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Efficacy and Safety of Delayed Prolonged-Release Tacrolimus Initiation in *De Novo* Hepatitis C Virus-Negative Orthotopic Liver Transplant Recipients: A Single-Center, Single-Arm, Prospective Study

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Delaying initiation of tacrolimus after liver transplantation (LT) is a potential renal-sparing strategy. We assessed safety and efficacy of delayed initiation of prolonged-release tacrolimus (PR-T) in *de novo* LT.

Material/Methods: This was a single-center, single-arm, prospective, 12-month observational study of hepatitis C virus-negative orthotopic LT patients. Immunosuppression included PR-T (initially 0.1 or 0.2 mg/kg/day) initiated on Day 3 post LT, basiliximab (20 mg) on post-transplantation Day 0 and Day 4, and intraoperative corticosteroids (500 mg). Patients received maintenance corticosteroids and mycophenolate mofetil (MMF) according to center protocol. MMF dose was adjusted according to thrombocyte count. The primary endpoint was the estimated glomerular filtration rate (eGFR) measured using the Modification of Diet in Renal Disease 4-variable formula at 12 months. Secondary endpoints included biopsy-confirmed acute rejection (BCAR) and dialysis requirement. Adverse events were recorded.

Results: Sixty-nine patients (mean age 55.0 years) were included. Most patients started MMF on Day 1 (60.9%) or Day 2 (10.1%), and PR-T on Day 3 (55.1%) or Day 4 (29.0%). Mean tacrolimus trough levels (ng/mL) were: Day 7, 9.5±6.3; Day 10, 9.4±5.4; Month 1, 8.0±3.1; Month 3, 7.8±3.7; Month 6, 8.0±4.1; and Month 12, 7.2±3.1. Mean 12-month eGFR was 77.2±24.5 mL/min/1.73 m^2; 72.5% of patients had eGFR >60 mL/min/1.73 m^2 at 12 months; 89.9% had no eGFR measurements <40 mL/min/1.73 m^2 during the study. Renal insufficiency (any eGFR <60 mL/min/1.73 m^2) was diagnosed in 27.5% of patients; one patient required dialysis. There were no BCAR episodes; the infection rate was 36.2%, and 3 patients died. Overall, 19 patients (27.5%) developed *de novo* diabetes mellitus, 18 patients (26.1%) had hypercholesterolemia, and 12 patients (17.4%) had hypertriglyceridemia.

Conclusions: Quadruple therapy with delayed administration of PR-T was well tolerated and efficacious, and was associated with acceptable renal function over 12 months.

MeSH Keywords: **Immunosuppression • Liver Transplantation • Prospective Studies • Renal Insufficiency**

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Background

Advances in immunosuppression regimens after solid-organ transplantation have significantly improved patient and graft survival [1]. However, approximately 25% of patients experience chronic renal failure 10 years after liver transplantation (LT) [2]. Among the many post-transplantation factors that influence kidney function, there remains concern that long-term use of calcineurin inhibitor (CNI)-based immunosuppression may be associated with renal function deterioration [3,4]. In particular, ciclosporin has been shown to reduce renal blood flow and microperfusion in kidney transplant recipients [5,6].

CNI avoidance or withdrawal after transplantation would prevent development of CNI-related kidney dysfunction. However, such strategies reduce long-term graft and patient survival [7,8], due to inadequate rejection prophylaxis provided by other immunosuppressive regimens. Therefore, immunosuppression regimens that minimize renal dysfunction have instead been proposed [4], including delaying the initiation of CNI, and dose reduction or minimization strategies [9].

The CNI tacrolimus has become the current mainstay of immunosuppression regimens in LT. It is available as immediate-release and prolonged-release formulations, both of which have demonstrated positive outcomes following LT [9–17]. Furthermore, the limited available data suggest that delaying the initiation of tacrolimus may sustain renal function without increasing the risk of transplant rejection. For example, a quadruple immunosuppression regimen with antibody induction, mycophenolate mofetil (MMF), delayed immediate-release tacrolimus, and corticosteroids with gradual tapering, resulted in a lower rejection rate versus standard tacrolimus-based regimens, and low toxicity in hepatitis C virus (HCV)-negative LT recipients [18,19]. Additionally, while the license recommends commencing treatment with prolonged-release tacrolimus approximately 12–18 hours after the completion of surgery for the prophylaxis of liver transplant rejection, delayed initiation has been trialed. In *de novo* LT recipients, delaying the initiation of prolonged-release tacrolimus to Day 5 post transplantation resulted in significantly better renal function at Week 24 compared with administration of prolonged-release tacrolimus immediately post transplantation [9].

As few studies have evaluated delayed initiation of prolonged-release tacrolimus in *de novo* LT patients, this single-center, single-arm study may inform clinical practice; it was conducted to evaluate the safety, efficacy, and 12-month evolution of kidney function, with delayed initiation of prolonged-release tacrolimus in *de novo* HCV-negative LT recipients.

Material and Methods

Study design and patients

This was an observational, single-center, single-arm, prospective study conducted at the Bellvitge University Hospital in Barcelona, Spain, between March 2011 and December 2014. The study was approved by the Institutional Review Board of Bellvitge University Hospital, and was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice. All patients provided informed written consent.

Both LT donors and recipients were screened for HCV before patient enrollment. The study included all consecutive HCV-negative patients aged >18 years who had received their first ABO-compatible LT. HCV-positive patients were excluded from the study because the standard immunosuppression regimen in these patients at our institution is a corticosteroid-free regimen. Multiple-organ transplantation patients, those with a prior transplantation, and those with current substance abuse were also excluded.

Immunosuppressive treatment

All study patients received induction therapy with 20 mg of intravenous basiliximab on Day 0 and Day 4, and a dose of corticosteroids intraoperatively (intravenous methylprednisolone 500 mg or equivalent) during graft reperfusion. Patients received maintenance corticosteroids and MMF according to center protocol. The standard tapering regimen of corticosteroids was as follows: 0.5 mg/kg/day for 5 days, 0.25 mg/kg/day until the end of Month 1, and 0.14 mg/kg/day during Months 2 and 3. Patients then discontinued corticosteroids. MMF was initiated according to thrombocyte count on Day 1: 1000 mg/12 hours if >100 000, 500 mg/12 hours if 50 000–100 000, or no MMF on Day 1 if <50 000. MMF was adjusted throughout the study according to thrombocyte count, trough levels of prolonged-release tacrolimus, and adverse events, including opportunistic infections. Delayed prolonged-release tacrolimus (Advagraf®, Astellas Pharma Europe BV, Netherlands) was initiated in accordance with center practice on the third day after LT at 0.2 mg/kg/day if serum creatinine levels on Day 3 were <130 µmol/L. If creatinine was 130–180 µmol/L, the initial prolonged-release tacrolimus dose was reduced to 0.1 mg/kg/day. Prolonged-release tacrolimus was further delayed if serum creatinine was >180 µmol/L and was initiated when serum creatinine was ≤180 µmol/L. Doses were adjusted in order to maintain target trough levels of tacrolimus and to avoid under- or over-immunosuppression throughout the study. Target tacrolimus trough levels in the first 6 months were 6–8 ng/mL if prolonged-release tacrolimus was combined with MMF, and 10–15 ng/mL if not combined. From Months 6 to 12, target

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levels were 4–6 ng/mL and 6–10 ng/mL with and without MMF, respectively.

Follow-up and study endpoints

Patients were followed up for 12 months after their respective LT. The baseline visit (Day 0) was the day of surgery. Perioperative data were collected during hospital admission at 3, 7, and 15 days after LT. Subsequent visits were scheduled at 1, 3, 6, and 12 months; results are also presented for Month 2, where available. Adverse events were recorded throughout the study and were considered serious if they resulted in death, were immediately life-threatening, resulted in persistent or significant disability/incapacity or substantial disruption of the ability to perform normal activities, resulted in congenital anomaly or birth defect, required inpatient hospitalization, or lead to prolonged hospitalization.

Data were prospectively collected and transferred to the anonymized study database. Pre-transplantation variables included demographic and laboratory data, and clinical history related to kidney and liver disease. Variables recorded during follow-up included the details of the immunosuppressive regimen and tacrolimus trough levels in serum, routine clinical and laboratory data, kidney function variables, concomitant treatments, biopsy-confirmed acute rejection (BCAR) episodes and details thereof, kidney insufficiency diagnosis (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at any point during the study), and adverse events.

The primary outcome was kidney function at 12 months, measured by eGFR, using the Modification of Diet in Renal Disease (MDRD) 4-variable formula. Secondary outcomes included eGFR (MDRD-4) at 12 months stratified by tacrolimus serum level in the first 10 days after transplantation (<5, 5–10, and >10 ng/mL), serum creatinine level, achievement of target levels of tacrolimus in serum, incidence of BCAR, need for dialysis during the study period, and adverse events. The safety analysis included parameters of special interest (diabetes, hypertension, and lipid metabolism). New-onset diabetes was defined by the following criteria: use of insulin for >30 consecutive days, plasma glucose ≥200 mg/dL at any time of day with symptoms of diabetes, fasting plasma glucose ≥126 mg/dL, and/or a fasting plasma glucose >200 mg/dL after a challenge with 75 g glucose. These criteria were confirmed on a different day, with the same or another criterion, unless an evident hyperglycemic decompensation became apparent.

Statistical analysis

As this study included all eligible patients in our center within the established inclusion period (the intention-to-treat population), sample size was not statistically determined. All efficacy variables were analyzed on an intent-to-treat basis, and all patients were included in the analysis of safety variables. A descriptive analysis was performed, and the results subsequently presented as mean and standard deviation (SD) for continuous variables, and frequency and percentages for categorical variables. For analysis of the primary efficacy endpoint, patients who discontinued treatment or were lost to follow-up were treated as missing observations. For other variables, the last valid value for patients lost to follow-up was carried forward to the next time point until the end of the study. In the case of death, missing data for these patients were excluded from analysis. All variables were analyzed using the intention-to-treat population.

Results

Overall, 69 patients were included (51 male; 18 female) with mean age 55.0±9.9 years. Mean donor age was 57.3±16.7 years. Demographic and clinical data of the recipients before transplantation and the details of donors are summarized in Table 1. Patients had a mean pre-transplant Model for End-Stage Liver Disease (MELD) score of 18.9±7.6, and 21.7% of patients had a clinical history of diabetes mellitus. The average duration of patient stay in an intensive care unit immediately post LT was 4.2±6.3 days, and the mean duration of hospital admission was 15.3±11.0 days. No deaths occurred during the immediate postoperative hospital stay.

Immunosuppression

The days of MMF and prolonged-release tacrolimus initiation are presented in Figure 1. In most patients, MMF was initiated between Day 1 (60.9%) and Day 2 (10.1%). By Day 10, 66 patients (95.7%) had initiated MMF, and the latest day of MMF initiation was Day 15. Three patients (4.3%) started prolonged-release tacrolimus on Day 2. In most patients, prolonged-release tacrolimus was initiated between Day 3 (55.1%) and Day 4 (29.0%). In the 7 patients (10.1%) who had serum creatinine >180 µmol/L, prolonged-release tacrolimus was initiated between Day 5 and Day 10. All patients had initiated prolonged-release tacrolimus by Day 10. Almost half of the cohort (n=33; 47.8%) followed standard 3-month treatment with maintenance corticosteroids. Patients with extended corticosteroid treatment (n=36) received maintenance corticosteroids for a mean duration of 7.1±3.5 months.

Tacrolimus mean doses and blood levels during follow-up, and the mean doses of MMF used during the study period are presented in Figure 2. Overall mean ±SD tacrolimus trough levels (ng/mL) were: Day 7, 9.5±6.3; Day 10, 9.4±5.4; Month 1, 8.0±3.1; Month 3, 7.8±3.7; Month 6, 8.0±4.1; and Month 12, 7.2±3.1. Eighteen patients (26.1%) achieved target levels of tacrolimus

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Table 1. Clinical and demographic characteristics of recipients and donors.

Characteristics	
Recipients	**N=69**
Mean ±SD age, years	55.0±9.9
Gender, male	51 (73.9)
Mean ±SD pre-transplant MELD score	18.9±7.6
Mean ±SD pre-transplant MELD-Na score	3.9±8.7
Pre-transplantation kidney disease	
Hepatorenal syndrome I	5 (7.2)
Hepatorenal syndrome II	5 (7.2)
Refractory ascites	18 (26.1)
History of acute kidney failure	29 (42.0)
Chronic kidney disease	6 (8.7)
Clinical history	
Arterial hypertension	17 (24.6)
Diabetes mellitus	15 (21.7)
Donors	**N=69**
Mean ±SD age, years	57.3±16.7
Gender, male	35 (50.7)
Mean ±SD weight, kg	74.9±13.8

No patients with previous surgery due to portal hypertension. All data are n (%) unless otherwise specified. MELD – Model for End-Stage Liver Disease; MELD-Na – Model for End-Stage Liver Disease-sodium; SD – standard deviation.

5 days after initiation, 27.5% were within target trough levels at Day 10, and 49.3% at Month 1. Table 2 summarizes the proportion of patients within the target range throughout the study: 26.1–40.6% of patients had tacrolimus trough levels above the target range at some point during the study follow-up period. All patients had received MMF by Day 15. The mean ±SD dose of MMF was 1.0±0.5 g/12 hours on the day of transplantation, increasing to 1.3±0.4 g/12 hours at 12 months.

Kidney function

Mean ±SD eGFR (mL/min/1.73 m^2) was 102.8±43.1 before transplantation, decreasing to 86.8±42.3 on Day 1 post transplantation, but was similar to pre-transplantation levels by Day 3 (106.3±54.7) (Figure 3). At 1-month post transplantation, the mean eGFR had fallen to 84.3±31.7, and had decreased further at Month 12 (77.2±24.5) (Figure 3). At 12 months, 72.5%, 17.4%, and 5.8% of patients had eGFR >60, 40–60, and <40 mL/min/1.73 m^2, respectively. For 62 patients (89.9%), no measurements of eGFR were below 40 mL/min/1.73 m^2 at any time during the study.

There was a trend towards better renal function at Month 12, with higher tacrolimus serum levels at Day 10 (mean ±SD eGFR 71.3±27.5, 76.6±20.2, and 86.2±25.5 mL/min/1.73 m^2 in patients with tacrolimus serum levels of <5, 5–10, and >10 ng/mL, respectively). When stratified by tacrolimus serum levels of <10 and ≥10 ng/mL at Month 1, mean ±SD eGFR at 12 months was 77.4±24.7 and 73.7±23.2 mL/min/1.73 m^2, respectively.

Overall, mean ±SD serum creatinine concentration increased from 89.9±43.4 µmol/L pre-transplantation to 114.0±74.9 µmol/L on Day 1 post transplantation, after which there was a decrease to 85.8±38.8 µmol/L by Day 7. Between Months

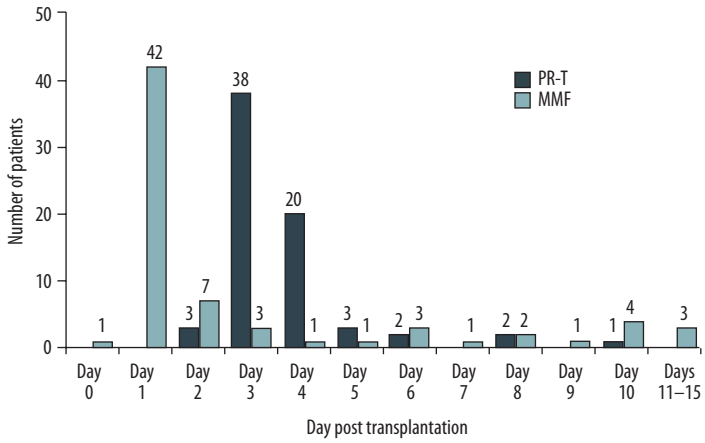

Figure 1. Days of initiation of PR-T and MMF. MMF – mycophenolate mofetil; PR-T – prolonged-release tacrolimus.

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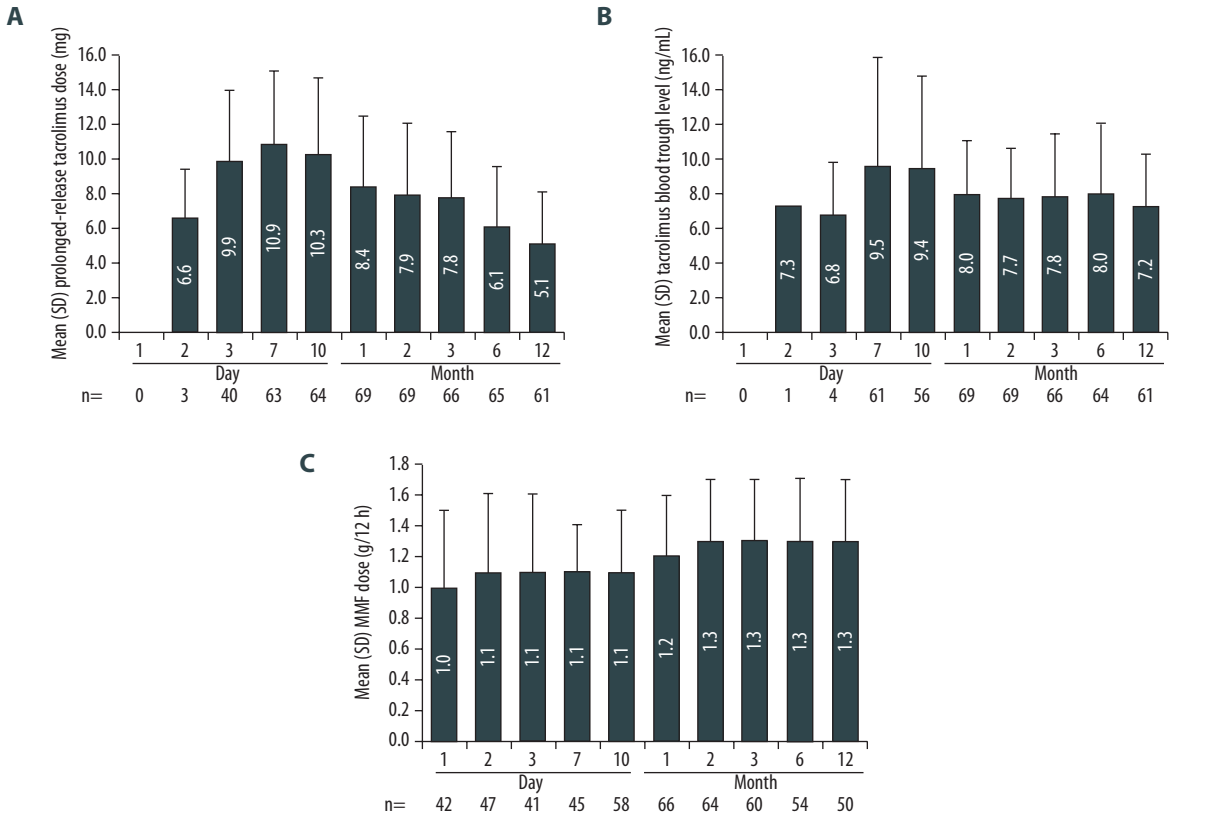

Figure 2. Mean dose and trough levels. (**A**) Mean doses of prolonged-release tacrolimus. (**B**) Mean trough tacrolimus blood levels. The earliest day of tacrolimus initiation was Day 2, and most patients initiated tacrolimus between Day 3 (n=38; 55.1%) and Day 4 (n=20; 29.0%). (**C**) Mean doses of MMF. The n numbers under each graph represent the number of patients with available data. LT – liver transplantation; MMF – mycophenolate mofetil; SD – standard deviation.

Table 2. Proportion of patients in target tacrolimus trough range during follow-up visits.

n=69	Day 7	Day 10	Month 1	Month 2	Month 3	Month 6	Month 12
Below target	22 (31.9)	10 (14.5)	7 (10.1)	15 (21.7)	11 (15.9)	19 (27.5)	20 (29.0)
Within target range	18 (26.1)	19 (27.5)	34 (49.3)	33 (47.8)	33 (47.8)	19 (27.5)	23 (33.3)
Above target	21 (30.4)	27 (39.1)	28 (40.6)	21 (30.4)	22 (31.9)	26 (37.7)	18 (26.1)
No levels available	8 (11.6)	13 (18.8)	0 (0.0)	0 (0.0)	3 (4.35)*	5 (7.25)*	8 (11.6)*

Target levels: first 6 months: 6–8 ng/mL if combined with MMF, and 10–15 ng/mL if not combined with MMF. From Months 6 to 12: 4–6 ng/mL when combined with MMF, and 6–10 ng/mL if not combined with MMF. All data are n (%). * Includes patients who died during follow-up. MMF – mycophenolate mofetil.

1 and 12, overall mean creatinine level ranged between 95.0 µmol/L and 105.5 µmol/L (Figure 3).

Although 27.5% of patients overall were diagnosed with renal insufficiency, only one patient required dialysis, and this was during the first postoperative week.

Biopsy-confirmed rejection, adverse events, and discontinuation

There were no reports of BCAR. However, data on suspected acute rejection episodes (those without biopsy) were not recorded. A total of 25 patients (36.2%) had infection at some point during follow-up, and most patients with infection experienced only one event in 12 months (23.2% of patients

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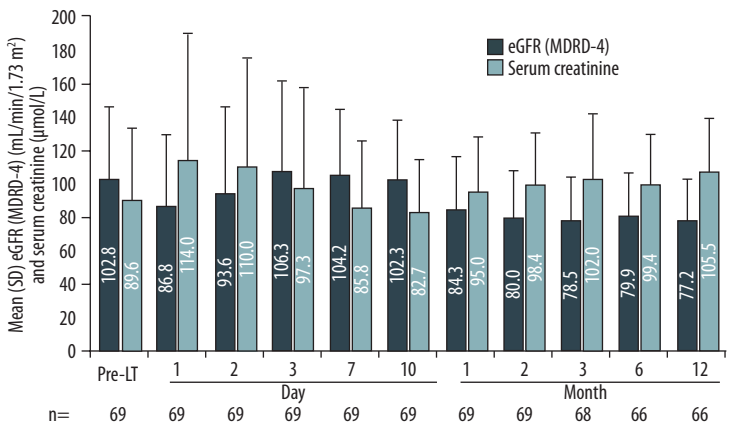

Figure 3. Evolution of kidney function by eGFR (MDRD-4) and serum creatinine level. Mean ±SD eGFR and serum creatinine during follow-up. Number of patients=69 except for Month 3 (n=68), Month 6, and Month 12 (n=66). The n numbers under the graph represent the number of patients with available data. eGFR – estimated glomerular filtration rate; LT – liver transplantation; MDRD – Modified Diet in Renal Disease; SD – standard deviation.

Table 3. Clinical data and blood parameters before transplantation and during the 12 months of follow-up.

	Pre-LT	Month 1	Month 3	Month 6	Month 12**
Weight, kg	79.9±16.3	72.4±13.2	72.5±12.2*	73.6±12.5**	75.0±12.7
Mean BP, mmHg	86.0±13.2	93.4±13.5	94.8±10.9*	93.9±11.8**	92.5±12.2
Hemoglobin, mmol/L	10.8±2.5	11.0±1.7	11.6±1.8*	11.8±1.7**	12.2±1.7
WBC, $\times 10^9$/L	4.6±2.6	6.8±2.8	5.1±2.3*	4.9±2.2**	5.2±2.0
Platelet count, $\times 10^9$/L	116.8±88.0	201.8±98.8	172.6±72.0*	173.5±82.1**	173.7±74.9
Fasting glucose, mmol/L	5.8±1.3	6.1±1.8	6.2±1.9*	6.1±1.6**	6.4±2.0
Urea, mmol/L	6.8±3.8	8.8±3.9	8.7±2.6*	8.5±2.9**	8.3±2.7
Total cholesterol, mmol/L	3.9±1.5	5.1±1.5	4.8±1.3***	4.3±0.9**	4.4±1.1
Triglycerides, mmol/L	0.9±0.4*	1.6±0.7*	1.4±0.6***	1.4±0.7**	1.4±0.6
HbA_{1c}, %	5.1±1.1	5.4±1.0***	5.8±1.2#	5.7±1.1##	5.8±1.2

All data are mean ±SD. N=69, unless otherwise indicated. * n=68; ** n=66; *** n=67; # n=64; ## n=65. BP – blood pressure; HbA_{1c} – glycated hemoglobin; LT – liver transplantation; SD – standard deviation; WBC – white blood cell count.

overall). In the total study population, 27.5% of patients had bacterial infection (25 episodes in 19 patients). There were 14 episodes of viral infection in 12 patients (17.4%), of which 6 were identified as cytomegalovirus (CMV) infection, 6 herpes virus, and 2 were unknown.

Table 3 summarizes laboratory results and clinical data from pre-transplantation to 12 months post transplantation for all patients. Numeric increases from pre-transplantation to Month 1 were found in mean cholesterol, triglycerides, and glycated hemoglobin (HbA_{1c}) levels, but these values remained stable from Months 3 to 12.

Nineteen patients (27.5%) developed post-transplantation *de novo* diabetes mellitus. Eighteen patients (26.1%) had hypercholesterolemia, and 12 (17.4%) had hypertriglyceridemia post transplantation. Other adverse events of special interest were *de novo* thrombocytopenia in 23 patients (33.3%) and low white blood cell count in 12 patients (17.4%). Overall, 139 serious adverse events affecting 49 patients were reported; those occurring in more than 4% of patients are summarized in Table 4.

Of the 20 patients who discontinued treatment with prolonged-release tacrolimus, 13 discontinued due to tacrolimus trough levels above target range, 3 due to renal insufficiency, 2 due to neurotoxicity and 2 due to unknown reasons.

Prolonged-release tacrolimus was reintroduced in 13 patients. Tacrolimus dose levels were adjusted down for those patients who had initially been discontinued due to higher-than-target tacrolimus trough levels. In cases of worsening of renal function, MMF dose was increased. Seven patients who required complete withdrawal of prolonged-release tacrolimus were converted to mammalian target of rapamycin inhibitors; prolonged-release tacrolimus was discontinued at least 2 months after LT.

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Table 4. Serious adverse events occurring in >4% of patients.

Serious adverse event	Number of patients (%) N=69	
Any serious adverse events	49	(71.0)
De novo hypertension	17	(24.6)
De novo diabetes mellitus	17	(24.6)
Cholangitis	10	(14.5)
Bacteremia	7	(10.1)
Arterial thrombosis	5	(7.2)
Bile duct stenosis	5	(7.2)
Renal insufficiency	5	(7.2)
Herpetic infection	4	(5.8)
Respiratory insufficiency	4	(5.8)
CMV infection	4	(5.8)
Sepsis	3	(4.3)
Respiratory infection	3	(4.3)

CMV – cytomegalovirus.

Three patients died during the 12-month follow-up, 2 of whom died within 3 months of their LT due to infection (infectious endocarditis and sepsis, respectively), and one after 6 months (ischemic cholangitis). No death was considered related to treatment with prolonged-release tacrolimus.

Discussion

In our cohort, delayed initiation of prolonged-release tacrolimus in the context of a quadruple immunosuppressive regimen with basiliximab induction showed acceptable efficacy and safety results during the immediate postoperative period and during the first year after LT. There were no cases of BCAR, and renal function was maintained over 12 months of follow-up, with only one patient requiring dialysis.

Kidney function was preserved during the postoperative period with our approach; over 70% of patients had an eGFR >60 mL/min/1.73 m^2 after 12 months and, in almost 90% of the patients, eGFR did not fall below 40 mL/min/1.73 m^2 during the 12-month study period. Our results are consistent with findings from other studies using a similar regimen with immediate-release tacrolimus [18,19]. More recently, the multicenter, randomized, Phase III DIAMOND study was published, which assessed whether immunosuppressive regimens with delayed initiation of prolonged-release tacrolimus until Day 5, or a reduced initial dose of prolonged-release tacrolimus, improved renal function versus prolonged-release tacrolimus initiated at a dose of 0.2 mg/kg/day immediately post LT [9]. The DIAMOND study demonstrated that delaying the initiation of prolonged-release tacrolimus to Day 5 post transplantation, in combination with MMF, corticosteroids and basiliximab induction, maintained eGFR over 24 weeks (73.3 mL/min/1.73 m^2) [9]. Our results suggest that delayed initiation of prolonged-release tacrolimus can maintain renal function over 12 months post transplantation. This is an important finding, as it has been demonstrated that renal function during the first year post transplantation is predictive of long-term renal function and patient survival [20].

Although renal insufficiency (eGFR <60 mL/min/1.73 m^2) was diagnosed in 27.5% of patients at some point during the study, only one patient required dialysis after transplantation – and this was during the first postoperative week. This is notable given that many patients had pre-transplantation kidney diseases and this group of patients are particularly susceptible to deterioration of renal function. As mean eGFR at Month 12 tended to be better with higher tacrolimus serum levels at Day 10, and was not apparently associated with Month 1 tacrolimus levels, the use of tacrolimus is unlikely to be responsible for the observed rate of kidney insufficiency in this study. Indeed, Yoshida et al. showed that early post-transplantation differences in tacrolimus trough levels with a standard tacrolimus regimen versus delayed introduction of tacrolimus, resulted in similar eGFR and creatinine clearance at Month 12 [18]. Importantly, there are many other risk factors for kidney insufficiency in orthotopic LT patients. For example, several intraoperative factors have been reported to significantly predict postoperative kidney function, including intraoperative hypotension (odds ratio [OR] 4.7; *P*=0.016), and the need for noradrenaline (OR 0.085; *P*=0.010) [21]. As our study did not specifically include assessment of risk factors for renal insufficiency, this is an area for future research.

As well as experiencing stable kidney function, no patients experienced BCAR in our study, which is consistent with the efficacy of prolonged-release tacrolimus previously reported [9,11]. Three deaths were recorded within the 12-month follow-up period, and infection was the primary cause of death (2 of the 3 deaths reported in our study were related to infectious endocarditis and sepsis), which is consistent with previous studies in LT patients receiving prolonged-release tacrolimus [9–11].

Interestingly, despite the low target levels of tacrolimus used in this study, altered lipid metabolism was detected in some patients (18 patients had hypercholesterolemia, and 12 experienced hypertriglyceridemia), and 19 patients developed *de novo* diabetes mellitus. Although not assessed in this study, it is possible that *de novo* diabetes mellitus developed primarily

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in the patients with tacrolimus levels above the target range (26.1–40.6% of patients across the study). Further analysis and a larger patient population would be required to confirm the hypothesis.

The proportion of patients achieving target trough tacrolimus levels throughout this study was relatively low (26.1–49.3% of patients) compared with the DIAMOND study [9]. However, these results should be interpreted in the proper context. The target ranges in our study were considerably narrower than those in other reports, particularly in patients receiving concomitant MMF (all patients for at least part of the study). For example, the difference between the maximum and minimum of the target tacrolimus range was 2–5 ng/mL (depending on MMF use), compared with 7–10 ng/mL in the DIAMOND study, and 5 ng/mL in the single-center study by Ortiz et al. [9,17]. Based on the target tacrolimus range recommended in the DIAMOND study (5–15 ng/mL during the first 6 weeks post transplantation, and 5–12 ng/mL up to Week 24 [9]), all mean tacrolimus trough levels were within target during our study. Notably, despite the narrower target tacrolimus trough range in our study compared with the DIAMOND study, eGFR was comparable between the studies at Month 6, which suggests that tacrolimus trough level may not be a limiting factor for renal function *per se*.

Our study has several limitations, including having a small, single-center cohort. The study had a single arm and, as such, it was not possible to compare delayed initiation of tacrolimus with initiation of tacrolimus at transplantation. Furthermore, the study was not powered to assess risk factors for renal insufficiency at Month 12. The LT patients included in this study had a high eGFR, a low MELD score, and patients with HCV were excluded; therefore, it may be difficult to extrapolate these results to other populations. While this observational study – our first experience of working with delayed initiation of prolonged-release tacrolimus – lacked a comparator group, the monitoring was carried out prospectively, and thus provides useful preliminary data regarding the safety of delayed initiation of tacrolimus in *de novo* LT recipients.

Conclusions

Our results suggest that prolonged-release tacrolimus is an efficacious and tolerable alternative for HCV-negative *de novo* LT recipients, when used as part of quadruple induction therapy, and with tailored dosing of each drug. This strategy resulted in a stable eGFR between Months 1 and 12 post transplantation, with acceptable patient and graft outcomes.

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Conflicts of interest

LL, JF, and ER report grants from Astellas, during the conduct of the study and personal fees from Astellas outside the submitted work. CB reports grants from Astellas, during the conduct of the study and personal fees from Janssen outside the submitted work. EGV and JB report grants from Astellas, during the conduct of the study. XX reports personal fees from Gilead, outside the submitted work. AGC has no conflicts to disclose.

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