Three-year Outcomes in De Novo Liver Transplant Patients Receiving Everolimus With Reduced Tacrolimus: *Follow-Up Results From a Randomized, Multicenter Study*

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Background. Data are lacking regarding the long-term effect of preemptive conversion to everolimus from calcineurin inhibitors early after liver transplantation to avoid renal deterioration. **Methods.** In a prospective, multicenter, open-label study, de novo liver transplant patients were randomized at day 30 to (i) everolimus + reduced exposure tacrolimus (EVR + Reduced TAC), (ii) everolimus + tacrolimus elimination (TAC Elimination), or (iii) standard exposure tacrolimus (TAC Control). **Results.** Randomization to TAC Elimination was terminated prematurely due to a higher rate of treated biopsy-proven acute rejection (tBPAR) during TAC withdrawal. Of 370 patients who completed the 24-month core study on-treatment, 282 (76.2%) entered an additional 12-month extension phase. The composite efficacy failure endpoint (tBPAR, graft loss or death) occurred in 11.5% of EVR+Reduced TAC patients versus 14.6% TAC Controls from randomization to month 36 (difference, -3.2%; 95% confidence interval, -10.5% to 4.2%; $P = 0.334$). Treated BPAR occurred in 4.8% versus 9.2% of patients ($P = 0.076$). From randomization to month 36, mean (SD) estimated glomerular filtration rate decreased by 7.0 (31.3) mL/min per 1.73 m^2 in the EVR+Reduced TAC group, and 15.5 (22.7) mL/min per 1.73 m^2 in the TAC Control group ($P = 0.005$). Rates of adverse events, serious adverse events, and discontinuation due to adverse events were similar in both groups during the extension. **Conclusions.** A clinically relevant renal benefit after introduction of everolimus with reduced-exposure tacrolimus at 1 month after liver transplantation was maintained to 3 years in patients who continued everolimus therapy to the end of the core study, with comparable efficacy and no late safety concerns.

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It has long been recognized that liver transplant recipients are at high risk for chronic renal failure,[1] with 1 in 5 patients progressing within 5 years.[2] One of the few modifiable risk factors for posttransplant renal dysfunction is exposure to calcineurin inhibitor (CNI) therapy. The majority of studies which have studied CNI-sparing regimens in liver transplant

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populations examined changes to the immunosuppressive regimen only after renal dysfunction developed.[3] Less well-explored are preemptive immunosuppressive strategies to avoid renal deterioration. Randomized trials have demonstrated that reduced-CNI regimens with concomitant mycophenolate mofetil from the time of transplant can provide effective immunosuppression with improved renal function versus a standard-exposure CNI protocol.[4-6] An alternative approach is to harness the immunosuppressive synergism[7] between the mammalian target of rapamycin inhibitor everolimus and CNI to reduce CNI exposure, which appears to be a promising approach. Two randomized trials of everolimus with early CNI discontinuation after liver transplantation have shown similar efficacy to a standard CNI-based regimen, but with higher estimated glomerular filtration rate (eGFR) at 1 year after transplantation.[8,9] Data are required, however, concerning the long-term effect of conversion to everolimus after liver transplantation.

The randomized H2304 trial compared everolimus with reduced-exposure tacrolimus or tacrolimus elimination, both from month 1 after transplantation versus a standard tacrolimus regimen in a population of 719 liver transplant recipients.[10] At 12 and 24 months after transplantation, patients randomized to everolimus showed a significant and clinically relevant improvement in renal function versus the control arm.[10,11] After completion of the 24-month core study, patients were followed-up until month 36 to evaluate the long-term safety and efficacy of everolimus with CNI reduction in de novo liver transplant recipients. Efficacy, safety, and renal outcomes at 3 years after transplantation are reported here.

MATERIALS AND METHODS

Study Design and Conduct

The H2304 study methodology has been published in full previously.[10] This was a 24-month prospective, randomized, 3-arm, parallel group, open-label trial in which de novo liver transplant patients were recruited at transplant centers in 19 countries worldwide.[10] After a run-in period to 30 days after transplantation, during which the immunosuppression regimen was identical for all patients, patients were randomized (1:1:1) to (i) EVR+Reduced TAC (ii) TAC Control, or (iii) TAC Elimination. Patients who completed the 24-month core study on-treatment were eligible to enter an extension study which followed up patients until month 36 after transplantation. The core study started in January 2008, with the final 36-month patient visit in May 2013.

Eligibility Criteria

Full inclusion criteria have been published previously.[10] Patients aged 18 to 70 years were eligible for the core study if they received a primary full-size liver transplant from a deceased donor and had been treated with tacrolimus and corticosteroids (with or without mycophenolic acid) since transplantation, unless hepatocellular carcinoma (HCC) was present which did not fulfill Milan criteria.[12,13] Key additional inclusion criteria at randomization were (i) eGFR 30 mL/min per 1.73 m^2 or higher by the 4-variable Modification of Diet in Renal Disease (MDRD4) formula[14]; (ii) no abnormal liver function[10]; (iii) tacrolimus trough concentration 8 ng/mL or higher in the week before randomization. All patients who completed the month 24 visit of the core study and who had been continuously treated with the assigned regimen were eligible to enter the extension study.

Randomization

Patients were stratified before randomization according to pretransplant hepatitis C virus (HCV) status and the stratum of eGFR (MDRD4 formula). Randomization to the TAC Elimination arm was stopped in April 2010, when approximately 690 patients had been randomized in total after a recommendation from the independent Data Monitoring Committee.[10]

Immunosuppression

In the EVR+Reduced TAC arm, everolimus dose was adjusted to target a trough (C_0) concentration in the range of 3 to 8 ng/mL with a target tacrolimus trough concentration of 3 to 5 ng/mL. In the TAC Control arm, the target tacrolimus trough concentration was 8 to 12 ng/mL until month 4 after transplantation and 6 to 10 ng/mL thereafter. Corticosteroids were administered according to local practice with a minimum oral dose of 5 mg prednisolone/day to be continued until at least month 6 after transplantation. At the end of the core 24-month study, immunosuppression was to continue unchanged during the extension study.

Study Endpoints

The main efficacy endpoints of the extension study (at month 36 after transplantation) were renal function estimated by eGFR (MDRD4 formula), the composite efficacy endpoint of treated biopsy-proven acute rejection (tBPAR), graft loss or death since randomization, and progression of HCV-related allograft fibrosis (Ishak-Knodell score) in HCV-positive patients. Treated BPAR was defined as treated acute rejection with rejection activity index of 3 or higher according to Banff 1997 criteria.[15]

Statistical Analysis

Because of the premature discontinuation of recruitment to the TAC Elimination group and extensive conversion of patients in this arm to standard therapy, the statistical analyses focused on the EVR+Reduced TAC and TAC Control groups.

No inferential statistical comparisons were performed. The efficacy endpoints that occurred in the extension study were summarized for all extension patients. Efficacy events which occurred since randomization were further analyzed by the Kaplan-Meier method for the intent-to-treat population, consisting of all patients randomized in the core study. In the Kaplan-Meier analyses, the patients who did not enter the extension study were censored at their last contact day. Slopes of renal function were assessed using a mixed-effect model for longitudinal data in the extension study with postrandomization eGFR as the response variable, treatment, randomization eGFR and HCV status, day of creatinine sample collection, and the interaction of day by treatment as fixed effects, and with intercept and patient as the random effects.

RESULTS

Patient Population

In total, 580 of 719 randomized patients (80.7%) completed the month 24 visit of the core study. Of the 370 patients (63.8%) who remained on their assigned immunosuppressive regimen at month 24, 282 (76.2%) provided

informed consent to enter the extension study (Figure 1). The baseline characteristics of the treatment groups were well balanced (Table 1) and showed no marked differences to the core study population.[7]

Immunosuppression

Mean everolimus C_0 concentration was within target range (3 to 8 ng/mL) for the EVR+Reduced TAC group during the extension study (Table S1, SDC, http://links.lww.com/TP/B99). At months 24 and 36, everolimus C_0 was below 3 ng/mL in 9.6% and 10.3% of the patients, and tacrolimus C_0 below the target range (6 to 10 ng/mL) in 29.4% and 34.1% of the patients. In the TAC Control group, 35.4% and 43.4% had tacrolimus C_0 level below 6 ng/mL at months 24 and 36, although mean tacrolimus C_0 was within the target (6 to 10 ng/mL) (Table S1, SDC, http://links.lww.com/TP/B99).

Corticosteroids were administered in 13.2% (n = 14) of the patients in the EVR+Reduced TAC group and 20.8% (n = 26) of TAC Control patients at some point during the extension study. Mean steroid dose was slightly higher in the EVR+Reduced TAC group (Table S1, SDC, http://links.lww.com/TP/B99).

Efficacy

The composite efficacy failure endpoint of tBPAR, graft loss, or death occurred in 11.5% of EVR+Reduced TAC patients and 14.6% of TAC Controls between randomization and month 36 in the intent-to-treat population (Kaplan-Meier estimates). The between-group difference was −3.2% in favor of EVR+Reduced TAC (95% confidence interval, −10.5% to 4.2%; $P = 0.334$) (Table 2, see Figure S1a, SDC, http://links.lww.com/TP/B99). This result was similar to that observed at month 12[10] and month 24.[11] The incidence of tBPAR from randomization to month 36 was 4.8% in the EVR+Reduced TAC group versus 9.2% in the TAC Control group ($P = 0.076$) (see Figure S1b, SDC, http://links.lww.com/TP/B99).

Overall, efficacy events were rare during months 24 to 36. Two patients died in the EVR+Reduced TAC group due to hyperglycemia and sudden death. In the TAC Control arm, there was 1 graft loss during months 24 to 36 caused by hepatic artery thrombosis. There was no tBPAR in the EVR +Reduced TAC group, and 2 episodes of tBPAR (Banff scores, 6 and 7) in the TAC Control arm. Biopsy-proven acute rejection was reported in 1 (0.9%) patient in the EVR+Reduced TAC group (Banff score, 4) during the extension study and in 5 (4.0%) patients in the TAC Control group; maximum severity in the 2 groups during the extension study was Banff scores 4 and 7, respectively.

Renal Function

Mean (SD) eGFR (MDRD4) at time of transplant was 102.0 (56.1) mL/min per 1.73 m^2 in the EVR+Reduced TAC group versus 92.1 (44.5) mL/min per 1.73 m^2 in the TAC Control arm ($P = 0.371$). The incidence of BPAR before randomization was 8.2% in both groups, with identical immunosuppression. By the time of randomization, eGFR was 85.0 (35.8) mL/min per 1.73 m^2 in the EVR+Reduced TAC group versus 78.0 (28.1) mL/min per 1.73 m^2 in the TAC Control group ($P = 0.203$) (Table S2, SDC, http://links.lww.com/TP/B99). From 1 month after randomization to month 36, mean eGFR was significantly higher in the EVR+Reduced TAC group (Figure 2A, Table S2, SDC, http://links.lww.com/TP/B99). At month 36, mean (SD) eGFR was 78.7 (25.7) mL/min per 1.73 m^2 in the EVR +Reduced TAC group versus 63.5 (18.3) mL/min per 1.73 m^2 in the TAC Control group ($P < 0.001$) (Table S3, SDC, http://links.lww.com/TP/B99). From randomization to

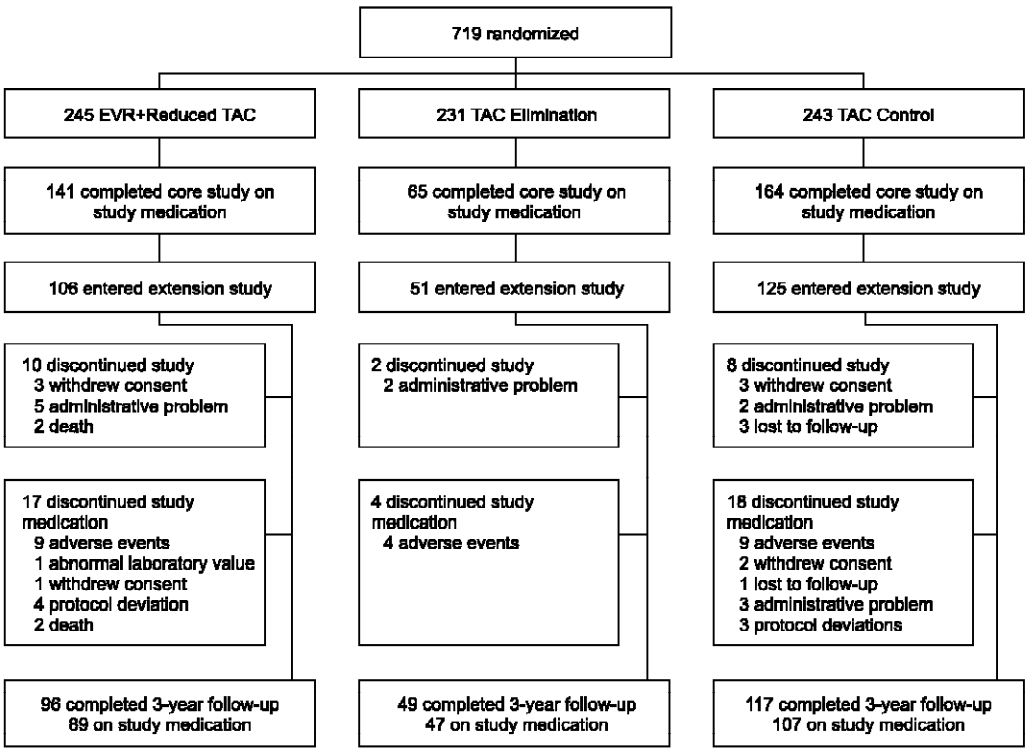

FIGURE 1. Patient disposition.

TABLE 1.

Demographics and baseline characteristics (extension study population)

	EVR+Reduced TAC, N = 106	TAC Elimination, N = 51	TAC Control, N = 125
Age, y	53.5 (9.6)	54.9 (10.1)	55.2 (8.1)
Male sex, n (%)	77 (72.6)	33 (64.7)	87 (69.6)
Race, n (%)			
Caucasian	95 (89.6)	44 (86.3)	99 (79.2)
Black	0 (0.0)	1 (2.0)	4 (3.2)
Asian	2 (1.9)	1 (2.0)	4 (3.2)
Other	9 (8.5)	5 (9.8)	18 (14.4)
Body mass index, kg/m^2[a]	24.8 (3.9)	25.4 (4.7)	24.5 (3.9)
HCV positive, n, %[a]	26 (24.5)	16 (31.4)	37 (29.6)
Diabetes at randomization, n, %[a]	36 (34.0)	22 (43.1)	53 (42.4)
Primary disease leading to liver transplantation, n, %			
Alcoholic cirrhosis	36 (34.0)	12 (23.5)	24 (19.2)
HCV	22 (20.8)	12 (23.5)	27 (21.6)
Hepatocellular carcinoma	22 (20.8)	6 (11.8)	18 (14.4)
Other	26 (24.5)	21 (41.2)	56 (44.8)
MELD score[b]	19.0 (8.4)	19.4 (8.0)	19.4 (7.9)
Donor age, y	51.0 (18.6)	46.3 (17.3)	48.2 (17.5)
Cold ischemia time, h	8.5 (5.4)	7.5 (3.2)	7.7 (3.0)
Cystatin C, mg/L[a]	1.2 (0.4)	1.2 (0.2)	1.3 (0.4)
eGFR at randomization (MDRD4, mL/min per 1.73 m^2)[a]			
Mean (SD)	85.0 (35.8)	83.3 (38.5)	78.0 (28.1)
Median (min, max)	78.9 (25.4, 247.7)	74.8 (24.2, 246.7)	74.1 (21.1, 193.2)
eGFR at randomization (MDRD4), n, %			
<30 mL/min per 1.73 m^2	2 (1.9)	1 (2.0)	2 (1.6)
30 to 45 mL/min per 1.73 m^2	10 (9.6)	1 (2.0)	9 (7.3)
45 to <60 mL/min per 1.73 m^2	14 (13.2)	8 (16.0)	18 (14.6)
≥60 mL/min per 1.73 m^2	80 (75.5)	40 (80.0)	94 (76.4)

[a] Among patients who attended the month 36 visit.
[b] MELD score based on laboratory values only.
Continuous variables are shown as mean (SD) unless otherwise stated
MELD, model for end-stage liver disease.

month 36, mean (SD) eGFR decreased by 7.0 (31.3) mL/min per 1.73 m^2 in the EVR+Reduced TAC group, and by 15.5 (22.7) mL/min per 1.73 m^2 in the TAC Control group (P = 0.005). Based on the longitudinal data analysis, eGFR in the EVR+Reduced TAC arm increased slightly during the study (slope = 0.04 mL/min per 1.73 m^2 per month), whereas it decreased in the TAC Control group (slope = −0.26 mL/min per 1.73 m^2 per month).

Mean (SD) eGFR at month 36 in the patients who remained on their randomized study drug to month 36 was 79.7 (25.8) mL/min per 1.73 m^2 in the EVR+Reduced TAC group versus 63.0 (18.0) mL/min per 1.73 m^2 in the TAC Control arm (P < 0.001).

From month 6 onward, mean eGFR (MDRD4) was highest in the TAC Elimination group (Figure 2B, **Table S2, SDC**, http://links.lww.com/TP/B99). By month 36, mean (SD)

TABLE 2.

Efficacy endpoints from randomization to month 36 (ITT population)

				EVR+ Reduced TAC versus TAC control	
	EVR+ Reduced TAC N = 245	TAC Elimination N = 231	TAC Control N = 243	difference (97.5% CI)	P[a]
Composite efficacy endpoint[b]					
n	26	56	32	—	—
Incidence (KM %)	11.5	27.5	14.6	−3.2 (−10.5, 4.2)	0.334
Secondary endpoints					
Graft loss, n (KM %)	9 (3.9)	6 (2.8)	8 (4.0)	0.0 (−4.3, 4.3)	0.987
Death, n (KM %)	14 (6.5)[c]	15 (7.3)	10 (4.4)	2.1 (−2.9, 7.0)	0.348
tBPAR, n (KM %)	11 (4.8)	43 (21.5)	20 (9.2)	−4.4 (−9.9, 1.2)	0.076
BPAR, n (KM %)	15 (7.3)	53 (26.8)	34 (17.7)	−10.4 (−19.0, −1.9)	0.006

[a] Z-test (no-difference).
[b] tBPAR, graft loss or death.
[c] Including 2 patients who never received everolimus.
95% CI, 95% confidence interval; ITT, intent-to-treat; KM, Kaplan-Meier estimate.

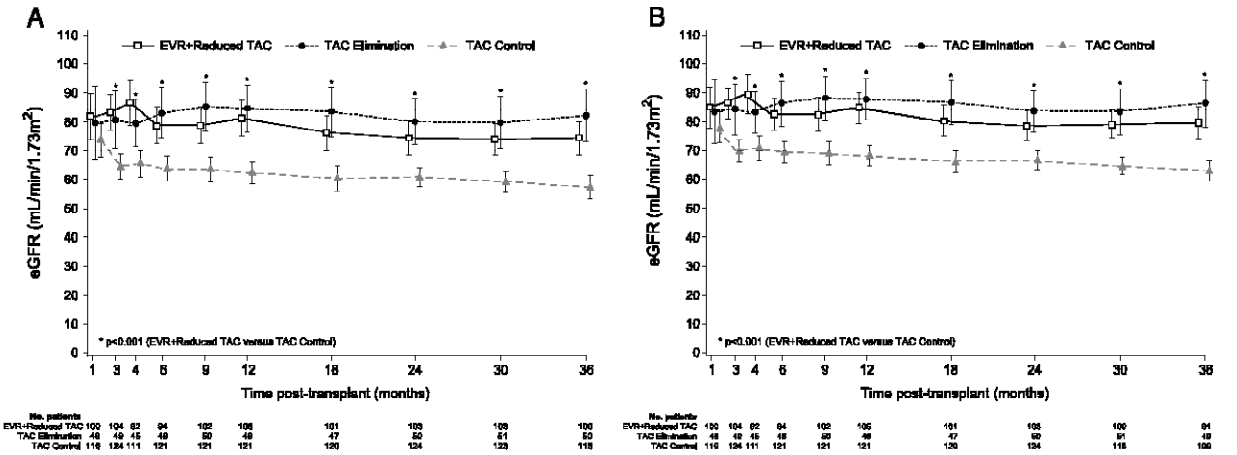

FIGURE 2. Estimated GFR (MDRD4) to month 36 according to treatment group (A) extension study population and (B) on-treatment population. Values are shown as mean and 95% confidence interval.

eGFR was 85.5 (28.1) mL/min per 1.73 m^2 in the TAC Elimination arm versus 63.5 (18.3) mL/min per 1.73 m^2 in the TAC Control arm.

Proteinuria (defined as 1.0 to <3.0 g/day) was present in three patients each in the EVR+Reduced TAC and TAC Control groups at month 36, but no patient had nephrotic syndrome (defined as ≥3.0 g proteinuria/day). The mean urine protein to creatinine ratio increased slightly in both the EVR +Reduced TAC and TAC Control groups during months 24 to 36; the between-group difference remained nonsignificant (Table S3, SDC, http://links.lww.com/TP/B99). No patients in either group discontinued study drug due to proteinuria during the extension phase. Renal failure was reported as an adverse event during the extension phase in 7.5% (n = 8) and 14.4% (n = 18) patients in the EVR+Reduced TAC and TAC Control groups, respectively.

HCV-Positive Patients

Twenty-six patients in the EVR+Reduced TAC group (24.5%) and 37 TAC Control patients (29.6%) were HCV-positive at the start of the extension phase of whom 14 and 22 patients, respectively, were genotype 1. The mean (SD) HCV RNA level was 6.8 (0.7) in the EVR+Reduced TAC group and 6.4 (0.8) in the TAC Control group at month 24, compared to 6.6 (0.8) and 6.8 (0.6), respectively, at month 36 (log_{10}-transformed values). Analysis of the Ishak-Knodell score between treatment groups during the extension phase was not considered meaningful due to the low number of protocol biopsies performed at month 36 (EVR+Reduced TAC group 10, TAC Elimination 3, TAC Control group 13).

Safety

During months 24 to 36, 82.1% and 76.8% of patients in the EVR+Reduced TAC and TAC Control groups, respectively, experienced 1 or more adverse event ($P = 0.335$) (Table 3). Serious adverse events occurred in 30.2% of patients in the EVR+Reduced TAC group and 22.4% of patients in the TAC Control group ($P = 0.228$) during the extension phase, the most frequent of which were diarrhea (2.8% and 1.6%), pyrexia (2.8% and 1.6%), and pneumonia (1.9% and 2.4%). Nine patients in both treatment groups (EVR +Reduced TAC 8.5%, TAC Control 7.2%) discontinued study medication due to adverse events during the extension phase. No single type of adverse event in either group led to study drug discontinuation in more than one patient.

The HCC recurred in 1 patient in both treatment groups during the extension period. During the extension phase, 1 or more neoplasm was reported in 3 patients in the EVR +Reduced TAC (recurrent HCC; malignant lung neoplasm; malignant lung neoplasm with squamous cell carcinoma [SCC] of the lung) and nine patients in the TAC Control arm (HCC; diffuse large B-cell lymphoma; basal cell carcinoma [BCC] with SCC of the skin; BCC with SCC of the skin and sebaceous adenoma; BCC with benign neoplasm of the skin; melanotic nevus; intraductal papillary mucinous neoplasm [2 patients]; angiosarcoma). Cardiovascular events occurred in 3 patients in the EVR+Reduced TAC group and 6 patients in the TAC Control arm.

Three patients in each of the 2 groups developed pneumonia. Viral infections were reported in 2 patients in the EVR +Reduced TAC arm and 5 patients in the TAC Control arm. There were no reported cases of cytomegalovirus infection or cytomegalovirus disease during the extension phase in either group.

Seventeen patients (16.0%) in the EVR + Reduced TAC group and 9 patients (7.2%) in the TAC Control group were receiving lipid-lowering therapy at month 36. High-density lipoprotein-cholesterol increased to a greater extent during the extension study in the EVR+Reduced TAC group than in the TAC control arm (mean [SD] 0.08 [0.30] mmol/L versus 0.01 [0.22] mmol/L; $P = 0.024$). There were no other significant differences for change in lipid values between the 2 treatment groups. By month 36, new-onset diabetes mellitus had occurred in 1 patient in the EVR+Reduced TAC group and 2 patients in the TAC Control arm. Hematological parameters, liver enzyme levels, biochemical parameters (except for lipids) and blood pressure showed no marked differences between treatment arms at month 36, other than total bilirubin (Table S4, SDC, http://links.lww.com/TP/B99).

DISCUSSION

Three-year follow-up data from the extension phase of this randomized trial show that liver transplant patients receiving everolimus with reduced-exposure tacrolimus from 1 month after transplantation experience a significant renal benefit versus a standard tacrolimus regimen. The difference in eGFR

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