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Efficacy and safety of a switch from twice-daily tacrolimus to once-daily generic tacrolimus in stable liver transplant patients

Jong Man Kim[1], Pyoung-Jae Park[2,3], Geun Hong[4], Dong Jin Joo[5], Kwan Woo Kim[6], Je Ho Ryu[7], Young Seok Han[8], Jai Young Cho[9], Gi-Won Song[10], Bong-Wan Kim[11], Dong-Sik Kim[2], Seong Hoon Kim[12], Sang Tae Choi[13], Young Kyoung You[14], Kyung-Suk Suh[15], Yang-Won Na[16], Koo Jeong Kang[17], Jae-Won Joh[1]

[1]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]Department of Surgery, Korea University College of Medicine, Seoul, Korea
[3]Department of Surgery, Korea University Guro Hospital, Seoul, Korea
[4]Department of Surgery, Ewha Woman's University School of Medicine, Seoul, Korea
[5]Department of Surgery, Yonsei University College of Medicine, Seoul, Korea
[6]Department of Surgery, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Korea
[7]Department of Surgery, Pusan National University College of Medicine, Busan, Korea
[8]Department of Surgery, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[9]Department of Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[10]Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[11]Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Ajou University School of Medicine, Suwon, Korea
[12]Center for Liver Cancer, National Cancer Center, Goyang, Korea
[13]Department of Surgery, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, Korea
[14]Department of Surgery, College of Medicine, The Catholic University of Korea, Seoul, Korea
[15]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea
[16]Department of Surgery, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea
[17]Department of Surgery, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Korea

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Corresponding author: Jae-Won Joh
Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, 06351 Seoul, Korea
Tel: +82-2-3410-3466
Fax: +82-2-3410-0040
E-mail: jw.joh@samsung.com

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Background: Once-daily tacrolimus reduces non-compliance relative to twice-daily tacrolimus. However, little is known about the safety and efficacy of conversion from twice-daily tacrolimus to generic once-daily tacrolimus in liver transplantation (LT). Herein, we investigated the efficacy and safety of a switch from twice-daily tacrolimus to generic once-daily tacrolimus in patients with stable liver graft function.
Methods: This prospective, multicenter, open-label, single-arm study was conducted in 17 medical centers for 1 year from July 2019 to July 2020 (NCT04069065). Primary endpoint was the incidence of biopsy-proven acute rejection (BPAR) for 24 weeks after conversion. Secondary endpoints were graft failure, patient death, and adverse events (AEs).
Results: Of 151 screened LT patients, 144 patients were enrolled. BPAR, graft failure, and patient death did not occur in this patient population. There were no statistical differences in blood tests, liver function tests, or biochemical tests between visits in any of the patients. Median tacrolimus trough level decreased abruptly from 4.7 ng/mL to 3.2 ng/mL after generic once-daily tacrolimus conversion, but median tacrolimus dose increased due to low tacrolimus trough level. Ninety-two adverse events occurred in 54 patients. Liver enzyme levels increased in seven patients (4.9%) after the switch to generic once-daily tacrolimus, but the liver function tests of these patients normalized thereafter. There were three cases of severe AEs not related to investigational drug.
Conclusions: Present study suggests that conversion from twice-daily tacrolimus to generic once-daily tacrolimus is effective and safe in stable LT patients.

Keywords: Tacrolimus; Liver transplantation; Therapeutic equivalence; Immunosuppression

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HIGHLIGHTS

- **Biopsy-proven acute rejection, graft failure, and patient death did not occur after conversion to generic once-daily tacrolimus in stable liver transplant patients.**
- **Therefore, present study suggests that switch from twice-daily tacrolimus to generic once-daily tacrolimus is effective and safe.**

INTRODUCTION

Tacrolimus is an effective immunosuppressant in liver transplantation (LT) and is most often prescribed as twice-daily immediate-release tacrolimus [1-3]. Once-daily extended-release tacrolimus was developed to enhance adherence to treatment because nonadherence is a common and major cause of transplant failure [4,5]. The formulation of once-daily extended-release tacrolimus with ethyl cellulose and hypromellose results in a prolonged drug release profile after administration [6,7]. In addition, the release of tacrolimus typically occurs more distally along the gastrointestinal tract, which results in slower absorption kinetics of tacrolimus compared with twice-daily immediate-release tacrolimus [6,7]. Several studies performed in Korean populations have shown comparable systemic drug exposure, as well as efficacy and safety profiles, after 1:1 (mg:mg) dose conversion from twice-daily tacrolimus to once-daily extended-release brand-name tacrolimus in stable liver transplant recipients [8-11].

The cost of immunosuppressants and care in transplant patient remains high despite efforts to reduce these costs [12]. The patent for tacrolimus expired in 2008. Since then, generic tacrolimus, which has met all standards for bioequivalence and is therapeutically equivalent to brand-name tacrolimus, has been introduced worldwide [13,14]. Generic tacrolimus is now widely prescribed for liver transplant recipients in many countries.

Tacrobell (Chong Kun Dang Pharmaceutical, Seoul, Korea) is a generic formulation of twice-daily tacrolimus that was approved in 2004 by the Korea Ministry of Food and Drug Safety (KMFDS) [15]. The criteria for approval of a generic formulation by the KMFDS are similar to those of the U.S. Food and Drug Administration and the European Medicinal Agency [16]. The KMFDS requires the manufacturer to conduct a bioequivalence study in healthy volunteers as a clinical trial [15-17]. Twice-daily generic tacrolimus was demonstrated to be safe and effective for LT patients in Korea [15,17,18].

However, the efficacy and safety of generic once-daily tacrolimus, Tacrobell SR (Chong Kun Dang Pharmaceutical), for adult LT patients in Korea have not yet been reported. We therefore investigated the impact of transition from twice-daily tacrolimus to generic once-daily tacrolimus in patients with a stable liver graft.

METHODS

Study Design

This prospective, multicenter, single-arm group study was conducted in 17 medical centers for one year from July 2019 to July 2020. Written informed consent was obtained from all patients following approval from each institute's Institutional Review Board (IRB No. SMC-2019-05-006). All participants received generic once-daily tacrolimus from twice-daily tacrolimus. This study was registered at ClinicalTrial.gov (NCT04069065).

Patients

Study participants had received a first LT from living or deceased donors more than one year prior to the start of this study. Inclusion criteria were: age ≥20 years, use of twice-daily tacrolimus at screening, stable kidney function (serum creatinine level, ≤2.0 mg/dL), stable liver function (serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels within normal ranges), and maintenance of the same immunosuppressive dosing regimen more than 1 month before enrollment. Patients who received any drugs known to interfere with tacrolimus pharmacokinetics and those enrolled in other immunosuppressant study protocols were not eligible for the study. Exclusion criteria included non-Korean, multiorgan recipients or a previous transplant of any organ; liver donated after cardiac death; trough level of tacrolimus at screening ≤2 ng/mL; an acute rejection episode within 6 months before enrollment; leukopenia (<1,500/mm^3) and/or serum creatinine > 2.0 mg/dL prior to enrollment; use of any other investigational drug within 4 weeks before screening; a history of malignancy other than hepatocellular carcinoma (HCC) or skin cancer; donor with positive hepatitis B surface antigen (HBsAg) liver graft; positive HIV status of donor or recipient; history of liver support system; unstable concurrent medical condition; presence of severe gastro-

intestinal complications such as diarrhea or severe peptic ulcer disease at screening; clinically significant infection; women of childbearing potential unwilling to use an effective form of contraception for the duration of the study; women who were pregnant or lactating; persons unable to communicate because of psychological problems.

Tacrolimus Concentrations

Once-daily tacrolimus was administered at 8 AM, and the dose was adjusted according to the daily trough level of the drug (C0 or Cmin). Trough levels of tacrolimus were measured by liquid chromatography-tandem mass spectrometry using a Waters 2795 Alliance HT system (Waters Ltd., Watford, UK) and a Micromass Quattro Micro API mass spectrometer (Waters Corp., Milford, MA, USA). Before and after conversion, all tacrolimus doses were adjusted according to the trough level of the drug to obtain a therapeutic window of 2–8 ng/mL.

Immunosuppression

Immunosuppressive therapy after LT was based on the combination of calcineurin inhibitor (tacrolimus) and/or mycophenolate mofetil. All patients were converted to once-daily generic tacrolimus on a 1:1 mg basis for the total daily dose. However, some dose adjustments were permitted depending on the patient's condition, and other immunosuppressants were allowed to be used according to standard practice at scheduled every visit. Serum trough levels of tacrolimus and clinical assessments for safety and rejection were completed four weeks after the conversion; then, parameters were evaluated routinely according to the patient follow-up schedules. Doses of tacrolimus at baseline and during follow-up were adjusted on an individual basis according to the serum trough level of the drug.

Assessment

Study visits took place within 4 weeks before enrollment (screening), at enrollment (visit 1), and at 2 weeks (visit 2), 4 weeks (visit 3), 12 weeks (visit 4), and 24 weeks (visit 5) after enrollment. At each visit, a complete physical examination was performed, laboratory values indicative of kidney and liver function were assessed, and hematology parameters and trough levels of tacrolimus were measured. Blood pressure, weight, and any problems between visits were documented. We examined renal function based on serum creatinine level and the estimated glomerular filtration rate (eGFR) calculated using the modification of diet in renal disease (MDRD) formula [19]. Drug compliance was measured by the oral pill counts returned of the prescribed drug. Data were recorded, entered into an electronic database, and re-evaluated by external monitors. Study monitoring and database analyses were performed, and all adverse and serious adverse events were documented.

Endpoints

Primary efficacy endpoint was biopsy-proven acute rejection (BPAR) and secondary endpoints were graft failure, patient death, and adverse events (AEs) until 24 weeks after enrollment. Allograft loss was presumed to have occurred if a patient required re-transplantation. Safety assessments included incidences of AEs and serious AEs (SAEs). Serial laboratory results and the proportion of patients with clinically notable abnormalities were reported.

Statistical Analysis

Previous clinical trial of once-daily tacrolimus reported that the failure rate of efficacy in once-daily tacrolimus was 22.4% [20]. Based on the results of this study, the tolerance for non-inferiority was set at 11.2% compared with 50% of the control effect. A sample size of 146 for a single-arm group was determined to be required to assess the primary endpoint assuming a one-sided significance level (α) of 2.5%, power of 80%, 11.2% non-inferiority compared with 50% of the control effect based on previous study, and a 25% dropout rate. Statistical analyses were conducted using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). Data are expressed as medians and ranges or as frequencies (percentages). Categorical variables were analyzed using the chi-square test or Fisher's exact test and continuous variables were analyzed using the Mann Whitney U-test. In the present study, P-values of <0.05 were considered significant.

RESULTS

Baseline Characteristics

Out of 151 screened liver transplant patients, 144 patients were enrolled; they comprised the full-analysis set (FAS) population. Two patients in the FAS were excluded due to protocol violation and eight patients were excluded in the per-protocol set (PPS) due to withdrawal of consent, investigator's judgement, and non-compliance. Investigator judgement cases (n=2) are cases in which it is difficult to participate in the study. Bone metastasis due to recurrent

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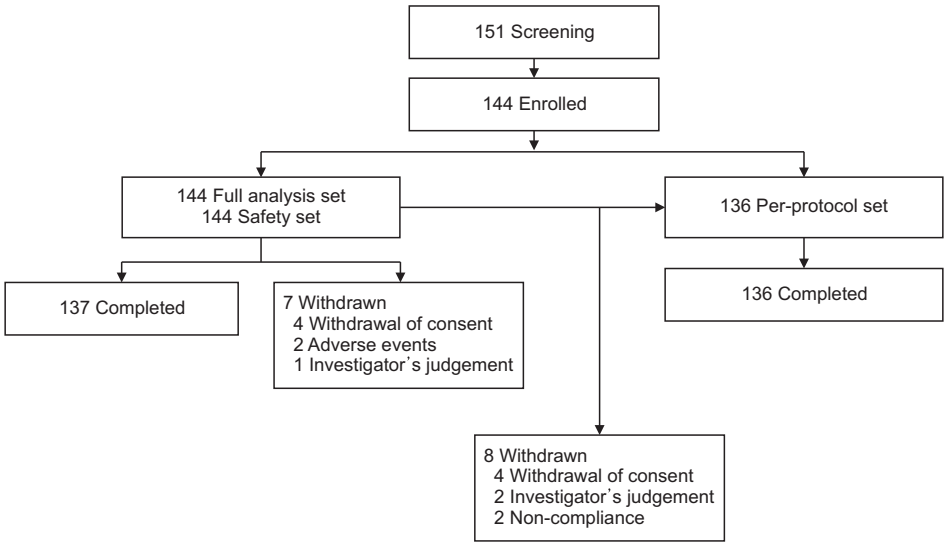

Fig. 1. Patient distribution and study population.

Table 1. Baseline characteristics

Liver transplantation	Value
Etiology	
HBV	76 (52.8)
Alcoholics	28 (19.4)
NBNC	33 (23.6)
HCV	2 (1.4)
Others	5 (3.5)
Co-existence of HCC	97 (67.4)
MELD score	16 (6–40)
Type of liver transplantation	
LDLT	84 (58.3)
DDLT	60 (41.7)
ABO-incompatible LDLT	16 (11.1)
Screening	
Sex (male)	102 (70.8)
Age (yr)	58 (22–75)
Body mass index (kg/m^2)	23.5 (16.5–31.4)
HBsAg (positive)	1 (0.7)
Anti-HCV (positive)	6 (4.2)
Period after liver transplantation (yr)	3 (1–12)
1–2	23 (16.0)
2–5	46 (31.9)
5–10	52 (36.1)
>10	23 (16.0)

Values are presented as number (%) or median (range).
HBV, hepatitis B virus; NBNC, non-B, non-C hepatitis; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; HBsAg, hepatitis B surface antigen.

HCC was diagnosed in one case and the other case was not suitable for the study because of high ALP due to biliary complications. Non-compliance cases were two cases. One participant took twice-daily tacrolimus after once-daily conversion. The other participant was injected with the contraindicated drug herpes zoster vaccine. A total of 142 patients in the FAS and 136 patients in the PPS completed the study follow-up and the study drug regimen (Fig. 1).

Baseline characteristics of patients at screening are summarized in Table 1. Most patients were male (70.8%, n=102) and the median age of patients was 58 years (range, 22–75 years). The incidence of living donor LT (LDLT) was higher than that of deceased donor LT (DDLT) (58.3% vs. 41.7%, respectively). The median model for end-stage liver disease (MELD) score was 16 (range, 6–40). The reason for the LT was HBV in more than half of the patients (52.8%, n=76), and 67.4% (n=97) of patients had the coexistence of HCC in explant liver. The incidence of ABO-incompatible (ABOi) LDLT was 11.1% (n=16). Median time from LT to screening was 3 years (range, 1–12 years). One patient had positive HBsAg and six patients had positive anti- HCV immunoglobulin G (anti-HCV IgG) at screening. However, no patients were positive for HBV DNA or HCV RNA.

Compliance and Trough Level of Tacrolimus

Median blood trough levels of mycophenolate mofetil at screening time, enrollment, 2, 4, 12, and 24 weeks in the FAS population are shown in Fig. 2, and median doses of tacrolimus at the same time points are shown. Median tac-

rolimus trough level decreased abruptly from 4.7 ng/mL at visit 1 to 3.2 ng/mL at visit 2 after once-daily generic tacrolimus conversion (P<0.001). Median tacrolimus dose from visit 2 to visit 3 increased due to low tacrolimus trough level. Median tacrolimus trough level and tacrolimus dose were maintained at constant levels after visit 3.

Participants with less than 80% compliance were considered low compliance patients and were excluded from the PPS. Median compliance of all participants was 100% (range, 80.4%–106.0%), and none of the participants had less than 80% compliance. Of the 128 patients in the PPS who received a tacrolimus dose <6 mg/day at screening, the dose for about 70% of patients was increased (Table 2).

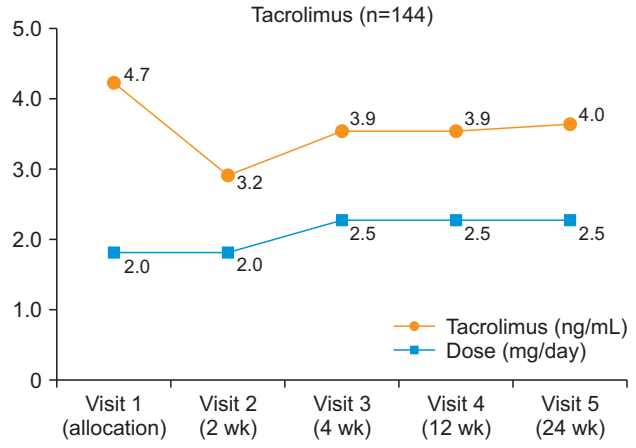

Fig. 2. Median trough level and median dose of tacrolimus at each visit.

Efficacy

BPAR, graft failure, and patient death did not develop in the PPS. median total bilirubin, AST, and ALT did not increase even though tacrolimus trough level decreased in visit 2 compared to visit 1 after generic once-daily tacrolimus conversion. Median total bilirubin, AST, and ALT did not increase after visit 3 (Table 3). In addition, median creatinine and eGFR levels remained stable even when tacrolimus dose and trough level increased.

Safety

Ninety-two AEs occurred in 54 patients (Table 4). A total of nine adverse drug reactions, including elevated liver enzymes, were reported in seven patients (4.9%) for which

Table 2. Tacrolimus dose change after extended-release tacrolimus conversion

Tacrolimus dose at screening (mg/day)	Maintenance/ reduction	Increase	Increased tacrolimus dose (mg/day)
<2 (n=48)	14 (29.2)	34 (70.8)	0.5 (0.25–3.25)
2–4 (n=59)	20 (33.9)	39 (66.1)	1.0 (0.5–4.5)
4–6 (n=21)	7 (33.3)	14 (66.7)	1.0 (0.5–2.0)
≥6 (n=7)	3 (42.9)	4 (57.1)	1.0 (1.0–3.0)
Total	44	91	-

Values are presented as number (%) or median (range).

Table 3. Laboratory findings at regular visits

Variable	Visit 1 (allocation, n=150)	Visit 2 (2 wk, n=141)	Visit 3 (4 wk, n=140)	Visit 4 (12 wk, n=137)	Visit 5 (24 wk, n=137)
White blood cell (/uL)	4.9 (2.0–10.4)	5.2 (2.4–10.4)	5.3 (1.6–11.3)	5.3 (2.6–11.3)	5.3 (2.0–10.9)
Hemoglobin (g/dL)	14.1 (9.1–18.5)	14.3 (9.1–18.5)	14.4 (9.2–19.5)	14.5 (8.5–18.9)	14.4 (8.7–18.3)
Platelet count (/uL)	174 (55–309)	175 (43–320)	177 (46–315)	179 (45–316)	171 (58–302)
BUN (mg/dL)	16.7 (8–37)	16 (6–38)	17.4 (8–37)	16 (6.1–48.5)	17 (6.1–57.4)
Creatinine (mg/dL)	1.0 (0.6–1.8)	1.0 (0.6–2.1)	1.0 (0.6–1.9)	1.0 (0.6–2.1)	1.0 (0.6–1.8)
eGFR (mL/min/1.73m^2)	75 (37–127)	72 (33–127)	75 (35–121)	72 (32–121)	73 (29–148)
Glucose (mg/dL)	111 (75–289)	110 (50–239)	110 (71–272)	111 (80–229)	110 (78–247)
HbA1c (%)	5.6 (4.1–8.7)	-	-	5.6 (4.3–9.9)	5.7 (4.3–9.5)
AST (U/mL)	23 (11–96)	23 (10–264)	23 (12–116)	23 (12–273)	24 (12–142)
ALT (U/mL)	18 (6–129)	19 (6–425)	18 (6–200)	21 (5–173)	20 (6–133)
Total bilirubin (mg/dL)	0.8 (0.3–2.7)	0.8 (0.2–3.0)	0.8 (0.2–2.3)	0.8 (0.2–2.6)	0.8 (0.3–2.6)
Potassium (mEq/L)	4.5 (3.4–5.8)	4.5 (3.6–5.7)	4.6 (3.5–5.8)	4.5 (3.5–6.0)	4.4 (3.5–6.0)
Phosphorous (mg/L)	3.1 (2.1–4.5)	3.1 (1.9–4.5)	3.0 (1.9–4.6)	3.1 (1.8–4.4)	3.1 (1.4–4.5)
Uric acid (mg/dL)	5.8 (2.8–11.5)	5.7 (2.7–11.1)	5.6 (2.8–10.0)	5.5 (2.8–10.7)	5.5 (1.9–9.2)

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; AST, aspartate transaminase; ALT, alanine transaminase.

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Table 4. Detailed adverse events

Classification	No. of patients (n=54)	No. of cases (n=92)	Adverse event
Gastrointestinal disorder	14	19	Diarrhea (9), abdominal discomfort (3), abdominal pain (2), gastritis (2), etc (1)
Investigation	13	17	Abnormal liver function tests (16), increased creatinine (1)
Infections and infestation	13	16	Pharyngitis (6), upper respiratory tract infection (3), influenza (3), herpes zoster (1)
Respiratory, thoracic, and mediastinal disorder	8	9	Cough (6), chronic bronchitis (1), oropharyngeal pain (1), rhinorrhea (1)
Nervous system disorder	5	5	Paresthesia (2), cerebral infarction (1), dizziness (1), herpetic neuralgia (1)
Musculoskeletal and connective tissue disorder	4	4	Musculoskeletal pain (2), arthralgia (1), osteoarthritis (1)
Others	18	22	Incisional hernia (1), fibroma (1), dysuria (1), nocturia (1), pruritus (1), otolithiasis (1), eyelid ptosis (1), etc (1)

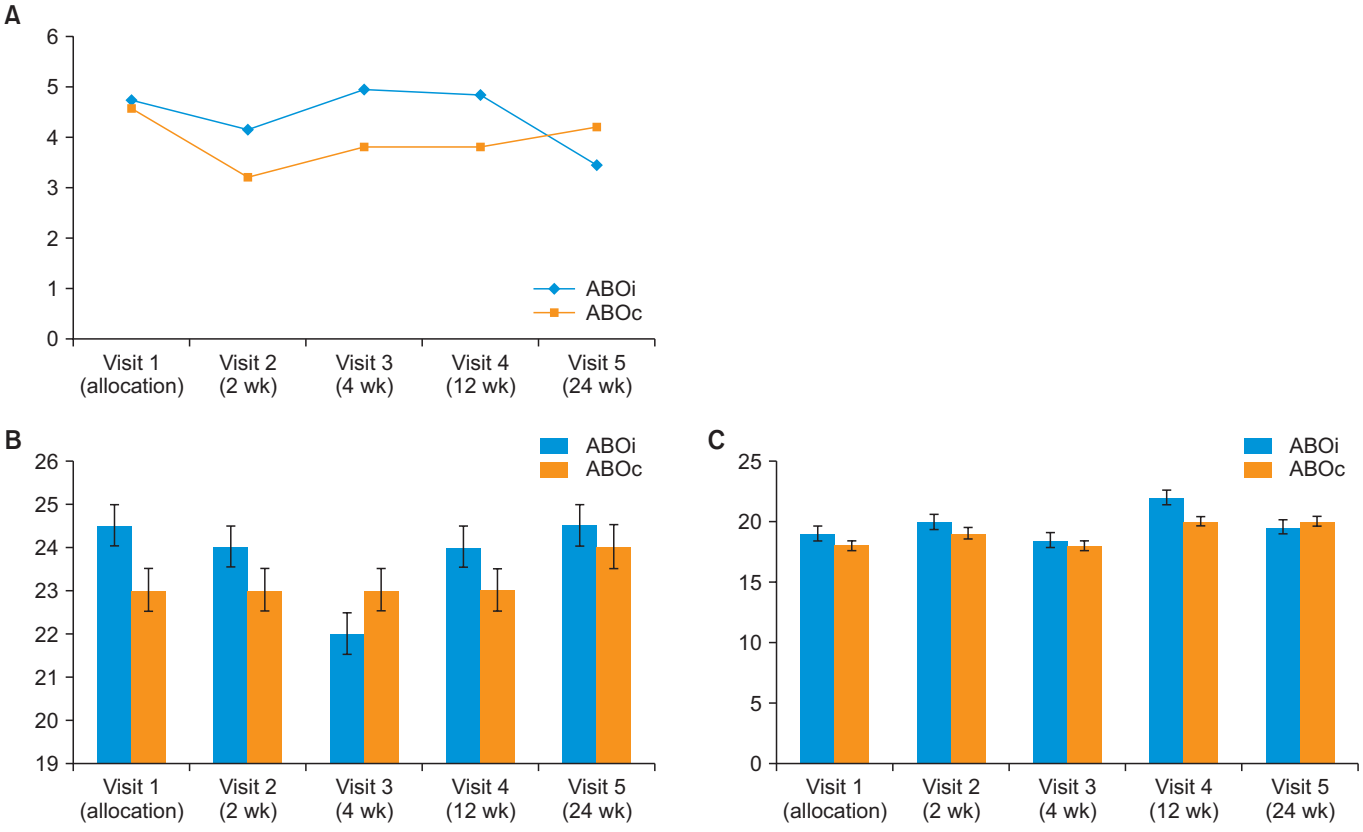

Fig. 3. ABO-incompatible (ABOi) living donor liver transplantation and ABO-compatible (ABOc) liver transplantation. (A) Tacrolimus trough level. (B) Aspartate aminotransferase. (C) Alanine aminotransferase.

a causal relationship with the investigational drug could not be excluded. There were three cases of severe AEs (cerebral infarction, incisional hernia, and intestinal obstruction) unrelated to the investigational drug. There was no change in tacrolimus dose in the three cases of severe adverse events. Incisional hernia and intestinal obstruction were recovered by surgery, and the symptoms of cerebral infarction patients improved with active drug treatment in the early stages. Liver enzyme levels increased in seven patients after the switch to generic once-daily tacrolimus switch, but the liver function tests of these patients normalized during tacrolimus dose increase or observation.

The effect of ABOi LDLT

During the study period, the median tacrolimus trough levels of patients with ABOi LDLT were higher than those of patients with ABO-compatible (ABOc) LT, but there were no statistical differences at every visits between the two groups. In addition, the elevation of liver function enzymes was reported seven patients with ABOc LT, but there were no liver function tests elevation among patients with ABOi LDLT. Median AST and median ALT at each visit were not different between the two groups (Fig. 3).

DISCUSSION

In this prospective study, we investigated the efficacy and safety of a switch from twice-daily tacrolimus to generic once-daily tacrolimus in stable LT recipients. BPAR, graft failure, or death did not occur among the study participants. There were three severe AEs, but these were unrelated to the use of generic once-daily tacrolimus. Elevated liver enzyme levels were found in seven patients, but there were no acute rejection cases. The current study provides strong evidence that generic once-daily tacrolimus is safe and efficacious in LT patients with stable liver graft function more than 1 year after LT.

The safety and efficacy of once-daily and twice-daily tacrolimus are comparable [3,7,9,21,22]. Conversion from twice-daily to once-daily tacrolimus is associated with an equivalent exposure and steady state and trough levels; however, these two treatments have different pharmacokinetic profiles and bioavailability [7].

Median trough level decreased by about 30% after 1:1 conversion from twice-daily tacrolimus to once-daily tacrolimus in our study. Approximately 70% of all participants had a decreased tacrolimus trough level, thus the tacrolimus dose was increased in these patients. Previous studies reported that median tacrolimus trough level decreased by about 15%–20% after a switch to 1:1 once-daily tacrolimus [9-11]. Interestingly, median tacrolimus trough level decreased by about 40% in the cytochrome P450 (CYP) 3A5 expressor group [8]. It is difficult to compare only the tacrolimus trough level because the correlation of the area under the curve (AUC) value of tacrolimus concentration to C0 or C2 is different depending on the presence or absence of the CYP3A5 expressor [8]. In addition, while twice-daily tacrolimus is absorbed in the proximal jejunum, once-daily tacrolimus is absorbed in the entire small intestine, thus the AUC of tacrolimus concentration is difficult to predict. The frequency of the CYP3A5 expressor has been reported to be about 50%-60% in Asian populations [8,23]. Participants in our study whose dose of tacrolimus was increased due to a decrease in tacrolimus trough level are likely CYP3A5 expressors.

LFT abnormalities were observed in seven patients (4.9%), which were the most common AE in the present study. Liver function of these patients, however, improved after tacrolimus dose adjustment or spontaneously. Previous study reported that the incidence of liver dysfunction after conversion to brand-name once-daily tacrolimus was 17.9% in the expressor group and 3.1% in the non-expressor group [8]. Another retrospective study reported that the incidence of LFT abnormalities was 7.8% [10]. The incidence of LFT abnormalities was low in our study, suggesting that generic once-daily tacrolimus does not adversely affect liver graft function.

Generic immunosuppressants offer significant cost savings for liver transplant programs and recipients; however, there has been considerable concern among transplant hepatologists and patients about the equivalence of generic and brand-name drugs [12,24]. Bioequivalence is a prerequisite for the use of generic drugs [25]. Some transplant hepatologists and surgeons have shown hesitation converting from brand-name twice-daily tacrolimus to generic once-daily tacrolimus. However, conversion from brand-name twice daily tacrolimus to generic once-daily tacrolimus has been shown to have comparable efficacy and safety [15,18]. Consistent with these previous studies, we demonstrated that a switch from brand-name or generic twice-daily tacrolimus to once-daily tacrolimus in liver transplant patients with stable liver graft function was safe and effective.

Present study had several limitations. First, we did not compare generic tacrolimus with brand-name tacrolimus after conversion to once-daily tacrolimus because this was a single-arm study. Second, CYP3A5 polymorphisms affect tacrolimus trough level and pharmacokinetics, but no information regarding CYP3A5 polymorphisms of donors or recipients was available. Tacrolimus pharmacokinetics were also not investigated when taking twice-daily tacrolimus. Third, our study targeted Koreans and once-daily generic tacrolimus conversion requires validation in non-Korean patients. Lastly, costs and drug compliance associated with a switch from twice-daily tacrolimus to once-daily tacrolimus were not investigated.

In conclusion, no significant differences in either effica-

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cy or safety were observed after a switch from twice-daily immediate-release tacrolimus to generic once-daily tacrolimus in stable LT recipients. Thus, reducing the dosing frequency of tacrolimus using generic once-daily tacrolimus may optimize adherence and quality of life among LT patients.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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ORCID

Jong Man Kim https://orcid.org/0000-0002-1903-8354
Pyoung-Jae Park https://orcid.org/0000-0001-6624-7522
Geun Hong https://orcid.org/0000-0003-2597-1068
Dong Jin Joo https://orcid.org/0000-0001-8405-1531
Kwan Woo Kim https://orcid.org/0000-0002-7432-6949
Je Ho Ryu https://orcid.org/0000-0002-9377-3074
Young Seok Han https://orcid.org/0000-0003-4075-730X
Jai Young Cho https://orcid.org/0000-0002-1376-956X
Gi-Won Song https://orcid.org/0000-0002-1581-7051
Bong-Wan Kim https://orcid.org/0000-0001-9059-0451
Dong-Sik Kim https://orcid.org/0000-0002-0608-1580
Seong Hoon Kim https://orcid.org/0000-0001-7921-1801
Sang Tae Choi https://orcid.org/0000-0001-5164-6889
Young Kyoung You https://orcid.org/0000-0002-7363-8131
Kyung-Suk Suh https://orcid.org/0000-0002-9535-7349
Yang-Won Na https://orcid.org/0000-0001-8161-9849
Koo Jeong Kang https://orcid.org/0000-0003-1385-8308
Jae-Won Joh https://orcid.org/0000-0003-1732-6210

Author Contributions

Conceptualization: JMK, JWJ. Data curation: JMK, PJP, GH, DJJ, KWK, JHR, YSH, JYC, GWS, BWK, DSK, SHK, STC, YKY, KSS, YWN, KJK. Formal analysis: JMK, JWJ. Funding acquisition: JWJ. Methodology: JMK, PJP, GH, DJJ, KWK, JHR, YSH, JYC, GWS, BWK, DSK, SHK, STC, YKY, KSS, YWN, KJK. Project administration: JMK. Visualization: JMK, JWJ. Writing–original draft: JMK, JWJ. Writing–review & editing: PJP, GH, DJJ, KWK, JHR, YSH, JYC, GWS, BWK, DSK, SHK, STC, YKY, KSS, YWN, KJK.

REFERENCES

1. U.S. Multicenter FK506 Liver Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med 1994;331:1110-5.
2. Kuypers DRJ. Intrapatient variability of tacrolimus exposure in solid organ transplantation: a novel marker for clinical outcome. Clin Pharmacol Ther 2020;107:347-58.
3. Brunet M, van Gelder T, Åsberg A, Haufroid V, Hesselink DA, Langman L, et al. Therapeutic drug monitoring of tacrolimus-personalized therapy: second consensus report. Ther Drug Monit 2019;41:261-307.
4. Kuypers DR, Peeters PC, Sennesael JJ, Kianda MN, Vrijens B, Kristanto P, et al. Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. Transplantation 2013;95:333-40.
5. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R, et al. Nonadherence consensus conference summary report. Am J Transplant 2009;9:35-41.
6. Caillard S, Moulin B, Buron F, Mariat C, Audard V, Grimbert P, et al. Advagraf(®), a once-daily prolonged release tacrolimus formulation, in kidney transplantation: literature review and guidelines from a panel of experts. Transpl Int 2016;29:860-9.
7. Iwasaki M, Yano I, Fukatsu S, Hashi S, Yamamoto Y, Sugimoto M, et al. Pharmacokinetics and pharmacodynamics of once-daily tacrolimus compared with twice-daily tacrolimus in the early stage after living donor liver transplantation. Ther Drug Monit 2018;40:675-81.
8. Kim JM, Ryu JH, Lee KW, Hong SK, Yang K, Choi GS, et al. Effect of CYP3A5 on the once-daily tacrolimus conversion in stable liver transplant patients. J Clin Med 2020;9:2897.
9. Kim JM, Kwon CH, Joh JW, Sinn DH, Lee S, Choi GS, et al. Conversion of once-daily extended-release tacrolimus is safe in stable liver transplant recipients: a randomized prospective study. Liver Transpl 2016;22:209-16.
10. Suh SW, Lee KW, Jeong J, Kim H, Yi NJ, Suh KS. Risk

factors for the adverse events after conversion from twice-daily to once-daily tacrolimus in stable liver transplantation patients. J Korean Med Sci 2016;31:1711-6.
11. Kim SH, Lee SD, Kim YK, Park SJ. Conversion of twice-daily to once-daily tacrolimus is safe in stable adult living donor liver transplant recipients. Hepatobiliary Pancreat Dis Int 2015;14:374-9.
12. Molnar AO, Fergusson D, Tsampalieros AK, Bennett A, Fergusson N, Ramsay T, et al. Generic immunosuppression in solid organ transplantation: systematic review and meta-analysis. BMJ 2015;350:h3163.
13. Taube D, Jones G, O'Beirne J, Wennberg L, Connor A, Rasmussen A, et al. Generic tacrolimus in solid organ transplantation. Clin Transplant 2014;28:623-32.
14. Spence MM, Nguyen LM, Hui RL, Chan J. Evaluation of clinical and safety outcomes associated with conversion from brand-name to generic tacrolimus in transplant recipients enrolled in an integrated health care system. Pharmacotherapy 2012;32:981-7.
15. Yu YD, Lee SG, Joh JW, Kwon CH, Kim DG, Suh KS, et al. Results of a phase 4 trial of Tacrobell® in liver transplantation patients: a multicenter study in South Korea. Hepatogastroenterology 2012;59:357-63.
16. Son SY, Jang HR, Lee JE, Yoo H, Kim K, Park JB, et al. Comparison of the long-term efficacy and safety of generic Tacrobell with original tacrolimus (Prograf) in kidney transplant recipients. Drug Des Devel Ther 2017;11:203-10.
17. Park K, Kim YS, Kwon KI, Park MS, Lee YJ, Kim KH. A randomized, open-label, two-period, crossover bioavailability study of two oral formulations of tacrolimus in healthy Korean adults. Clin Ther 2007;29:154-62.
18. Kim JM, Joh JW, Choi GS, Lee SK. Generic tacrolimus (Tacrobell ®) shows comparable outcomes to brand-name tacrolimus in the long-term period after adult deceased donor liver transplantation. Drug Des Devel Ther 2019;13:4431-8.
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461-70.
20. TruneČka P, Klempnauer J, Bechstein WO, Pirenne J, Friman S, Zhao A, et al. Renal function in de novo liver transplant recipients receiving different prolonged-release tacrolimus regimens-the DIAMOND Study. Am J Transplant 2015;15:1843-54.
21. Fischer L, Trunečka P, Gridelli B, Roy A, Vitale A, Valdivieso A, et al. Pharmacokinetics for once-daily versus twice-daily tacrolimus formulations in de novo liver transplantation: a randomized, open-label trial. Liver Transpl 2011;17:167-77.
22. Beckebaum S, Iacob S, Sweid D, Sotiropoulos GC, Saner F, Kaiser G, et al. Efficacy, safety, and immunosuppressant adherence in stable liver transplant patients converted from a twice-daily tacrolimus-based regimen to once-daily tacrolimus extended-release formulation. Transpl Int 2011;24:666-75.
23. Schutte-Nutgen K, Tholking G, Suwelack B, Reuter S. Tacrolimus: pharmacokinetic considerations for clinicians. Curr Drug Metab 2018;19:342-50.
24. Al Ameri MN, Whittaker C, Tucker A, Yaqoob M, Johnston A. A survey to determine the views of renal transplant patients on generic substitution in the UK. Transpl Int 2011;24:770-9.
25. Alloway RR, Vinks AA, Fukuda T, Mizuno T, King EC, Zou Y, et al. Bioequivalence between innovator and generic tacrolimus in liver and kidney transplant recipients: a randomized, crossover clinical trial. PLoS Med 2017;14:e1002428.

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