

## Efficacy and safety of prolonged-release versus immediate-release tacrolimus in *de novo* liver transplant recipients in South Korea: a randomized open-label phase 4 study (MAPLE)

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**Background:** Prolonged-release tacrolimus is associated with better long-term graft and patient survival than the immediate-release formulation in liver transplant patients. However, no clinical data are available to assess the efficacy and safety of early conversion from twice-daily, immediate-release tacrolimus to once-daily, prolonged-release tacrolimus in *de novo* liver transplant recipients in Korea.

**Methods:** A 24-week, randomized, open-label study was conducted in 36 liver transplant recipients. All patients received immediate-release tacrolimus (0.1–0.2 mg/kg/day, divided into two doses) for 4 weeks after transplantation, at which time 50% of the patients were converted, at a ratio of 1 mg to 1 mg, to prolonged-release tacrolimus (once-daily). The primary efficacy endpoint was the incidence of biopsy-confirmed acute rejection (BCAR) from weeks 4 to 24 after transplantation (per-protocol set). Medication adherence, adverse event profiles, laboratory tests, vital signs, and physical changes were also recorded.

**Results:** BCAR frequency at 24 weeks was similar between the two treatment groups; two cases (mean ± standard deviation, 0.14 ± 0.53 cases) of BCAR were reported in one patient treated with prolonged-release tacrolimus (n=14), while no such cases were reported among patients treated with immediate-release tacrolimus (n=12). The tacrolimus blood concentration at weeks 12 and 24, medication adherence, and adverse event profiles were also similar between the formulations, with no unusual laboratory test results, vital signs, or physical changes reported.

**Conclusions:** Early conversion to a simplified, once-daily, prolonged-release tacrolimus regimen may be an effective treatment option for liver transplant recipients in Korea. Larger-scale studies are warranted to confirm non-inferiority to immediate-release tacrolimus formulation in *de novo* liver transplant recipients.

**Keywords:** Immunosuppressive agents; Humans; Liver transplantation; Prolonged-release tacrolimus; Republic of Korea; Treatment outcome

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## INTRODUCTION

Tacrolimus treatment has become the cornerstone of immunosuppressive regimens to prevent allograft rejection after liver transplantation [1]. While advances in immunosuppressive regimens have significantly improved patient and graft survival [2], it remains difficult to further optimize post-transplantation outcomes. Clinical use of tacrolimus is complicated by high inpatient variability in whole-blood tacrolimus levels and medication non-adherence [3-5].

Various oral tacrolimus formulations are available after liver transplantation [6], including immediate-release capsules, which are taken twice daily, and newer, prolonged-release formulations, which are taken once daily in the morning. Prolonged-release tacrolimus is associated with greater treatment adherence than immediate-release formulations. It also shows lower inpatient variability and can improve long-term transplant outcomes [2,7-11], as reported in a large retrospective analysis conducted by the European Liver Transplant Registry, which compared the two formulations in primary liver transplant recipients from 21 European centers. In multivariate analyses, the once-daily formulation was associated with superior 3-year graft and patient survival compared with the twice-daily formulation [2].

Multiple studies have shown that stable liver transplant recipients can be converted from immediate-release to prolonged-release tacrolimus without impacting efficacy or safety [4,12-17], and that patients prefer once-daily dosing [17]. Most of these studies, including those conducted in Korea [16,17], have involved conversion to prolonged-

release tacrolimus 1 year after transplantation. However, no published, prospective, clinical data have assessed the efficacy and safety of early conversion to prolonged-release tacrolimus in *de novo* liver transplant recipients in Korea.

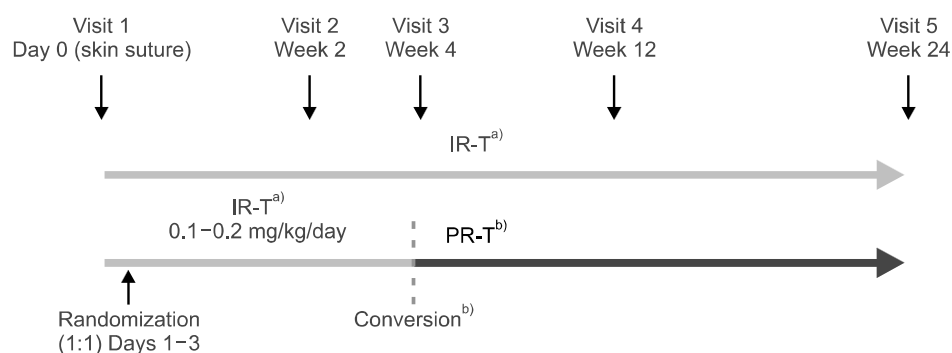
In the present study, we carried out the first direct comparison of the two oral tacrolimus formulations in Korean *de novo* liver transplant recipients who had converted from immediate-release to prolonged-release tacrolimus 4 weeks after transplantation.

## METHODS

### Study Design and Patients

This was a 24-week, randomized, open-label, phase 4 study conducted at four tertiary hospitals in South Korea from January 2013 to January 2017. The study was conducted in accordance with Korean Good Clinical Practice, the guidelines of the International Council for Harmonisation, and the Declaration of Helsinki (ClinicalTrials.gov: NCT 03423225). Written informed consent to participate in the study was obtained from all patients.

Adult men and women aged between 20 and 65 years who had terminal hepatic failure and were scheduled to receive a liver transplant were eligible to enter the study. The exclusion criteria were (1) previous organ transplant, (2) auxiliary transplant or use of a bioartificial liver, (3) allergy or resistance to macrolide antibiotics or tacrolimus, (4) immunosuppressive treatment or chemotherapy before transplant, unless the patient had been treated for a hepatic disorder for less than 1 month and treatment had been discontinued at the time of transplantation, and (5) malignancy within the past 5 years. Women of childbearing age



**Fig. 1.** Overview of study design. IR-T, immediate-release tacrolimus; PR-T, prolonged-release tacrolimus. <sup>a)</sup>Prior to surgery, or within 3 days after surgery; <sup>b)</sup>Conversion from IR-T on a 1:1 (mg:mg) total-daily-dose basis.

were required to provide a negative serum pregnancy test and to take double contraception.

### Study Treatment

Eligible patients received immediate-release tacrolimus (Prograf; Astellas Pharma Europe Ltd., Chertsey, UK) from day 0 to week 4. They were then equally randomized (1:1) to receive either prolonged-release tacrolimus (Advagraf; Astellas Pharma Europe, Leiden, the Netherlands) or immediate-release tacrolimus until week 24 (Fig. 1). A randomization schedule for each study center was completed by Linical Korea Ltd. (Seoul, Korea) and randomization codes were generated using a block randomization method stratified by investigational site.

Either before surgery or within 3 days of transplantation, all patients received immediate-release tacrolimus capsules at an initial dose of 0.1–0.2 mg/kg/day, divided into two doses. At the week 4 visit, the allocated patients were converted on a 1:1 dosage basis to prolonged-release tacrolimus capsules [18].

From day 0 to 30, individual tacrolimus doses were adjusted based on target tacrolimus whole-blood trough levels of 5–15 ng/mL. After day 30, the target whole-blood trough levels were 3–12 ng/mL. Steroids, mycophenolate mofetil, azathioprine, and basiliximab were permitted as concomitant medications.

### Endpoints

Efficacy and safety assessments were carried out at weeks 12 and 24. The primary efficacy endpoint was the incidence of biopsy-confirmed acute rejection (BCAR) from weeks 4 to 24 after transplantation. Secondary efficacy endpoints included the incidence of BCAR from weeks 4 to 12, the severity and frequency of BCAR, patient and graft survival, and tacrolimus trough levels. Adverse events, adverse drug reactions, and abnormal clinical findings were assessed in all patients who received at least one dose of study drug. The severity of adverse events was classified as: (1) mild, does not interfere with normal activities; (2) moderate, significantly interferes with normal activities; or (3) severe, requires intensive treatment and may be life-threatening. Vital signs (weight, blood pressure, body temperature, and pulse), laboratory parameters,

and physical changes were assessed at each study visit, and adherence with the study medication was assessed in terms of the number of returned capsules.

### Statistical Analysis

Based on previous studies [19–21], the anticipated post-surgery acute rejection rate was approximately 15% up to week 4 and 50% up to week 24; the acute rejection rate from week 4 to 24 was therefore estimated at 35% (50%–15%). Assuming a 10% dropout rate, a total of 88 patients (44 per treatment arm) were required to yield a power of at least 80% to detect a significant difference (5% significance level) in confirmed week 4–24 acute rejection rates between the two groups.

The main analysis population to evaluate treatment efficacy was the per-protocol set (PPS), which comprised patients who had received at least one dose of study medication after randomization and who had completed the study without major protocol deviation. To assess the robustness of the primary analysis result, supportive analyses were carried out on the full-analysis set: the overall population who had received at least one dose of study medication. Safety analyses were carried out on the safety set (all patients who had received at least one dose of study medication) and were based on the actual treatment administered, irrespective of group assignment.

The primary objective of this study was to demonstrate that prolonged-release tacrolimus was not inferior to immediate-release tacrolimus in terms of the BCAR incidence from weeks 4 to 24 after transplantation. Non-inferiority was assessed using a pre-specified margin of 30%. That is, if the upper 95% confidence limit of the difference between the immediate-release and prolonged-release treatment groups was <30%, noninferiority was confirmed. Differences in incidence were calculated using Fisher's exact test. Between-group differences in tacrolimus trough levels were tested using either the two-sample t-test or Wilcoxon rank-sum test. The statistical significance of between-group differences in adverse events and adverse drug reactions was tested using either the chi-square test or Fisher's exact test. Statistical evaluations were performed using the SAS statistical software package ver. 9.3 (SAS Institute Inc., Cary, NC, USA).

The overall adherence rate was calculated as a percentage by dividing the number of capsules administered by the planned number of capsules per day multiplied by the overall duration of administration.

## RESULTS

### Study Population

We had difficulties in recruiting sufficient patient numbers, so we closed study enrollment early. Ultimately, 36 patients were randomized (prolonged-release tacrolimus: n=19, immediate-release tacrolimus: n=17), 26 of whom completed the study and were included in the PPS. Two patients in each treatment group were not treated, and three in each had protocol deviations (Fig. 2). The reasons for withdrawal were as follows: violation of inclusion/exclusion criteria (prolonged-release tacrolimus group: n=2), graft loss (immediate-release tacrolimus group: n=1), and others (immediate-release tacrolimus group: n=1, prolonged-release tacrolimus group: n=2). Because the sample size was smaller than planned, the study had insufficient power to make the planned between-group comparisons.

A total of 12 major protocol deviations (six in the prolonged-release and six in the immediate-release tacrolimus groups) occurred in 10 patients, namely concomitant prohibited medication (n=2), less than 80% adherence (n=2), withdrawal (n=6; violation of inclusion/exclusion

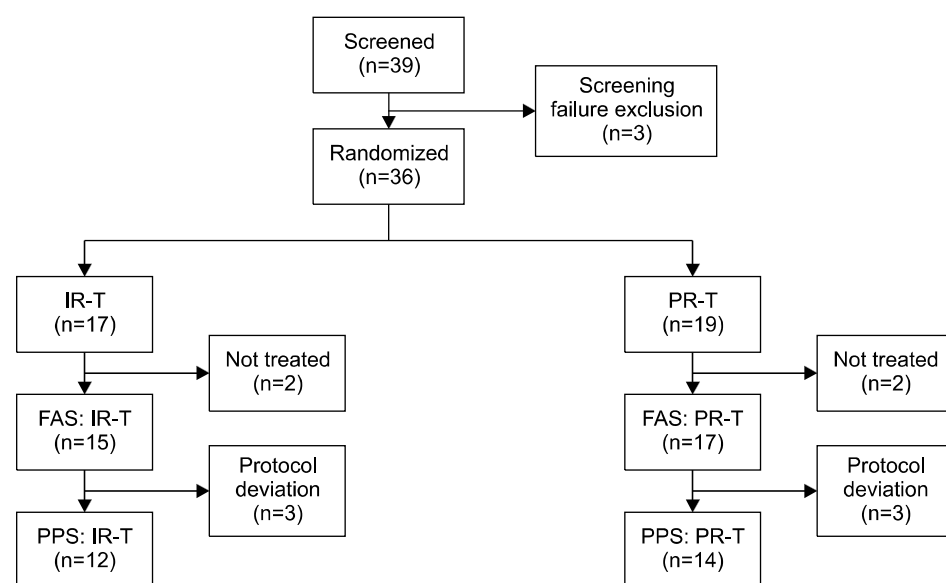
criteria [n=2], death [n=2], graft loss [n=1], incompatible blood groups [n=1]), violation of administration method

**Table 1.** Baseline patient demographics and characteristics

Characteristics	Prolonged-release tacrolimus (n=17)	Immediate-release tacrolimus (n=15)	P-value
Male sex	11 (64.7)	11 (73.3)	0.712 <sup>a)</sup>
Age (yr)			0.449 <sup>b)</sup>
Mean ±SD	55.0±8.3	52.7±8.9	
Median (range)	56.0 (42.0-65.0)	56.0 (33.0-65.0)	
Height (cm)			0.174 <sup>a)</sup>
Mean ±SD	162.5±9.06	167.0±9.3	
Median (range)	162.0 (148.0-180.0)	167.0 (151.0-181.0)	
Blood (RH)			
RH+	17 (100.0)	15 (100.0)	
RH-	0	0	
Blood type (ABO)			0.102 <sup>b)</sup>
A	4 (23.5)	4 (26.7)	
B	7 (41.2)	3 (20.0)	
AB	1 (5.9)	6 (40.0)	
O	5 (29.4)	2 (13.3)	
Infection status			
HIV, positive	0	0	
HBV, positive	9 (52.9)	9 (60.0)	0.688 <sup>c)</sup>
HCV, positive	3 (17.7)	1 (6.7)	0.603 <sup>b)</sup>
CMV, positive	14 (82.4)	14 (93.3)	0.603 <sup>b)</sup>
EBV, positive	14 (82.4)	9 (64.3)	0.413 <sup>b)</sup>

Values are presented as number (%) unless otherwise indicated. SD, standard deviation; RH, Rhesus type; HIV, human immunodeficiency virus antigen/antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

<sup>a)</sup>Two-sample test; <sup>b)</sup>Fisher's exact test; <sup>c)</sup>Chi-square test.



**Fig. 2.** Patient flow throughout the study. Overall, 26 patients completed the study (PPS). The reasons for withdrawal were (1) violation of inclusion/exclusion criteria (prolonged-release tacrolimus group: n=2), (2) graft loss (immediate-release tacrolimus group: n=1), and (3) others (immediate-release tacrolimus group: n=1, prolonged-release tacrolimus group: n=2). IR-T, immediate-release tacrolimus; FAS, full-analysis set (patients who received at least one dose of investigational product); PPS, per-protocol set (patients who received at least one dose of study medication and completed the study without major protocol deviation); PR-T, prolonged-release tacrolimus.

(n=1), and violation of inclusion/exclusion criteria (n=1).

At baseline, there were no major differences between the treatment groups in any demographic characteristics, including blood group and virus infection status (Table 1). After taking the study medication, a similar proportion of patients received concomitant immunosuppressant medication (17 patients in the prolonged-release tacrolimus group and 14 in the immediate-release group).

### Tacrolimus Trough Level

At baseline, i.e., at the time of switching (week 4), tacrolimus trough levels (mean±standard deviation [SD]) were higher in the prolonged-release tacrolimus group than in the immediate-release tacrolimus group (8.8±2.2 and 6.9±1.4, respectively). The trough levels at weeks 12 and 24 were similar (Table 2). Changes in trough levels from baseline to weeks 12 and 24 were also similar between the two treatment groups (Table 2).

### Biopsy-Confirmed Acute Rejection

One patient in the prolonged-release tacrolimus group experienced two cases of moderate rejection; the frequency (mean±SD; PPS) was 0.07±0.27 (one case in one patient) at week 12 and 0.14±0.53 (two cases in one patient) at week 24. This patient's acute rejection was treated using

**Table 3.** Incidence of biopsy-confirmed acute rejection at week 24

Variable	Prolonged-release tacrolimus	Immediate-release tacrolimus	Difference <sup>a)</sup> (95% CI)	P-value
PPS				1.000 <sup>b)</sup>
Number	14	12		
BCAR	1 (7.1)	0	7.1 (-6.4 to 20.6)	
FAS				1.000 <sup>b)</sup>
Number	17	15		
BCAR	1 (5.8)	0	5.9 (-5.3 to 17.1)	

Values are presented as number (%) unless otherwise indicated. CI, confidence interval; PPS, per-protocol set; BCAR, biopsy confirmed acute rejection; FAS, full-analysis set.

<sup>a)</sup>Difference in incidence between prolonged-release and immediate-release tacrolimus and 95% two-sided confidence interval for the difference; <sup>b)</sup>Fisher's exact test.

**Table 2.** Whole-blood tacrolimus concentration and change from baseline tacrolimus concentration at week 12 and week 24 (PPS)

Variable	Prolonged-release tacrolimus (n=14)	Immediate-release tacrolimus (n=12)	P-value
Baseline (week 4)			0.018 <sup>a)</sup>
Mean±SD	8.8±2.2	6.9±1.4	
Median (range)	8.8 (3.9 to 12.9)	6.9 (4.7 to 9.6)	
Week 12			0.903 <sup>a)</sup>
Mean±SD	6.7±3.2	6.6±2.3	
Median (range)	6.6 (2.9 to 14.9)	6.0 (3.3 to 11.0)	
Week 24			0.837 <sup>b)</sup>
Mean±SD	7.1±2.8	7.9±4.0	
Median (range)	7.3 (2.7 to 12.8)	6.2 (4.2 to 16.9)	
Change from baseline at week 12			0.212 <sup>a)</sup>
Mean±SD	-2.1±4.1	-0.3±2.4	
Median (range)	-2.8 (-9.4 to 6.1)	-0.6 (-3.4 to 5.1)	
P-value for within-group difference in observed value between baseline and week 12	0.081 <sup>c)</sup>	0.632 <sup>c)</sup>	
Change from baseline at week 24			0.110 <sup>a)</sup>
Mean±SD	-1.7±3.4	0.93±4.6	
Median (range)	-2.2 (-6.1 to 5.5)	-1.1 (-4.1 to 11.0)	
P-value for within-group difference in observed value at baseline and week 24	0.088 <sup>c)</sup>	0.501 <sup>c)</sup>	

Values are in ng/mL.

PPS, per protocol set; SD, standard deviation.

<sup>a)</sup>Two sample t-test; <sup>b)</sup>Wilcoxon rank-sum test; <sup>c)</sup>Paired t-test.

corticosteroid pulse therapy; however, the patient's condition did not improve, and a liver biopsy was performed. From the biopsy results, the investigator judged that the patient's elevated aspartate transaminase (AST)/alanine transaminase (ALT) ratio and T-bilirubin levels were due to biliary stricture and inserted a percutaneous, trans-hepatic biliary drainage tube into the patient. The patient's AST/ALT and T-bilirubin levels subsequently decreased, and they were discharged. The cause of the acute rejection was reported as biliary stricture.

No patients in the immediate-release tacrolimus group experienced BCAR (Table 3). The upper 95% confidence limit of the between-group difference was below the pre-defined threshold of 30% (20.6%). However, the study had insufficient power to claim non-inferiority, which was the primary objective. Identical results were observed for the BCAR rate at week 12, and both findings were supported in the results from the full-analysis set.

#### Patient/Graft Survival

One patient in the prolonged-release tacrolimus group died due to sepsis (unrelated to the study drug). The patient survival rates at week 24 were 94.1% (95% confidence interval, 65.0% to 99.2%) and 100.0% in the prolonged-release and immediate-release tacrolimus groups, respectively. No patients in either group had retransplantation or death as a result of graft loss.

#### Medication Adherence

Medication adherence was high and similar between

groups: 94.8% in the prolonged-release and 94.4% in the immediate-release tacrolimus group (Table 4).

#### Safety

Of the 32 randomized patients in the safety set, 26 (81.3%) developed 102 adverse events; 65 of these events occurred in 15 patients (88.2%) in the prolonged-release tacrolimus group, and 37 occurred in 11 patients (73.3%) in the immediate-release tacrolimus group. Adverse events with an incidence  $\geq 10\%$  were generally similar in each treatment group (Table 5). The majority of adverse events (94.1%) were mild or moderate in severity. One patient in the prolonged-release tacrolimus group, experienced a treatment-related adverse event (sepsis) and subsequently died, but the adverse event was considered unrelated to study drug. Five patients (15.6%; four in the prolonged-release group and one in the immediate-release tacrolimus group) had 10 episodes of elevated liver function tests and/or bilirubin levels. Of these patients, all were taking concomitant methylprednisolone, four were taking mycophenolate, and two had also been prescribed deflazacort (glucocorticoid). After elevated liver function test/bilirubin had been identified, tacrolimus dosage was increased in one patient in the prolonged-release group, decreased in one patient in the prolonged-release group, and maintained in one patient in the prolonged-release group. The dosage was unavailable in two of the patients. Adverse drug reactions were experienced by five patients (29.4%) in the prolonged-release group and two patients (13.3%) in the immediate-release group. No unusual laboratory

**Table 4.** Medication adherence in the full-analysis set

Variable	Prolonged-release tacrolimus (n=17)	Immediate-release tacrolimus (n=15)	P-value
Medication adherence (%)			0.240 <sup>a)</sup>
Mean $\pm$ SD	94.8 $\pm$ 4.8	94.4 $\pm$ 7.5	
Median (range)	99.4 (41.3–110.8)	95.8 (76.6–104.0)	
Medication adherence category			1.000 <sup>b)</sup>
< 80%	1 (5.9)	1 (6.7)	
$\geq 80\%$ to < 90%	2 (11.8)	2 (13.3)	
$\geq 90\%$	14 (82.4)	12 (80.0)	

Values are presented as number (%) unless otherwise indicated. SD, standard deviation.

<sup>a)</sup>Wilcoxon rank-sum test; <sup>b)</sup>Fisher's exact test.

**Table 5.** Frequently occurring adverse events with an incidence  $\geq 10\%$  in each treatment group (SAF)

Adverse event	Prolonged-release tacrolimus (n=17)	Immediate-release tacrolimus (n=15)	Total (n=32)
Abdominal pain	2 (11.8)/2	2 (13.3)/2	4 (12.5)/4
Constipation	0	2 (13.3)/2	2 (6.3)/2
Diarrhea	1 (5.9)/1	2 (13.3)/2	3 (9.4)/3
Pyrexia	2 (11.8)/4	1 (6.7)/3	3 (9.4)/7
Bile duct stenosis	2 (11.8)/2	0	2 (6.3)/2
CMV infection	3 (17.7)/3	0	3 (9.4)/3
Upper respiratory tract infection	1 (5.9)/1	2 (13.3)/2	3 (9.4)/3
Blood bilirubin increased	2 (11.8)/2	0	2 (6.3)/2
Liver function test increased	3 (17.7)/7	1 (6.7)/1	4 (12.5)/8
Electrolyte imbalance	2 (11.8)/2	0	2 (6.3)/2
Myalgia	2 (11.8)/2	1 (6.7)/1	3 (9.4)/3
Headache	2 (11.8)/2	2 (13.3)/2	4 (12.5)/4
Tremor	0	2 (13.3)/2	2 (6.3)/2
Hypertension	2 (11.8)/2	0	2 (6.3)/2

Values are presented as number (%) / number of events. SAF, safety set; CMV, cytomegalovirus.

test results, vital signs, or physical changes were reported.

## DISCUSSION

Evidence suggests that treatment with prolonged-release tacrolimus may improve long-term graft and patient survival compared with the immediate-release formulation in primary liver transplant recipients [2]. Early conversion to prolonged-release tacrolimus may help maximize these benefits. To our knowledge, this was the first prospective trial to compare early conversion to prolonged-release tacrolimus with continued immediate-release tacrolimus in *de novo*, South Korean liver transplant recipients. The results showed that once-daily, prolonged-release tacrolimus was effective when administered from 4 weeks after transplantation, and that it was similar to immediate-release tacrolimus with respect to BCAR rates during the 24-week study period. No major differences in safety outcomes occurred between the prolonged-release and immediate-release tacrolimus formulations, and no new safety signals were observed in South Korean liver trans-

plant recipients.

Because we had difficulty recruiting sufficient patients, we closed enrollment after only 36 patients had entered the study. Several issues may have contributed to this insufficient enrollment, including an outbreak of Middle East Respiratory Syndrome (MERS) that occurred during the trial, the strict inclusion/exclusion criteria, and the late addition of investigational sites. Due to the small sample size, our study had insufficient power to make comparisons between the treatment arms. Thus, our results are exploratory only, and require confirmation in a larger-scale trial. However, they are consistent with a previous study in a large (n=475), predominantly Caucasian population of *de novo* liver transplant recipients [6], in which prolonged-release tacrolimus started immediately after liver transplantation was not inferior to immediate-release tacrolimus with respect to rejection rates over 24 weeks. An open-label extension of the study then demonstrated similar efficacy and safety profiles for prolonged-release and immediate-release tacrolimus over 12 months of treatment [6].

In the present study, no patients required re-transplantation or died due to graft loss. Only one patient died of a non-drug related adverse event (sepsis). The patient survival rate at 24 weeks was similar between the treatment groups, and in the prolonged-release tacrolimus group, the rate (94.1%) was consistent with the 6-month rates reported in a recently published trial that assessed three different prolonged-release tacrolimus regimens (89.1%-90.4%) [22], as well as with other previous studies in *de novo* liver transplant recipients [6,23-25].

Whole-blood tacrolimus concentrations decreased after conversion to prolonged-release tacrolimus but remained within the target range and were stable between 12 and 24 weeks. This pattern of reduced tacrolimus trough levels after conversion to the prolonged-release formulation was consistent with other conversion trials in stable patients who had undergone liver transplant [12-16], and it may indicate that the prolonged-release formulation is absorbed at more distal regions of the gastrointestinal tract, where conditions for drug absorption are generally less favorable. Although similar BCAR rates and target trough levels were seen in both groups, clinicians must monitor

tacrolimus concentrations closely at first to identify patients requiring dose adjustment after conversion to prolonged-release tacrolimus. In this regard, although patients randomized to be converted to prolonged-release tacrolimus showed significantly higher tacrolimus trough levels at week 4 in the present study ( $8.8 \pm 2.2$  vs.  $6.9 \pm 1.4$  ng/mL), the levels were well within the target range (5–15 ng/mL). Since the two patient groups had similar baseline characteristics and had been treated with exactly the same immediate-release tacrolimus regimen up to week 4, this difference in trough levels was most likely a natural variation resulting from the small population size. We doubt this difference had any clinical significance or would have affected outcomes, especially as no significant difference in tacrolimus concentrations was seen between the groups at weeks 12 and 24.

Previous studies have shown that patients prefer prolonged-release tacrolimus and that they adhere better to such regimens [4,15,17,26]. However, the present study showed no difference in adherence between the groups (prolonged-release, 94.8%; immediate-release, 94.4%), perhaps because the patient population was small and the study was only carried out over 24 weeks.

Conversion to prolonged-release tacrolimus was well-tolerated, with a low incidence of treatment-related adverse events. Those adverse events that did occur were similar to those already associated with the immediate-release formulation, as previously reported [4,6,18].

Several studies have suggested that prolonged-release tacrolimus can be administered immediately after liver transplantation, provided that the tacrolimus trough level is strictly monitored and adjusted [6,27]. However, little practical information is available about initiating prolonged-release tacrolimus, and experts are cautious about using prolonged-release tacrolimus immediately after surgery when gastric motility changes might disturb its absorption [28]. We decided to initiate prolonged-release tacrolimus 4 weeks after transplantation based on changes to tacrolimus pharmacokinetics that occur in the early posttransplantation period [29]; furthermore, transplant physicians are already accustomed to using twice-daily tacrolimus and maintaining tacrolimus dose from 4 weeks after transplantation.

The present study had a number of limitations that should be addressed in a confirmatory trial. For example, the open-label design of the trial may have introduced bias, and the 24-week duration would not reveal differences in adverse event profiles emerging over the longer term. In addition, the study had insufficient power to confirm that prolonged-release tacrolimus is not inferior to immediate-release tacrolimus. Additionally, the 30% non-inferiority margin may have been too large, as it was double the non-inferiority margin used in a previous large-scale study that compared the two formulations with respect to BCAR [6].

Despite these limitations, the present study does add to the limited available data comparing tacrolimus formulations in *de novo* liver transplant recipients. Furthermore, it was conducted among Asian patients, who have been under-represented in the tacrolimus studies conducted to date.

The present study, carried out in *de novo* liver transplant recipients, suggested that early posttransplant conversion from twice-daily tacrolimus to a simplified once-daily dosing regimen with prolonged-release tacrolimus is an effective treatment option for liver transplant recipients in South Korea. These findings warrant confirmation in larger-scale studies.

## CONFLICT OF INTEREST

This study was funded by Astellas Pharma Inc. and YJL and HJ are employees of Astellas Pharma Inc. No other potential conflict of interest relevant to this article was reported.

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