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Adefovir- or Lamivudine-Induced Renal Tubular Dysfunction after Liver Transplantation

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Abstract: To reduce hepatitis B virus reinfection after liver transplantation (LT), patients often receive antihepatitis B immunoglobulin (HBIG) alone or combined with antiviral nucleoside/nucleotide analogs (NUCs); however, proximal renal tubular dysfunction (RTD) that was induced by NUCs in liver recipients was rarely reported. Here, we analyzed RTD and renal impairment (RI) following adefovir (ADV) and lamivudine (LAM) treatment in liver recipients.

We retrospectively reviewed medical records of patients treated with HBIG alone (group 1, n = 42) or combined with ADV or LAM (group 2, n = 21) after LT. We compared RTD and RI incidence during the 12 months after LT. An RTD diagnosis required manifestation of at least 3 of the following features: hypophosphatemia, RI, hypouricemia, proteinuria, or glucosuria.

No significant differences were observed regarding sex, age, donor type, model of end-stage liver score, and estimated glomerular filtration rate at pre-LT between the 2 groups. Hepatitis B virus recurrence within 12 months was 4.8% in both groups ($P = 1.000$); however, the RTD incidence was 0% in group 1 and 19.0% in group 2 ($P = 0.010$). RI occurrence did not differ between the groups. The only risk factor for RI was HBIG administration combined with both LAM and ADV (odds ratio 11.27, 95% confidence interval 1.13–112.07, $P = 0.039$, vs HBIG alone).

RTD occurred more frequently in patients treated with HBIG combined with LAM or ADV compared with HBIG alone. Thus, LAM or ADV therapy can induce RTD after LT, and when administered, liver recipients should be monitored.

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Abbreviations: ADV = adefovir dipivoxil, CNI = calcineurin inhibitor, eGFR = estimated glomerular filtration rate, ETV = entecavir, HBIG = antihepatitis B immunoglobulin, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LAM = lamivudine, LT = liver transplantation, NUCs = nucleoside/nucleotide analogues, RI = renal impairment, RTD = renal tubular dysfunction, S-Cr = serum creatinine, TAC = tacrolimus.

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INTRODUCTION

Prevention of hepatitis B virus (HBV) recurrence is important after liver transplantation (LT) in patients infected with the virus. To reduce HBV reinfection following LT, antihepatitis B immunoglobulin (HBIG) alone or in combination with antiviral nucleoside/nucleotide analogs (NUCs) is often used as prophylaxis[1,2]; however, NUCs are known to be nephrotoxic.[3] In particular, chronic hepatitis B patients treated with adefovir dipivoxil (ADV) or lamivudine (LAM) have frequently reported renal dysfunction and hypophosphatemia.[4–6] The liver recipients are more vulnerable to nephrotoxicity than other patients due to pretransplant liver cirrhosis, perioperative bleeding and hypotension, posttransplant calcineurin inhibitor (CNI) use, and infection.[7,8] Renal dysfunction after LT is a very common adverse effect[8] and key prognostic factor of post-LT survival.[9] Although nephrotoxic agents in liver recipients are used with caution, several studies have reported nephrotoxicity following LAM and ADV treatment.[10–12] The aim of the current study was to investigate LAM- and ADV-induced nephrotoxicity in liver recipients through retrospective review and analysis of incidence, clinical features, risk factors, prognosis of proximal renal tubular dysfunction (RTD), and renal impairment (RI).

PATIENTS AND METHODS

Patients and Groups

Medical records of liver recipients with HBV who underwent LT in Yonsei University Severance Hospital between September 2005 and December 2012 were retrospectively reviewed. To minimize confounder effects to estimated glomerular filtration rate (eGFR), we excluded the following patients with the following characteristics: <15 years old, multiorgan transplantation, retransplantation, hepatitis C virus coinfection, perioperative mortality, cyclosporine treatment instead of tacrolimus (TAC), and low eGFR (<60 mL/min/1.73 m^2). We reviewed 63 liver transplant recipients who had undergone prophylactic treatment with HBIG, LAM, or ADV continuously without change for a minimum of 12 months. Liver recipients were divided into 2 groups according to whether they were treated with or without ADV and LAM. Group 1 included recipients who were administered HBIG alone, whereas Group 2 consisted of patients who received HBIG combined with ADV or LAM for HBV prophylaxis. The study protocol was approved by the independent institutional review board of Yonsei University College of Medicine (IRB No.: 4-2014-0747).

TABLE 1. Baseline Characteristics of Liver Recipients Who Received Prophylactic Treatment With HBIG Alone (Group 1) or in Combination With LAM or ADV (Group 2)*

Patient Characteristics	Group 1 (n = 42)	Group 2 (n = 21)	*P* value
Male recipients, n (%)	36 (85.7%)	16 (76.2%)	0.483
Male donors, n (%)	32 (76.2%)	15(71.4%)	0.762
Age of recipients, y	52.5 ± 6.5	51.1 ± 5.9	0.409
Age of donors, y	34.7 ± 10.5	35.9 ± 13.1	0.703
Living donor, n (%)	35 (83.3%)	16 (76.2%)	0.513
BMI, kg/m^3	23.7 ± 2.6	24.1 ± 2.4	0.505
Hypertension, n (%)	8 (19.0%)	5 (23.8%)	0.357
Diabetes, n (%)	8 (19.0%)	6 (28.6%)	0.710
CTP score	8.1 ± 2.2	8.1 ± 2.0	0.866
MELD score	12.3 ± 5.6	11.9 ± 6.6	0.765
HCC pre-LT	22 (52.4%)	9 (42.9%)	0.512
S-Cr, mg/dL	0.84 ± 0.16	0.87 ± 0.16	0.515
eGFR, mL/min/1.73 m^2	103.24 ± 024.94	96.32 ± 6.32 4	0.282
Intraoperative transfusion, packs	4.9 ± 5.0	5.7 ± 4.1	0.551

ADV = adefovir dipivoxil, BMI = body mass index, eGFR = estimated glomerular filtration rate, HBIG = antihepatitis B immunoglobulin, HCC = hepatocellular carcinoma, LAM = lamivudine, MELD = Model for End-stage Liver Disease, S-Cr = serum creatinine.
* Data are expressed as the mean ± standard deviation for continuous variables and number (proportion) for categorical variables.

Measurement and Definition of Renal Dysfunction

To evaluate nephrotoxicity due to LAM or ADV treatment, we compared incidence of RTD and RI for 12 months after LT between the groups. Although RTD and Fanconi syndrome have been defined differently in the literature, we used the definition of RTD suggested by Gara et al.[4] In particular, RTD is characterized by hypophosphatemia (ie, serum phosphate <2.5 mg/dL and ≥0.5 mg/dL from baseline) with at least 2 other de novo manifestations of tubular dysfunction defined as follows[4]: increase in serum creatinine (S-Cr) >1.2 mg/dL and ≥0.5 mg/dL from baseline; hypouricemia (ie, serum uric acid <3.7 mg/dL and ≥0.5 mg/dL from baseline); proteinuria; and glycosuria without diabetes mellitus.

We defined RI as a sustained increase in S-Cr >1.2 mg/dL and ≥0.5 mg/dL from baseline.[4,13]

To evaluate renal function, S-Cr and eGFR were compared between pre-LT and 12 months post-LT in each group and between groups. eGFR was calculated based upon S-Cr, race, and age using the updated Modification-of-Diet-in-Renal-Disease equation.[14] CKD stage expressed as base on kidney disease outcomes quality initiatives (K/DQI) guidelines.[15]

Antihepatitis B Regimens and Immunosuppression

We routinely treated HBV-infected LT recipients with HBIG alone or in combination with NUC as follows. During the anhepatic phase, 10,000 IU (20,000 IU if HBe Ag + or HBV DNA + at pre-LT) of HBIG was infused. During the first week after LT, 10,000 IU of HBIG was infused daily. For the next month, 10,000 IU of HBIG was infused once per week. Thereafter, 10,000 IU of HBIG was infused once per 4 to 6 weeks to maintain a trough serum level >500 IU/L. LAM (100 mg) and ADV (10 mg) were administrated orally in patients with normal renal function. These doses were reduced in patients with creatinine clearance was <50 mL/min.

The standard protocol for maintaining immunosuppression consisted of TAC, steroids, and mycophenolate mofetil in our institution. Double regimens (eg, TAC and steroid) were considered for patients with gastrointestinal conditions, leukopenia, cytomegalovirus infection, and for women in their childbearing years. The trough level of TAC in triple regimens was 6 to 12 ng/mL for the first month and 5 to 8 ng/mL thereafter. In double regimens, the trough level of TAC was 8 to 15 ng/mL for the first month and 6 to 10 ng/mL thereafter.

Serum and Urine Monitoring in Outpatients after LT

All HBV-infected patients were examined for complete blood count and routine chemistries, including serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, direct and total bilirubin, creatinine, blood urea nitrogen, phosphate, calcium, uric acid, albumin, total protein, and phosphate every 4 to 6 weeks. The serum level of hepatitis surface antibody (Hbs Ab) was also assessed every 4 to 6 weeks. Another HBV serologic panel [hepatitis surface antigen (HBs Ag), hepatitis envelope antigen (HBe Ag), and hepatitis enevelope antibody (HBe Ab)] and HBV DNA were tested at least once per year. Alpha-fetoprotein and protein induced by vitamin K antagonist-II (PIVKA-II) was measured every 2 or 3 months in recipients with hepatocellular carcinoma (HCC). Urinalysis was also checked every 2 or 3 months.

Statistical Analysis

Data are expressed as the mean (± standard deviation) for continuous variables and number (proportion) for categorical variables. Statistical analysis was performed using the SPSS 20 (SPSS Inc., Chicago, IL). Categorical variables were tested using Fisher exact test or chi-square test between groups. Continuous variables were tested using independent Student t tests. Differences in eGFR and S-Cr between pre-LT and 12 months post-LT in each group were compared using the paired Student *t* test. Changes in distribution of CKD stages in each group were evaluated by the Wilcoxon signed-rank test. Survival rates were calculated using Kaplan–Meier analysis and the log-rank test was used to compare the probabilities in subgroups. The risk factor of RI was calculated by logistic regression. A *P* value <0.05 was considered statistically significant.

TABLE 2. Changes in Renal Function between Pre-LT and 12 Months Post-LT Based on HBV Prophylaxis Regimens*

Renal Function	Group 1			Group 2			*P* Value (Group 1 vs 2)[a]
	Pre-LT	1-Year Post-LT	*P* Value	Pre-LT	1-Year Post-LT	*P* Value	
S-Cr, mg/dL	0.84 ± 0.16	1.23 ± 0.28	<0.001	0.87 ± 0.16	1.23 ± 0.31	<0.001	0.736
eGFR, mL/min/1.73 m^2	103.24 ± 25.34	66.19 ± 25.33	<0.001	96.32 ± 21.31	66.18 ± 18.60	<0.001	0.295

eGFR = estimated glomerular filtration rate, LT = liver transplantation, S-Cr = serum creatinine.
* Data represent the mean ± standard deviation.
[a] *P* values were calculated to compare renal function between groups (change from baseline).

RESULTS

The number of LT recipients who had undergone prophylactic treatment with HBIG alone or in combination with LAM or ADV totaled 63, of which 52 were male and 51 received an organ from a living donor. The mean age was 52.0 ± 6.3 years, with 42 and 21 recipients assigned into groups 1 and 2, respectively. No significant differences were observed between the groups regarding sex, age, body mass index, hypertension, diabetes mellitus, Child–Turcotte–Pugh score, the Model for End-stage Liver disease score, S-Cr and eGFR pre-LT, and intraoperative transfusion. The demographic characteristics of the liver recipients are summarized in Table 1.

We began our retrospective study by examining the recurrence of HBV and HCC. Our analysis revealed that the rate of HBV recurrence within 12 months was 4.8% in both groups ($P = 1.000$). The rate of hepatocellular carcinoma (HCC) recurrence during this time period was similar to HBV recurrence, with 7.1% and 4.8% of patients in groups 1 and 2, respectively ($P = 1.000$), re-experiencing HCC. The level of HBV DNA in patients who had developed HBV recurrence was higher than 10^4 and 2 patients were positive for HBe Ag before transplantation. All 3 patients were switched to treatment with HBIG plus entecavir (ETV) from HBIG alone or in combination with LAM. Two patients died due to HCC recurrence but 1 patient survived with normal liver function. Patients who experienced HBV recurrence exhibited a mean survival rate of 39 months (ranging from 27 to 75 months).

Next, we assessed the effect of LT on eGFR. The mean eGFR at 12 months after transplantation was significantly reduced compared with before transplantation in each group ($P < 0.001$). The changes of eGFR and S-Cr observed were not significantly different between the groups. The details of renal function are shown in Table 2. The distribution according to CKD stages changed over time in each group. The proportion of CKD stage 1 was significantly decreased in both groups after 12 months, whereas the proportion of CKD stage 3 increased ($P < 0.001$, Figure 1.)

Examination of RTD revealed that 4 patients were diagnosed with this condition after LT. Only group 2 consisted of RTD patients (0.0% vs 19.0%, $P = 0.010$). All patients diagnosed with RTD exhibited symptoms of hypophosphatemia and hypouricemia. Among them, 1 patient with HCC recurrence died at 60 months after LT. The clinical manifestations of all RTD recipients are shown in Table 3.

The percentage of RI that occurred within 12 months was 26.2% and 28.6% in groups 1 and group 2, respectively ($P = 1.000$). The only risk factor for RI was administration of HBIG combined with both LAM and ADF (OR 11.27, 95% CI 1.13–112.07, $P = 0.039$, compared with HBIG alone) by logistic regression analysis. The ages of the donors and recipients, sex, donor type, intraoperative transfusion, the Model for End-stage Liver disease score, Child–Turcotte–Pugh score, hypertension, diabetes mellitus, and pre-LT eGFR did not exhibit statistically significant differences.

Finally, no significant differences were found in survival rate between groups 1 and 2 (87.1% vs 85.7% at 3 years, 87.1% vs 75.9% at 5 years, $P = 0.395$). This rate was not affected by RTD (66.7% and 81.2% at 5 years, $P = 0.831$) or RI (86.7% and 86.4% at 3 years, 86.7% and 80.8% at 5 years, $P = 0.831$).

DISCUSSION

Renal dysfunction is a common complication after LT,[7] and the decrease in post-LT eGFR over time is associated with post-LT survival.[9] Careful use of nephrotoxic drugs after LT should be considered because liver recipients are vulnerable to kidney injuries.[7] Nephrotoxicity following CNI treatment has been well established in liver recipients[16]; however, nephrotoxicity due to

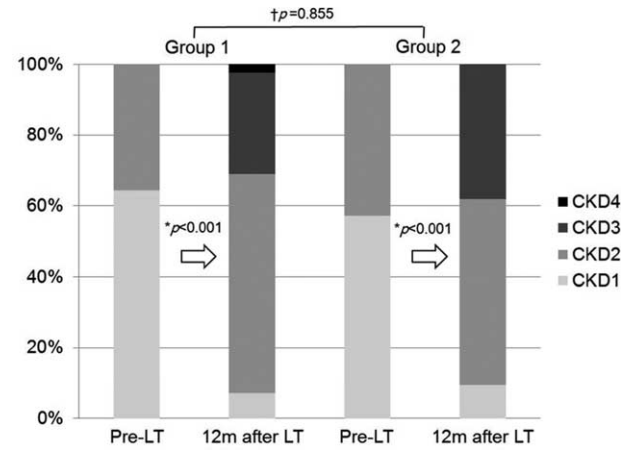

FIGURE 1. Distribution according to stages of CKD based on kidney disease outcomes quality initiatives guidelines15 at pre-LT and 12 months post-LT. In both groups, the proportion of CKD stage 1 was significantly decreased and that of CKD stage 3 was remarkably increased at 12 months after liver transplantation; however, no significant differences in changes of CKD stages, from baseline to 12 month after LT, were observed between the groups. CKD = chronic kidney disease, LT = liver transplantation. * *P* value calculated by Wilcoxon signed-rank test in each group. † *P* value calculated by comparing changes from baseline using Fisher exact test.

TABLE 3. Clinical Features of 4 Liver Recipients Who Developed RTD*

No	Age	Sex	Phos (mg/dL)	Cr (mg/dL)	Uric Acid (mg/dL)	Urine Protein	Urine glucose	NUC	Status	Follow-Up (Months)
1	47	M	3.9/1.1	1.10/1.20	4.6/1.5	−/−	−/4+	LAM → ETV	Alive	92
2	43	M	3.0/1.7	0.90/0.90	4.1/2.3	−/−	−/+	LAM → ETV	Alive	74
3	48	M	3.7/2.2	1.00/2.04	4.1/2.2	−/2+	2+/3+	LAM + ADF → ETV	Alive	39
4	47	F	3.0/2.5	0.70/0.74	3.7/3.3	−/−	−/1+	LAM	Dead	60

ADF = adefovir dipivoxil, Cr = Creatinine, ETV = entecavir, LAM = lamivudine, NUC = nucleoside/nucleotide, Phos = phosphate, RTD = renal tubular dysfunction.

* Data are expressed as the value at baseline/value at diagnosis of RTD.

NUC treatment is less understood. Small number of case studies regarding RTD of NUC was reported in liver recipients.[11,12]

ADV is nucleotide analog of adenosine monophosphate that is highly effective in viral suppression in both treatment-naive and LAM-resistant chronic hepatitis B (CHB) patient.[17] Although ADV nephrotoxicity was dose-dependent, administration of 10 mg was also reported as an independent predictor for significant renal dysfunction (defined as eGFR $\leq$50 mL/min/1.73 m^2).[6] LAM is a nucleoside analog that targets the reverse transcriptase of HBV and probably remains the most widely used NUC due to its low cost[18]; however, long-term lamivudine therapy results in viral resistance due to YMDD mutations.[19] Therefore, combination treatment of ADV with LAM has been recommended for treating LAM-resistant HBV. Renal function declines over time with LAM treatment[20] and RTD is common, especially in patients treated with LAM and ADV.[5]

In contrast to CNI toxicity, which is a major factor of chronic kidney disease after LT that affects vasoconstriction,[16,21] the nephrotoxicity of NUC influences the renal proximal tubule.[3] The characteristics of CNI-induced tubular damage include renal tubular functional alternation and metabolic disturbance like hyperkalemia, hypomagnesemia, distal renal tubular acidosis, and hyperuricemia.[21] On the contrary, the clinical features of RTD due to NUC treatment are hypophosphatemia, hypouricemia, increased S-Cr, glucosuria, and proteinuria.[3–5]

In our study, 4 recipients from group 2 were diagnosed with RTD within 12 months after transplantation. The cumulative incidence of RTD after 1 year was 19.0%, which was higher than the 15% after 10 years reported by Gara et al[4] and the 6.8% after 1 year published by Tanaka et al[5]; however, these studies evaluated nontransplant patients, whereas our study investigated the effects of these NUCs on liver transplant recipients. We propose several possibilities to explain why RTD incidence was found to be higher in our study. First, liver recipients are more susceptible to kidney injury than nontransplant patients with CHB due to a combination of hemodynamic instability, CNI toxicity, nephrotoxic drug, and acute tubular necrosis.[7] The mean eGFR at 12 months post-LT in recipients administered HBV prophylaxis was decreased from baseline in our study (Table 2 and Figure 1). Sharma et al[9] also reported that eGFR of liver recipients decreased over time after LT.

Second, a synergistic effect due to interaction between immunosuppressants, NUCs, and other nephrotoxic drugs can cause more severe nephrotoxicity. Due to the small number of RTD patients included in our study, we could not find any other significant risk factors of RTD except HBV prophylaxis with ADV or LAM; however, all RTD patients were administered immunosuppressants with dual regimens including TAC and a steroid. The level and dosage of CNI is generally higher than that of triple regimens including TAC, steroids, and mycophenolate mofetil. The synergic effect between a NUC and CNI is not well understood; however, development of renal Fanconi syndrome due to TAC and LAM treatment has been reported.[11] We hypothesize that a synergic effect can occur between CNI and NUC that causes nephrotoxicity.

Third, RTD incidence may also be high due to improper dosing of NUC. Because NUC nephrotoxicity is well established, the European Association for the Study of the Liver recommended that dosage should be adjusted in all patients with impaired renal function (defined as creatinine clearance $\leq$50 mL/min)[22]; however, improper dosing is not the main cause of RTD because we excluded a patient with a pre-LT eGFR <60 mL/min/1.73 m^2. We confirmed the dosage taken by the patient who developed RTD according to creatinine clearance.

A treatment regimen of HBIG combined with NUCs is commonly prescribed; however, the most effective prophylactic option following LT remains controversial.[1,2] The recurrence rate of HBV was reported in 0% to 32% patients in HBIG monotherapy.[1] In our study, no significant differences in HBV recurrence rate were observed between patients treated with HBIG alone and in combination with LAM or ADV. The cumulative incidences of HBV recurrence were 4.8% in both groups 1 and 2 during the initial 12 months after LT. There were limitations to control variables that could affect HBV recurrence, such as HBe Ag and the level of HBV DNA at pre-LT because we focused primarily on nephrotoxicity due to LAM and ADV; however, we suggest that HBIG monotherapy can be considered for patients diagnosed with RTD after LT because this condition can be induced by NUCs.

HBV prophylaxis regimens, RI, and RTD did not affect survival rate in our study. Sharma et al[9] reported that a decrease in post-LT eGFR over time was the only independent predictor of survival as patients were divided into 3 groups according to pre-LT eGFR ($\geq$60 mL/min/1.73 m^2, 30–59 mL/min/1.73 m^2 and <30 mL/min/1.73 m^2). In contrast, we excluded a patient with eGFR <60 mL/min/1.73 m^2 before transplantation to evaluate NUC nephrotoxicity in liver recipients with normal renal function. Furthermore, we selected patients who did not change their HBV prophylaxis regimen for a minimum of 12 months to determine the difference in nephrotoxicity between HBIG alone and in combination with LAM or ADV. This can be 1 reason why the current study does not demonstrate a negative effect of RI and RTD to graft survival. Also, RTD did not affect survival because this condition can be reversed with cessation of nephrotoxic drugs; GFR was also

preserved unlike glomerulonephropathy.[23,24] In our study, none of the RTD patients progressed to symptomatic hypophosphatemia such as osteomalacia. Three RTD patients showed improvements in serum phosphate, creatinine, uric acid, and glucosuria after switching to ETV. These results are consistent with Gara et al, who also reported that 6 RTD patients exhibited improvement after switching from ADV or tenofovir to ETV.[4] Therefore, changing antiviral agents is a good option when liver recipients develop RTD.

CONCLUSIONS

It has been convinced that the regimens of HBIG combined with LAM or ADV had nephrotoxicity in LT recipients. Our study revealed that HBV prophylaxis regimen including HBIG combined with ADV or LAM could be associated RTD and characterized by hypophosphatemia, hypouricemia, RI, glucosuria, and proteinuria in liver transplant recipients. A regimen of HBIG combined with both ADV and LAM could be a risk factor for RI, which is characterized clinically by elevated S-Cr. RTD and RI arising from LAM or ADV use should be considered and monitored in patients who received HBV prophylaxis after LT.

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