HbsAg^-$. Moreover, we compared the outcomes of the patients whose HBV DNA was positive with the patients whose HBV DNA was negative. Additionally, we compared the outcomes of different antiviral treatments.

Patients and Methods

A total of 204 patients who underwent renal transplantation in our center between 2001 and 2014 were included in the study. The patients were divided into 2 groups. Group 1 was the $HbsAg^-$ group [n = 136; male-female ratio, 97:39 (71.3% versus 28.7%)], and group 2 was the $HbsAg^+$ group [n = 68; male-female ratio: 53:15 (77.9% versus 22.1%)]. Shown in Table 1 are the mean patient ages (group 1 versus group 2, respectively: 36 ± 11 years versus 37 ± 10 years; $P = 0.708$); patient sex distributions ($P = 0.313$); donor body mass indexes (group 1 versus group 2: 25.7 ± 4.3 versus 25.2 ± 3.1; $P = 0.595$); glomerular filtration rates (GFRs) of the transplanted kidney (measured with DTPA scintigraphy; group 1 versus group 2: 44.4 ± 14.4 versus 43.4 ± 16.5; $P = 0.819$); etiology of the chronic kidney diseases ($P = 0.189$); distribution of the renal replacement treatments ($P = 0.323$); source of the donors [cadaveric/living, respectively: group 1, 16:120 (11.8% versus 88.2%); group 2: 13:55 (19.1% versus 80.9%); $P = 0.156$]; lymphocyte crossmatch results ($P = 0.594$); number of mismatches ($P = 0.774$); immunosuppressive treatment protocols ($P = 0.402$); and distribution of the induction treatment ($P = 0.838$). Hypertension, glomerulonephritis, and diabetes mellitus were the leading three diseases in the etiology of chronic kidney diseases (for the patients with a known etiology).

Measurement of plasma HBV DNA by real-time polymerase chain reaction

HBV DNA was isolated from plasma specimens using the RealArt HBV RG RT-PCR (Reverse Transcription Polymerase Chain Reaction) kit (Qiagen, Valencia, California) with adaptations to the manufacturer's protocol. The HBV DNA real-time assay was performed with the real-time PCR instrument Rotor-Gene 3000 (Qiagen, Hilgen, Germany).

Table 1 Demographic features for 2 groups

Parameters	HBV^- group (n = 136)	HBV^+ group (n = 68)	*P* value
Recipient sex, n (%)			0.313
Male	97 (71.3)	53 (77.9)	
Female	39 (28.7)	15 (22.1)	
Gender donors, n (%)			0.802
Male	68 (50)	33 (48.5)	
Female	68 (50)	35 (51.5)	
Age of recipients, y (mean±SD)	36 ± 11	37 ± 10	0.708
Age of donors, y (mean±SD)	41 ± 11	44 ± 15	0.208
BMI of donors (mean±SD)	25.7 ± 4.3	25.2 ± 3.1	0.595
Source of donors, n (%)			0.156
Cadaveric	16 (11.8)	13 (19.1)	
Living	120 (88.2)	55 (80.9)	
GFR of transplanted kidney, mL/min (mean±SD)	44.4 ± 14.4	43.4 ± 16.5	0.819
Etiology of CKD, n (%)			0.189
DM	10 (7.4)	4 (5.9)	
HT	19 (14)	14 (20.6)	
CGN	15 (11)	12 (17.6)	
Cystic renal disease	9 (6.6)	4 (5.9)	
Unknown	39 (28.7)	23 (33.8)	
Other	44 (32.3)	11 (16.2)	
RRT modalities, n (%)			0.323
Preemptive	20 (14.8)	12 (17.6)	
HD	98 (72.6)	45 (66.2)	
PD	15 (11.1)	7 (10.3)	
HD + PD	2 (1.5)	4 (5.9)	
LCM^-/IgM^+, n (%)	133/3 (97.8/2.2)	65/3 (95.6/4.4)	0.594
Mismatch numbers, n (%)			0.774
0	8 (5.9)	2 (2.9)	
1	1 (0.7)	2 (2.9)	
2	13 (9.6)	6 (8.8)	
3	44 (32.4)	22 (32.4)	
4	25 (18.4)	13 (19.1)	
5	27 (19.9)	11 (16.2)	
6	18 (13.2)	12 (17.6)	
İmmunosupressive protocols, n (%)			0.402
TAC + MPA	80 (58.8)	34 (50)	
CSA + MPA	34 (25)	15 (22.1)	
TAC + SRL + MPA	3 (2.2)	5 (7.4)	
TAC + EVE + MPA	3 (2.2)	2 (2.9)	
CSA + EVE + MPA	7 (5.1)	5 (7.4)	
CSA + SRL + MPA	9 (6.6)	7 (10.3)	
Induction therapy, n (%)			0.838
No	35 (25.7)	15 (22.1)	
Daclizumab	15 (11)	6 (8.8)	
Basiliximab	63 (46.3)	33 (48.5)	
ATG	23 (16.9)	14 (20.6)	
Total follow-up time, months (mean±SD)	64.6 ± 43.7	63.2 ± 37.9	0.940

ATG, antithymocyte globulin; BMI, body mass index; CGN, chronic glomerulonephritis; CKD, chronic kidney disease; CSA, cyclosporine; DM, diabetes mellitus; EVE, everolimus; HD, hemodialysis; HT, hypertension; IgM, immunoglobulin M; LCM, lymphocyte crossmatch; MPA, mycophenolic acid; PD, peritoneal dialysis; RRT, renal replacement therapy; SRL, sirolimus; TAC, tacrolimus.

Measurement of serum hepatitis B serologic markers

Electrochemiluminescence immunoassay technique (Roche Modular Analytics E170 Immunoassay Analyser, Roche Diagnostics GmbH, Mannheim, Germany) was used to measure HBV markers (HBsAg, HBsAb, HBeAg, and HBeAb) according to the manufacturer's instructions.

Measurements of biochemical parameters

Serum levels of creatinine, glucose, albumin, alanine aminotransferase (ALT), and urinary total protein

were measured with a Roche Cobas 8000 autoanalyzer (Roche Diagnostics) using modified Jaffe, standard hexokinase, bromocresol purple colorimetric, enzymatic assay, and benzethonium chloride methods, respectively. The estimated GFR value was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[26]

In $HbsAg^+$ group, all of the patients were $HbsAg^+$ and $HbsAb^-$; 64 patients were $HbeAg^-$ and $HbeAb^+$; and 4 patients were $HbeAg^+$ and $HbeAb^-$. HBV DNA was positive in 51 patients, whereas it was negative in 17 patients. The patients who were HBV DNA^+ received preemptive antiviral treatment, whereas HBV DNA^- patients received prophylactic antiviral treatment only after the renal transplantation. A total of 57 patients (83.8%) were treated with lamivudine, 4 patients (5.9%) with entecavir, and 7 patients (10.3%) with tenofovir for hepatitis B infection.

After transplantation, the patients were followed up weekly in the first 3 months, once every 2 weeks in the 3- to 6-month period, monthly in the 6- to 12-month period, once every 45 days in the 12- to 18-month period, once every 2 months in the 18- to 24-month period, and then once every 3 months. All of the patients who were $HbsAg^+$ were consulted to the gastroenterology department before transplantation. All determinations and imagings that were associated with HBV serology were performed. Patients who received approval for transplantation from the gastroenterology department were informed in detail, and another written consent was obtained. During the follow-up, all of the patients were monitored closely in terms of probable liver complications. A 5-fold increase in serum ALT levels and an increase of HBV DNA titer were determined as episode of acute hepatitis, only after excluding the possible diseases in which ALT levels were increased.

Tacrolimus (0.15 mg/kg/d in 2 equal doses), cyclosporine (6–8 mg/kg/d in 2 equal doses), sirolimus (2 mg/d), and everolimus (2× 1 mg/d) were administered for immunosuppression, and the dosage was adjusted according to the serum drug levels. On the day of operation, 1000 mg of prednisolone was administered intravenously prior to the operation, and it was continued as 500, 250, 160, 80, 40, and 20 mg on consecutive days. It was given 20 mg/d up to the 30th day; 17.5 mg/d in the second month; 15 mg/d in the third month; 10 mg/d in the fourth to sixth months; 7.5 mg in the sixth to twelfth months; and 5 mg/d after 1 year. In calcineurin inhibitor (CNI) and m-TOR inhibitor (m-TORi) combination therapies, CNI + mycophenolic acid (MPA) derivatives were used in first 5 days, and on the fifth day MPA was stopped and m-TORi treatment was added and continued up to the 80th day. On the 80th day, MPA derivatives were added to the therapy, with 25% dose reduction, and at the end of the third month, therapy was continued as m-TORi + MPA + prednisolone with dose titration.

Diagnosis of acute rejection was confirmed with biopsy, and Banff classification was used for determination. Pulse prednisolone was administered for treatment of acute rejection, and antithymocyte globulin was given to the patients who did not response to prednisolone. Plasmapheresis was administered to the resistant cases. Loss of the patient was noted as graft loss as well. The patients with graft loss were excluded from the study after the time of graft loss. Proteinuria was measured by collecting urine for 24 hours. GFR was measured by MDRD formula. New-onset diabetes mellitus after transplantation (NODAT) was diagnosed according to the 2003 American Diabetes Association criteria.[27] Additionally, subgroup analysis was performed for $HbsAg^+$ patients, immunosuppressive treatment protocols (classic CNI-based regimen and mTORi-based regimen), transplantations from deceased donors and living donors, and recipients whose HBV DNA titers were positive or negative.

Statistical Analysis

The study data were analyzed using SPSS 15.0 (SPSS Inc, Chicago, Illinois) software. Continuous variables were expressed as mean ± SD, and categoric variables were expressed as number (%). Student *t*-test was used for continuous variables, and χ^2 test was used for categoric variables. All hypotheses were bidirectional, and critical alpha value was accepted as 0.05. Patient and graft survival after transplantation were calculated using Kaplan-Meier survival curves and compared using the log-rank test.

Results

There was no significant difference between the groups in terms of demographic data and immunologic risk profiles (Table 1). The mean preoperative HBV DNA titer of the patients was 69.5 copies per milliliter (range, 0–744,960 copies per milliliter). No acute viral hepatitis developed in $HbsAg^-$ patients,

Table 2 Comparison of different clinical outcomes between groups

Parameters	HBV^- group	HBV^+ group	*P* value
DGF, n (%)	4 (4.2)	15 (22.1)	0.005
Acute rejection rate, n (%)	29 (21.4)	6 (8.8)	0.072
Graft loss, n (%)	14 (10.3)	5 (7.4)	0.496
Patient loss, n (%)	5 (3.7)	1 (1.5)	0.379
CAD, n (%)	4 (2.9)	2 (2.9)	1
NODAT, n (%)	14 (10.3)	5 (7.4)	0.496
Graft survival, %			0.579
1-y	96	96.8	
3-y	92.4	96.8	
5-y	91.3	93.9	
10-y	83.8	87.5	
Patient survival, %			0.349
1-y	97.7	97.1	
3-y	97.7	97.1	
5-y	96.3	97.1	
10-y	94.7	97.1	
Acute hepatitis, n (%)	0	4 (5.9)	0.004
Latest control			
Cr, mg/dL, median (min–max)	1.3 (0.6–13)	1.2 (0.6–6)	0.098
Glucose, mg/dL, mean±SD	98 ± 39	95 ± 44	0.170
GFR (MDRD), mL/min, mean±SD	56.8 ± 27.2	66.6 ± 29.1	0.016
Albumin, g/dL, mean±SD	4.3 ± 0.5	4.3 ± 0.4	0.865
ALT, U/L, median (min–max)	16 (4–79)	22 (5–149)	0.006
Proteinuria, mg/d, median (min–max)	188 (55–7460)	171 (40–4700)	0.467

CAD, chronic allograft dysfunction; Cr, creatinine; DGF, delayed graft function.

whereas 4 of the patients (5.9%) who were $HbsAg^+$ developed acute viral hepatitis ($P = 0.004$; Table 2). Three of the patients who developed acute viral hepatitis were being treated with lamivudine, and one of the patients was being treated with tenofovir. The mean preoperative HBV DNA titer of these patients was 69 copies per milliliter (range, 0–3250 copies per milliliter). The mean time for developing acute hepatitis was 21 months (range, 4–89 months) after transplantation. During the acute hepatitis period, serum ALT levels increased at least up to 5-fold, and the mean DNA titer was 320,002,560 copies per milliliter (range, 1146–989,400,000 copies per milliliter). During follow-up, patients with acute hepatitis improved after the reduction of immunosuppression and other conservative actions. The serum ALT levels came down to normal levels. The mean HBV DNA titer of these patients at their last follow-up was 688 copies per milliliter (range, 0–15,590,000 copies per milliliter). None of the $HbsAg^+$ patients, including the patients who developed acute viral hepatitis, and none of the control group patients developed cirrhosis, hepatocellular carcinoma, or other liver-associated complications and mortality.

Biopsy-proven acute rejection rates of the groups were not statistically different [group 1, 29 (21.4%) versus group 2, 6 (8.8%); $P = 0.072$; Table 2]. Additionally, the drugs that were used for treatment of acute rejection, and the response rates of the groups to the treatment were similar.

There was no significant difference between the groups in terms of graft loss rates [group 1, 14 (10.3%) versus group 2, 5 (7.4%); $P = 0.496$]. The etiology of the graft loss was rejection in 9 patients and patient loss in 5 patients in group 1, whereas it was rejection in 4 patients and patient loss in 1 patient in group 2. No graft loss was developed in patients who developed acute hepatitis. Graft survival rates of the groups were similar (group 1 versus group 2, respectively: 96% versus 96.8% in the first year; 92.4% versus 96.8% in the third year; 91.3% versus 93.9% in the fifth year; and 83.8% versus 87.5% in the tenth year; $P = 0.579$; Table 2 and Fig. 1).

Patient loss rates for the groups were also similar [group 1, 5 (3.7%) versus group 2, 1 (1.5%); $P = 0.379$]. Patient loss was due to myocardial infarction for 2 patients, pulmonary embolism in 1 patient, and infection in 1 patient in group 1, whereas 1 patient died of myocardial infarction in group 2. Patient survival rates of the groups were similar (group 1 versus group 2, respectively: 97.7% versus 97.1% at the first year; 97.7% versus 97.1% at the third year; 96.3% versus 97.1% in the fifth year; and 94.7% versus 97.1% at the tenth year; Table 2 and Fig. 1).

Delayed graft function rates were higher in group 2 [group 1, 4 (4.2%) versus group 2, 15 (22.1%); $P = 0.005$). The rates of chronic allograft dysfunction [group 1, 4 (2.9%) versus group 2, 2 (2.9%)] and development of NODAT [group 1, 14 (10.3%) versus group 2, 5 (7.4%)] were similar between the groups (Table 2). In terms of malignancy after transplantation, only 1 patient in group 1 developed basal cell carcinoma. Cytomegalovirus infection developed in 3 patients in group 1, and virus–associated nephropathy developed in 1 patient in group 1.

In the patients' last follow-up, serum creatinine levels, fasting blood glucose levels, and albumin levels were similar between the groups. GFR and serum ALT levels were higher in $HbsAg^+$ group (Table 2).

Subgroup analyses of the immunosuppressive treatment protocols revealed that the acute hepatitis

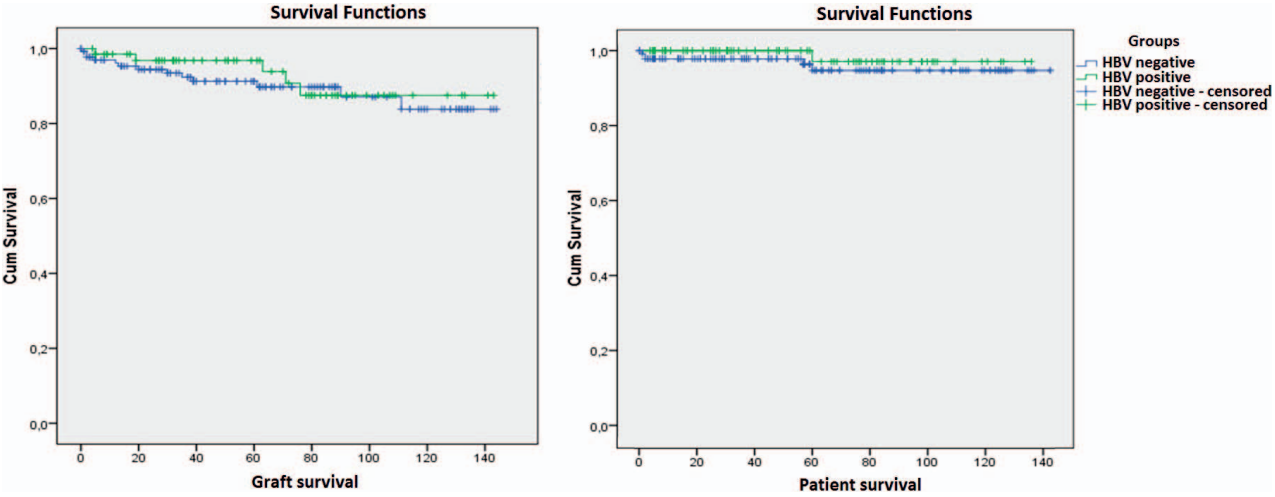

Fig. 1 Graft and patient survival curves for groups.

development rate was significantly higher in an mTORi-based regimen than in a classical CNI-based regimen [group 1, 3 (15.8%) versus group 2, 1 (2.0%); $P = 0.031$]. Another subgroup analysis was performed in the $HbsAg^+$ group between the patients whose HBV DNA titer was positive (n = 51) and the patients whose HBV DNA titer was negative (n = 17). There was no statistical difference between these groups in terms of episodes of acute hepatitis ($P = 1$), acute rejection rates ($P = 0.139$), graft loss ($P = 0.789$), patient loss ($P = 0.561$), graft survival ($P = 0.630$), and patient survival ($P = 0.489$).

Discussion

Our study revealed that, graft survival rate, patient survival rate, and acute rejection rate were similar between $HbsAg^+$ and $HbsAg^-$ Rtx recipients, but acute hepatitis rate was higher in $HbsAg^+$ recipients. None of the patients developed liver cirrhosis, liver failure, hepatocellular carcinoma, or other liver-associated complications; mortality or graft loss due to liver-associated complication; or HBV-related glomerular pathology.

Delayed graft function rate was higher in the $HbsAg^+$ group, whereas chronic allograft dysfunction rate, NODAT rate, cytomegalovirus infection rate, and BK virus nephropathy rate were similar between the groups.

Viral replication and reactivation can develop in HBV^+ Rtx recipients because of immunosuppressive drugs, and this can result in many liver pathologies, such as liver cirrhosis and liver failure.[1,9,10,23,28,29] Acute viral hepatitis develops more often in patients who are $HbsAg^+$.[30] Some studies have revealed the correlation between preoperative viral load and progression of liver complications and hepatocellular failure after Rtx.[9,10] In our study, acute viral hepatitis development rate was higher in $HbsAg^+$ patients, but none of the patients developed liver-associated complications.

Additionally, liver functions came down to normal values through a conservative approach, and no complications developed. So, we did not need to change the antiviral treatment. We thought that this result may be due to the patient groups, the choice of immunosuppressive drug and desired drug levels, the preoperative viral loads of the patients, or the treatments for rejection after Rtx. The current adopted approach in recipients who develop acute hepatitis is to reduce or stop immunosuppressive treatment or to switch CNIs to m-TOR inhibitors. But in our study, acute hepatitis rate was higher in recipients who were using m-TOR–based immunosuppressive treatment.

We compared the patients whose preoperative HBV DNA titer was negative with the patients whose preoperative HBV DNA titer was positive (in various levels) by subgroup analysis. Acute hepatitis rate, acute rejection rate, graft, and patient survival rate were found to be similar to those for $HbsAg^-$ patients. We thought that this may be due to the specifications of the patient group and may be a result of administering antiviral treatment to all patients.

Viral reactivation usually develops in the first year after transplantation.[9,31–33] Usage of higher doses of immunosuppressive drugs after Rtx in the

first year is the major cause of this situation. In our study, acute hepatitis developed in the first year in 1 patient, and in the second year in the other patients.

In a study that determined the antiviral drugs' effectiveness in $HbsAg^+$ Rtx recipients, it was shown that HBV DNA clearance was increased, ALT levels came down to normal, and progression of liver disease was slowed down with antiviral treatment.[17] In another study, effectiveness of prophylactic and preemptive antiviral treatments was compared. No liver disease–associated mortality was developed in the antiviral treatment–positive group. Patient and graft survival rates of the groups were similar, but reactivation rate was shown to be higher in the prophylactic antiviral treatment group.[34] In another study, risk of hepatocellular carcinoma or liver complications and acute rejection rate were found to be reduced with lamivudine treatment, whereas graft and patient survival rates increased.[18] In our study, except for the 4 patients who developed acute viral hepatitis and finally achieved remission, no liver complication developed. We thought that this was closely associated with the use of antiviral drugs in all patients. In accordance with previous studies, our study revealed that Rtx can be performed safely in the $HbsAg^+$ chronic kidney disease patients, with administration of antiviral treatment.

There are many studies with different results that determine the effects of HbsAg positivity on patient survival rate in Rtx recipients.[11] Some studies revealed that 5-year patient survival rate was worse in $HbsAg^+$ patients, whereas another study revealed that HbsAg positivity had no impact on patient survival rate.[12–16] However, a study has revealed that 5-year patient and graft survival rates were similar between $HbsAg^+$ and $HbsAg^-$ patients.[1] Ahn *et al*[16] revealed that 27 $HbsAg^+$ recipients' (who were treated with lamivudine) graft and patient survival rates were similar to those of the $HbsAg^-$ patients. HbsAg positivity was shown to be an independent risk factor on 10-year patient survival rate,[17] and lamivudine treatment was shown to improve survival rate.[19,35] In our study, we found that there was no significant difference between the groups in terms of patient and graft survival rates. We thought that it was a result of administration of antiviral treatment.

Although there are not many studies on acute rejection rate in $HbsAg^+$ Rtx recipients, lamivudine treatment was shown to decrease the rejection rate.[4] In our study, acute rejection of the groups were similar.

In our study, comparisons in terms of graft functions revealed that GFR at the last follow-up was higher in the $HbsAg^+$ group, whereas postoperative first-, third-, sixth-, and twelfth-month GFR, and third-year GFR were similar between the groups.

In conclusion, graft and patient survival rates of $HbsAg^+$ recipients and $HbsAg^-$ recipients are similar, but the acute hepatitis rate is higher in $HbsAg^+$ recipients. Additionally, antiviral treatment plays an important role in preventing liver-associated complications after Rtx.

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