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Modifying Tacrolimus-related Toxicity After Liver Transplantation Comparing Life Cycle Pharma Tacrolimus Versus Extended-released Tacrolimus: A Multicenter, Randomized Controlled Trial

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Background. The aim of this open-label, multicenter, randomized controlled study was to investigate whether the life cycle pharma (LCP)-tacrolimus compared with the extended-release (ER)-tacrolimus formulation results in a difference in the prevalence of posttransplant diabetes, hypertension and chronic kidney disease (CKD) at 12 mo after liver transplantation. **Methods.** Patients were 1:1 randomized to either of the 2 tacrolimus formulations. The primary endpoint was defined as a composite endpoint of any of 3 events: sustained (>3 mo postrandomization) posttransplant diabetes, new-onset hypertension, and/or CKD, defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 for >3 m during the follow-up. **Results.** In total, 105 patients were included. In the intention-to-treat analysis, a statistically significant lower proportion of liver transplant recipients in the LCP-tacrolimus group reached the composite primary endpoint at 12 mo compared with the ER-tacrolimus group (50.9% [27/53], 95% confidence interval [CI], 37.9%-63.9% versus 71.2% [37/52], 95% CI, 57.7%-81.7%; risk difference: 0.202; 95% CI, 0.002-0.382; $P = 0.046$). No significant difference was found in the per protocol analysis. In the intention-to-treat and per protocol population, fewer liver transplant recipients in the LCP-tacrolimus group developed CKD and new-onset hypertension compared with the ER-tacrolimus group. No differences in rejection rate, graft and patient survival were found. **Conclusions.** A statistically significant and clinically relevant reduction in the prevalence of the composite primary endpoint was found in the LCP-tacrolimus group compared with the ER-tacrolimus group in the first year after liver transplantation with comparable efficacy.

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Tacrolimus is the cornerstone of the immunosuppressive regimen after liver transplantation (LT). The use of tacrolimus has substantially decreased the risk of acute rejection and has improved short-term outcomes, but these short-term gains are not matched by similar gains in long-term outcomes.[1-3] Tacrolimus was approved in 1994 by the European Medicines Agency and Food and Drug Administration as twice-daily capsules (Prograf; Astellas Pharma). In 2007, the first once-daily extended-release (ER)-tacrolimus formulation (Advagraf; Astellas Pharma) received approval, and in 2014, a second

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H.J.M. and S.D.M. designed the study. M.B.M., B.v.H., W.G.P., I.P.J.A., B.d.W., S.D.M., E.V.-H., L.E., D.A.H., C.M.d.H., and H.J.M. were involved in the execution of the study. M.B.M. and H.J.M. had access to and verified the underlying data. M.B.M. and N.S.E. analyzed the data. M.B.M. wrote the article with input from all other authors. All authors participated in data interpretation, article writing, review, and approval of the final version of the article for submission.
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prolonged-release once-daily tacrolimus formulation, life cycle pharma (LCP)-tacrolimus, (Envarsus; Chiesi Farmaceutici S.p.A.) was approved. The introduction of once-daily tacrolimus formulations improved the medication adherence in liver transplant recipients.[4,5] Around the world, the choice for a tacrolimus formulation varies among transplant centers and no preference is pronounced.

Tacrolimus is associated with a wide range of side effects with potential negative impact on long-term outcomes in liver transplant recipients. Cumulative exposure and peak blood concentration of tacrolimus are 2 factors associated with side effects that are potentially modifiable.[6-8] Nephrotoxicity, post-transplant diabetes (PTDM), hypertension, and neurotoxicity are the most common side effects specific to calcineurin inhibitors (CNIs), aside from the risk of infection and the development of de novo malignancy, which are shared by most immunosuppressive agents.[9] Several studies show that in the first years after LT the incidence of PTDM ranges from 10% to 30% and the incidence of hypertension ranges from 40% to 60%.[10] Furthermore, up to 50% of LT recipients will develop chronic kidney disease (CKD) defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2.[11,12] Apart from the direct nephrotoxic effects of tacrolimus, diabetes, hypertension and, in the past, recurrent hepatitis C infection have an additive effect on the development of CKD.[13] A number of strategies has been developed to minimize the risk on tacrolimus toxicity including different dosing regimens and combinations with multiple immunosuppressive agents allowing for lower (cumulative) tacrolimus exposure.[12]

LCP-tacrolimus is a prolonged-release tacrolimus formulation utilizing a new drug delivery technology (MeltDose).[14,15] This formulation has lower peak-through blood level fluctuations and a higher bioavailability compared with the other tacrolimus formulations, resulting in a lower dose requirement to reach a certain tacrolimus exposure.[14,16,17] Rayar et al[18] showed that a high intrapatient variability of tacrolimus exposure in LT recipients was associated with poorer outcomes. Furthermore, the tacrolimus immediate-release (IR) formulation (Prograf) and ER-tacrolimus formulation are associated with a characteristic high peak concentration (C_{max}) following dosing, which may be associated with increased neurotoxicity.[19] Whether the high peak concentration (C_{max}) is also associated with the increased cardiovascular risk profile of tacrolimus is unknown.

To date, no head-to-head comparison between the 2 once-daily tacrolimus formulations has been performed to evaluate differences in clinically relevant outcomes. Therefore, the aim of this randomized controlled study was to investigate whether LCP-tacrolimus compared with ER-tacrolimus results in a difference in the prevalence of PTDM, new-onset hypertension, and CKD at 12 mo after transplantation.

MATERIALS AND METHODS

Study Design and Participants

This study was an open-label, multicenter, randomized controlled trial. Patients were enrolled between April 2019 and October 2021 and prospectively followed for 12 mo or until death. Patients were randomized at discharge or within 4 wk (whichever came first) after LT from IR-tacrolimus to LCP-tacrolimus or ER-tacrolimus.

Adult patients, between 18 and 75 y, were included after a primary LT. All participants gave written informed consent before any study-related activity. The main exclusion criteria were multiorgan transplantation, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 at the moment of randomization, hepatic artery thrombosis, known hypersensitivity to tacrolimus, and the use of a mammalian target of rapamycin-inhibitor or the need for an IR-tacrolimus formulation.

The study was performed at 2 centers in the Netherlands: The Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands, and Leiden University Medical Center, Leiden, The Netherlands. The study was approved by the institutional Ethical Committees of these institutions, registered in the EudraCT database (EudraCT: 2018-002856-34) and conducted in accordance with the latest version of the declaration of Helsinki.

Study Endpoints

The primary endpoint was defined as a composite endpoint of any of 3 events: sustained (>3 mo postrandomization) PTDM, new-onset hypertension, and/or CKD.

PTDM was defined according to the definition of diabetes by the World Health Organization (ie, fasting plasma glucose value of 7 mmol/L or random venous plasma glucose concentration ≥11.1 mmol/L measured at least on 2 different occasions or HbA1C >48 mmol/mol) and excludes the diagnosis of diabetes before LT.[20,21] Because the majority of patients receive high-dose prednisolone in the immediate posttransplant period, PTDM was defined by a sustained hyperglycemia after the first 3 mo post-LT.

New-onset hypertension was defined as a systolic blood pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg measured during ≥2 office blood pressure measurements. This definition excluded the presence of hypertension before LT.

CKD was defined as grade ≥3 (eGFR <60 mL/min/1.73 m^2) for >3 mo during the follow-up according to the KDIGO classification.[22] The renal function was measured by serum

involved in the development, execution and analysis of the trial. The manuscript was reviewed before submission by Chiesi Pharmaceuticals.

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EudraCT: 2018-002856-34.

Requests for access to the study data can be emailed to the corresponding author.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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creatinine and the estimated glomerular filtration rate was calculated using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation.[23]

Secondary endpoints included the individual components of the composite endpoint, prevalence of LT recipients having an eGFR <60 or <30 mL/min/1.73 m^2 at 3, 6, and 12 post-LT, graft survival, recipient survival, number of episodes, and severity of rejections and safety. Furthermore, the cumulative exposure to tacrolimus was calculated by the area under curve of trough concentrations based on work by Rodríguez-Perálvarez et al[7,8] and for the patient treated according to the protocol the intrapatient variability (IPV) in tacrolimus in the first 6 and 12 mo was quantified as the coefficient of variation as described by van der Veer et al.[24] Serious adverse events (SAEs) were described according to the Medical Dictionary for Regulatory Activities. Infections included every viral or bacterial infection that occurred during the study period excluding cholangitis.

Randomization and Masking

Participants were randomly assigned (1:1) to either LCP-tacrolimus or ER-tacrolimus according to a computer-generated randomization list by CastorEDC.[25] Stratification was done by center, to ensure an equal distribution of both arms in the 2 participating centers. Blinding of participants and physicians was not applied.

Procedures

After the transplantation participants received after basiliximab induction, corticosteroids, and mycophenolic acid (MPA). From day 5 after transplantation, IR-tacrolimus was started. The tacrolimus trough level at the time of randomization had to be ≤6 ng/mL and MPA had to be discontinued. During the study follow-up, the dose of both tacrolimus formulations was adapted according to trough levels, aiming for a trough level between 8 and 10 µg/L in the first 3 mo and a trough level between 6 and 8 µg/L thereafter. Dose adjustments of both formulations resulting in lower or higher trough levels were allowed in the case of severe side effects or rejection. In the case of deterioration of the kidney function, tacrolimus monotherapy could be switched to MPA or a mammalian target of rapamycin-inhibitor in combination with low-dose tacrolimus. Subjects switching tacrolimus therapy will not be replaced, according to the intention-to-treat (ITT) principle. Corticosteroids were lowered or discontinued within 180 d after randomization at the discretion of the treating physician.

Data Collection

Variables collected included recipient sociodemographic, clinical, and transplantation parameters, SAEs, and trough levels of tacrolimus.

Statistical Analysis

The percentage of LT recipients reaching the primary composite endpoint in the ER-tacrolimus arm was estimated at 68% (based on historical data, not published, at the Erasmus University Medical Center). The percentage of LT recipients reaching the primary composite endpoint in the LCP-tacrolimus arm was expected to be 30% percentage points lower compared with the control group. To have 80% power to detect a significant difference at the 95% confidence level (CI) using the Pearson chi-square test with continuity correction 96 patients are required. However, to compensate for any unexpected loss, 10 additional patients were included resulting in a total of 106 patients deemed to be required.

Variables were described using counts (%) for nominal and ordinal variables and mean (SD) or median (interquartile range [IQR]) for the continuous variables, depending on the shape of the distribution.

The risk differences for the primary and secondary outcomes between the 2 treatment arms were compared using the Pearson chi-square test (with continuity correction). The corresponding *P* values were obtained via Monte Carlo simulation with 1 million simulations. Secondary endpoints were analyzed using the Pearson chi-square test, Mann–Whitney U test or Student *t*-test. For all statistical tests, a (2-sided) *P* value of <0.05 was considered to indicate statistical significance.

A generalized mixed-effect model was fitted to examine the kidney function during the course of the study. Besides the treatment arm, visit number, and their interaction, the model included covariates shown to be relevant in previous studies: tacrolimus trough levels, recipient age and sex, pre- and posttransplantation hypertension, and diabetes. Participant-specific random intercepts were included to account for correlation among repeated measurement nested within each participant. The shape of the association with the kidney function was investigated using natural cubic splines. Missing data were considered as missing completely at random. To visualize the estimated associations, the expected kidney function across the course of the study was calculated while fixing the values of all other covariates to the median or reference category.

The analysis was performed as an ITT and per protocol (PP). Patients with protocol violations in immunosuppressive therapy, a retransplantation, or death were excluded in the PP analysis. All data were collected in CastorEDC and analyses were conducted with R software (version 4.2.1).[25,26]

RESULTS

Table 1 presents the baseline characteristics. A total of 105 patients was included, of whom 52 were randomized to the ER-tacrolimus and 53 to the LCP-tacrolimus arm (Figure 1). Most of the patients was transplanted because of HCC (31/105, 29.5%), primary sclerosing cholangitis (18/105, 17.1%), or (non)alcoholic steatohepatitis (17/105, 16.2%). The mean eGFR at randomization in the ER-tacrolimus and LCP-tacrolimus groups was 82 ± 17.8 and 79 ± 20.4 mL/min/1.73 m^2. More patients with pretransplant hypertension were included in the ER-tacrolimus group compared with the LCP-tacrolimus group (32.7% versus 20.8%).

Composite Primary Endpoint and Separate Components

Figure 2 shows the proportion of LT recipients reaching the composite primary endpoint and the separate components of the composite primary endpoint in the ITT and PP populations. In the ITT population, a statistically significant lower proportion of LT recipients in the LCP-tacrolimus group reached the composite primary endpoint at 12 mo compared with the ER-tacrolimus group (50.9% [27/53]; 95% CI, 37.9%-63.9% versus 71.2% [37/52]; 95% CI, 57.7%-81.7%; risk difference: 0.202; 95% CI, 0.002-0.382; *P* = 0.046). In the PP population, the

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TABLE 1.

Baseline characteristics

	ER-tacrolimus (n = 52)	LCP-tacrolimus (n = 53)
Recipient demographics at randomization		
Age, y, median (IQR)	58.50 (46.75–65.25)	56.50 (46.25–63)
Gender, male, n (%)	41 (78.8)	35 (66)
Body mass index, kg/m^2, mean ± SD	26.13 ± 5.28	25.82 ± 4.56
Ethnicity, n (%)		
Caucasian	46 (88.5)	49 (92.5)
Other[a]	4 (7.6)	4 (7.5)
Unknown	2 (3.8)	1 (1.9)
Primary disease, n (%)		
Hepatocellular carcinoma	19 (36.5)	12 (22.6)
(Non)alcoholic steatohepatitis	7 (13.5)	10 (18.9)
Primary sclerosing cholangitis	10 (19.2)	8 (15.1)
Acute liver failure	3 (5.8)	3 (5.7)
Cryptogenic cirrhosis	3 (5.8)	3 (5.7)
Metabolic diseases	—	4 (7.5)
Viral hepatitis	3 (5.8)	3 (5.7)
Other[b]	7 (13.5)	11 (20.8)
Hematology laboratory results		
Hemoglobin, mmol/L, mean ± SD	6.3 ± 0.9	6.1 ± 0.8
Leucocytes, 10^9/L, mean ± SD	9.5 ± 4.8	9.5 ± 4.7
Platelets, 10^9/L, mean ± SD	263 ± 125	249 ± 122
INR, mean ± SD	1.6 ± 0.5	1.2 ± 0.3
Factor V, median (IQR)	1.71 (1.39–1.71)	1.47 (1.16–1.66)
Chemistry lab		
Albumin, g/L, mean ± SD	32.9 ± 4.7	33.7 ± 4.2
Bilirubin, µmol/L, median (IQR)	19 (12.8–31.8)	19 (12.3–27.5)
Creatinine, µmol/L, mean ± SD	77 ± 26	82 ± 36
eGFR, mL/min/1.73 m^2, mean ± SD	82 ± 18	79 ± 20
Cholesterol total, mmol/L, mean ± SD	3.65 ± 1.06	3.48 ± 0.95
LD lipoprotein, mmol/L, mean ± SD	1.96 ± 0.86	1.90 ± 0.86
Triglyceride, mmol/L, mean ± SD	2.08 ± 0.85	1.87 ± 0.74
Glucose, mmol/L, median (IQR)	6.65 (5.55–8.45)	7.15 (5.70–9.28)
HbA1c, mmol/mol, mean ± SD	35.3 ± 10.7	33.8 ± 6.4
Blood pressure		
Diastolic, mm Hg, mean ± SD	77 ± 10	75 ± 11
Systolic, mm Hg, mean ± SD	130 ± 15	127 ± 17
Heart rate, beats per minute, mean ± SD	82 ± 14	84 ± 13
Tacrolimus trough blood level, µg/L, mean ± SD	6.94 ± 3.05	7.51 ± 3.29
Pharmacogenetics, n (%)		
Normal CYP3A4 metabolism	33 (63.5)	36 (67.9)
Intermediar CYP3A4 metabolism	4 (7.7)	2 (3.8)
Unknown CYP3A4 metabolism	15 (28.8)	16 (30.2)
CYP3A5 expressor	9 (17.3)	7 (13.2)
CYP3A5 nonexpressor	28 (53.8)	31 (58.5)
Unknown CYP3A5 status	15 (28.8)	16 (30.2)
Recipient demographics pretransplantation		
Pre-existing diabetes, yes, n (%)	11 (21.2)	13 (24.5)
Pre-existing hypertension, yes, n (%)	17 (32.7)	11 (20.8)

[a]Other includes Asian and Afro-American.

[b]Other includes primary biliary cirrhosis, secondary biliary cirrhosis, autoimmune cirrhosis, cholangiocarcinoma, Caroli disease, polycystic liver disease, and neuroendocrine tumor liver metastases.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate based on the CKD-EPI formula; ER, extended-release; INR, international normalized ratio; IQR, interquartile range; LCP, life cycle pharma.

observed difference was not statistically significant (41.4% [12/29]; 95% CI, 25.5%-59.3% in the LCP-tacrolimus group versus 64.3% [18/29]; 95% CI, 45.8%-79.3% in the ER-tacrolimus group; risk difference: 0.229; 95% CI, −0.051 to 0.467; $P = 0.11$).

In the ITT population, fewer LT recipients in the LCP-tacrolimus group developed CKD, new-onset hypertension, and PTDM compared with the ER-tacrolimus group: CKD 26.4% (14/53); 95% CI, 16.4%-39.6% versus 42.3% (22/52); 95% CI, 29.9%-55.8%; risk difference: 0.159; 95% CI, −0.035 to 0.339; $P = 0.10$ and new-onset hypertension 38.1% (16/42); 95% CI, 24.9%-53.2% versus 54.3% (19/35); 95% CI, 38.2%-69.5%; risk difference: 0.162; 95% CI, −0.076 to 0.379; $P = 0.18$ and PTDM 20% (8/40); 95% CI,

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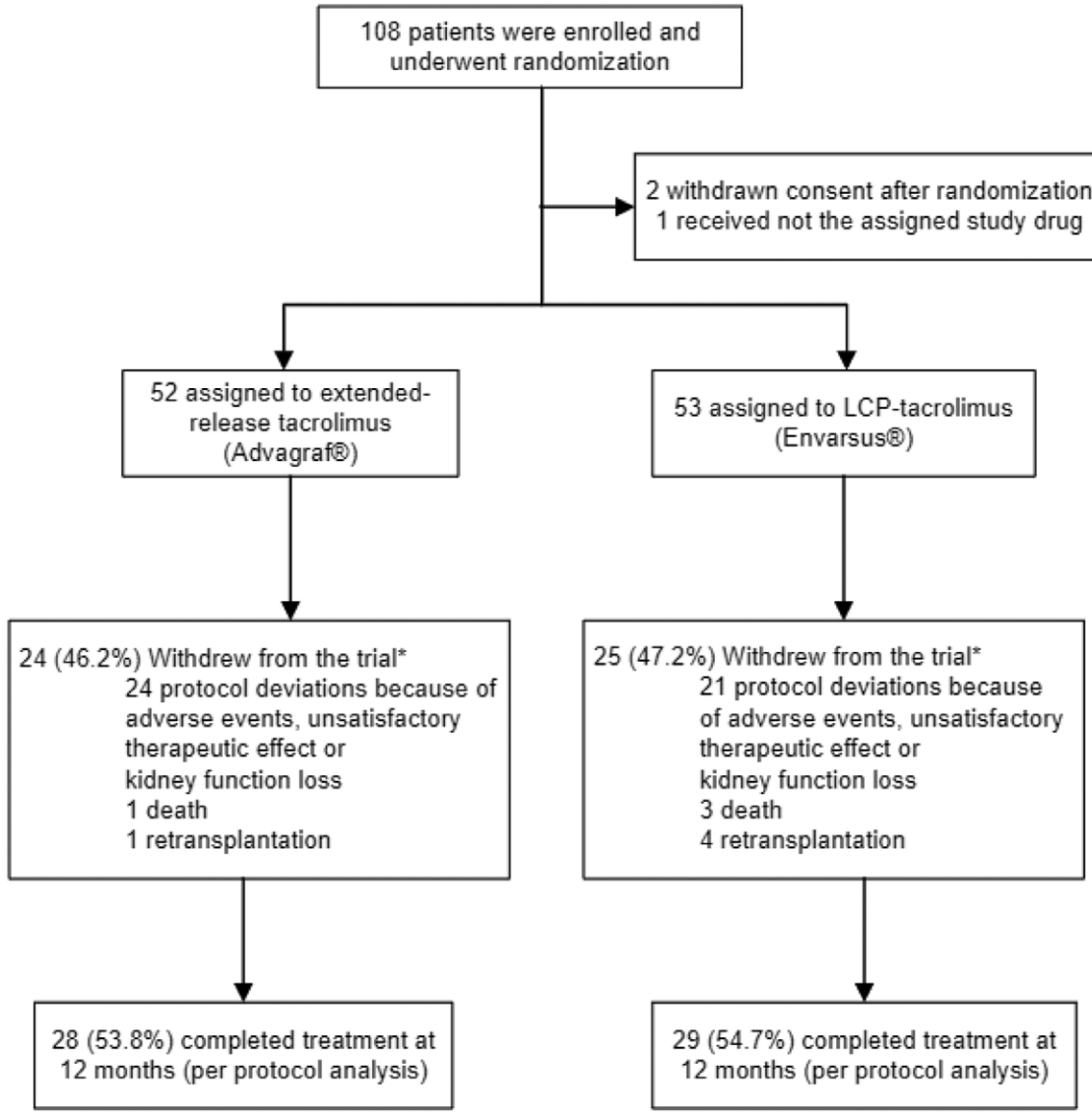

FIGURE 1. Enrollment, randomization, and follow-up. *Some LT recipients experiencing protocol deviations died or had a retransplantation. LCP, life cycle pharma; LT, liver transplantation.

10.5%-34.8% versus 26.8% (11/41) 95% CI, 15.7%-41.9%; risk difference: 0.068; 95% CI, −0.133 to 0.262; $P = 0.60$.

In the PP population, less LT recipients in the LCP-tacrolimus group developed CKD and new-onset hypertension compared with the ER-tacrolimus group: CKD 10.3% (3/29); 95% CI, 3.6%-26.4% versus 28.6% (8/28); 95% CI, 15.3%-47.1%; risk difference: 0.182; 95% CI, −0.051 to 0.399; $P = 0.10$ and new-onset hypertension 38.1% (8/21), 95% CI, 20.8%-59.1% versus 52.2% (12/23); 95% CI, 32.9%-70.7%; risk difference: 0.141; 95% CI, −0.173 to 0.421; $P = 0.38$. No evidence was found for a difference in the development of PTDM between both groups: 13% (3/23); 95% CI, 4.5%-32.1% versus 13% (3.23); 95% CI, 4.5%-32.1%; risk difference: 0; 95% CI, −0.237 to 0.237; $P = 1$.

Sensitivity analyses for new-onset hypertension and PTDM showed similar event rates in both groups when LT recipients with pretransplant hypertension or diabetes were included in the analysis (and considered not to have new-onset disease) as well as when every LT recipients with hypertension or diabetes was considered new-onset hypertension or PTDM.

Figure 3A and B visualizes the individual kidney function measurements, the observed means per group, and the estimated group trajectories across the study period based on the linear mixed-effect model. The results of the models are shown in Table S1 (**SDC**, http://links.lww.com/TXD/A636). In the ITT and PP populations, after the transplantation, the mean eGFR gradually declined during the study period. No evidence for differences in the mean eGFR was found between the LCP-tacrolimus group compared with the ER-tacrolimus group during the study period. The linear mixed-effect models confirmed this.

In the PP population, the percentage of LT recipients having an eGFR <60 mL/min/1.73 m^2 at 3 mo post-LT was 15.4% (4/29) in the LCP-tacrolimus group and 25% (7/28) in the ER-tacrolimus group ($P = 0.13$), at 6 mo post-LT 17.2% (5/29) in the LCP-tacrolimus group and 25% (7/28) in the ER-tacrolimus group ($P = 0.24$) and at 12 mo post-LT 25% (7/29) in the LCP-tacrolimus group and 28.6% (8/28) in the ER-tacrolimus group ($P = 0.68$). At 3 mo, no LT recipients had an eGFR <30 mL/min/1.73 m^2 and at 6 and 12 mo 1 LT

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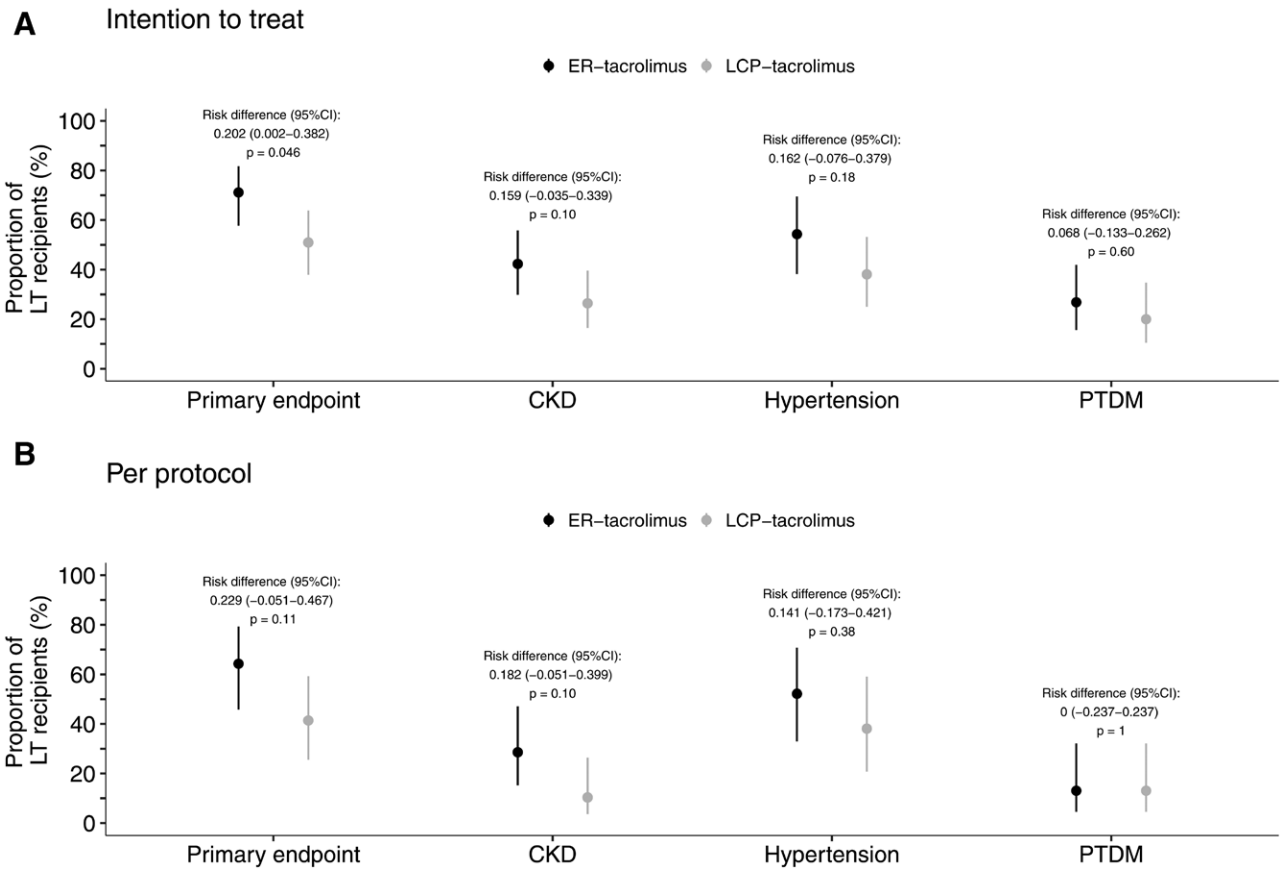

FIGURE 2. LT recipients reaching the composite primary endpoint and developing chronic kidney disease, new-onset hypertension and new-onset diabetes after transplantation. A, Intention-to-treat and (B) PP show the proportion of LT recipients with 95% CI reaching the composite primary endpoint and developing the separate components of the composite primary endpoint in the intention-to-treat population and PP population: CKD defined as grade ≥3 (eGFR <60 mL/min/1.73 m^2) for >3 mo during the follow-up, new-onset hypertension and PTDM. In the ITT population the composite primary endpoint at 12 mo was reached in 50.9% (27/53); 95% CI, 37.9%-63.9% of the LT recipients in the LCP-tacrolimus group vs 71.2% (37/52); 95% CI, 57.7%-81.7% of the LT recipients in the ER-tacrolimus group; risk difference: 0.202; 95% CI, 0.002-0.382; $P = 0.046$. In the PP population, the composite primary endpoint at 12 mo was reached in 41.4% (12/29); 95% CI, 25.5%-59.3% of the LT recipients in the LCP-tacrolimus group vs 64.3% (18/29), 95% CI, 45.8%-79.3% of the LT recipients in the ER-tacrolimus group; risk difference: 0.229; 95% CI, –0.051 to 0.467; $P = 0.114$. CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ER, extended-release; LCP, life cycle pharma; LT, liver transplantation; ns, nonsignificant; PP, per protocol; PTDM, posttransplant diabetes.

recipient in the LCP-tacrolimus group and 0 LT recipient in the ER-tacrolimus group had an eGFR <30 mL/min/1.73 m^2.

Secondary Endpoints: Rejection, Graft, and Patient Survival

During the follow-up, no differences in the amount of rejection episodes between the study groups were found (Table 2). In the LCP-tacrolimus group, 6 LT recipients developed 7 episodes of rejection and, in the ER-tacrolimus group, 5 LT recipients developed 5 episodes of rejection. Rejections were treated according to local protocols with corticosteroids and no antithymocyte globulin was used.

In the LCP-tacrolimus group, more LT recipients died or had a retransplantation compared with the ER-tacrolimus group: death 5.6% (3/54) versus 1.9% (1/52) and retransplantation 7.4% (4/54) versus 1.9% (1/52). No death or retransplantation was considered study drug-related: 3 LT recipients died because of multiorgan failure, 1 died because of a traumatic intracranial hemorrhage, 4 LT recipients were retransplanted because of ischemic-type biliary lesions, and 1 LT recipient was retransplanted because of hepatic artery thrombosis.

Immunosuppression

During the study, the mean trough levels for tacrolimus were within the target range for both groups for the ITT and PP populations (Figure 3C and D). At the end of the study, in the ITT and PP populations, the mean tacrolimus trough levels in the LCP-tacrolimus group was statistically significant higher compared with the ER-tacrolimus group: ITT population 7.6 ± 3.1 versus 6.3 ± 2.2 μg/L, $P = 0.026$ and PP population 8.3 ± 3.1 versus 6.7 ± 2.1 μg/L, $P = 0.033$.

The median cumulative exposure to tacrolimus based on the area under the curve of trough concentrations was higher at month 12 for the LCP-tacrolimus group compared with the ER-tacrolimus group: ITT population 2697 μg·d/L (IQR 2316–2949) versus 2357 μg·d/L (IQR 1946–2806); $P = 0.018$ and PP population 2707 μg·d/L (IQR 2383–2975) versus 2612 μg·d/L (IQR 2219–2976); $P = 0.39$. No differences were found in the cumulative exposure to tacrolimus at month 3.

At 6 and 12 mo, the intrapatient variability calculated with the coefficient of variation was not different between the groups (**Figure S1, SDC,** http://links.lww.com/TXD/A636).

Every LT recipient received 500 mg of methylprednisolone intraoperatively. The median number of days of prednisolone

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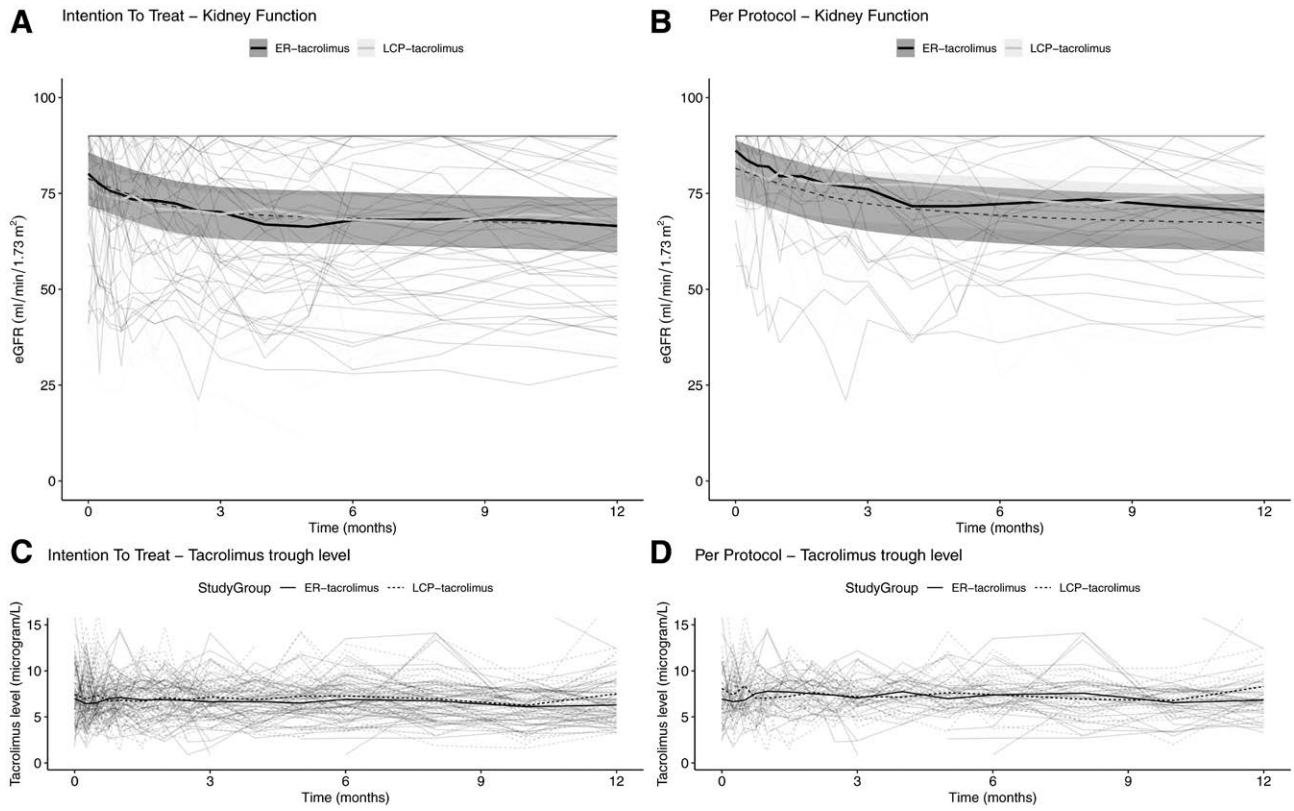

FIGURE 3. Kidney function and tacrolimus levels in the ITT and PP population. A, Individual eGFR trajectories (CKD-EPI formula) and group-wise mean with 95% CI during the course of the study of the ITT population represented as solid lines. The dashed lines and shaded areas indicate the expected values and corresponding 95% CI from the generalized mixed-effect model (values for the covariates: tacrolimus trough levels, recipient age and sex, hypertension, diabetes were set to the population median or reference category). Random participant effects were included to account for repeated measurement nested within each participant. The shape of the association with the kidney function was investigated using natural cubic splines. Missing data were considered as missing completely at random. B, Individual eGFR trajectories (CKD-EPI formula) and group-wise mean with 95% CI during the course of the study of the PP population represented as solid lines. The dashed lines and shaded areas indicate the expected values and corresponding 95% CI from the generalized mixed-effect model (values for the covariates: tacrolimus trough levels, recipient age and sex, hypertension, diabetes were set to the population median or reference category). Random participant effects were included to account for repeated measurement nested within each participant. The shape of the association with the kidney function was investigated using natural cubic splines. Missing data were considered as missing completely at random. C, Mean tacrolimus trough level (µg/L) during the study of the ITT population. D, Mean tacrolimus trough level (µg/L) during the study of the PP population. CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ITT, intention to treat; PP, per protocol.

TABLE 2.

Serious Adverse events according to the Medical Dictionary for Regulatory Activities

	ER-tacrolimus		LCP-tacrolimus	
	No. patients with event (n = 51)	No. events (n = 76)	No. patients with event (n = 53)	No. events (n = 84)
Serious adverse events				
Fever[a]	11 (22%)	23 (30.3%)	8 (15.1%)	14 (16.7%)
Cholangitis and bile duct obstruction	4 (7.8%)	6 (7.9%)	9 (17.0%)	10 (11.9%)
Infections[b]	6 (11.7%)	9 (11.8%)	6 (11.3%)	7 (8.3%)
Liver transplant rejection	5 (9.8%)	5 (6.6%)	6 (11.3%)	7 (8.3%)
Kidney injury/failure	3 (5.9%)	4 (5.3%)	4 (7.5%)	7 (8.3%)
Hepatic artery thrombosis	—	—	1 (1.9%)	1 (1.2%)
Other	22 (43.1%)	29 (38.2%)	19 (35.8%)	38 (45.2%)
Outcome				
Death	1 (2.0%)	—	3 (5.7%)	—
Resolved—no sequelae	24 (47.1%)	62 (81.6%)	26.0 (49.1%)	63 (75.0%)
Resolved—with sequelae	26 (51.0%)	14 (18.4%)	24 (45.3%)	21 (25.0%)

[a]Fever with an unspecified cause and no overlap with the SAEs for cholangitis or infections.
[b]Infections include every viral or bacterial infection occurred during the study period excluding cholangitis.
ER, extended-release; LCP, life cycle pharma; SAE, serious adverse event.

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after transplantation, the median cumulative dose and the median dose per day prednisolone during the study in both groups were not different. In the LCP-tacrolimus group, the number of days prednisolone was 146 d (IQR 114–180 d), the median cumulative dose prednisolone was 1030 mg (IQR 830–1260) and the median dose per day prednisolone was 7.1 mg/d (IQR 6.5–8). In the ER-tacrolimus group, the number of days of prednisolone was 151 d (IQR 117–175 d), the median cumulative dose prednisolone was 1095 mg (IQR 865–1320) and the median dose per day prednisolone was 7.2 mg/d (IQR 6.8–8). During the study, in the ER-tacrolimus group, 46.2% (24/52) of the LT recipients switched therapy because of toxicity (renal insufficiency or tremors) or rejection: 22 LT recipients to the combination of ER-tacrolimus and mycophenolic acid, 1 LT recipient to the combination of IR-tacrolimus and everolimus, and 1 LT recipients from ER-tacrolimus to LCP-tacrolimus. In the LCP-tacrolimus group, 40.4% (21/54) of the LT recipients switched therapy during the study because of toxicity (renal insufficiency or tremors), rejection or the recurrence of hepatocellular carcinoma: 19 LT recipients to the combination of LCP-tacrolimus and mycophenolic acid and 2 LT recipients to LCP-tacrolimus and sirolimus. None of these patients was switched back during the study period.

Safety

Table 2 shows the SAEs and the outcomes of the SAEs during the study period. In total, 160 SAEs were reported: 47.5% (76/160) in the ER-tacrolimus group and 52.5% (84/160) in the LCP-tacrolimus group. SAEs most frequently reported were fever 23.1% (37/160), cholangitis and bile duct obstruction 10% (16/160) and infections 10% (16/160).

DISCUSSION

In this randomized controlled study, it was observed that significantly less LT recipients in the LCP-tacrolimus group reached the composite primary endpoint at 12 mo compared with the ER-tacrolimus group at no increased costs in terms of efficacy or safety.

An important recommendation in the Consensus on Managing Modifiable Risk in Transplantation guideline is the frequent monitoring for unwanted side effects of immunosuppression, such as renal impairment, PTDM, obesity, arterial hypertension and hyperlipidemia.[6] Therefore, we focused in this study on differences in clinically relevant outcomes for both long-acting tacrolimus formulations currently available.

In this study, the use of LCP-tacrolimus had a major positive impact on CNI-related nephrotoxicity. The use of LCP-tacrolimus resulted in a 15.9%–18.2% reduction in the prevalence of CKD grade ≥3 (eGFR <60 mL/min/1.73 m^2) for >3 mo post-LT. Furthermore, the prevalence of CKD grade ≥3 at 3 and 6 mo post-LT was 15%–17% in the LCP-tacrolimus group, whereas in the ER-tacrolimus group in this study, as in previous studies, the prevalence ranged from 30% to 50%.[11,12] Interestingly, the mean eGFR during the whole study period was not different between both study groups. This is caused by the fact that when the eGFR of liver transplant recipients deteriorated most transplant physicians reduced the tacrolimus dose or switched the recipient to combination therapy of immunosuppressive drugs. This resulted in an increase of the eGFR over time and by calculating the mean eGFR, information of liver transplant recipients with an eGFR below average is not shown anymore. Whereas by calculating the percentage of liver transplant recipients with CKD a more appropriate view on the development of CKD during the study period is available.

Another interesting finding is the fact that we found less new-onset hypertension in the LCP-tacrolimus group. After solid organ transplantation, immunosuppressive agents play a major role in the development of new-onset hypertension. Both tacrolimus and corticosteroids are associated with blood pressure elevation. Tacrolimus-induced hypertension has been related to increased sympathetic nervous system activity and increased peripheral vascular resistance, whereas corticosteroid-induced hypertension is related to sodium and water retention.[27] In this study, corticosteroids have less contribution to the development of new-onset hypertension because the corticosteroids were lowered or discontinued within a median of 150 d. Furthermore, no difference in the median number of days of prednisolone after transplantation, cumulative dose, and median dose/day prednisolone was found. Finally, based on the difference in the prevalence of pre-existing hypertension in both groups, we performed a sensitivity analysis. This analysis showed similar results when LT recipients with pretransplant hypertension were included in the analysis and when every LT recipients with hypertension in this study was analyzed as new-onset hypertension. Therefore, the significantly reduced prevalence of new-onset hypertension in the LCP-tacrolimus group is suggested to be a result of the new drug delivery technology with a lower C_{max} of this tacrolimus formulation.

Over the last decennia, the exposure to tacrolimus in LT recipients decreased with target trough levels declining from >10 μg/L to the current target range of 6–8 μg/L for 3–12 mo post-LT. Previous studies by Rodriguez-Perálvarez et al[7,8] have shown that an increased cumulative exposure to tacrolimus for the years results in increased toxicity (eg, nephrotoxicity and the incidence of cancer). In this study, the mean tacrolimus trough level and the cumulative exposure to tacrolimus at month 12 were statistically significant higher in the LCP-tacrolimus group compared with the ER-tacrolimus group. In line with a study by Del Bello et al,[28] we found that the IPV in the LCP-tacrolimus group was not different compared with the ER-tacrolimus group. Conflicting results regarding the impact of a high IPV in tacrolimus exposure on the long-term outcomes are available.[24,29] Even though patients in the LCP-tacrolimus group had a higher cumulative exposure to tacrolimus, we found a statistically significant and clinically relevant reduction in the prevalence of the composite primary endpoint.

The development of LCP-tacrolimus was driven based on the large fluctuations in plasma concentration with the other tacrolimus formulations. It has been suggested that high tacrolimus peak concentrations (C_{max}) following dosing may be associated with increased neurotoxicity.[19] Preclinical studies investigating the mechanism behind the development of tacrolimus-related toxicity (eg, CKD, hypertension, diabetes, and neurotoxicity) in relation to peak concentrations are lacking. In this study, we did not evaluate the tacrolimus peak concentrations or actual exposure by measuring the area under the curve after ingestion. However, because the IPV in tacrolimus was comparable between the groups and the calculated cumulative exposure was higher for LCP-tacrolimus, we believe that the lower LCP-tacrolimus peak

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concentration is the factor that explains the more favorable cardiovascular risk profile. Overall, the tacrolimus peak concentration and the cumulative exposure to tacrolimus over time are the factors associated with the development of tacrolimus-related toxicity. However, the exact mechanism behind the development of tacrolimus-related toxicity needs to be determined.

This is the first head-to-head comparison of the 2 long-acting tacrolimus formulations available for the prevention of rejection after transplantation evaluating CNI-related nephrotoxicity or metabolic side effects. No other study showed a significant improvement in the cardiovascular risk profile with the use of LCP-tacrolimus. Most studies that have been performed focused either on the conversion of IR formulation to LCP-tacrolimus, or investigated only pharmacokinetics, had a retrospective and short-term design or analyzed other primary endpoints (eg, death andgraft failure of biopsy-proven acute rejection).[15,30-32]

This study has a major limitation, namely the fact that almost half of the LT recipients in both groups switched immunosuppressive therapy because of toxicity (renal insufficiency or tremors), rejection or the recurrence of HCC. Although a larger number of LT recipients was switched to another immunosuppressive regimen, mostly combination therapy, this could have introduced selection bias, complicating the interpretation of the results. This type of selection bias has been addressed in several other studies investigating immunosuppressive drugs in transplant recipients.[12,33,34] Overall, the results in our ITT analysis might be underestimating the actual effect of tacrolimus on the composite primary endpoint. Although the ITT and PP analysis needs to be cautiously interpreted, our results are consistent in the ITT and PP analysis. Because we studied 2 formulations of tacrolimus and not 2 different immunosuppressive regimens, the result is still relevant and reflects the daily clinical practice in transplant care.

Further research evaluating the long-term clinical side effects in a larger population and the effect on the quality of life is necessary to determine whether LCP-tacrolimus should be the preferred tacrolimus formulation after LT. Currently, the EnGraft-trial enrolling 268 patients is running to evaluate the bioavailability, efficacy and safety of LCP-tacrolimus compared with ER-tacrolimus during a 3-y period. The results are awaited in the following years.[35]

In conclusion, a statistically significant and clinically relevant reduction in the prevalence of the composite primary endpoint was found in the LCP-tacrolimus group compared with the ER-tacrolimus group in the first year after LT with comparable efficacy. Furthermore, less LT recipients using LCP-tacrolimus develop CKD and new-onset hypertension compared with the ER-tacrolimus group in the first year after LT.

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REFERENCES

1. Todo S, Fung JJ, Starzl TE, et al. Liver, kidney, and thoracic organ transplantation under FK 506. *Ann Surg*. 1990;212:295–305. Discussion 306.
2. Rana A, Ackah RL, Webb GJ, et al. No gains in long-term survival after liver transplantation over the past three decades. *Ann Surg*. 2019;269:20–27.
3. Ruijter BN, Inderson A, van den Berg AP, et al. Randomized trial of ciclosporin with 2-h Monitoring vs. tacrolimus with trough monitoring in liver transplantation: DELTA study. *J Clin Transl Hepatol* 2023;11:839–849.
4. Maurer MM, Ibach M, Plewe J, et al. Reducing the pill burden: immunosuppressant adherence and safety after conversion from a twice-daily (IR-Tac) to a novel once-daily (LCP-Tac) tacrolimus formulation in 161 liver transplant patients. *Biomedicines*. 2022;10:272.
5. Verma M, Zaki R, Sadeh J, et al. Improved medication adherence with the use of extended-release tacrolimus in liver transplant recipients: a pilot randomized controlled trial. *J Transplant*. 2023;2023:7915781.
6. Neuberger JM, Bechstein WO, Kuypers DR, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and Clinical Checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. *Transplantation*. 2017;101(4S Suppl 2):S1–S56.
7. Rodríguez-Perálvarez M, Guerrero M, De Luca L, et al. Area under trough concentrations of tacrolimus as a predictor of progressive renal impairment after liver transplantation. *Transplantation*. 2019;103:2539–2548.
8. Rodríguez-Perálvarez M, Colmenero J, González A, et al; Chronic Immunosuppression, Cancer Spanish Consortium. Cumulative exposure to tacrolimus and incidence of cancer after liver transplantation. *Am J Transplant*. 2022;22:1671–1682.
9. Watt KD, Pedersen RA, Kremers WK, et al. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant*. 2010;10:1420–1427.
10. Laryea M, Watt KD, Molinari M, et al. Metabolic syndrome in liver transplant recipients: prevalence and association with major vascular events. *Liver Transpl*. 2007;13:1109–1114.
11. Allen AM, Kim WR, Therneau TM, et al. Chronic kidney disease and associated mortality after liver transplantation—a time-dependent analysis using measured glomerular filtration rate. *J Hepatol*. 2014;61:286–292.
12. Mulder MB, van Hoek B, van den Berg AP, et al. Three-year results of renal function in liver transplant recipients on low-dose sirolimus and tacrolimus: a multicenter, randomized, controlled trial. *Liver Transpl*. 2023;29:184–195.
13. Fussner LA, Heimbach JK, Fan C, et al. Cardiovascular disease after liver transplantation: when, what, and who is at risk. *Liver Transpl*. 2015;21:889–896.
14. Tremblay S, Nigro V, Weinberg J, et al. A steady-state head-to-head pharmacokinetic comparison of all FK-506 (tacrolimus) formulations (ASTCOFF): an open-label, prospective, randomized, two-arm, three-period crossover study. *Am J Transplant*. 2017;17:432–442.
15. Budde K, Bunnapradist S, Grinyo JM, et al; Envarsus Study Group. Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of phase III, double-blind, randomized trial. *Am J Transplant*. 2014;14:2796–2806.
16. Garnock-Jones KP. Tacrolimus prolonged release (Envarsus(R)): a review of its use in kidney and liver transplant recipients. *Drugs*. 2015;75:309–320.
17. Staatz CE, Tett SE. Clinical pharmacokinetics of once-daily tacrolimus in solid-organ transplant patients. *Clin Pharmacokinet*. 2015;54:993–1025.
18. Rayar M, Tron C, Jézéquel C, et al. High intrapatient variability of tacrolimus exposure in the early period after liver transplantation is associated with poorer outcomes. *Transplantation*. 2018;102:e108–e114.
19. Eidelman BH, Abu-Elmagd K, Wilson J, et al. Neurologic complications of FK 506. *Transplant Proc*. 1991;23:3175–3178.
20. Wilkinson A, Davidson J, Dotta F, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant*. 2005;19:291–298.
21. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553.
22. Eknoyan G, Lameire N, Eckardt K, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2013;3:5–14.
23. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR

estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis*. 2010;55:622–627.
24. van der Veer MAA, Nangrahary N, Hesselink DA, et al. High intrapatient variability in tacrolimus exposure is not associated with immune-mediated graft injury after liver transplantation. *Transplantation*. 2019;103:2329–2337.
25. Castor EDC. Castor Electronic Data Capture. 2019. Available at: https://www.castoredc.com.
26. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2019. Available at https://www.R-project.org/.
27. Rubin MF. Hypertension following kidney transplantation. *Adv Chronic Kidney Dis*. 2011;18:17–22.
28. Del Bello A, Gaible C, Longlune N, et al. Tacrolimus intrapatient variability after switching from immediate or prolonged-release to extended-release formulation, after an organ transplantation. *Front Pharmacol*. 2021;12:602764.
29. Shuker N, Shuker L, van Rosmalen J, et al. A high intrapatient variability in tacrolimus exposure is associated with poor long-term outcome of kidney transplantation. *Transpl Int*. 2016;29:1158–1167.
30. Sánchez Fructuoso A, Ruiz JC, Franco A, et al. Effectiveness and safety of the conversion to MeltDose(®) extended-release tacrolimus from other formulations of tacrolimus in stable kidney transplant patients: a retrospective study. *Clin Transplant*. 2020;34:e13767.
31. Baccarani U, Velkoski J, Pravisani R, et al. MeltDose technology vs once-daily prolonged release tacrolimus in de novo liver transplant recipients. *Transplant Proc*. 2019;51:2971–2973.
32. Alloway RR, Eckhoff DE, Washburn WK, et al. Conversion from twice daily tacrolimus capsules to once daily extended-release tacrolimus (LCP-Tacro): phase 2 trial of stable liver transplant recipients. *Liver Transpl*. 2014;20:564–575.
33. Kneidinger N, Valtin C, Hettich I, et al. Five-year outcome of an early everolimus-based quadruple immunosuppression in lung transplant recipients: follow-up of the 4EVERLUNG study. *Transplantation*. 2022;106:1867–1874.
34. Glanville AR, Aboyoun C, Klepetko W, et al; European and Australian Investigators in Lung Transplantation. Three-year results of an investigator-driven multicenter, international, randomized open-label de novo trial to prevent BOS after lung transplantation. *J Heart Lung Transplant*. 2015;34:16–25.
35. Wöhl DS, James B, Götz M, et al; EnGraft Trial Group. EnGraft: a multicentre, open-label, randomised, two-arm, superiority study protocol to assess bioavailability and practicability of Envarsus® versus Advagraf™ in liver transplant recipients. *Trials*. 2023;24:325.

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