Pharmacokinetics of Mizoribine in Adult Living Donor Liver Transplantation

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ABSTRACT

We investigated the pharmacokinetics of mizoribine in the acute phase after adult living donor liver transplantation (LDLT). Between February 2004 and October 2009, 16 recipients received immunosuppressive therapy that included mizoribine (100 to 200 mg/d) after undergoing LDLT. We determined the serum levels of mizoribine before (C0) and 3 (C3), 4 (C4), and 10 (C10) hours after administration on postoperative days 3, 7, and 21. We assessed area under the concentration time curve (AUC) (hour · μg/mL), normalized serum concentration (NSC) at C0 [concentration (μg/mL)/dose (mg/kg body weight)], and estimated glomerular filtration rate (eGFR). The mizoribine concentration showed increases at C3 and C4 followed by a decrease at C10 on all days. AUC was 4.3, 5.9, and 8.3 in the 200-mg/d dose group on days 3, 7, and 21, respectively. NSC at C0 increased for 3 weeks after LDLT. There was a significant correlation between the NSC at C0 and eGFR on day 21, but not on days 3 and 7. There were no correlations between the NSC at C0 and either aspartate aminotransferase, total bilirubin, albumin, trough cyclosporine, or trough tacrolimus on any day. The pharmacokinetics of mizoribine in the acute phase after LDLT seems to be affected by postoperative day and renal function.

MIZORIBINE IS AN ORAL IMMUNOSUPPRESsive agent approved in Japan, Korea, and China for the prevention of graft rejection in renal transplantation. Its immunosuppressive potential is promising, and three-drug combination therapy with a calcineurin inhibitor, a steroid, and mizoribine is sometimes used for patients after renal transplantation.[1–3] The application of mizoribine has now been extended to lupus nephritis, chronic rheumatoid arthritis, and nephritic syndrome treatment in Japan.[4] Using antimetabolites as immunosuppressants in combination therapy may be beneficial for reducing the dose and side effects of calcineurin inhibitors or steroids after living donor liver transplantation (LDLT).[5,6] Due to the absence of information on the pharmacokinetics of mizoribine in liver transplantation, the options for secondary and tertiary agents in immunosuppressive combination therapy are limited to azathioprine (AZA) and mycophenolate mofetil (MMF). It is critical to ensure that the concentrations of the immunosuppressive agent used is maintained within an appropriate range, especially in the acute phase after LDLT, because even a minor failure in management postsurgically, when liver graft volume and function are not fully recovered, can be lethal. Since mizoribine is excreted from the kidneys, and since AZA and MMF are metabolized or activated in the liver, it is worthwhile to investigate the pharmacokinetics of these antimetabolites in patients with hepatic dysfunction. In this study, we monitored mizoribine levels on postoperative day 3, 7, and 21 and assessed the pharmacokinetics of mizoribine in the acute phase of LDLT.

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0041-1345/–see front matter
http://dx.doi.org/10.1016/j.transproceed.2012.01.139

PATIENTS AND METHODS

Patients

Between February 2004 and October 2009, 16 transplant recipients were treated with an immunosuppressive regimen that included mizoribine after undergoing LDLT. The backgrounds of the patients are summarized in Table 1. The immunosuppressive regimen was a three-drug combination therapy. In cases of hepatitis C positivity, basiliximab was used instead of a steroid. In cases of ABO blood-type incompatibility, the three-drug combination therapy and additional regimens were employed; patients were preoperatively administered rituximab twice, and a steroid, prostaglandin El, and gabexate mesilate were administered through the portal vein for 3 weeks postoperatively. Mizoribine was given orally twice a day at a dose of 100 mg/d in the initial three cases, and 200 mg/d in the other 13 cases. Tacrolimus was chosen as the calcineurin inhibitor for the initial cases of hepatitis C positivity and ABO blood type incompatibility, and cyclosporine was used in the other cases.

Serum samples were collected before and 3, 4, and 10 hours after dosing on postoperative days 3, 7, and 21. All serum samples were analyzed to determine the mizoribine concentration. The concentrations before and 3, 4, and 10 hours postadministration were defined as C0, C3, C4, and C10, respectively. Blood samples were centrifuged for 5 minutes at 1500g, and all serum samples were stored at −80°C prior to being assayed. Informed consent was obtained from each patient or family, and the study protocol conformed to the ethical guidelines of Keio University School of Medicine.

Mizoribine Assay

Concentrations of mizoribine in serum were measured by Asahi Kasei Pharma Corporation (Tokyo, Japan) using high-performance liquid chromatography (HPLC). The serum was deproteinized and filtered (Ultra-Free C3LCC, Millipore, Tokyo). Filtrate (10 μL) was injected into an HPLC column (Shim-Pack CLC-NH2 15 cm × 6.0 mm internal diameter, Shimadzu, Kyoto). The mobile phase consisted of 66.7 mmol/L phosphate buffer (pH 2.5) and acetonitrile (27.5:72.5), and the flow rate was set at 1.3 mL/min. The drug was detected at a wavelength of 280 nm using a UV detector, and the detection limit was 0.02 μg/mL.

Table 1. Patient Background

Liver diseases	
Virus-related liver cirrhosis	11
Fulminant hepatitis	2
Primary biliary cirrhosis	2
Budd-Chiari syndrome	1
Sex	
Male	10
Female	6
Age (y)	49.5 ± 9.5
Body weight (kg)	60.6 ± 10.5
ABO blood type compatibility	
Identical	8
Compatible	4
Incompatible	4
Immunosuppressive regimen	
Cyclosporine, steroid, and mizoribine	8
Cyclosporine, basiliximab, and mizoribine	2
Tacrolimus, steroid, and mizoribine	2
Tacrolimus, basiliximab, and mizoribine	3
Cyclosporine to tacrolimus convert on day 14, steroid, and mizoribine	1
Mizoribine dose (minimum to maximum, mg/kg/day)	0.60–4.0

Blood Biochemistry

The serum levels of aspartate aminotransferase (AST), total bilirubin (TB), creatinine, albumin, and trough levels of cyclosporine and tacrolimus were determined by a biochemistry laboratory in our hospital.

Pharmacokinetic Parameters and Estimated Glomerular Filtration Rate

The area under the concentration-time curve (AUC) (hour · μg/mL) was estimated for the 100-mg/d dose patients, 200-mg/d dose patients, and all patients by summing three trapezoidal areas (C0 to C3, C3 to C4, and C4 to C10). Each trapezoid area was calculated by multiplying the concentration (μg/mL) by time (hours). The concentration of mizoribine was normalized according to dose and body weight using the following equation: [normalized serum concentration (NSC)] = [concentration of mizoribine (μg/mL)]/[dose of mizoribine (mg/kg)]. The area under the NSC-time curve [(hour · μg/mL)/(mg/kg)] was estimated for all patients by summing three trapezoidal areas (0 to 3 hours, 3 to 4 hours, and 4 to 10 hours). Each trapezoid area was calculated by multiplying the NSC [(μg/mL)/(mg/kg)] by time (hour). The highest concentration among C0, C3, C4, and C10 was defined as Cmax (μg/mL). The time from C0 to Cmax was defined as Tmax (hours). Clearance of mizoribine (Cl, L/h) was estimated by the following method: (1) elimination rate constant (kel) was calculated using the equation; kel (hour^{-1}) = −([natural logarithm of C10] − [natural logarithm of C4])/(10 − 4); (2) C12 was estimated using the equation: C12 = C10 × exp$^{(-\text{kel}\times 2)}$; (3) the AUC of C0 to C12 was estimated by adding three trapezoidal areas (C0 to C3, C3 to C4, and C4 to C10) and one additional trapezoid (C10 to estimated C12); and (4) Cl was estimated using the equation; Cl (L/h) = [mizoribine dose per intake (mg)]/[estimated AUC of C0 to C12 (hour · μg/mL)]. The glomerular filtration rate (GFR) was estimated using the following equation: estimated GFR (eGFR, mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ (if female, × 0.739).[7]

Adverse Events

A diagnosis of acute cellular rejection (ACR) was reached when patients showed elevation of hepatic enzymes and needle liver biopsy results showed more than moderate-grade ACR. Patients were diagnosed as having symptomatic infection if they had prolonged high fever and infection marker positivity (bacteria, cytomegalovirus, etc), or asymptomatic infection if they had the infection marker positivity without high fever. Patients were diagnosed as having hepatic dysfunction if they had reelevation of hepatic enzymes, and as having renal dysfunction if they underwent serum filtration.

Statistical Analysis

Results are expressed as means ± standard deviations (SDs) unless noted otherwise. For parametric data, differences between groups were evaluated using Student *t* test for unpaired data, based on the assumption that the data were derived from populations with equal SDs. Correlations were evaluated using the Spearman rank test. Differences were considered significant at *P* values less than .05.

RESULTS

Serum Mizoribine Concentrations

Figure 1a shows mean mizoribine concentrations in all patients in this study on postoperative days 3, 7, and 21. The levels were increased at C3 and C4 followed by a decrease at C10 on postoperative days 3, 7, and 21. The highest concentrations were 0.40, 0.65, and 0.90 μg/mL at C4 on postoperative days 3, 7, and 21, respectively. The C3/C0 ratios were 1.80 ± 0.73, 2.07 ± 1.68, and 1.94 ± 0.50 on postoperative days 3, 7, and 21; the respective C4/C0 ratios were 2.07 ± 1.33, 1.88 ± 1.14, and 1.79 ± 0.57, and the C10/C0 ratios were 1.54, 1.35, and 0.86. Figures 1b and 1c show mean mizoribine concentrations on postoperative days 3, 7, and 21 in the 200 and 100-mg/d dose groups,

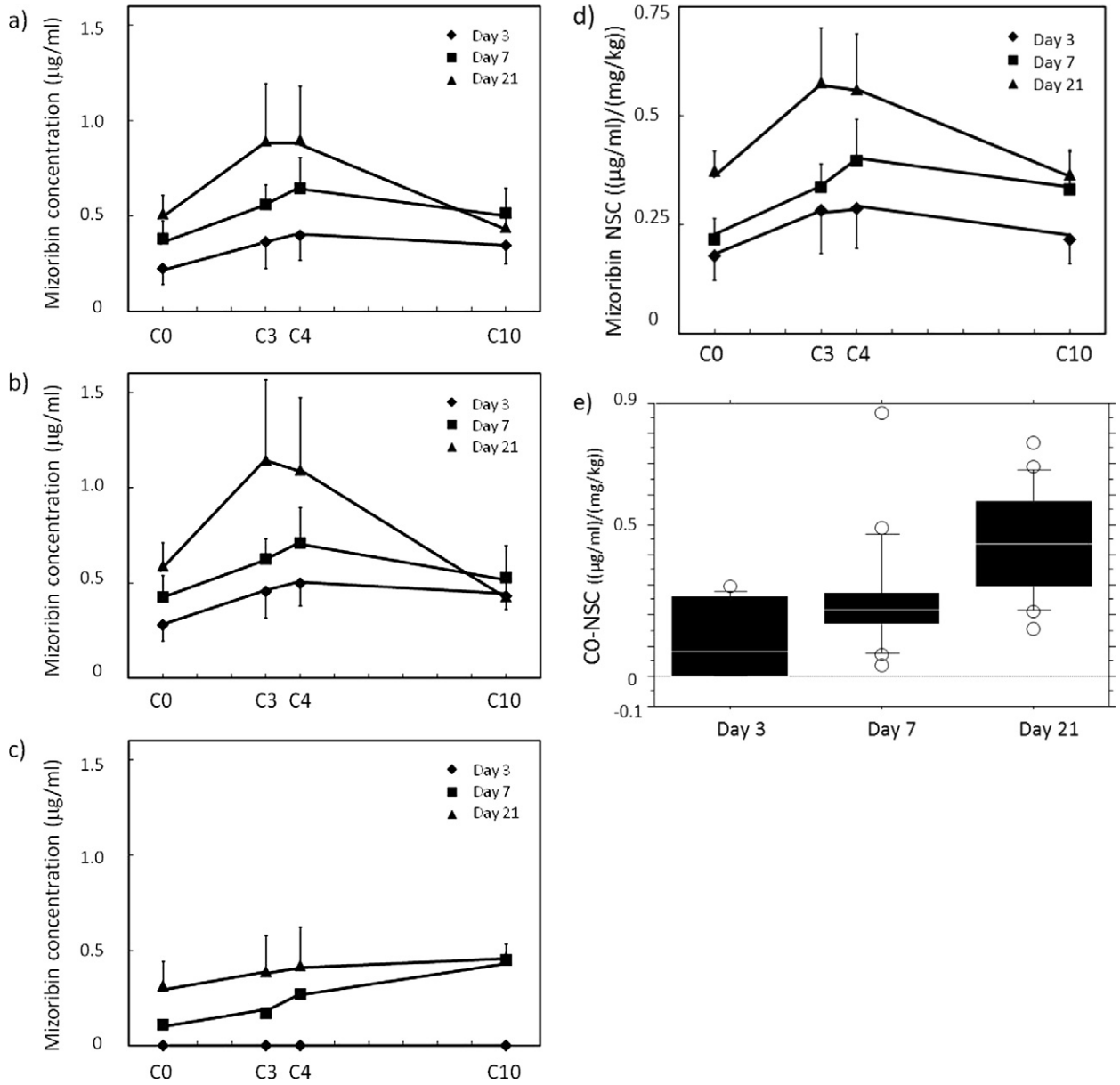

Fig 1. Mizoribine concentrations. C0, C3, C4, and C10 on postoperative days 3, 7, and 21 in (**a**) all patients, (**b**) 200-mg/d dose patients, and (**c**) 100-mg/d dose patients. (**d**) NSC at C0, C3, C4, and C10 on postoperative days 3, 7, and 21 in all patients. Results are expressed as mean + SEM or mean − SEM. C0, C3, C4, and C10; serum mizoribine concentration before and 3, 4, and 10 hours after mizoribine administration, respectively. (**e**) A quantile box plot of NSC at C0 on postoperative days 3, 7, and 21. The box for each day represents the interquartile range (25–75th percentile) and the line within this box is the median value. Bottom and top bars of the whisker indicate the 10th and 90th percentiles, respectively. Outlier values are indicated as open circles. NSC, normalized serum concentration; SEM, standard error of the mean.

respectively. Figure 1d shows NSC in all patients on postoperative days 3, 7, and 21. The NSC at C0 was increased in a time-dependent manner from day 3 to 21 and was significantly higher on postoperative day 21 compared to days 3 and 7 ($P < .05$; mean ± SD values of NSC at C0: 0.18 ± 0.14, 0.22 ± 0.14, and 0.37 ± 0.13 on days 3, 7, and 21, respectively). Figure 1e shows a quantile box plot of NSC at C0 on postoperative days 3, 7, and 21.

Pharmacokinetic Parameters

AUC, area under the NSC time curve, C0, Cmax, Tmax, and Cl are shown in Table 2. Results are expressed as mean ± SD. Maximum, median, and minimum values are indicated parenthetically in order.

Estimated Glomerular Filtration Rate

A quantile box plot of Fig 2 shows eGFR on postoperative days 3, 7, and 21. The mean ± SD eGFR values were 78 ± 23, 78 ± 31, and 64 ± 32 on days 3, 7, and 21, respectively. There were no significant differences among these values.

Effect of Parameters on Mizoribine Concentration

There was a significant correlation between the NSC at C0 and eGFR on day 21 (Fig 3c, $R^2 = 0.495$, $P < .05$), but not on days 3 and 7 (Fig 3a, 3b). There were no correlations between the NSC at C0 and either AST, TB, albumin, trough cyclosporine, or trough tacrolimus on any day (the R^2 values were extremely low and P values were >.05 in these analyses). There were no differences between the mizoribine trough NSCs at C0 in patients with tacrolimus and cyclosporine. There were no differences between the mizoribine trough NSCs at C0 in patients with and without steroids.

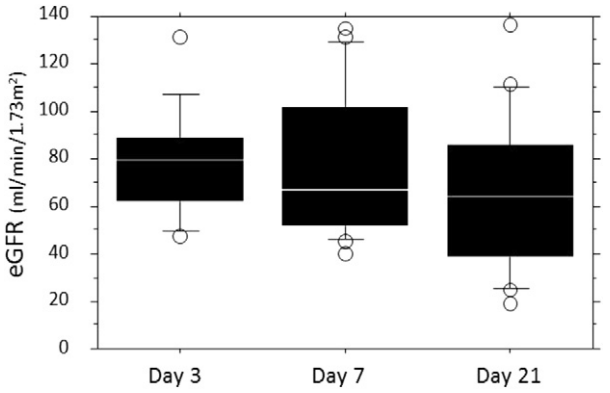

Fig 2. A quantile box plot of eGFR on postoperative days 3, 7, and 21. The box for each day represents the interquartile range (25–75th percentile) and the line within this box is the median value. Bottom and top bars of the whisker indicate the 10th and 90th percentiles, respectively. Outlier values are indicated as open circles. eGFR, estimated glomerular filtration rate.

Table 2. Pharmacokinetic Parameters

	100 mg/d	200 mg/d	All patients
Area under the concentration time curve (h · μg/mL)			
Postoperative day 3	0	4.3	3.4
Postoperative day 7	2.8	5.9	5.4
Postoperative day 21	4.1	8.3	7.0
Area under the NSC time curve [(h · μg/mL)/(mg/kg)]			
Postoperative day 3			2.4
Postoperative day 7			3.3
Postoperative day 21			4.7
C0 (μg/mL)			
Postoperative day 3	0 (0, 0, 0)	0.28 ± 0.19 (0.51, 0.38, 0.36)	0.22 ± 0.20 (0.51, 0.36, 0)
Postoperative day 7	0.18 ± 0.09 (0.24, 0.17, 0.11)	0.43 ± 0.28 (0.89, 0.35, 0.13)	0.36 ± 0.26 (0.89, 0.26, 0.11)
Postoperative day 21	0.34 ± 0.16 (0.47, 0.40, 0.16)	0.60 ± 0.26 (1.07, 0.56, 0.28)	0.52 ± 0.26 (1.07, 0.39, 0.16)
Cmax (μg/mL)			
Postoperative day 3	0 (0, 0, 0)	0.59 ± 0.22 (0.89, 0.61, 0.36)	0.59 ± 0.22 (0.89, 0.61, 0.36)
Postoperative day 7	0.35 ± 0.15 (0.45, 0.34, 0.24)	0.48 ± 0.50 (1.64, 0.59, 0.36)	0.66 ± 0.42 (1.64, 0.58, 0.24)
Postoperative day 21	0.49 ± 0.16 (0.67, 0.42, 0.38)	1.08 ± 0.82 (2.69, 0.83, 0.44)	0.88 ± 0.72 (2.69, 0.67, 0.38)
Tmax (h)			
Postoperative day 3		4.2 ± 4.1 (4, 3, 0)	4.2 ± 4.1 (4, 3, 0)
Postoperative day 7	5.0 ± 7.0 (10, 5, 0)	2.8 ± 1.4 (4, 3, 0)	3.4 ± 2.9 (10, 3, 0)
Postoperative day 21	5.6 ± 3.7 (10, 4, 3)	4.5 ± 2.7 (10, 3.5, 3)	4.8 ± 2.9 (10, 4, 3)
Cl (L/h)			
Postoperative day 3		20.7 ± 6.3 (28.2, 18.7, 12.7)	20.7 ± 6.3 (28.2, 18.7, 12.7)
Postoperative day 7	23.4 ± 14.4 (33.6, 23.4, 13.2)	18.0 ± 9.4 (30.1, 10.7, 7.1)	19.9 ± 9.7 (33.6, 19.2, 7.1)
Postoperative day 21	11.8 ± 4.3 (15.7, 12.6, 7.1)	14.3 ± 9.5 (30.4, 11.8, 5.1)	13.4 ± 7.6 (30.4, 12.2, 5.1)

NSC, normalized serum concentration; C0, serum mizoribine concentration before mizoribine administration; Cmax, highest concentration of serum mizoribine; Tmax, time from mizoribine administration to Cmax; Cl, clearance of mizoribine.

Adverse Events and Patient Outcomes

The incidence of adverse events is shown in Table 3. The seven cases of asymptomatic infection were patients who tested positive for cytomegalovirus infection but did not present with fever. All patients survived more than 3 weeks after operation.

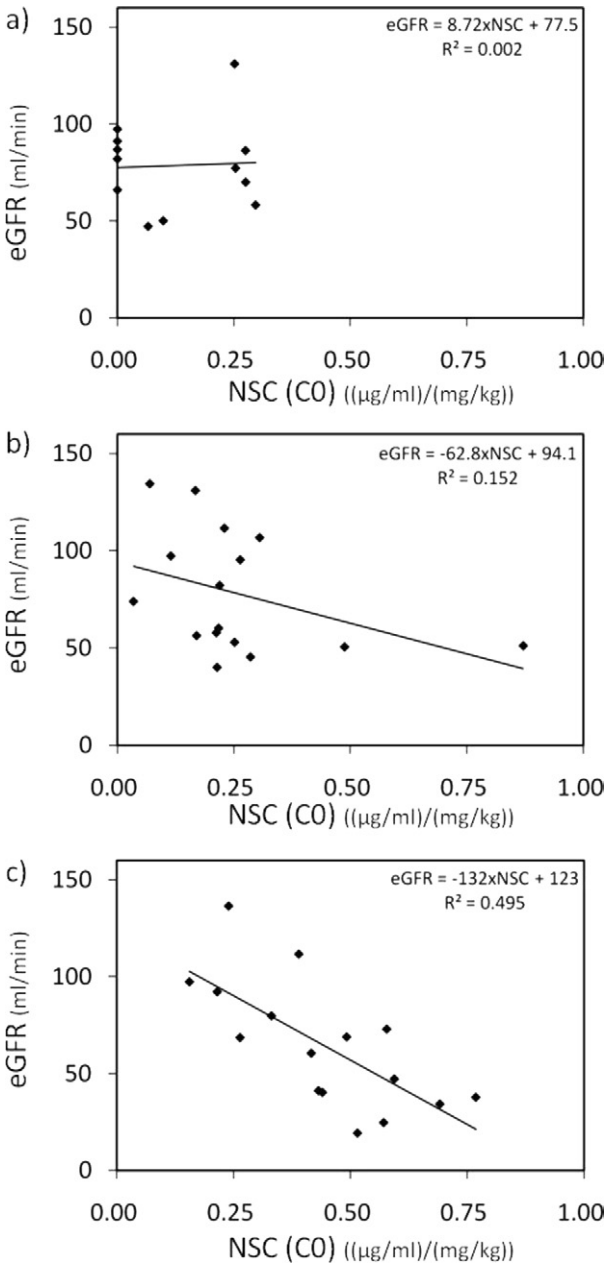

Fig 3. Correlation between mizoribine NSC at C0 and eGFR. Correlation between mizoribine NSC at C0 and eGFR on postoperative days 3 (**a**), 7 (**b**), and 21 (**c**). NSC, normalized serum concentration; eGFR, estimated glomerular filtration rate.

Table 3. Incidences of Adverse Events

	No. of cases
Mortality	0 (0%)
Antibody-mediated rejection	0 (0%)
Acute cellular rejection	1 (6%)
Central nervous disorder	1 (6%)
Hepatic dysfunction	1 (6%)
Pancytopenia	1 (6%)
Symptomatic infection	2 (12%)
Renal dysfunction	3 (18%)
Asymptomatic infection	7 (43%)

DISCUSSION

Our preliminary study in initial cases after LDLT showed that peak concentrations of mizoribine occurred 3 or 4 hours postadministration. Sugitani and colleagues reported that peak drug concentrations were reached approximately 3 hours after intake in patients who were treated with mizoribine more than 1 month after renal transplantation, at which time their condition had stabilized.[3] Therefore, we decided to collect serum samples before and 3, 4, and 10 hours after oral mizoribine administration to assess peak drug levels. The analysis showed that the highest concentration was 0.40, 0.65, and 0.90 μg/mL at C4 on postoperative days 3, 7, and 21, respectively, and the peak level was approximately twice the level at C0 on all days. Sugitani et al studied patients who took higher doses of mizoribine (4 to 6 mg/kg/d) and reported that the peak concentration was 2.87 μg/mL, the peak level was approximately twice the trough level, and there were few adverse events.[3] Our study employed LDLT patients who took lower doses of mizoribine (0.60 to 4.0 mg/kg/d) and showed that the peak concentrations were much lower than those reported by Sugitani et al. The lower concentrations in our study might be a result of not only the lower mizoribine dose used but also differences in intestinal absorption and renal excretion between subject populations. Since the incidence of adverse events in our study and that of Sugitani et al was acceptably low in both cases, a potential alternative mizoribine protocol for LDLT could include a higher dose of mizoribine to achieve higher trough and peak drug levels. However, the optimal serum concentration of mizoribine in organ transplantation patients has never been determined. In a study by Sonda et al, which employed the mixed lymphocyte reaction assay to assess the effects of mizoribine on peripheral lymphocytes from healthy adults, the inhibition rates were 2.4%, 36.4%, 43.8%, 52.6%, 62.2% at mizoribine concentrations of 0.05, 0.1, 0.5, 1.0, 5.0 μg/mL, respectively (8). According to these data, the drug doses used by Sugitani et al and in our study may have had an immunosuppressive effect on lymphocytes. Future clinical studies should determine the optimal serum concentration of mizoribine when it is used as a second or third agent in combination immunosuppressive therapy.

This study also showed that the NSC at C0 increased from postoperative day 3 to 21, suggesting that the NSC at

C0 did not reach a steady state until 3 weeks after the operation. The time to reach steady-state drug levels is generally calculated by multiplying the half-life of the drug by 3 to 5, if the excretion rate is stable. The half-life of mizoribine is 1.6 hours in patients with normal renal function (creatinine clearance $>$ 70 mL/min) and 4.6 hours in patients with severely impaired renal function (creatinine clearance $<$ 40 mL/min),[9] and it can be estimated that steady-state levels of mizoribine were reached within a few days postadministration in LDLT patients. The present finding that the NSC at C0 did not reach to a steady state until 3 weeks postoperatively suggests that the time to reach steady state was markedly prolonged in the LDLT patients. The pharmacokinetics of mizoribine depends on both intestinal absorption and renal excretion.[4] eGFR showed that levels were virtually unchanged on days 3 and 7 and slightly decreased on day 21. It is known that intestinal absorption is impaired in patients who have undergone long-duration laparotomy. Absorption may also be impaired in LDLT, which sometimes takes more than 10 hours to perform and involves major surgical procedures on the intestine. Therefore, we reason that the prolonged time to reach steady-state levels of mizoribine within 3 weeks after LDLT could be mainly attributable to poor absorption due to delayed gastric emptying and reduced intestinal motility following surgery. Recent studies have investigated the potential impact of bile flow[10] and the drug transporter of concentrative nucleoside transporter 1 polymorphisms[11] on mizoribine absorption. These factors might contribute to interindividual differences in the plasma disposition of mizoribine. Assessing the status of cholestasis in the liver and intestine of patients by measuring bile flow from biliary drainage tubes and genotyping for concentrative nucleoside transporter may provide additional insight into postoperative mizoribine absorption.

Because mizoribine is excreted by the kidneys, the serum concentration of mizoribine achieved during therapy should correlate with renal function. In fact, there was a significant relationship between trough NSC at C0 and eGFR on day 21. It is noteworthy that the correlation between NSC at C0 and eGFR was found only on day 21, but not on days 3 and 7. Sonda et al reported that the dose of mizoribine should be adjusted according to renal function in patients after renal transplantation.[8] We assume that this suggestion may not apply in the acute phase (several weeks) after LDLT because it may take time for mizoribine absorption to fully recover. It is reasonable that the serum concentration of mizoribine was independent of hepatic function represented by the hepatic markers of AST or TB, because mizoribine is neither metabolized nor activated in the liver. We investigated other possible factors that could be associated with mizoribine concentrations. One very important aspect and potential confounder in all pharmacokinetic studies after transplantation is the albumin concentration. However, mizoribine does not bind to proteins and, in fact, this study demonstrated that there was no relationship between trough NSC at C0 and albumin concentration on days 3, 7, and 21. Another aspect of interest is the impact of concomitant immunosuppressants such as steroids and calcineurin inhibitors on mizoribine concentrations. Hohage and colleagues reported that cyclosporine withdrawal resulted in a significant increase in the trough levels and AUC of mycophenolic acid in a group of renal transplant recipients with impaired renal function.[12] It is not known whether calcineurin inhibitors have a pharmacological effect on mizoribine concentrations. This study showed that there were no differences between the mizoribine trough NSCs at C0 in patients treated with tacrolimus and cyclosporine. Similarly, there were no differences between the mizoribine trough NSCs at C0 in patients with and without steroids. Therefore, this study did not find any factors associated with mizoribine concentration other than except renal function.

The efficacy and safety of mizoribine when used after LDLT is of great interest. Although mizoribine is now our preferred choice as a third agent in combination therapy, we previously used AZA or MMF as the third immunosuppressive agent together with a calcineurin inhibitor and a steroid in LDLT patients. It cannot be determined from this study if the immunosuppressive effect and incidence of adverse events with mizoribine are equivalent to those with AZA and MMF because the backgrounds of patients in whom mizoribine, AZA, and MMF were used are not comparable. We did not encounter lethal or severe adverse events arising from the use of mizoribine in this study. The finding that there was no relationship between NSC at C0 and AST or TB also provides information about the pharmacodynamics of mizoribine (ie, low-dose mizoribine may have a minimal adverse effect on hepatic function). Although our conclusions are limited by the small sample size in this study and a lack of comparative studies, it appears that low doses of mizoribine may be used safely after liver transplantation.

In the present study, we reported the pharmacokinetics of mizoribine in the acute phase after LDLT. The trend from C0 to C10 clearly showed that there were daily troughs and peaks, as was shown in a past study on renal transplantation by Sugitani and associates.[3] However, in our study both the peak and trough levels were much lower than those reported by Sugitani et al, probably because our protocol employed a relatively low dose of mizoribine. A new finding is that trough level increases for 3 weeks postoperatively. We assume that mizoribine adsorption is poor in the very early postoperative phase and, therefore, it takes 3 weeks until the serum concentration of this agent reaches a steady state. Mizoribine undergoes renal excretion, and its serum concentration should show a correlation with renal function if absorption is stable. It may not be possible to apply this correlation in the initial days following surgery, and a higher dose may be needed to compensate for poor absorption. The dose may need to be adjusted for renal excretion if more than 3 weeks passes after surgery. It is expected that mizoribine would have minimal adverse effects on hepatic function after surgery. Although there is

a period of poor mizoribine absorption in the very early postoperative phase, it could be a valuable alternative to agents that are metabolized or activated hepatically in cases where a renally excreted antimetabolite is preferable.

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