Liver Transplantation

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Sequential Cohort Analysis After Liver Transplantation Shows de Novo Extended Release Tacrolimus Is Safe, Efficacious, and Minimizes Renal Dysfunction

Tiong Yeng Lim, MD,1 Mark J. McPhail, MD, PhD,1 Amar Shah, MD,1 Sara Mahgoub, MD,1 Jeremy Nayagam, MD,1 Matthew Cramp, MD,2 William Bernal, MD,1 Krish Menon, MD,1 Wayel Jassem, MD, PhD,1 Deepak Joshi, MD, PhD,1 Michael A. Heneghan, MD,1 Kosh Agarwal, MD,1 Nigel D. Heaton, MD,1 Abid Suddle, MD,1 John G. O’Grady, MD,1 and Varuna R. Aluvihare, MD, PhD1

Background. The use of once-daily extended-release tacrolimus (ERT) is associated with improved long-term graft and patient survival when compared with twice-daily tacrolimus (BDT), but the underlying reasons for differential survival are unclear. The aim of the study was to compare clinical outcomes known to impact on posttransplant survival for de novo BDT and ERT in liver transplantation (LT) recipients. Methods. We conducted a single-center, prospective sequential cohort analysis of adult patients undergoing LT during a change in protocol from de novo BDT to ERT, with a 6-month post-LT follow-up. Results. A total of 160 transplanted patients were evaluated; 82 were in the BDT group and 78 were in the ERT group. The cohorts were matched for standard variables and a similar proportion in each group received induction interleukin-2 receptor antibody (36% and 31%). There were no significant differences in the measured outcomes of patient and graft survival, biopsy-proven acute rejection episodes, post LT diabetes, and toxicity. A significantly lower number of patients developed chronic kidney disease Stage3–4 in the ERT cohort compared with BDT cohort. In patients with pre-LT renal dysfunction who received antibody induction, estimated glomerular filtration rate decreased significantly in the BDT but not the ERT group. Conclusions. We show that once-daily ERT is as safe and efficacious as BDT in de novo LT but optimally conserves renal function post-LT.

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of care BDT to ERT are lacking.7,8 Despite these studies, the potential factors determining improved long-term survival, when comparing ERT with BDT remain unclear.

The aim of our study was to compare the safety, efficacy, and clinically relevant variables known to impact on patient survival for de novo ERT and BDT after LT. To our knowledge, this is the first study to delineate factors that may underlie apparent survival advantage, when comparing the performance of de novo ERT and BDT.

**MATERIALS AND METHODS**

**Study Design**

This is a single-center, prospective open-label study of adult and adolescent patients undergoing LT. Sequential patients transplanted from November 2015 to June 2016 were initiated on BDT and sequential patients transplanted from July to April 2017 were initiated on ERT. We aim to compare the early clinical outcomes between the 2 groups including acute cellular rejection rate, renal impairment, and metabolic complications. Clinical data including sex, ethnicity, disease indication for transplantation, age at transplantation, and blood and biopsy results were collected from clinical notes, electronic patient records, and prescribing systems.

The primary outcome of the study was the development of de novo chronic kidney disease (CKD) >2 by 6 months post LT. Therefore, this parameter underwent formal power calculation. Assuming a rate of 30% in the BDT group and 10% in the ERT group with a 90% power and alpha of 0.05 would require 80 patients per group and a total of 160 patients.

Exclusion criteria were multiorgan (n = 5), retransplantations (n = 19), patients on anti-retroviral treatment (n = 5). This study followed the principles of the Declaration of Helsinki and received ethics committee approval. Patients transplanted from one referral center were excluded due to local prescribing practice which prevented the use of ERT.

**Laboratory Results and Clinical Outcomes**

Results were collected from electronic patient records. Whole blood predose (trough) tacrolimus concentrations (at ~12 hours for BDT and ~24 hours for ERT) were assayed by liquid chromatography-tandem mass spectrometry with a detection limit of 0.5 ng/mL. Dose-equalized tacrolimus concentrations (DEC) were calculated by the division of the predose concentration by the daily tacrolimus dose. An unadjusted Model for End-Stage Liver Disease score was calculated at the time of transplantation.10

Clinical outcome variables recorded include patient survival, graft survival, biopsy-proven acute rejection (BPAR) rate, renal function, and immunosuppression-related metabolic morbidity. Graft loss was defined as retransplantation or death with a nonfunctioning graft.

Serum creatinine concentrations and estimated glomerular filtration rate (eGFR) were used as indicators of renal function. Pretransplant renal dysfunction was defined as an eGFR of <60 mL/min (based on the Modification of Diet in Renal Disease-4 formula, MDRD). CKD was defined and classified according to Kidney Disease: Improving Global Outcomes guidelines.11 BPAR episodes requiring supplemental immunosuppressive therapy (with corticosteroids or antibody treatment) were documented from the patients’ clinical and laboratory records.

De novo diabetes was diagnosed when fasting plasma glucose was repeatedly at >126 mg/dL, glycated hemoglobin ≥6.5% or when oral hypoglycemic or insulin treatment was prescribed, based on the widely used WHO criteria for diagnosing diabetes mellitus. Additionally, dyslipidemia and hypertension were diagnosed when lipid-lowering and antihypertensive medications were initiated. Anti-hypertensive treatment was initiated if the patient showed sustained elevation of blood pressure ≥140/90 mm Hg. Patients were classified for hyperlipidemia according to the recommendations of the European Consensus, 1987. Serum cholesterol and TG levels were considered elevated if they were 250 and 150 mg/dL, respectively, in at least 2 consecutive samples.

**Immunosuppression Protocol**

An initial dose of 5 mg ERT was administered at 12 to 24 hours post-LT and once daily thereafter. For patients who were unable to swallow tacrolimus early post-LT, the capsule was opened and dissolved in water and administered via the NG tube, as is standard practice with the BDT formulation. For patients with eGFR < 50 mL/min at time of listing or on day of LT, ERT was initiated at 2 mg once daily based on institutional protocol. In this context, supplementary immunosuppression with the interleukin-2 receptor antibody (IL2RA) basiliximab (Novartis), was given at 20 mg/day on day 1 and 4 post-LT. For the BDT group, patients were administered 2 mg of BDT at 12 to 24 hours post-LT and twice daily thereafter. Patients who received IL2RA were initiated at a lower dose of 1 mg twice daily.

Mycophenolate mofetil (MMF) was added to the immunosuppressive regimen following acute rejection (AR) and/or in patients with renal impairment as a renal-sparing regimen at doses ranging from 250 mg to 1 g b.d. by weight.

No dose modifications to the ERT were made until day 4 when a steady state will have been achieved. Based on institutional protocol, the maximum doses were 12 mg/day for ERT and 6 mg b.d. for BDT, respectively. A target trough (24-hour post dose) level of 5–10 µg/L (2–5 μg/L for patients who received basiliximab). In the case of an AR episode, first-line therapy was methylprednisolone 1000 mg/day for 3 days. Anti-thymocyte globulin (ATG) was used to treat corticosteroid-resistant AR at a dose of 1.5 mg/kg intravenously for 7 to 10 days.

**Statistical Analysis**

Statistical analysis was performed with GraphPad Prism 6.0 for Mac (GraphPad Software, La Jolla, CA) and SPSS 17 (IBM, Armonk, NY). Continuous data were presented as median, with interquartile range unless otherwise stated, and were assessed for normality using the D’Agostino Pearson test. Comparisons between the 2 groups were made using the Mann-Whitney U test and the Wilcoxon rank sum test was for unpaired and paired data respectively. Multiple comparisons were made using the Kruskal-Wallis test, with post hoc comparisons of individual groups performed with a repeated-measures analysis of variance for sequential data with log transformation if necessary. Categorical data were compared using Fisher exact test. Two-tailed tests were applied, and significance was assumed at $P < 0.05$. 
RESULTS

Patient Characteristics

A total of 160 patients were included in the study; 82 in the BDT and 78 in the ERT. Seven patients underwent out of protocol switch from ERT to BDT during their initial admission (median = Day 10 post-LT, range 1–13). Two patients were switched following BPAR at days 9 and 11 post-LT, respectively, while 5 patients were switched due to early target tacrolimus levels being below protocol range or lack of availability of ERT in referral area (median 2.1 μg/L, range 0.6–6.5). These patients were not included in the subsequent analysis between the BDT and ERT groups.

The majority of patients in both groups were males, and the most common etiology of liver disease is alcohol-related cirrhosis. Twenty-six percent of the BDT was transplanted for an indication of hepatocellular carcinoma, compared with 23% in the ERT. The main patient demographics and disease characteristics are summarized in Table 1. There was no statistically significant difference between the characteristics of the 2 groups, except the donor age (55 y in BDT versus 60 y in ERT, \(P = 0.032\)). There was no significant difference in allocation of donor-after-brain-death grafts between the 2 cohorts. The median length of inpatient stay was 15 days in both cohorts. The duration of stay in intensive care was 3 days in the BDT cohort and 2 days in the ERT cohort.

Survival

There were 6 deaths during the follow-up period; 3 in the BDT and 3 in the ERT cohorts. In the BDT cohort, 1 patient died at day 35 post-LT from multi-organ failure due to recurrent sepsis, the second patient who had a simultaneous coronary artery bypass graft and LT died at day 38 from multi-organ failure, and the third patient died from a pulmonary embolus and gastrointestinal bleed at day 174 post-LT. The patients in the ERT died at days 4, 33, and 95 post-LT from a pulmonary embolus, complications of Guillain-Barre Syndrome, and subarachnoid hemorrhage, respectively.

Immunosuppression

A similar proportion of patients in each group received IL2RA, according to the protocol above (36% in BDT versus 31% in ERT). The median total daily dose of tacrolimus at discharge was 8 mg in the BDT group and 9 mg in the ERT group. The concentrations of tacrolimus normalized for the dose (DEC) were lower in the ERT compared with the BDT, but this equalized from 1-month post-LT (Figure 1). In addition, DEC was more stable in the ERT throughout the first 15 days post-LT compared with the BDT where DEC started statistically significantly higher (median DEC 1.36 versus 0.63 μg/L/mg/day, \(P < 0.001\)). This was more pronounced in the cohorts that received IL2RA, where the total daily tacrolimus dose was lower. The DEC in both groups increased from 1-month post-LT despite reductions in total tacrolimus doses to 1.44 and 1.40 μg/L/mg/day, respectively, at 6 months post-LT. The number of patients breaching protocol based post-LT tacrolimus levels by end of week 6 (tacrolimus level of >10 μg/L), was not significantly different between the BDT and ERT cohorts (Table S1, SDC, http://links.lww.com/TXD/A240). The trough tacrolimus levels for each cohort are shown in Figure 2.

Acute Rejection

The incidence of BPAR episodes was not significantly different in both groups (20% in BDT versus 29% in ERT, \(P > 0.20\)).

| Characteristic | BDT | ERT | \(P\) |
|---------------|-----|-----|------|
| Total # patients (male, %) | 82 (60%) | 78 (60%) | 0.873 |
| Age, y, median (range) | 56 (16–72) | 54 (21–71) | 0.544 |
| Etiology, n (%): |  |  |  |
| • Acute liver failure | 5 (6) | 2 (3) | 0.444 |
| • Alcoholic liver disease | 19 (23) | 24 (31) | 0.291 |
| • Autoimmune hepatitis | 3 (4) | 8 (10) | 0.124 |
| • Cryptogenic | 5 (6) | 1 (1) | 0.211 |
| • Nonalcoholic fatty liver disease | 11 (13) | 10 (13) | 1.000 |
| • Primary biliary cholangitis | 5 (6) | 4 (5) | 1.000 |
| • Primary sclerosing cholangitis | 4 (5) | 7 (9) | 0.361 |
| • Hepatitis B \(\pm\) D | 3 (4) | 4 (5) | 0.715 |
| • Hepatitis C | 15 (18) | 7 (9) | 0.109 |
| • Other | 12 (15) | 11 (14) | 1.000 |
| Hepatocellular carcinoma | 21 (26) | 18 (23) | 0.717 |
| LOS, days | 15 (8–75) | 15 (9–69) | 0.664 |
| Intensive care unit LOS, days | 3 (1–29) | 2 (1–41) | 0.547 |
| Donor age, years \(\alpha\) | 55 (17–79) | 60 (11–83) | 0.032 |
| Graft, DBD (%) | 52 (63) | 47 (60) | 0.382 |
| Cold ischemic time, min\(^{1}\) | 500 (99–1140) | 510 (240–900) | 0.652 |
| MELD | 15 (6–41) | 15 (7–40) | 0.856 |
| UKELD | 51 (39–67) | 52 (42–66) | 0.548 |
| Baseline eGFR (mL/min) | 93 (73–104) | 101 (77–112) | 0.677 |
| Inducted with interleukin-2 receptor antibody | 30 (36) | 24 (31) | 0.505 |

\(\alpha\) Cold ischemic time, mins.
BDT, twice-daily tacrolimus group; DBD, donation after brain death; eGFR, estimated glomerular filtration rate; ERT, extended-release tacrolimus group; LOS, coefficient of variation; MELD, model for end-stage liver disease; UKELD, United Kingdom model for end-stage liver disease.
with similar median time of 10 days post-LT (Table 2). The number of BPAR occurring within 30 days of LT was also similar (15% versus 24%, $P = 0.16$). Most rejections were histologically moderate; with 11 patients (13%) in the BDT receiving corticosteroid boluses compared with 17 patients (22%) in the ERT ($P = 0.21$; Figure 3). Two patients in each group required a second cycle of corticosteroids. Four patients in the BDT received ATG for steroid-refractory ACR while none in the ERT received ATG. There was no significant difference in the frequency of rejection episodes between males and females in either group ($P = 0.60$). One patient in the BDT was relisted for transplantation at 6 months post-LT for severe rejection that failed to respond to both pulsed corticosteroids and ATG.

**Renal Function**

For renal function outcomes, patients who received induction with IL2RA as part of a renal-sparing immunosuppressive regimen were analyzed separately to those on standard immunosuppressive regimen. The renal function, as measured by eGFR level, in all groups was not significantly different at all time-points measured. However, in the non-induced cohort, eGFR level decreased significantly at 6 months compared with pretransplantation levels in both groups; from of 101.5 to 79.0 mL/min in BDT cohort ($P < 0.001$), compared with 111.5 to 77.6 mL/min in the ERT cohort ($P < 0.001$). In the cohorts that received IL2RA, mean eGFR reduced significantly from a baseline of 78.1 to 63.0 mL/min ($P = 0.004$) in the BDT cohort, compared with 73.4 to 65.6 mL/min ($P = 0.215$) in the ERT cohort (Figure 4).

The number of patients with CKD stage ≥2 at 6 months increased from baseline in both groups. However, the proportion of patients with new-onset CKD stage 3–4 at 6-months post-LT was significantly higher in the BDT compared with the ERT (26% versus 7%, $P = 0.006$, Table 3).

**Adverse Events**

The incidence of de novo metabolic complications during follow-up is shown in Table 3. The most frequent of these is hypertension, which occurred in 30% of the BDT and

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**FIGURE 1.** Median (IQR) DECs in patients receiving BDT and ERT. A. Comparison of DEC in cohort not treated with interleukin-2 receptor antagonist. B. Comparison of DEC in cohort that received interleukin-2 receptor antagonist. BDT, twice-daily tacrolimus; DEC, dose-equalized tacrolimus concentration; ERT, extended-release tacrolimus; IQR, interquartile range.
21% novo type 2 DM in 17% and 9% in each group, respectively. Thirdly, 5% of the BDT and 6% of the ERT were started on a lipid-lowering agent for dyslipidemia during the same period. There was no significant difference between the incidences of each complication between the 2 groups.
Two patients in the BDT cohort developed presumed neurotoxicity; 1 patient was switched to cyclosporine on Day 12 post-LT for persistent confusion while another patient was switched to ERT on Day 8 for severe headaches and loose stools. One additional patient in the BDT was switched to cyclosporine on Day 6 post-LT for myopathy. No patients in the ERT discontinued tacrolimus due to toxicity.

Variability of Exposure
We assessed the intra-patient variability (IPV) of exposure to tacrolimus in each patient by calculating the coefficient of variation (CoV), which is the SD of all DECs after the first week of transplant, divided by mean DEC (CoV = SD/mean). As not all patients received a constant drug dose during the follow-up period, the CoV was calculated using the DEC. There was no significant difference in median SD of DEC between ERT and BDT (Figure 5).

**DISCUSSION**

Since it was licensed for use in 2007, ERT has been shown to improve long-term graft and patient survival in LT recipients, as well as having good efficacy in preventing rejection. While specific features of ERT (lower maximum serum concentration, or Cmax, and IPV) and improved adherence have been proposed as possible underlying mechanisms for this apparent superiority, available data do not permit an adequate explanation for differences in outcome. Nonadherence appears to become more significant in the late post-LT phase, indicating that this is an unlikely explanation for the early graft and patient survival evidenced in this study. In addition, since the cohort of patients exposed to ERT in the above study were defined by exposure within 1 month of transplant, it remains unclear what proportion were exposed de novo and what proportion underwent early switch from BDT. Our study did not show a difference in graft or patient survival to 6 months post-LT, which is consistent with published data indicating benefit may accrue later in the post-LT course, but may also reflect the fact that the study was not adequately powered for this end point.

Renal failure post LT is a major determinant of long-term outcomes. Early post-LT renal impairment at 6 months is predictive of chronic renal failure. For patients completing the study, renal function was comparable in all cohorts at 6 months although they were significantly worsened from baseline in both groups that did not receive induction therapy. However, the number of patients who developed new-onset CKD Stage 3–4 was significantly higher in the BDT compared with the ERT, suggesting de novo use of ERT may improve renal outcomes in patients with un-impaired pre-LT function.

In addition, for those patients with preexisting renal dysfunction who received IL2RA and low-dose tacrolimus, only the eGFR level in the BDT decreased significantly from pre-LT, despite both cohorts receiving comparable dose-modified renal sparing immunosuppression protocols. The most likely explanation for a lack of significant difference in eGFR 6-month values between the BDT and ERT cohorts, is that they started from different baselines but experienced different trajectories to get to the 6-month time point. The difference in statistical significance of eGFR trajectory between the ERT and BDT cohorts is explained by a larger group of patients in the inducted ERT cohort that underwent an improvement in renal function, when compared with the BDT cohort (data not shown).

The tacrolimus trough level reached the therapeutic target range at a similar time (median Day 7) in both groups that were not inducted, but the lower exposure to tacrolimus we observed over the first 7 days post-LT for the ERT cohort, when compared with the BDT cohort, may explain the difference in new-onset renal dysfunction (CKD stage 3–4) we observed between the cohorts. The tacrolimus trough level in the inducted-BDT reached therapeutic target range after Day 9 due to protocol based low-dose tacrolimus exposure, based on the RESPECT study. In contrast, the inducted-ERT had a significantly lower exposure to tacrolimus during the first 15 days, despite a comparable dose modification to BDT in this setting, which may explain the reduced attrition of renal function we observed in this group. Renal impairment is a significant cause of late morbidity and mortality among LT recipients. While a non-significant trend to higher MMF use in the ERT cohort was observed, reduced early CNI exposure rather than differential MMF use per se, is the likely cause of better preservation of renal function in the ERT cohort, in accordance with published data. Interestingly, although patients who received IL2RA induction received a lower dose tacrolimus regimen compared with those who did not receive induction, the majority of BPAR occurred in the latter group.

The patients switched out of protocol from ERT to BDT were excluded from the analysis but they are unlikely to have influenced renal outcome since the majority were switched for below protocol tacrolimus levels. Furthermore, statistical differences in graft type between the ERT and BDT cohorts would be expected to favor better preservation from renal injury in the latter cohort. Our data argue that de novo ERT should be considered in patients who are at risk of developing CKD or have pre-LT renal dysfunction and need anti-IL2 induction therapy with reduced early tacrolimus exposure. Furthermore, given the well-known impact of post-LT renal failure on long-term patient outcomes, the differences in renal function we describe between patients on ERT and BDT, might reasonably be expected to lead to differential patient survival on extended follow-up in our cohorts.

Non-adherence to immunosuppression regimen is associated with increased risk of rejection, and the de novo use of ERT in kidney transplant recipients has been shown to improve adherence. Recently, de novo initiation of ERT in LT also showed noninferiority compared with BDT, although the tacrolimus target levels used were higher than currently
used in clinical practice (10–20 μg/L).\textsuperscript{23,24} Our study from a large UK transplant center showed that de novo use of ERT is as safe and efficacious as BDT in LT. There were no significant differences in graft and patient survival rates between the BDT and ERT cohorts. The safety of ERT has been shown following late conversion from tacrolimus BID at 12 and 24 months as well as in the de novo setting.\textsuperscript{19}

The profiles of DECs in this study mirrors our previous findings in both the early and late-conversion cohorts.\textsuperscript{6} In the BDT, an immediate fall in median DEC was seen after LT in both non-inducted and inducted cohorts although this was more pronounced in the latter. In contrast, we observed a much smaller change in median DEC in the ERT cohort, which stayed between 0.45 and 0.8 μg/L/day in the first 15 days post-LT. This difference likely reflects the changes in the oral clearance of tacrolimus that are determined by changes in both its bioavailability and rate of metabolism. In accordance with our previous study, a small but greater proportion of patients failed to achieve protocol based early target levels on ERT when compared with BDT post-LT.

There was no significant increase in BPAR in patients receiving de novo ERT, despite the reduced DEC when compared with BDT. This further supports the use of ERT in the de novo setting.

IPV has been shown to correlate with long-term kidney graft outcomes.\textsuperscript{25,26} The IPV, as represented here by the CoV, was not significantly different between both groups, which may explain the lack of difference in AR episodes between the

\begin{figure}
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\includegraphics[width=\textwidth]{figure4.png}
\caption{Evolution of mean eGFR post-LT between patients who received de novo BDT vs once-daily tacrolimus (ERT) in (A) cohort that was not treated with IL2RA and (B) cohort treated with interleukin-2 receptor antagonist. * eGFR decreased significantly in the BDT cohort from a pretransplant mean of 102.6 ± 5.9 mL/min to 80.6 ± 4.6 mL/min (\(P < 0.001\)), compared with 113.2 ± 6.4 mL/min to 80.6 ± 4.6 mL/min in the ERT cohort (\(P < 0.001\)). For the groups that received IL2RA, mean eGFR reduced significantly from a baseline of 79.6 ± 5.3 mL/min to 65.2 ± 4.3 mL/min (\(P = 0.006\)) in the BDT cohort, compared with 75.2 ± 5.7 mL/min to 68.5 ± 6.0 mL/min (\(P = 0.09\)) in the ERT cohort. BDT, twice-daily tacrolimus; eGFR, estimated glomerular filtration rate; ERT, extended-release tacrolimus; IL2RA, interleukin-2 receptor antibody; LT, liver transplantation.}
\end{figure}
Table 3. Summary of adverse outcomes recorded at 6 months post-liver transplant

| Outcome                        | BDT | ERT | P    |
|--------------------------------|-----|-----|------|
| Total available                | n=77| n=75|      |
| Renal impairment (CKD stage 3–4) |     |     |      |
| - Pre-existing                 | 19 (25%) | 16 (21%) | 0.702 |
| - New-onset/# at risk          | 15/58 (26%) | 4/59 (7%) | 0.006 |
| Diabetes mellitus              |     |     |      |
| - Preexisting                  | 24 (32%) | 15 (19%) | 0.147 |
| - New-onset/# at risk          | 9/53 (17%) | 5/53 (9%) | 0.390 |
| Hypertension                   |     |     |      |
| - Preexisting                  | 13 (17%) | 11 (14%) | 0.827 |
| - New-onset/# at risk          | 19/64 (30%) | 14/67 (21%) | 0.315 |
| Dyslipidemia                   |     |     |      |
| - Preexisting                  | 3 (4%) | 6 (7%) | 0.320 |
| - New-onset/No. at risk        | 4/74 (5%) | 4/72 (6%) | 1.000 |

BDT, twice-daily tacrolimus group; CKD, chronic kidney disease; ERT, extended-release tacrolimus group.

FACTS

- Diabetes mellitus
- Renal impairment (CKD stage 3–4)
- Dyslipidemia
- Hypertension

In conclusion, we show the use of ERT in de novo LT is safe. The incidence of new onset CKD stages 3 and 4 and attrition of renal function in the context of preexisting renal dysfunction did however differ between patients on BDT and ERT. These findings may help explain in part the apparent survival advantage at 3 years conferred by ERT when compared with BDT in LT.1 Further findings suggest that de novo use of ERT can be considered in all patients with minor exceptions, commencing even when patients are nil-by-mouth, with nasogastric tube in situ in the intensive care setting post-LT. However, based on our study and previous studies, de novo ERT should be specifically considered in patients at risk of post-LT renal dysfunction and those at high risk of nonadherence.20 Long-term follow-up data are needed, as well as validation in an independent cohort of patients.

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References

1. Todo S, Fung JJ, Demetris AJ, et al. Early trials with FK 506 as primary treatment in liver transplantation. Transplant Proc. 1990;22:13–16.
2. Group EFMLS. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. Lancet. 1994;344:423–428.
3. Group TUSMFLS. A Comparison of Tacrolimus (FK 506) and Cyclosporine for Immunosuppression in Liver Transplantation. N Engl Journal of Medicine. 1994;331:1110–1115.
4. Advagraf European Public Assessment Reports (EPAR) 2007. Scientific Discussion. 2007. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000712/WC500022237.pdf. Accessed December 2018.
5. Adam R, Karam V, Delvart V, et al; European Liver Intestine Transplant Association (ELITA). Improved survival in liver transplant recipients receiving prolonged-release tacrolimus in the European liver transplant registry. Am J Transplant. 2015;15:1267–1282.
6. Considine A, Tredger JM, Heneghan M, et al. Performance of modified-release tacrolimus after conversion in liver transplant patients indicates potentially favorable outcomes in selected cohorts. Liver Transpl. 2015;21:29–37.
7. van Hooff JP, Alloway RR, Truneéka P, et al. Four-year experience with tacrolimus once-daily prolonged release in patients from phase II conversion and de novo kidney, liver, and heart studies. Clin Transplant. 2011;25:E1–12.
8. Gastaca M, Valdivieso A, Bustamante J, et al. Favorable long-term outcomes of liver transplant recipients treated de novo with once-daily tacrolimus: results of a single-center cohort. Liver Transpl. 2016;22:1391–1400.
9. European Medicines Agency. Guideline on Bioanalytical Method Validation. 2012. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf. Accessed December 2018.
10. Karnath PS, Kim WR; Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). Hepatology. 2007;45:797–805.
11. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
12. De Geest S, Burkharter H, Bierben L, et al; Psychosocial Interest Group, Swiss Transplant Cohort Study. The swiss transplant cohort study’s framework for assessing lifelong psychosocial factors in solid organ transplants. Prog Transplant. 2013;23:235–246.
13. Gorwa TA, Mai ML, Melton LB, et al. End-stage renal disease (ESRD) after orthotopic liver transplantation (OLTx) using calcineurin-based
immunotherapy: risk of development and treatment. *Transplantation.* 2001;72:1934–1939.

14. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med.* 2003;349:931–940.

15. Wilkinson A, Pham PT. Kidney dysfunction in the recipients of liver transplants. *Liver Transpl.* 2005;11:S47–S51.

16. Guitard J, Ribes D, Kamar N, et al. Predictive factors for chronic renal failure one year after orthotopic liver transplantation. *Ren Fail.* 2006;28:419–425.

17. Neuberger JM, Mamelok RD, Neuhaus P, et al; ReSpECT Study Group. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the ‘respect’ study. *Am J Transplant.* 2009;9:327–336.

18. Trunečka P, Klempnauer J, Bechstein WO, et al; DIAMOND† study group. Renal function in de novo liver transplant recipients receiving different prolonged-release tacrolimus regimens-the DIAMOND study. *Am J Transplant.* 2015;15:1843–1854.

19. Florman S, Alloway R, Kalayoglu M, et al. Conversion of stable liver transplant recipients from a twice-daily prograf-based regimen to a once-daily modified release tacrolimus-based regimen. *Transplant Proc.* 2005;37:1211–1213.

20. Leithead JA, Tariciotti L, Gunson B, et al. Donation after cardiac death liver transplant recipients have an increased frequency of acute kidney injury. *Am J Transplant.* 2012;12:965–975.

21. Beckebaum S, Iacob S, Sweid D, et al. Efficacy, safety, and immunosuppressant adherence in stable liver transplant patients converted from a twice-daily tacrolimus-based regimen to once-daily tacrolimus extended-release formulation. *Transplant Int.* 2011;24:666–675.

22. Colly A, Calmus Y, Chermak F, et al. Once-daily prolonged release tacrolimus in liver transplantation: experts’ literature review and recommendations. *Liver Transpl.* 2015;21:1312–1321.

23. Trunečka P, Bollot O, Seehofer D, et al.; Tacrolimus Prolonged Release Liver Study Group. Once-daily prolonged-release tacrolimus (ADVAGRAF) versus twice-daily tacrolimus (PROGRAF) in liver transplantation. *Am J Transplant.* 2010;10:2313–2323.

24. Fischer L, Trunečka P, Gridelli B, et al. Pharmacokinetics for once-daily versus twice-daily tacrolimus formulations in de novo liver transplantation: a randomized, open-label trial. *Liver Transpl.* 2011;17:167–177.

25. Borra LC, Roodnat JI, Kal JA, et al. High within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcome after kidney transplantation. *Nephrol Dial Transplant.* 2010;25:2757–2763.

26. Vanhove T, Vermeulen T, Annaert P, et al. High intrapatient variability of tacrolimus concentrations predicts accelerated progression of chronic histologic lesions in renal recipients. *Am J Transplant.* 2016;16:2954–2963.