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Safety and Efficacy of Once-Daily Prolonged-Release Tacrolimus in Living Donor Liver Transplantation: An Open-Label, Prospective, Single-Arm, Phase 4 Study

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: After liver transplantation (LT), nonadherence to immunosuppressants due to the complex regimen can lead to graft rejection and loss. This study assessed the efficacy and safety of conversion from twice-daily tacrolimus (Bid-Tac) to once-daily prolonged-release tacrolimus (OD-Tac) in living donor LT (LDLT) recipients.

Material/Methods: Among patients who underwent LDLT between November 2015 and October 2016, those who agreed to participate in this study were screened, and those with good general condition and stable liver functions were enrolled. Participants underwent a conversion from Bid-Tac to OD-Tac with a dose ratio of 1: 1 at about 10–14 weeks after LDLT and were followed-up for 24 weeks.

Results: Thirty-one patients were enrolled. The median number of conversion days after LDLT was 12.3 weeks (range, 10.3–13.8). Adherence was evaluated during the outpatient visits at weeks 2, 4, 8, 16, and 24 after Tac conversion, and 100% adherence was observed at all time points. There were no cases of acute rejection, graft loss, or patient death after Tac conversion. Nineteen cases of adverse events occurred in 11 patients (35.5%), none of which were severe. Alopecia was the most common, affecting 3 (9.7%) patients, followed by pruritus (n=2, 6.45%). There were no changes in renal function or in liver function test, serum glucose level, and lipid profile.

Conclusions: Early Tac conversion from Bid-Tac to OD-Tac is safe and feasible. However, further studies are needed to elucidate its long-term effects.

MeSH Keywords: **Liver Transplantation • Medication Adherence • Tacrolimus**

Abbreviations: **ALT** – alanine transaminase; **AST** – aspartate transaminase; **Bid-Tac** – twice-daily tacrolimus; **eGFR** – estimated glomerular filtration rate; **HDL** – high-density lipoproteins; **LDLT** – living donor liver transplantation; **LDL** – low-density lipoproteins; **LT** – liver transplantation; **OD-Tac** – once-daily prolonged-release tacrolimus; **Tac** – tacrolimus; **TG** – triglycerides

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Background

The liver is an essential organ for maintaining life, and due to its complex and diverse functions, no machine developed thus far can fully replace it. Thus, the only possible treatment for end-stage liver disease, including liver cirrhosis and hepatocellular carcinoma, or acute liver failure caused by fulminant hepatitis or acetaminophen overdose is liver transplantation (LT) from healthy living donors or (unhealthy) deceased donors.

Although the liver is not as antigenic as other organs, such as the kidney, lung, heart, and bowel, assessment and response to the rejection of transplanted liver grafts are important aspects of patient care. Immunosuppressive regimens based on steroids and tacrolimus (Tac) or combination therapy with cyclosporine are generally used in the early phase of LT, and secondary immunosuppressants (e.g., mycophenolate mofetil) may be added.

Meanwhile, Tac – also known as FK-506 or fujimycin – is a 23-membered macrolide lactone that inhibits the development and proliferation of T cells; it was first discovered in 1987 from Japanese soil specimens containing *Streptomyces tsukubaensis* [1,2]. Twice-daily Tac (Bid-Tac), which is commonly used in modern LT, may lead to nonadherence among patients, which in turn serves as a risk factor for rejection and graft loss [3–5]. In an effort to increase adherence to immunosuppressive therapy in LT patients, once-daily prolonged-release Tac (OD-Tac) was first introduced in Europe in 2007. OD-Tac has been reported to improve adherence [6–8], and the low inter- and intra-individual variability in exposure to OD-Tac has been associated with an increase of graft and patient survival [8–10].

Based on these superior benefits of adherence and low variability compared to Bid-Tac, late conversion from Bid-Tac to OD-Tac has been reported multiple times to be safe and feasible generally after 6 months of LT in patients with stabilized liver functions [11-18]. However, there is little data on the efficacy and safety of early conversion from Bid-Tac to OD-Tac in living donor liver transplantation patients within 6 months of LT. In this context, the present study aimed to thoroughly assess the safety and efficacy of conversion from Bid-Tac to OD-Tac at 10–14 weeks after LDLT.

Material and Methods

Patients and study design

This clinical trial was an open-label, prospective, single-arm, phase 4 study. Adult patients aged 20 years or older who underwent LDLT in our institute between November 2015 and October 2016 and provided informed consents were screened. Of these patients, those in a good general condition with stable liver functions were enrolled in this clinical trial. The details of the inclusion and exclusion criteria are described in Supplementary Table 1.

The participants of this study underwent a conversion from reference Bid-Tac (Prograf®, Astellas Pharma, Inc., Seoul, Korea) to OD-Tac (Advagraf®, Astellas Pharma Inc., Seoul, Korea) with a daily dosage ratio of 1: 1 at 10–14 weeks after LDLT. Tac was administered only once a day in the morning. The serum trough level of Tac was measured at each outpatient visit, and Tac dosage was adjusted to maintain a trough level of 5–8 ng/ml for the first 3 months (months 0–3) and below 5 ng/ml for the subsequent 3 months (months 3–6) after Tac conversion. In all cases, a right lobe of a donor liver was used [19–21]. This study was approved by our Institutional Review Board (NCC2015-0020) and was registered at ClinicalTrials.gov (NCT03423225).

Immunosuppression

For induction therapy, 20 mg of basiliximab is administered on the operation day and post-operative day 4. Immunosuppressive regimens are a combination of Tac, mycophenolate mofetil, and corticosteroids after high-dose steroid administration during the operation. After LT, initial therapeutic target levels of Tac were 8–12 ng/ml during the first and the second week and thereafter 8–10 ng/mL during the first 3months. After that, the tacrolimus trough level is adjusted to 5–6 ng/mL for 3–6 months and <5 ng/mL thereafter. Mycophenolate mofetil was started with a dose of 1.5 g/day. Corticosteroid was reduced to interruption for 6 months after LDLT.

Follow-up and surveillance

The participants enrolled in this study underwent a total of 7 rounds of tests, 1 at each of the following time points: screening, baseline, weeks 2, 4, 8, 16, and 24. Test categories included serum Tac trough level, creatinine, estimated glomerular filtration rate (eGFR), bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), glucose, cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), and triglycerides (TG). Adherence and adverse events were checked at every outpatient visit.

Statistical analysis

The results are presented as mean ± standard deviation or median (interquartile range) for continuous variables and percentage for categorical variables. Paired continuous data were analyzed with a Wilcoxon signed rank test. McNemar's test was used to compare paired proportions. A P value <0.05 was considered statistically significant. All calculations were made using the SPSS 24.0 statistical software package (IBM Corporation, Armonk, NY, USA).

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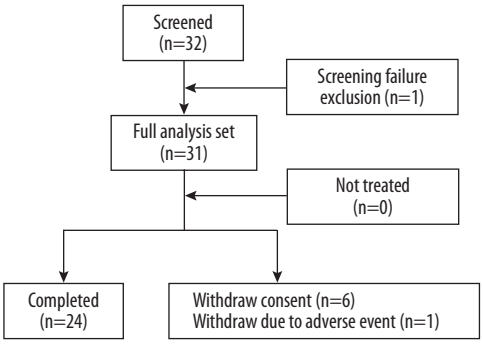

Figure 1. Patient deposition.

Results

Study population and baseline characteristics

A total of 32 patients were screened. One patient was excluded for having a history of acute rejection, resulting in a total of 31 patients in the final sample. Twenty-four of these patients completed the clinical trial, with 7 dropouts. Reasons for study withdrawal were an adverse event (n=1, moderate melena) and consent withdrawals (n=6) (Figure 1).

The mean age was 53.7±8.0 years. A total of 77.4% (n=24) of the patients were male, while 22.6% (n=7) were female. Hepatocellular carcinoma was the most frequent primary reason for LT (71.0%, n=22). The mean body weight was 62.0±14.6 kg, while mean height was 166.5±8.9 cm. There were 18 patients with hepatitis B virus infection (58.1%), 1 patient with hepatitis C virus infection (3.2%), and 2 patients with cytomegalovirus infection (6.5%). Six patients had diabetes mellitus (19.4%), while 5 patients had hypertension (16.1%). The mean OD-Tac exposure period was 152.4±50.6 days. The median number of weeks from LT to Tac conversion was 12.3 weeks (range, 10.3–13.8). Table 1 shows the baseline characteristics of the 31 patients enrolled in this clinical trial.

Adherence and Tac trough level

Adherence was 100% at all time points: at weeks 2, 4, 8, 16, and 24 after Tac conversion from Bid-Tac to OD-Tac. The mean period for OD-Tac exposure was 152.4±50.6 days. The daily dosage for OD-Tac was 4.9±1.9 mg. Tac trough level significantly differed at weeks 2, 4, 8, 16, and 24 from that prior to conversion (Figure 2A, all $P<0.001$). Tac dosage significantly differed at week 2 after conversion from that prior to conversion (Figure 2B, $P=0.011$).

Table 1. Baseline characteristics.

Variables	OD-Tac (n=31)
Age, (years)	53.7±8.0
Sex	
Female	7 (22.6)
Male	24 (77.4)
Primary reason for LT	
Carcinoma-hepatocellular	22 (71.0)
Carcinoma-other	4 (12.9)
Cirrhosis	4 (12.9)
Other	1 (3.2)
Weight, (kg)	62.0±14.6
Height, (cm)	166.5±8.9
Blood Type(RH)	
RH+	31 (100.0)
RH–	0 (0.0)
Blood type (ABO)	
A	9 (29.0)
B	10 (32.3)
AB	3 (9.7)
O	9 (29.0)
Viral infection status	
Hepatitis B virus	18 (58.1)
Hepatitis C virus	1 (3.2)
Cytomegalovirus	2 (6.5)
Epstein-Barr virus	0 (0.0)
Metabolism and nutrition disorders	
Diabetes mellitus	6 (19.4)
Hyperlipidemia	1 (3.2)
Hypertension	5 (16.1)
Exposure period of OD-Tac (days)	152.4±50.6

Data are presented as number (%) or mean ± standard deviation. LT – liver transplantation; OD-Tac – once-daily prolonged-release tacrolimus.

Efficacy and safety

There were no cases of acute rejection until study completion at week 24 after Tac conversion from Bid-Tac to OD-Tac.

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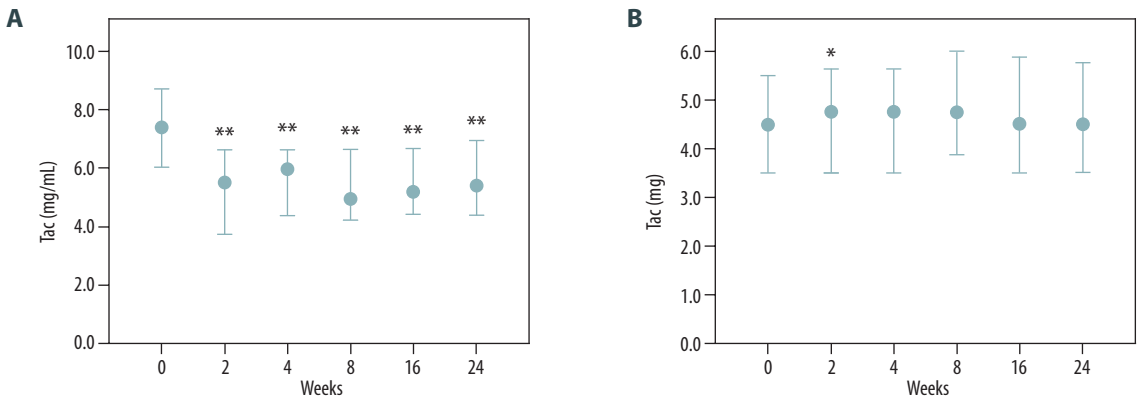

Figure 2. Tac (**A**) trough level and (**B**) daily dosage. Data are presented as median (circle) with a vertical line from the first quartile to the third quartile. * *P*<0.05; ** *P*<0.001. Tac – tacrolimus.

Table 2. Adverse events.

Adverse events	OD-Tac (n=31)
Gastrointestinal disorders	2 (6.5) [3]
Abdominal pain	1 (3.2) [1]
Melena	1 (3.2) [1]
Toothache	1 (3.2) [1]
General disorders and administration site conditions	1 (3.2) [2]
Face edema	1 (3.2) [1]
Edema	1 (3.2) [1]
Hepatobiliary disorders	1 (3.2) [1]
Jaundice	1 (3.2) [1]
Infections and infestations	2 (6.5) [2]
Periodontitis	1 (3.2) [1]
Upper respiratory tract infection	1 (3.2) [1]
Injury, poisoning and procedural complications	1 (3.2) [1]
Spinal compression fracture	1 (3.2) [1]
Investigations	1 (3.2) [1]
Liver function test abnormal	1 (3.2) [1]
Musculoskeletal and connective tissue disorders	1 (3.2) [1]
Arthralgia	1 (3.2) [1]
Nervous system disorders	1 (3.2) [1]
Headache	1 (3.2) [1]
Respiratory, thoracic and mediastinal disorders	1 (3.2) [1]
Cough	1 (3.2) [1]
Skin and subcutaneous tissue disorders	5 (16.1) [6]
Alopecia	3 (9.7) [3]
Pruritus	2 (6.5) [2]
Urticaria	1 (3.2) [1]

Data are presented the number of subjects (%) [number of events]. OD-Tac – once-daily prolonged-release tacrolimus.

Furthermore, there were no cases of graft loss or patient death during the entire study period.

Nineteen cases of adverse events occurred in 11 out of 31 patients (35.5%). Of them, 18 were mild adverse events and 1 was a moderate adverse event, with no severe adverse events. The most common adverse event was alopecia, which affected 3 patients (9.7%), followed by pruritus (n=2, 6.5%). Melena, a moderate adverse event, affected 1 patient (3.2%), and this patient was withdrawn from the study. One patient had jaundice and LFT abnormality due to biliary stricture (Table 2).

After conversion from Bid-Tac to OD-Tac, there were no changes in renal functions, such as creatinine and eGFR (Figure 3A, 3B). Furthermore, serum bilirubin, AST, ALT, and glucose changes were also not observed during the follow-up period (Figure 3C–3F). Tac conversion lipid profile, such as serum cholesterol, HDL, LDL, and TG, also did not significantly differ from pre-conversion parameters in most cases (Figure 4A–4D).

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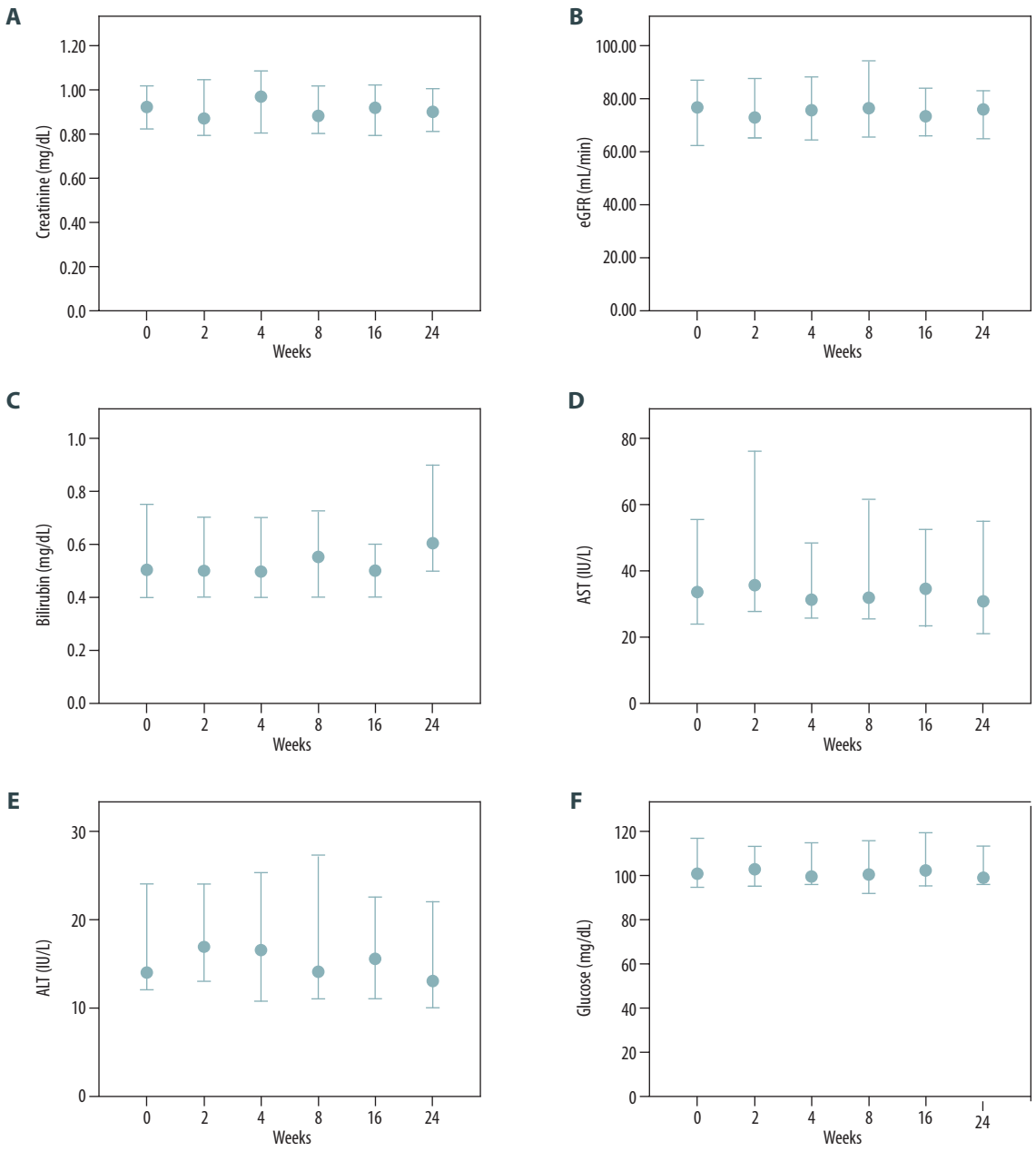

Figure 3. Comparison of laboratory data at the time of Tac conversion with those after 2, 4, 8, 16, and 24 weeks. (**A**) creatinine, (**B**) eGFR, (**C**) bilirubin, (**D**) AST, (**E**) ALT, and (**F**) glucose. Data are presented as median (circle) with a vertical line from the first quartile to the third quartile. ALT – alanine transaminase; AST – aspartate transaminase; eGFR – estimated glomerular filtration rate; Tac – tacrolimus.

Discussion

Adherence to immunosuppressants after LT is a decisive factor in preventing the risk of rejection and graft loss. It was reported that about 15–40% of adult patients showed nonadherence with immunosuppressant regimens [5]. Nonadherence to immunosuppressant after LT may induce rejection and graft loss, ultimately having adverse effects on long-term patient survival [3–5]. In our study, adherence was 100% at all outpatient visits at weeks 2, 4, 8, 16, and 24 after the conversion from Bid-Tac to OD-Tac. These results are in line with previous findings [7,15], again confirming the superiority of OD-Tac in terms of promoting adherence.

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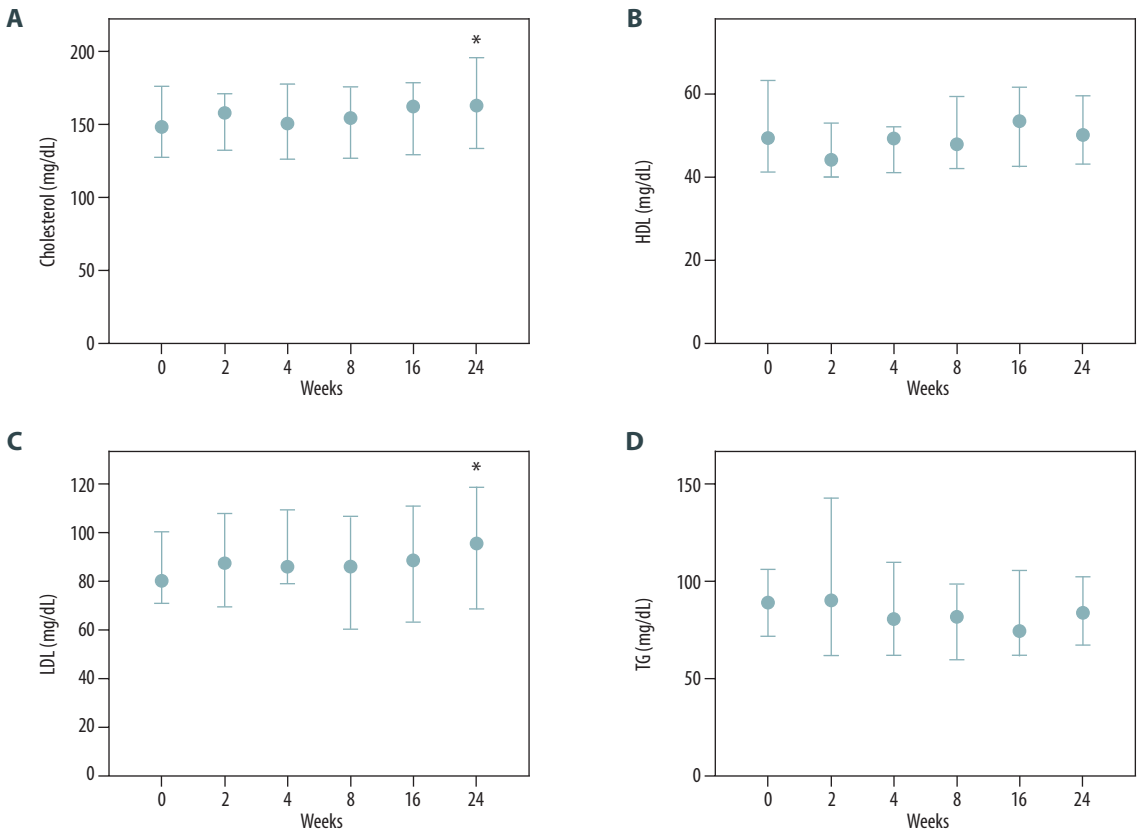

Figure 4. Comparison of laboratory data at the time of Tac conversion with those after 2, 4, 8, 16, and 24 weeks. (**A**) cholesterol, (**B**) HDL, (**C**) LDL, and (**D**) TG. Data are presented as median (open circle) with a vertical line from the first quartile to the third quartile. * $P<0.05$; ** $P<0.01$; *** $P<0.001$. HDL – high-density lipoproteins; LDL – low-density lipoproteins; Tac – tacrolimus; TG – triglycerides.

In addition to the benefits of adherence to immunosuppressants, OD-Tac has been reported to be superior to Bid-Tac in terms of inter-individual variability and intra-individual variability [9,10]. Moreover, a recent study suggested that OD-Tac is intimately related to the improvement of graft and patient survival [8]. Based on this superiority, there were some successful cases of *de novo* initiation of OD-Tac after LT [22–24], but it is yet to be popularized in Asian countries, including Korea. Fundamentally, Bid-Tac and OD-Tac formulations do not have different metabolism or excretion within the human body. One difference between the 2 Tac formulations is the absorption in the digestive tract; absorption occurs in the stomach and upper small bowel with Bid-Tac, while absorption occurs throughout the stomach and whole small bowel with OD-Tac. Hence, with unstable gastrointestinal motility, Tac trough level may also be unstable, which in turn is highly unfavorable for Tac, with its low therapeutic index [25,26]. Thus, considering that *de novo* initiation of OD-Tac after LDLT is performed immediately postoperatively, when there are significant motility changes in the digestive tract, and considering that LDLT using small partial liver grafts, which probably induces poor gastrointestinal absorption resulting from elevated portal pressure, is prevalent in Asian countries, including Korea, additional evidence must be obtained before performing *de novo* initiation of OD-Tac after LDLT as standard practice [27].

The efficacy and safety of late conversion from Bid-Tac to OD-Tac at least 6 months after LT in patients with stable liver functions have been documented by multiple studies [11–18]. However, few studies have documented the efficacy and safety of early conversion from Bid-Tac to OD-Tac within 6 months after LT. In a few previous studies, early conversion from Bid-Tac to OD-Tac was mostly performed within 1–2 months after LT [10,27], primarily because patients show better adherence to treatment in the earlier days after LT and adjusting Tac dose and performing therapeutic drug monitoring are easier for patients staying at the hospital after the operation [15,28]. However, as previously mentioned, OD-Tac agents are more profoundly affected by gastrointestinal absorptive functions than do Bid-Tac agents [25,26]. Therefore, this study attempted the

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conversion from Bid-Tac to OD-Tac in patients showing normal liver graft function at 10–14 weeks after LDLT, which is thought to be a period of relatively stable and consistent absorption capacity of the digestive tract.

In the present study, the Tac trough level decreased by 25.7% at week 2 after the conversion from BID-Tac to OD-Tac with a 1: 1 dosage ratio (Figure 2A, $P<0.001$). As a result, the dose of OD-Tac had to be increased by 18.8% (Figure 2B, $P=0.011$). This phenomenon has been reported in previous studies [10,19], and considering that Tac has a narrow therapeutic range, additional studies should be conducted to substantiate the optimal dosage ratio for the conversion from Bid-Tac to OD-Tac.

None of the patients in our study developed an acute rejection from the time of Tac conversion until completion of the study at week 24. Further, there were no cases of graft loss or patient death during the entire study period. With regard to efficacy, the rejection, graft, and patient survival results in the present study were similar to previous findings [9,10,15,30].

Further, there were no serious adverse events during the follow-up period after Tac conversion (Table 2). There were also no changes in the indicators of renal function, such as serum creatinine level and eGFR, in relation to Tac conversion (Figure 3A, 3B), as well as no changes in serum bilirubin, AST, ALT, and glucose level (Figure 3C–3F). Lipid profile, such as cholesterol, HDL, LDL, and TG level, also did not differ after Tac conversion. These results are in line with previous findings that OD-Tac and BID-Tac do not differ in terms of safety [9,10,15,27,29,31–34].

Conclusions

The findings from this study suggest that early conversion from BID-Tac to OD-Tac at 10–14 weeks after LDLT is safe and feasible. However, this study could not observe long-term effects due to having a short follow-up period, so additional studies are needed to shed more light on this matter.

Conflict of interest

None.

Supplementary Table

Supplementary Table 1. Inclusion and exclusion criteria.

Inclusion criteria
– Adults aged 20 years or older at the time of providing an informed consent
– Patients who underwent LDLT at least 10–14 weeks prior to the Tac conversion from Bid-Tac to OD-Tac
– Patients who had a minimal Tac concentration (Cmin) or trough level of between 3–10 ng/ml from the day of the most recent LDLT until the day of Tac conversion
– For premenopausal women, those with a negative serum or urine pregnancy test at the screening and consent to practice effective birth control during the course of the clinical trial (Oral contraceptive pills are prohibited)
– Clinically stable patients in the opinion of the tester
– Patients who provided written informed consents after receiving adequate explanation about the purpose and risks of the clinical trial
Exclusion criteria
– Patients who had previously received an organ transplantation other than liver or an auxiliary liver transplantation, or those who have used a bioartificial liver support system
– Patients who developed acute rejection after LDLT prior to Tac conversion
– Patients diagnosed with a novel malignant tumor after LDLT (Excluding those with basal cell carcinoma or squamous cell carcinoma of the skin that was successfully treated)
– Patients known to have a hypersensitivity to tacrolimus ingredients
– In the opinion of the tester, patients in an unstable medical state that may affect the purpose of this clinical trial
– Patients with any form of substance abuse, mental disorder, or condition that hinder effective communication with the tester as determined by the tester

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– Patients who are currently participating in another clinical trial or have received pharmaceuticals for another clinical trial within 28 days of the Tac conversion

– Patients who are currently undergoing or have undergone (within 28 days of Tac conversion) a therapy prohibited for the purpose of this study

– Pregnant or nursing women

– Patients known to be human immunodeficiency virus (HIV)-positive

– Patients with a high possibility of missing the scheduled visits per the research plan

– Patients determined by the tester to have a clinically significant renal dysfunction or patients whose serum creatinine level exceeded 1.6 mg/dL or estimated glomerular filtration rate (eGFR) was below 30 mL/min prior to Tac conversion

– Patients determined by the tester to have a clinically significant liver dysfunction or patients whose liver function test parameters increased more than three-fold of the normal range prior to Tac conversion

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