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Short- and Long-term Outcomes of De Novo Liver Transplant Patients Treated With Once-Daily Prolonged-Release Tacrolimus

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Background. Tacrolimus is the key immunosuppressive drug for liver transplantation. Once-daily prolonged-release tacrolimus (TAC-PR) exhibits good drug adherence but has difficulty controlling the trough level in the early phase of liver transplantation. The aim of this study was to compare the feasibility and efficacy of immediately starting oral TAC-PR versus traditional twice-daily tacrolimus (TAC-BID) in de novo liver transplantation recipients. **Methods.** The study included 28 patients treated with conventional TAC-BID and 60 patients treated with TAC-PR (median follow-up 70.5 months). Short-term and long-term outcomes were compared. **Results.** Patient characteristics were similar except for the incidence of hepatocellular carcinoma and type of graft. Dose adjustment was more frequently required for TAC-PR than TAC-BID (73.3% vs 42.9%, $P = 0.006$), but trough levels of TAC during the first 3 months after liver transplantation were controlled well in both groups. The rate of acute cellular rejection and long-term renal function were similar in both groups. In both groups, renal function worsened during the first 6 months after transplantation and remained stable until the end of the follow-up period. The 1-year, 3-year, and 5-year survival rates were 96.4%, 85.7%, and 85.7% for TAC-BID and 96.7%, 94.8%, and 94.8% for TAC-PR, respectively. The overall survival curve for TAC-PR was not inferior to that of TAC-BID. **Conclusions.** The TAC-PR protocol was feasible and effective with strict adjustment.

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Liver transplantation is an effective treatment modality for end-stage liver disease due to significant advances in surgical methods and immunosuppressive therapies.[1,2]

Tacrolimus is the key immunosuppressive agent for the prevention and treatment of allograft rejection in transplantation. The incidence of acute cellular rejection (ACR) after transplantation has decreased since tacrolimus was introduced.[3] Prolonged-release tacrolimus (TAC-PR) was developed to provide once-daily dosing with similar efficacy and safety as conventional twice-daily tacrolimus (TAC-BID). TAC-PR has various advantages compared with TAC-BID. TAC-PR has potentially less renal toxicity because its variability in 24-hour drug exposure is reduced and its C_{max} is less than TAC-BID.[4] Improvement of treatment adherence by using TAC-PR can contribute to better graft and patient survival.[2,5] However, the extended release formulation may make it difficult to control the trough level of tacrolimus during the early posttransplantation period because some factors, such as absorption and metabolism, are strongly influenced after operation.[6,7] Thus, clinicians are generally unwilling to use an oral extended release formulation of tacrolimus in intensive care units.[8] Therefore, various regimens for the administration of tacrolimus in de novo liver transplantation are performed by each facility.[9] However, the administration of TAC-PR during the early posttransplantation period may have several advantages because of its simplicity and unnecessary conversion of the TAC formula. We previously reported the short-term outcomes of TAC-PR in de novo liver transplant recipients.[10] Little practical information was

obtained about the long-term outcomes of de novo administration after liver transplantation.

The aim of the present study was to compare the safety and efficacy of immediately starting oral administration of TAC-PR to that of traditional TAC-BID in de novo liver transplant recipients in regard to both short- and long-term outcomes. To the best of our knowledge, this study is the first to conduct this comparison in detail.

MATERIALS AND METHODS

Patients

The study cohort consisted of 88 consecutive adult (>18 years of age) primary liver transplant recipients who underwent transplantation between January 2005 and August 2015. We performed 109 operations during this period but excluded patients who died within 3 months after transplantation, in which cases, tacrolimus was mainly administered by intravenous formula (9 cases) and who cyclosporine was initially introduced after the operation (12 cases). This study was conducted in accordance with the Declaration of Helsinki and approved by institutional review board.

Posttransplant Immunosuppressive Treatment

We changed the protocol for the initiation of tacrolimus. Twenty-eight patients between January 2005 and December 2008 received TAC-BID (Prograf, Astellas Pharma Japan Ltd, Tokyo, Japan) after transplantation, and 26 recipients between January 2009 and August 2011 received 1 dose of TAC-BID immediately after transplantation, followed by TAC-PR (Graceptor, Astellas Pharma Japan Ltd, Tokyo, Japan) in a once-daily protocol from postoperative day (POD) 1 as we described previously.[10] Thirty-four recipients immediately received TAC-PR after transplantation. We distributed the 88 cases into 2 groups: TAC-BID group (n = 28) and TAC-PR group (n = 60).

Initially, 0.05 mg/kg of each TAC was given through a nasogastric tube just after arrival at the intensive care unit after liver transplantation, and the tube was clamped for 1 hour. The TAC dose was adjusted based on the morning trough level from PODs 1 to 3, and then the subsequent doses of TAC were adjusted according to the trough level on the previous day. The dose was held or skipped when the trough level was greater than 20 ng/mL, and additional dose was administered when the trough concentration of TAC was suboptimal. Our target trough level of tacrolimus was 8 to 12 ng/mL within 21 days after liver transplantation, and reducing progressively to 6 to 10 ng/mL between 21 and 90 days after liver transplantation. After 3 months, 4 to 8 ng/mL was set as the target trough level. Corticosteroids were used together with TAC, starting with 1 g methylprednisolone during the surgery, then tapering from 100 to 5 mg/d in patients with primary biliary cirrhosis, primary sclerosing cholangitis, or autoimmune hepatitis, or tapering off in recipients with liver failure of other etiologies. Mycophenolate mofetil was added in patients with renal impairment, rejection episodes or others as needed. An elementary diet tube (8Fr, silicon, Create Medic Co., Ltd, Yokohama, Japan) was placed into the jejunum during the surgery and an elementary diet was started as soon as possible. Oral intake of medicine, including TAC, was started when water intake was fully possible and followed oral intake of food.

Short-term and Long-term Outcomes

Short-term outcomes compared between the 2 groups were the incidence of skipping or adding TAC, ACR, renal toxicity evaluated by estimated glomerular filtration rate (eGFR), and morbidities during the first 3 months after surgery. In this study, ACR means biopsy-proven ACR (BPAR) evaluated by the local pathologist, and graded according to the Banff International Consensus document.[11] The complications were scored and graded per the extended Clavien-Dindo classification of surgical complications, which was published by Japan Clinical Oncology Group, postoperative complications criteria, and more precisely described based on the original criteria of the Clavien-Dindo classification.[12] The incidence of adjusting TAC meant the number of patients who required adjusting TAC at least once.

Long-term outcomes compared between the 2 groups were the incidence of discontinuing tacrolimus, 5-year patient survival, morbidities related with immunosuppression, and long-term renal function.

Renal Dysfunction

We calculated glomerular filtration rate by the following formula: eGFR (mL/min per 1.73 m^2) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female).[13] We defined postoperative renal dysfunction in short-term outcome as the lowest eGFR within the first 3 months after transplantation being less than half of the preoperative eGFR. Chronic kidney disease (CKD) was defined and classified according to Kidney Disease: Improving Global Outcomes guidelines.[14]

Statistical Analysis

Statistical differences between groups were analyzed by the Mann-Whitney U test (continuous variables) or the χ^2 test (categorical variables). Patient survival curves were estimated by the Kaplan-Meier method and analyzed by the log-rank test. All statistical analyses were performed using JMP@12 (SAS Institute Inc., Cary, NC). P values less than 0.05 were considered significant.

RESULTs

Patient Characteristics

The final cohort consisted of 88 patients with a median follow-up of 70.5 (interquartile range, 38.6-104.0) months. The backgrounds and characteristics of transplant recipients are summarized in Table 1; they were similar except for the incidence of hepatocellular carcinoma (HCC) and type of graft. Overall, 25 (28.4%) patients had HCC, and significantly more patients in the TAC-BID group had HCC than patients in the TAC-PR group (46.4% vs 20.0%, P = 0.011). Preoperative radiological findings revealed 16 patients were within Millan criteria; 7 cases of TAC-BID group and 9 cases of TAC-PR group. After pathology examination, only 1 case in the TAC-PR group which was diagnosed as within Milan criteria proved not to match the criteria. Preoperative value of serum AFP tended to be higher in the TAC-BID group but not significant (958.3 ± 2203.7 ng/mL vs 93.1 ± 125.2 ng/mL, P = 0.505). The tumor differentiation grade of HCC was significantly aggressive in the TAC-BID group and the ratio of well or moderately differentiated HCC to poorly differentiated HCC were 2:7 versus 8:1 (P = 0.004).

As for type of graft, a right lateral section graft was only selected in the TAC-BID group. The major cause of liver disease

TABLE 1.

Baseline characteristics of patients

	TAC-BID	TAC-PR	
	(n = 28)	(n = 60)	*P*
Age, y	50.0 ± 13.9	52.1 ± 11.4	0.584
Sex, M/F	11/17	28/32	0.220
Primary diagnosis			0.426
Vital infection	15	26	
PBC/PSC	2/1	4/4	
Alcoholic	1	5	
Fulminant hepatitis	4	9	
NASH	0	6	
Other	5	6	
HCC	13 (46.4%)	12 (20.0%)	0.011
Milan criteria (yes:no)	7:6	9:3	0.271
Well/moderate:poorly	2:7	8:1	0.004
Type of donor			0.578
Living	23	52	
Deceased	5	8	
Type of graft			0.0018
Left lobe	8	28	
Right lobe	9	24	
Right lateral section	6	0	
Whole liver	5	8	
MELD score	19.0 ± 6.9	20.3 ± 8.4	0.672
Preoperative eGFR, mL/min	77.4 ± 26.4	73.3 ± 29.4	0.468
Operative time, min	805 ± 198	758 ± 144	0.522
Blood loss, mL	6259 ± 5218	7754 ± 5249	0.097

Data are presented as mean ± SD, number of patients, or n (%).

PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; NASH, nonalcoholic steatohepatitis; MELD, Model for End-stage Liver Disease; M, male; F, female.

in recipients were viral infection (n = 41, 46.6%), followed by fulminant hepatitis (n = 13, 14.8%). The preoperative Model for End-stage Liver Disease score and eGFR were similar between the groups.

Short-term Outcomes

Recipient short-term outcomes during the first 3 months after surgery are shown in Table 2. No significant difference was found, but patients in the TAC-PR group tended to have a lower incidence of BPAR by POD 90 (13.3% vs 28.6%, *P* = 0.084). All of the patients with BPAR were treated by steroid pulse and the addition of mycophenolate mofetil, and then acute rejection was improved immediately. Trough levels of tacrolimus were almost similar between the 2 groups throughout the 3 months (Figure 1). Trough levels in the TAC-PR group were slightly out of target trough level ranges on PODs 1, 2, and 5, as they were lower on PODs 1 and 2 and higher on POD 5. Thereafter, trough levels in the TAC-PR group were well controlled within the target ranges. The incidence of additional TAC due to low trough levels was higher in the TAC-PR group than the TAC-BID group (73.3% vs 42.9%, *P* = 0.006). However, the incidence of skipping TAC due to high trough levels tended to be rather lower in the TAC-PR group (25.0% vs 35.7%, *P* = 0.299). The rate of postoperative renal dysfunction was similar between the 2 groups (28.6% versus 25.0%, *P* = 0.723). The rate of overall postoperative surgical

morbidities (Clavien-Dindo ≥ IIIa) was also similar (46.4% vs 31.7%, *P* = 0.180).

Long-term Outcomes

Long-term outcomes including morbidities related with immunosuppression and renal function are compared in Table 3. Tacrolimus was withdrawn in 7 (8.0%) patients due to cranial neuropathy, development of renal dysfunction, or drug-induced liver injury. We found no difference in the incidence of discontinuing tacrolimus (10.7% vs 6.7%, *P* = 0.513). After the discontinuation of tacrolimus, cyclosporine was substituted as the main immunosuppression agent in all cases. We also compared immunosuppression-related morbidities. De novo tumors developed similarly in both groups (3.6% vs 3.3%, *P* = 0.954), whereas the recurrence of HCC was shown in 4 cases only in the TAC-BID group (14.3% vs 0.0%, *P* = 0.003). In these recurrent cases, tumor relapses were observed as extrahepatic metastasis, and times to recurrence after liver transplantation were respectively 6, 7, 11, and 20 months. Infection was present in 5 patients during follow-up. Three patients presented with bacterial infections, 1 patient presented with cytomegalovirus infection, and 1 patient with fungal infection. We found no difference in the incidence of patients presenting with infection (10.7% vs 3.3%, *P* = 0.164).

The evolution of mean eGFR in each group is shown in Figure 2. Glomerular filtration decreased from 77.4 and 73.3 mL/min per 1.73 m^2 before transplantation to 66.3 and 61.4 ml/min/1.73 m^2 at 6 months after transplantation in the TAC-BID and TAC-PR groups, respectively. Thereafter, the eGFR remained almost stable until the end of follow-up period. The mean eGFR 5 years after transplantation was 62.9 versus 61.6 ml/min/1.73 m^2 (*P* = 0.848). We found no significant difference at each time point from 0 to 60 months after transplantation. At the end of follow-up, a total of 24 (27.2%) patients had developed CKD (20, 2, and 2 patients in stage 3, stage 4, and stage 5, respectively) (Table 3). The incidence of CKD development was not significantly different between the 2 groups (28.6% vs

TABLE 2.

Short-term outcomes of patients

	TAC-BID	TAC-PR	
	(n = 28)	(n = 60)	*P*
BPAR	8 (28.6%)	8 (13.3%)	0.084
Addition of TAC	12 (42.9%)	44 (73.3%)	0.006
Skip of TAC	10 (35.7%)	15 (25.0%)	0.299
Postoperative renal dysfunction	8 (28.6%)	15 (25.0%)	0.723
Morbidities, Clavien-Dindo IIIa	13 (46.4%)	19 (31.7%)	0.180
Intra-abdominal bleeding	9	4	
Portal vein thrombus	2	1	
Hepatic artery complications	1	3	
Bile duct stenosis	0	3	
Infection	3	2	
Intracranial bleeding	0	3	
Upper GI bleeding	0	1	
Others	1	5	

Data are presented as n (%) or number of patients. Postoperative renal dysfunction was defined as minimal eGFR the first 3 months after surgery being less than half the preoperative eGFR.
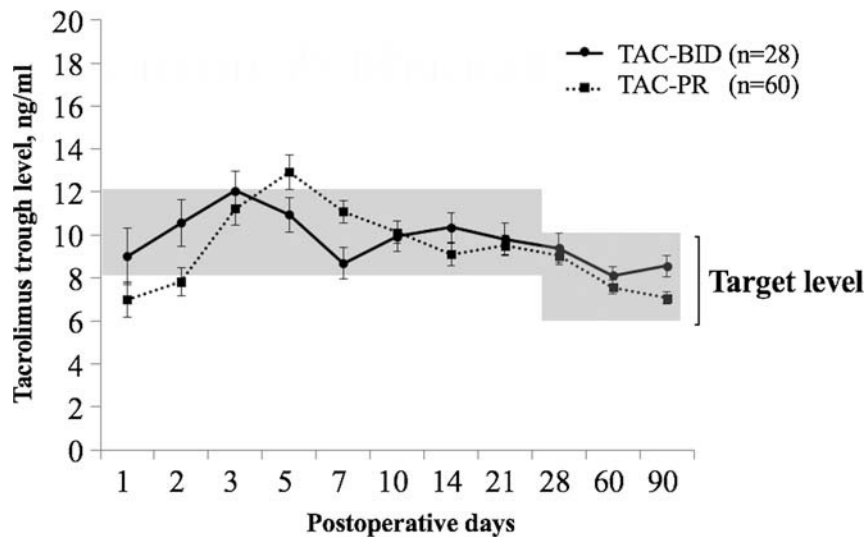
FIGURE 1. Trough levels of tacrolimus over 90 PODs. The gray zone indicates target trough level ranges. Error bars represent standard error of the mean.

26.7%, P = 0.852). Two patients in the TAC-PR group developed stage 5 CKD; 1 patient initially had stage 4 CKD, and 1 patient initially had stage 3 CKD and started hemodialysis due to thrombotic microangiopathy 15 months after transplantation.

Overall, 8 (9.1%) patients died during the follow-up period. The most common cause of mortality was HCC recurrence (n = 4, 4.5%), followed by sepsis (n =2, 2.3%). Patient survival at 1, 3, and 5 years were 96.4%, 85.7%, and 85.7% versus 96.7%, 94.8%, and 94.8%, respectively

TABLE 3.

Long-term outcomes of patients

	TAC-BID	TAC-PR	
	(n = 28)	(n = 60)	*P*
Discontinuation of tacrolimus	3 (10.7%)	4 (6.7%)	0.513
Cause of discontinuation			
Cranial neuropathy	2	2	
Renal dysfunction	1	1	
Drug-induced liver injury	0	1	
De novo tumor	1 (3.6%)	2 (3.3%)	0.954
HCC recurrence	4 (14.3%)	0 (0.0%)	0.003
Patients presenting with infection	3 (10.7%)	2 (3.3%)	0.164
Bacterial	2	1	
CMV	1	0	
Fungal	0	1	
Development of CKD	8 (28.6%)	16 (26.7%)	0.852
Stage 3	6	14	
Stage 4	2	0	
Stage 5 (HD)	0	2	
De novo DM or dyslipidemia	2 (7.1%)	3 (5.0%)	0.686
Mortality	5 (17.9%)	3 (5.0%)	0.051
Cause of mortality			
HCC recurrence	4	0	
HCV recurrence	1	0	
Sepsis	0	2	
Varix rupture	0	1	

Data are presented as n (%) or number of patients.
CMV, cytomegalovirus; HD, hemodialysis; DM, diabetes mellitus; HCV, hepatitis C virus.

(Figure 3). The overall survival of the TAC-PR group tended to be higher than that of the TAC-BID group (P = 0.096).

DISCUSSION

This retrospective study on heterogeneous groups of consecutive liver transplant recipients mostly from living donors demonstrates that immunosuppression based on TAC-PR initiated immediately after liver transplantation was feasible and favorable. Even though the necessity of additional TAC administration was greater in the TAC-PR group, the trough levels were almost within the target trough levels with less incidence of overshooting. In addition, a lower BPAR rate was achieved in the TAC-PR group. This is potentially valuable study because it is mostly performed on partial grafts from living donors. In Japan, living donor liver transplantation has a very important role due to chronic lack of brain-dead donors.[15] Oral administration of twice-daily TAC for de novo liver transplantation is still widely accepted because the graft size is small in living donor liver transplantation and more careful attention to the control of TAC administration should be necessary.[16] The administration of TAC-PR in the early phase of liver transplantation seemed to lead to postoperative adverse effects, such as acute rejection or infectious complications, due to difficulty controlling the trough level of TAC. The other regimens for TAC-PR administration in liver transplantation recipients are oral administration of traditional twice-daily TAC or temporary intravenous administration of TAC, and then conversion to TAC-PR. However, conversion of administration carries the risk of fluctuating the concentration of TAC. As long as the concentration is well controlled, the immediate start of TAC-PR should be better because of its simplicity and unnecessary conversion of the TAC formula.[17]

In this study, not only long-term outcomes, but also short-term outcomes, including the adjustment of TAC dose early after transplantation, were compared to evaluate the difference between the TAC-BID and TAC-PR protocol in detail. The incidence of additional TAC due to low trough levels was higher in the TAC-PR group than the TAC-BID group,
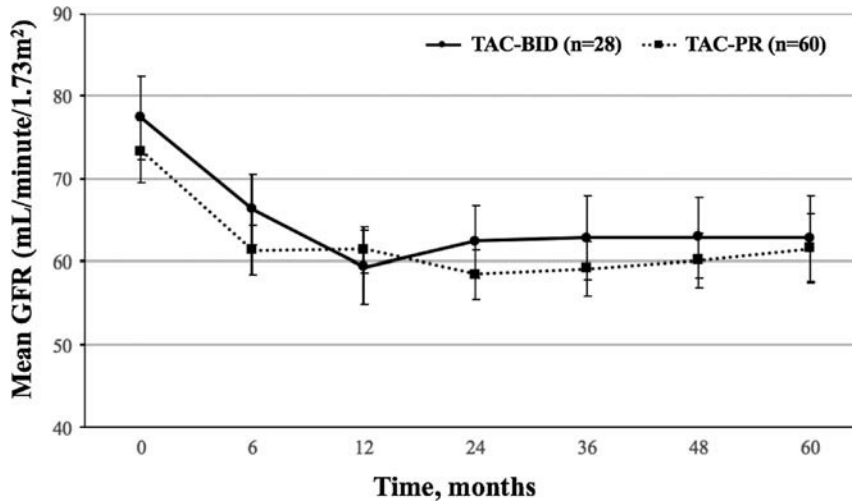
FIGURE 2. eGFR to month 60 per treatment group. Error bars represent standard error of the mean.

but this was probably because adjustments could be managed by increasing the evening dose of TAC in the TAC-BID group without adding TAC administration timing in most cases. Although the concentration of TAC did not tend to achieve the target trough levels until POD 2 in the TAC-PR group, we supposed that the delay to reach the target trough could be permitted because the high amount of corticosteroid was used during this acute phase. TAC has a narrow therapeutic index, and many clinical and genetic factors, such as cytochrome P450(CYP) 3A5 and ATP-binding cassette B1 polymorphisms can affect the pharmokinetics of TAC.[18] Especially in the early posttransplantation period, TAC blood levels are influenced by the dramatic change of absorption and metabolism. Our initial dose of TAC was relatively low, and we started with the same dose regardless of the formulation of TAC. After that, we adjusted the dose of TAC by monitoring the blood trough level. Our results support the immediate start of oral TAC-PR being feasible and safe compared with conventional TAC-BID in de novo liver transplantation.

Renal dysfunction after liver transplantation is a major problem,[19-22] and renal insufficiency is strongly associated with an increased relative risk of death more than 1 year after liver transplantation.[23,24] In our study, renal function gradually worsened during the first 6 months after transplantation and thereafter remained stable throughout the follow-up period. Overall, there were as many as 24 (27.2%) recipients developed CKD according to the Kidney Disease: Improving Global Outcomes guidelines. Among these 24 patients, 4 (4.5%) patients developed stage 4 or 5 CKD.

It is reported that the lower trough concentration of tacrolimus in the early posttransplant period by using TAC-PR was beneficial in reducing drug-related side effects without increasing the incidence of ACR by randomized controlled trial and systematic reviews.[25,26] In addition, lower tacrolimus trough levels possibly contribute to reduction in renal
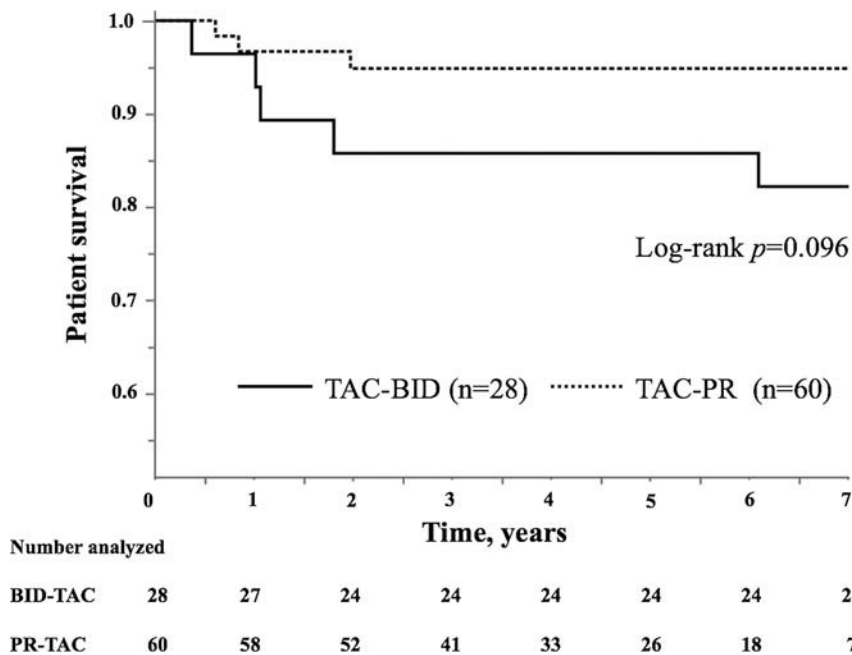

FIGURE 3. Kaplan-Meier analysis of patient survival over 7 years of treatment.

impairment,[17,27] lower HCC recurrence,[28] less progression of fibrosis,[29] and improvement of long-term patient and graft survival.[17,30] Early tacrolimus exposure, in the immediate posttransplant period, might be the key to improve renal function in future. In our study, target trough levels of tacrolimus were set to 8 to 12 ng/mL within the first 3 weeks after transplantation, and 6 to 10 ng/mL until 3 months after transplantation. We paid attention not to overshoot these target trough ranges.

In this study, HCC recurrence after liver transplantation was observed only in TAC-BID group, and the recurrence rate in TAC-BID group was 14.3%. In the baseline characteristics, the patients in TAC-BID group had more advanced stage and aggressive features of HCC. The rate of HCC over Milan criteria was higher in the TAC-BID group (46%) than the TAC-PR group (25%), and the preoperative value of AFP was higher in TAC-BID group. In addition, the pathological tumor differentiation was quite different in 2 groups; the rate of poorly differentiated HCC was significantly higher in the TAC-BID group. From these differences of baseline factors in 2 groups, it is supposed that HCC recurrence was shown only in patients of TAC-BID group. The influence on HCC recurrence by administering of immunosuppressive drug of TAC-BID versus TAC-PR could not be fully ascertained from this study due to the tumor characteristics differences in the 2 groups.

Our study has several limitations. In this study, 26 recipients who received 1 dose of TAC-BID immediately after transplantation, followed by TAC-PR in once-daily protocol from POD 1 were included in the TAC-PR group. We performed this protocol as a bridge to immediate start of TAC-PR from POD 0. As a result, our TAC-PR group included 2 subgroups. However, our policy concerning TAC administration was consistent, and we had kept almost the same way of administration. In addition, this was a single-center nonrandomized retrospective study, and we did not examine the incidence of nonadherence of TAC. As for immunosuppression nonadherence, we have plenty of evidence that nonadherence is associated with increased late ACR and graft loss in adult renal transplant populations, but similar evidence is scanty for adult liver transplant patients.[31-34] Improved adherence to TAC-PR might in turn lead to improved patient prognosis. There are few facilities where the immediate start of TAC-PR is introduced in de novo liver transplant recipients, and little information is available about the clinical experience. Our results clearly demonstrate that the TAC-PR protocol was well tolerated with closely controlled adjustment.

In conclusion, the TAC-PR protocol was feasible and favorable with strict adjustment compared with the traditional TAC-BID protocol in terms of both short- and long-term outcomes.

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