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Efficacy and Safety of Everolimus With Reduced Tacrolimus in Liver Transplant Recipients: 24-month Results From the Pooled Analysis of 2 Randomized Controlled Trials

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Background and Methods. Data from 2 randomized liver transplant trials (N = 772; H2304 [deceased donor, n = 488], H2307 [living donor, n = 284]) were pooled to further evaluate the efficacy and safety of everolimus with reduced tacrolimus (EVR + rTAC) versus standard tacrolimus (sTAC) regimen at month 24. **Results.** EVR + rTAC was comparable to sTAC for composite efficacy failure of treated biopsy-proven acute rejection, graft loss, or death (9.8% versus 10.8%; difference, −1.0%; 95% confidence interval, −5.4 to 3.4; $P = 0.641$) at month 24. EVR + rTAC was superior to sTAC for the mean change in estimated glomerular filtration rate (eGFR) from randomization to month 24 (−8.37 versus −13.40 mL/min/1.73 m^2; $P = 0.001$). A subanalysis of renal function by chronic kidney disease (CKD) stage at randomization showed significantly lower decline in eGFR from randomization to month 24 for patients with CKD stage 1/2 (eGFR ≥ 60 mL/min/1.73 m^2) in EVR + rTAC group versus sTAC (−12.82 versus −17.67 mL/min/1.73 m^2, $P = 0.009$). In patients transplanted for hepatocellular carcinoma (HCC) beyond Milan criteria, HCC recurrence was numerically lower although not statistically significant with EVR + rTAC versus sTAC group (5.9% [1 of 17] versus 23.1% [6 of 26], $P = 0.215$), while comparable in patients within Milan criteria (2.9% [3 of 102] versus 2.1% [2 of 96], $P = 1.000$), irrespective of pretransplant alpha-fetoprotein levels. **Conclusions.** EVR + rTAC versus sTAC showed comparable efficacy and safety with significantly better renal function, particularly in patients with normal/mildly decreased renal function (CKD stage 1/2) at randomization and a trend toward lower HCC recurrence in patients transplanted with HCC beyond Milan at month 24. Further long-term data would be required to confirm these results.

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INTRODUCTION

Liver transplantation has evolved as the treatment of choice for acute and chronic end-stage liver disease. The etiology and the procedures for liver transplantation differ due to organ availability and type of indications, leading to end-stage liver diseases between Western and Asian countries. Deceased donor liver transplantation (DDLT) account for >95% of transplantations in Western countries, whereas living donor liver transplantation (LDLT) account for >90% of transplantations in Asia.[1-5] Although

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alcoholic liver disease, followed by hepatitis C virus (HCV) and hepatocellular carcinoma (HCC), are the most common reasons for liver transplantation in the Western region, HCC remains the most common reason for liver transplantation in Asia.[1,2,6] Despite these differences in transplantation setting and medical root causes leading to liver transplantation, similar 5-year patient survival rates of over 75% have been achieved in both DDLT and LDLT settings.[1,7-10]

Calcineurin inhibitors (CNIs), cyclosporine A, and tacrolimus (TAC), have been the mainstay of maintenance immunosuppression following liver transplantation.[1,11] The use of CNIs has markedly improved liver graft survival, as well as patient survival. However, their long-term use is associated with chronic nephrotoxicity, increased risk of infections and (de novo) malignancies, and recurrence of HCC, which are among the major causes of patient death in patients with initially successful liver transplantation.[12-14]

Everolimus (EVR), a mammalian target of rapamycin inhibitor (mTORi), exerts synergistic immunosuppressive efficacy with CNIs, thereby allowing reduction of CNI exposure.[15] In addition to this immunosuppressive effect, the antiproliferative effect through inhibition of the mTOR pathway results in direct antitumor activity of EVR, which offers an additional approach in bridging the unmet clinical need in liver transplant recipients, mainly in patients with primary HCC.[16] Two randomized controlled trials by Novartis Pharma (Basel, Switzerland), namely, H2304 (NCT00622869) and H2307 (NCT01888432), explored the early introduction of EVR in combination with reduced TAC exposure at 1 month after liver transplantation. The 12-month to 36-month data from the H2304 trial and the 24-month results from the H2307 trial have demonstrated the benefits of renal function with EVR-facilitated early TAC exposure reduction without compromising the antirejection efficacy.[17-21] Both trials had a similar study design, albeit a slightly different study populations (Table S1, SDC, http://links.lww.com/TP/B975). The H2304 trial, primarily conducted in the United States and in Europe with no sites in Asia, involved DDLT recipients, majorly Caucasian, and only included patients transplanted for HCC who fulfilled Milan criteria. In contrast, the H2307 trial was primarily conducted in Asian countries, which involved LDLT recipients, majorly Asian by race, and included patients with HCC within as well as exceeding Milan criteria. In the H2304 study, >30% of patients were HCV positive, whereas only 17% of the patients were HCV positive in the H2307 study at baseline. Overall, mean glomerular filtration rate (eGFR) was higher at baseline in the H2307 study versus H2304 study.

Pooling 24-month data posttransplantation from these 2 major trials provided a unique opportunity to enhance the statistical power, to further evaluate the long-term efficacy and safety of EVR with reduced TAC (EVR + rTAC) versus standard TAC (sTAC) regimen, with particular interest on impact of these regimens on renal function, as well as HCC recurrence in patients transplanted with HCC within and beyond Milan criteria across the sites, irrespective of donor types.

MATERIALS AND METHODS

Study Conduct

Full study details and first outcome results of these trials have been published elsewhere.[17-21] Both trials were approved by the local ethics committees at all participating institutions and were conducted according to the recommendations of Good Clinical Practice (GCP) and the Declaration of Helsinki. All study participants gave their written informed consent to participate in the original trials, H2304 and H2307.

Study Population

Common inclusion criteria for both trials included (1) adult (age ≥18 years) recipients of a primary liver transplant who had been initiated on protocol-defined TAC-based immunosuppression; (2) acceptable allograft function at the time of randomization, defined as aspartate transaminase, alanine transaminase (ALT), and total bilirubin levels ≤3 times of the upper limit of normal; and (3) eGFR (abbreviated Modification of Diet in Renal Disease [MDRD]) ≥30 mL/min/1.73 m^2.

Randomization and Study Medication

Both studies were 24-month, multicenter, open-label, controlled trials with randomization at 30 ± 5 days posttransplantation. In the H2304 trial, randomization (1:1:1) was stratified by pretransplant HCV status and quartile

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S.G.L., L.J., F.S., A.S., W.L., P.D.S. F.N., K.S., L.F., D.J.J. J.F., J.J., T.K., D.G., and G.L. were study investigators and were responsible for the study design/conduct, data interpretation, drafting/revising, and approval of the final manuscript. M.M., B.R., C.S., and S.K. were responsible for the study design and protocol writing and were involved in data acquisition and analysis and drafting/revising and approval of the final manuscript.

Clinical trial identifier: H2304—NCT00622869; H2307—NCT01888432.

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ranges of eGFR to either (1) TAC elimination, (2) EVR + rTAC, or (3) sTAC group. Randomization to the TAC elimination group in the H2304 trial was prematurely stopped based on the recommendation of the independent Data Monitoring Committee due to a high rate of treated biopsy-proven acute rejections (tBPARs) clustered at the time of TAC elimination, and no data for this group will be shown in the present report.[17] In the H2307 trial, randomization (1:1) was stratified by HCC status to either (1) EVR + rTAC or (2) sTAC group. Otherwise, the study designs for H2304 and H2307 were identical.

Patients randomized to the EVR + rTAC group in both studies received an initial EVR dose of 2.0 mg/day, adjusted to a target trough level of 3–8 ng/mL throughout the study, while the TAC dose was tapered to 3–5 ng/mL in parallel. In contrast, in the sTAC group, the TAC target trough levels were maintained in the range of 8–12 ng/mL from randomization to month 4 and 6–10 ng/mL thereafter.

Study Endpoints

The primary endpoint in both trials was the composite efficacy failure rate of tBPAR, graft loss, or death at month 12 posttransplantation. The key focus of this pooled analysis of the H2304 and H2307 trials is to compare the composite efficacy failure rate of tBPAR, graft loss, or death, as well as renal function (using eGFR, as measured by means of the MDRD4 [4-variable modification of diet in renal disease] formula), HCC recurrence, and safety of the EVR + rTAC regimen against the sTAC therapy at month 24 posttransplantation. Discontinuation or adjustment in the study drug was based on physician's decision. Additionally, a subanalysis of renal function was conducted by chronic kidney disease (CKD) stage at randomization and model for end-stage liver disease (MELD) score at transplantation. HCC recurrence was subanalyzed using alpha-fetoprotein (AFP) levels and by Milan criteria at the time of transplantation.

Statistical Analysis

All efficacy analyses are based on the full analysis set (FAS) that followed intent-to-treat principle and included all randomized patients. Safety analyses are based on the safety population that consisted of all randomized patients who received at least one dose of the assigned study medication (EVR + rTAC versus sTAC). The TAC elimination group of the H2304 trial was not included in the analysis. Continuous parameters of age, body mass index, and MELD score at transplantation was compared by using *t* test. Categorical parameters of sex, race, primary disease leading to transplantation, and diabetes status at baseline were compared by using χ^2 test. The incidence of tBPAR, graft loss, death, and the composite of all at month 24 was assessed using the Kaplan–Meier formula with 2-sided *P* value and 95% confidence intervals (CIs) for the between-treatment difference in the FAS. In the Kaplan–Meier estimate, the censoring day for patients without an event was the last contact day, except for the on-treatment event analysis. For on-treatment event analysis, the censoring day for patients without an on-treatment event was the last day of study medication plus 2 days or the first day if the subject was not treated. The change in eGFR from randomization to month 24 was assessed by an analysis of covariance model, with treatment, study, and randomization eGFR as covariates in the FAS. Missing eGFR values at month 24 were imputed with the value at randomization if no postrandomization value was available or, otherwise, the worst value within the period in which the last assessment was done. For patient on renal replacement therapy, 15 mL/min/1.73 m^2 was imputed. A subanalysis of renal function by CKD stage and MELD score was conducted in the FAS. CKD stage was classified based on renal function (eGFR MDRD4).[22] A multivariate analysis was conducted using transplant cohort (DDLT versus LDLT), end-stage disease leading to liver transplantation (alcoholic cirrhosis versus HCC versus hepatitis C versus hepatitis B versus other), donor gender (female versus male), recipient gender (female versus male), donor age (continuous variable), recipient age (continuous variable), diabetes at baseline (yes versus no), MELD score (≤14 versus ≥15), and recipient race (Caucasian versus Asian versus other) as potential variables to identify their impact on the primary composite efficacy failure and renal function. HCC recurrence was analyzed in the safety population.

RESULTS

Patient Population

Among 772 randomized patients included in the pooled analysis (387 EVR + rTAC versus 385 sTAC), 656 (85.0%) completed the 24-month study (327 [84.5%] EVR + rTAC versus 329 [85.5%] sTAC). The major reasons for premature discontinuations were physician/subject decision (5.7% versus 5.5%), death (5.2% versus 3.6%), and technical or administrative problem (2.8% versus 3.4%) for the EVR + rTAC and sTAC groups, respectively. The treatment groups were well balanced in terms of baseline demographics and clinical characteristics (Table 1). Most patients were male and/or Caucasian, whereas alcoholic cirrhosis was the leading cause of liver transplantation followed by HCC and HCV. Patients who entered into H2304 trial had numerically higher MELD scores at transplantation than those in H2307 trial. The demographic and baseline characteristics between the groups were not significantly different after pooling both the studies.

Immunosuppression

At week 5, 56.1% of patients were within and 39.0% of patients were below the EVR target range, which changed to 81.3% within and 10.7% below at month 24. When we evaluated the distribution of EVR trough level by demographic/baseline parameters (such as ethnicity, graft function by CKD stages, and body weight), it was not very different from what we have observed for overall population. Mean EVR C0 levels were within the target range of 3–8 ng/mL throughout the study (Figure 1A). The proportion of patients with TAC trough levels >5 ng/mL was 79.6% at week 5, declining to 19.3% at month 24 in the EVR + rTAC group. In contrast, proportion of patients with TAC trough levels above the target range in the sTAC group was 16.2% at week 5 and 8.7% at month 24. Overall, the mean TAC trough concentrations exceeded the target range of 3–5 ng/mL in the EVR + rTAC group until month 6 and remained close to the upper threshold thereafter. In the sTAC group, the mean TAC trough

TABLE 1.

Baseline demographics and clinical characteristics

Parameters	EVR + rTAC, N = 387	sTAC, N = 385	*P*
Age, y, mean (SD)	53.8 (9.12)	53.9 (9.39)	0.9792
Gender			
Female, n (%)	103 (26.6)	107 (27.8)	0.7132
Male, n (%)	284 (73.4)	278 (72.2)	
Race, n (%)			
Caucasian	241 (62.3)	224 (58.2)	0.5888
Asian	115 (29.7)	117 (30.4)	
Others[a]	31 (8.0)	44 (11.4)	
Body mass index, kg/m^2, mean (SD)	24.4 (4.37)	23.9 (3.94)	0.1354
Primary disease leading to transplant, n (%)			
Alcoholic cirrhosis	99 (25.6)	78 (20.3)	0.6452
HCC	89 (23.0)	77 (20.0)	
Hepatitis C	73 (18.9)	67 (17.4)	
Hepatitis B	32 (8.3)	38 (9.9)	
Cryptogenic cirrhosis	20 (5.2)	26 (6.8)	
Other[b]	74 (19.1)	99 (25.7)	
Diabetes at baseline, n (%)	129 (33.3)	147 (38.2)	0.1599
MELD overall score at transplant, mean (SD)	17.2 (8.19)	17.1 (7.41)	0.9552
eGFR at transplant (MDRD4, mL/min/1.73 m^2), mean (SD)	98.6 (38.58)	98.7 (39.75)	0.9644

P values are provided for descriptive purpose only.
[a]Include African Americans, native Americans, other, and missing.
[b]Include acute liver failure, amyloidosis, autoimmune hepatitis, biliary atresia, Budd–Chiari syndrome, hemochromatosis, metabolic disease, nonalcoholic steatosis hepatitis, sclerosing cholangitis, polycystic liver disease, primary biliary cirrhosis, and other causes.
eGFR, estimated glomerular filtration rate; EVR, everolimus; HCC, hepatocellular carcinoma; MDRD4, 4-variable modification of diet in renal disease formula; MELD, model for end-stage liver disease; rTAC, reduced tacrolimus; sTAC, standard tacrolimus.

concentrations were within the target range throughout the study (Figure 1B). The median bodyweight-adjusted dose of steroid was similar between EVR + rTAC (0.20 mg/kg/day) and sTAC group (0.20 mg/kg/day) at randomization and at month 24 (0.08 versus 0.07 mg/kg/day).

Efficacy

The Kaplan–Meier incidence for composite efficacy failure (tBPAR, graft loss, or death) was 9.8% in the EVR + rTAC group versus 10.8% in the sTAC group, with a difference of −1.0% favoring EVR + rTAC group (95% CI, −5.4 to 3.4, $P = 0.641$ for no difference; Figure 2). tBPAR occurred in 15 (4.2%) patients versus 24 (6.4%) patients in EVR + rTAC versus sTAC groups, respectively (Table 2). Out of these 15 patients who experienced tBPAR in the EVR + rTAC group, 10 patients had EVR trough level of 3–8 ng/mL with corresponding TAC trough levels of 3–5 ng/mL in 3 patients, >5–<6 ng/mL in 4 patients, 6–10 ng/mL in 2 patients, and >10 ng/mL in 1 patient. In addition, 2 patients had EVR trough level of >8 ng/mL and TAC trough level of 3–5 ng/mL, who experienced tBPAR. The incidence of graft loss was comparable between both the treatment groups. Survival rates were high; a total of 20 patients died in the EVR + rTAC group versus 14 patients in the sTAC group; the primary cause of death was respiratory failure due to infections, sepsis, and/or multiple organ failure (8 versus 5 patients), liver failure (4 versus 5 patients), cardiac failure (3 versus 1 patient), cancer (de novo or recurrence; 3 versus 2 patients), and others/unknown (2 versus 1 patient). On-treatment death was reported for 9 patients in the EVR + rTAC group compared with 11 patients in the sTAC group.

The multivariate analysis showed presence of diabetes at baseline ($P = 0.0232$) and MELD score ≥15 ($P = 0.0352$) among the patients receiving EVR + rTAC regimen to be associated with significantly higher incidences of composite efficacy failure. However, none of these parameters had significant association with composite efficacy failure events in the sTAC group (Table 3).

Renal Function

The least square mean change in eGFR from randomization to month 24 was superior with EVR + rTAC versus sTAC (−8.37 versus −13.40 mL/min/1.73 m^2), with a difference of 5.03 mL/min/1.73 m^2 in favor of EVR + rTAC (95% CI, 2.02-8.05, $P = 0.001$). Consistent with the results in the FAS, the mean change in eGFR in the subpopulation of patients who remained on treatment was significantly better with EVR + rTAC versus sTAC (−7.34 versus −14.20 mL/min/1.73 m^2; difference 6.85 mL/min/1.73 m^2; 95% CI, 3.89-9.82, $P < 0.001$). The mean eGFR at randomization (week 4) was comparable between EVR + rTAC versus sTAC group. Starting at week 6 through to month 24, the mean eGFR remained significantly higher with EVR + rTAC versus sTAC (Figure 3). At week 6, the mean eGFR was 92.0 mL/min/1.73 m^2 in the EVR + rTAC group versus 79.8 mL/min/1.73 m^2 in the sTAC group ($P < 0.001$). The corresponding mean eGFR values at month 24 were 76.7 mL/min/1.73 m^2 versus 70.7 mL/min/1.73 m^2 ($P = 0.003$), respectively.

A subanalysis of change in eGFR from randomization to month 24 by MELD score at the time of transplantation showed a numerically lower decline, although not significant, with EVR + rTAC compared with sTAC in patients with MELD score ≤14 (−7.5 versus −12.3 mL/min/1.73 m^2, $P = 0.084$), MELD score 15–19 (−1.4 versus

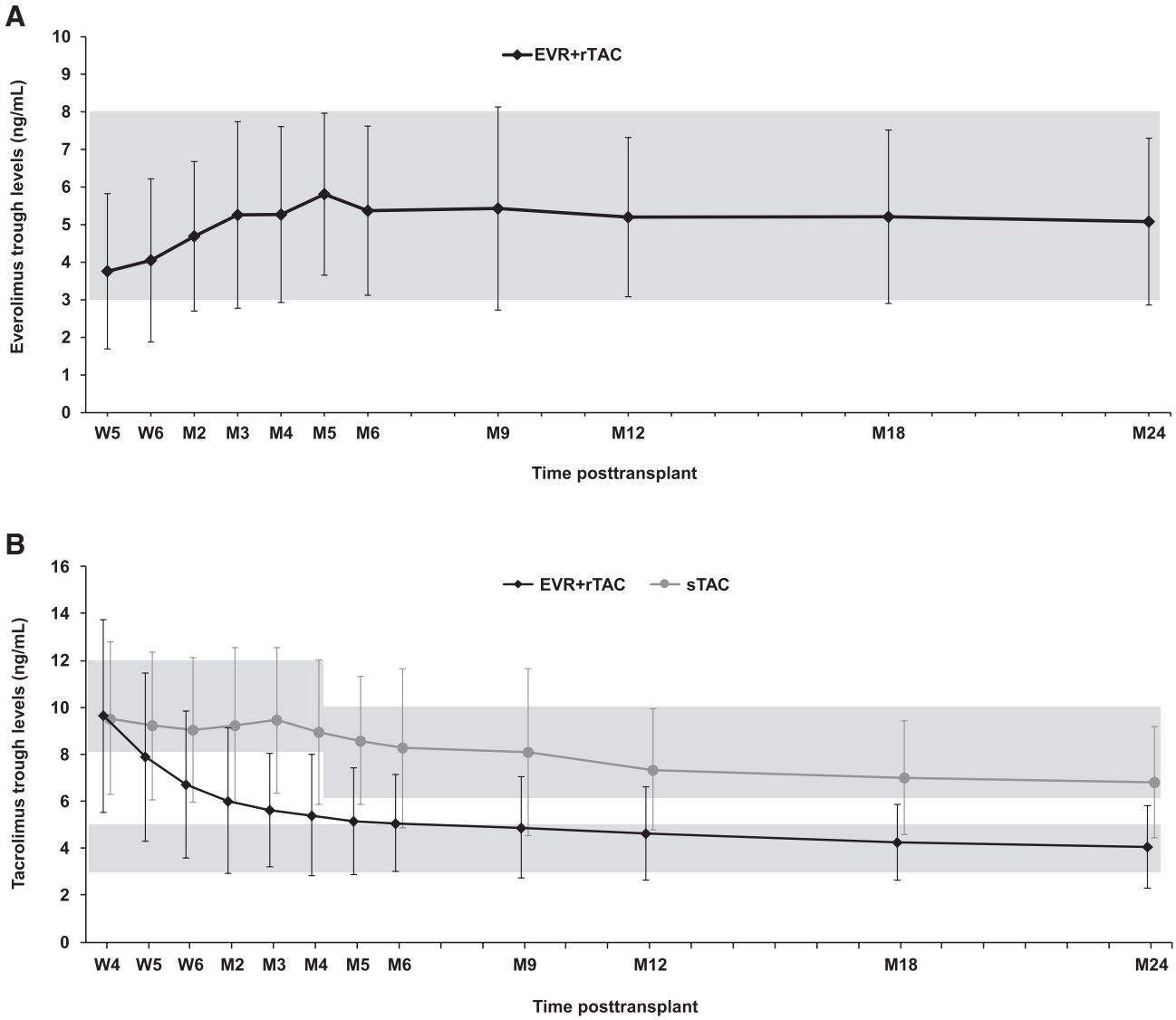
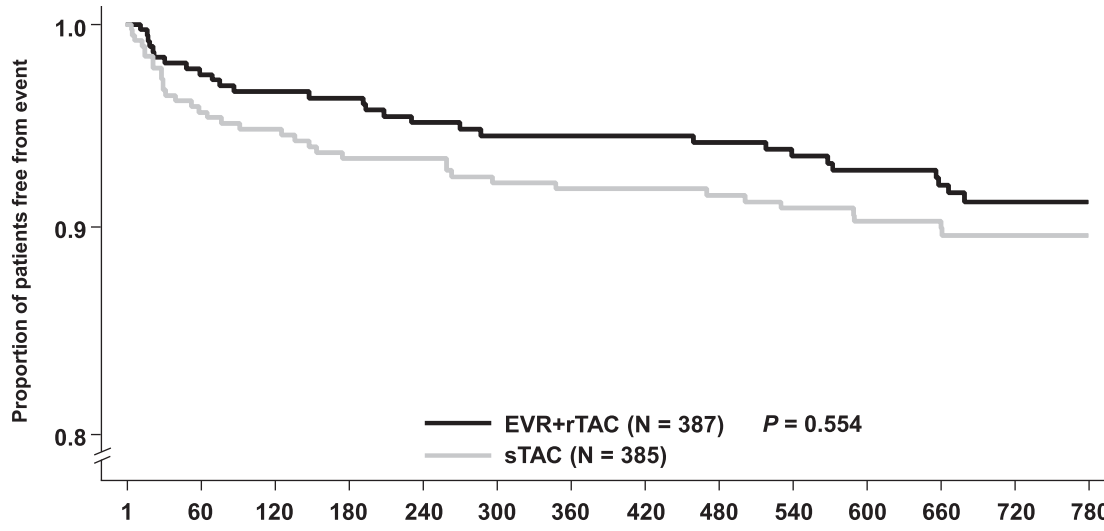


FIGURE 1. Everolimus (A) and tacrolimus (B) trough concentrations during the study. Values are shown as mean (SD). Shaded areas indicate target ranges. EVR, everolimus; M, month; rTAC, reduced tacrolimus; sTAC, standard tacrolimus; W, week.

–9.7 mL/min/1.73 m^2, $P = 0.060$), and MELD score 20–24 (–7.9 versus –12.8 mL/min/1.73 m^2; $P = 0.141$). However, the decline in eGFR was comparable in patients with MELD score 25–29 (–15.8 versus –16.6 mL/min/1.73 m^2, $P = 0.734$) and MELD score ≥30 (–15.9 versus –16.2 mL/min/1.73 m^2, $P = 0.671$; Figure 4).

A subanalysis of renal function by CKD stage at randomization showed comparable change in eGFR from randomization to month 24 for patients with CKD stage 4/5 (eGFR <30 mL/min/1.73 m^2; change: +11.54 mL/min/1.73 m^2 with EVR + rTAC versus +24.94 mL/min/1.73 m^2 with sTAC, $P = 0.487$), CKD stage 3B (eGFR 30–<45 mL/min/1.73 m^2; change: +17.93 mL/min/1.73 m^2 versus +9.56 mL/min/1.73 m^2 with sTAC, $P = 0.162$), and CKD stage 3A (eGFR 45–<60 mL/min/1.73 m^2; change: +3.12 mL/min/1.73 m^2 versus +2.12 mL/min/1.73 m^2 with sTAC, $P = 0.491$). For patients with CKD stage 1/2 (eGFR ≥60 mL/min/1.73 m^2) at randomization, the decline in eGFR from randomization to month 24 was significantly lower with EVR + rTAC versus sTAC (–12.82 mL/min/1.73 m^2 versus –17.67 mL/min/1.73 m^2, $P = 0.009$). Of 4 patients with CKD stage 4/5 at randomization in the EVR + rTAC group, renal function improved in 3 patients (2 patients had eGFR 30–<45 mL/min/1.73 m^2, 1 patient had eGFR ≥60 mL/min/1.73 m^2), while renal function remained stable in 1 patient (eGFR <30 mL/min/1.73 m^2). In the sTAC group, 2 patients had CKD stage 4/5 at randomization; renal function was improved in both the patients by month 24 (1 patient had eGFR 30–<45 mL/min/1.73 m^2 and 1 patient had eGFR 45–<60 mL/min/1.73 m^2). Overall, 10 patients in the EVR + rTAC group and 5 patients in the sTAC group had CKD stage 4/5 at month 24 (Table 4).

The multivariate analysis showed that the presence of diabetes at baseline ($P = 0.0322$) and MELD score ≥15 ($P = 0.0003$) among the patients receiving EVR + rTAC regimen were significantly associated with the lower renal function outcome up to month 24. Male recipients receiving sTAC treatment were significantly associated with the better renal function outcome (Table 5). However, recipient's age and eGFR at randomization were significantly associated with renal function outcomes, irrespective of the immunosuppression regimen they are receiving.



No. of patients at risk														
EVR+rTAC	387	350	334	321	310	298	294	289	281	276	272	253	20	6
sTAC	383	348	333	324	318	312	303	301	293	285	282	271	22	5

FIGURE 2. Kaplan–Meier plot for proportion of patients free from composite efficacy failure of tBPAR, graft loss, or death. EVR, everolimus; rTAC, reduced tacrolimus; sTAC, standard tacrolimus; tBPAR, treated biopsy-proven acute rejection.

TABLE 2.

Kaplan–Meier incidence rates of efficacy endpoints at mo 24

	EVR + rTAC, N = 387, n (%)	sTAC, N = 385, n (%)	EVR + rTAC vs sTAC	
			Difference (95% CI)	P[a]
tBPAR, graft loss, or death	36 (9.8)	40 (10.8)	–1.0 (–5.4 to 3.4)	0.641
tBPAR	15 (4.2)	24 (6.4)	–2.3 (–5.5 to 1.0)	0.168
Graft loss	9 (2.5)	8 (2.3)	0.2 (–2.1 to 2.5)	0.862
Death	20 (5.5)	14 (3.9)	1.6 (–1.5 to 4.7)	0.305
Graft loss or death	25 (6.8)	19 (5.3)	1.5 (–1.9 to 5.0)	0.387

[a]Z test for no difference.
EVR, everolimus; rTAC, reduced tacrolimus; sTAC, standard tacrolimus; tBPAR, treated biopsy-proven acute rejection.

HCC Recurrence

A total of 251 patients had HCC at the time of liver transplantation (123 EVR + rTAC and 128 sTAC). HCC was the primary reason for transplantation in 80 (20.7%) patients in the EVR + rTAC group and 70 (18.2%) patients in the sTAC group. HCC was the secondary reason for liver transplantation in 28 (7.2%) and 36 (9.4%) patients, although HCC was incidentally diagnosed in 15 (3.9%) and 23 (6.0%) patients, respectively. The majority of the participants in both study groups had HCC within Milan criteria (82.9% and 75.0%, respectively). The number of lesions and tumor size were similar between both treatment groups (Table 6).

Overall, HCC recurrence was observed in 4 of 123 (3.3%) patients in the EVR + rTAC group versus 8 of 128 (6.3%) patients in the sTAC group (risk difference, –3.0; 95% CI, –15.4 to 9.4, $P = 0.377$) at month 24. Of these, 2 patients had discontinued EVR before the recurrence of HCC. One patient discontinued EVR on day 439, and the HCC recurrence was diagnosed on day 754, whereas the second patient discontinued EVR on day 543, and HCC recurrence was diagnosed on day 588. A subgroup analysis showed that HCC recurrence was comparable between the EVR + rTAC and sTAC groups in patients who were within Milan criteria at the time of transplantation (2.9% [3 of 102] versus 2.1% [2 of 96]; risk difference, 0.9; 95% CI, –13.2 to 14.8; $P = 1.000$). In patients classified outside Milan criteria, HCC recurrence was numerically lower with EVR + rTAC compared with sTAC (5.9% [1 of 17] versus 23.1% [6 of 26]; risk difference, –17.2; 95% CI, –45.6 to 13.0; $P = 0.215$).

In a subanalysis of HCC recurrence by AFP levels, HCC recurrence was reported in 2 of 90 (2.2%) patients in EVR + rTAC group and 5 of 104 (4.8%) patients in sTAC group with a pretransplant AFP <400 µg/L (risk difference, –2.6; 95% CI, –16.6 to 11.5; $P = 0.453$). However, 1 of 5 (20.0%) and 2 of 3 (66.7%) patients with a pretransplant AFP ≥400 µg/L had HCC recurrence (risk difference, –46.7; 95% CI, –92.3 to 30.1; $P = 0.464$), respectively.

Safety

Adverse events (AEs) were, in general, comparable between EVR + rTAC and sTAC groups (97.2% versus 97.4%; risk ratio, 1.00; 95% CI, 0.97-1.02). Notably, peripheral edema, leukopenia, hypercholesterolemia, and hyperlipidemia were more frequent in the EVR + rTAC group (Table 7). However, tremor, renal failure, and back pain were more frequent in the sTAC group. Majority of

TABLE 3.

Multivariate Cox proportional hazard model for composite efficacy failure (full analysis set)

	EVR + rTAC		TAC control	
Parameters	**Hazard ratio (95% CI)**	***P***	**Hazard ratio (95% CI)**	***P***
Transplant				
LDLT vs DDLT	1.2 (0.29-4.60)	0.8424	0.6 (0.19-2.04)	0.4332
ESDCAT				
Hepatitis B vs alcoholic cirrhosis	0.4 (0.05-3.32)	0.4044	0.7 (0.13-3.40)	0.6246
Hepatitis C vs alcoholic cirrhosis	1.3 (0.43-3.63)	0.6816	1.4 (0.47-4.18)	0.5528
Hepatocellular carcinoma vs alcoholic cirrhosis	1.7 (0.63-4.63)	0.2929	1.3 (0.39-4.01)	0.7058
Others vs alcoholic cirrhosis	1.1 (0.41-3.14)	0.8032	1.7 (0.64-4.60)	0.2867
Donor sex				
Male vs female	0.9 (0.44-1.88)	0.8022	1.1 (0.57-2.20)	0.7388
Recipient sex				
Male vs female	1.1 (0.46-2.41)	0.9068	1.3 (0.57-2.83)	0.5503
Diabetes at baseline				
Yes vs no	2.3 (1.12-4.54)	0.0232	0.8 (0.41-1.70)	0.6217
MELD score at RND				
≥15 vs ≤14	2.4 (1.06-5.49)	0.0352	1.8 (0.84-3.89)	0.1289
Race				
Caucasian vs Asian	0.9 (0.23-3.84)	0.9343	0.8 (0.24-2.87)	0.7651
Other vs Asian	0.7 (0.11-5.21)	0.7610	0.4 (0.08-2.50)	0.3566
Donor age	1.0 (0.98, 1.03)	0.6447	1.0 (0.98, 1.02)	0.8538
Recipient age	1.0 (0.95, 1.03)	0.5777	1.0 (0.95, 1.01)	0.2334

DDLT, deceased donor liver transplant; ESDCAT, end-stage disease condition at transplant; EVR, everolimus; LDLT, living donor liver transplant; MELD, model end-stage liver disease; RND, randomization; rTAC, reduced-exposure tacrolimus; TAC, tacrolimus.

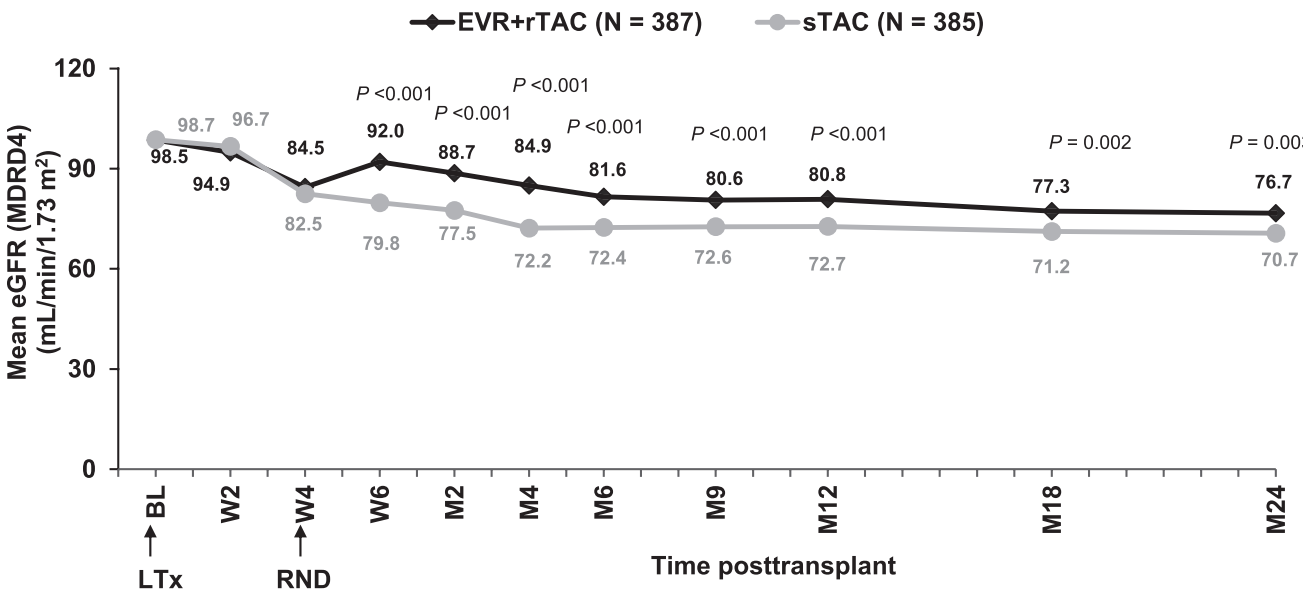


FIGURE 3. Renal function from baseline to month 24. *P* value based on the Wilcoxon rank-sum test. BL, baseline; eGFR, estimated glomerular filtration rate; EVR, everolimus; LTx, liver transplantation; M, month; MDRD4, 4-variable modification of diet in renal disease formula; RND, randomization; rTAC, reduced tacrolimus; sTAC, standard tacrolimus; W, week.

the AEs were mild to moderate in severity for both the treatment groups. In the EVR + rTAC group, 34.6% of recipients experienced severe AEs, whereas 28.2% of recipients in the sTAC group had severe AEs.

Serious adverse events (SAEs) occurred in 57.1% and 54.6% of patients in the EVR + rTAC and sTAC group, respectively. AEs leading to study treatment discontinuation were reported in 24.3% (n = 94) patients in the EVR + rTAC group versus 18.3% (n = 70) in the sTAC group. Proteinuria (2.8% versus 0.3%), renal failure (0.8% versus 2.1%), hepatitis C (1.6% versus 1.3%), and renal impairment (0.5% versus 1.8%) were the most frequent AEs leading to study treatment discontinuation. De novo malignancies in patients without HCC at the time of liver transplantation were reported in 7 (2.7%) patients in the EVR + rTAC group versus 10 (3.9%) in the sTAC group (risk ratio, 0.68; 95% CI, 0.26-1.75). Most of these events were non hematological malignant tumors.

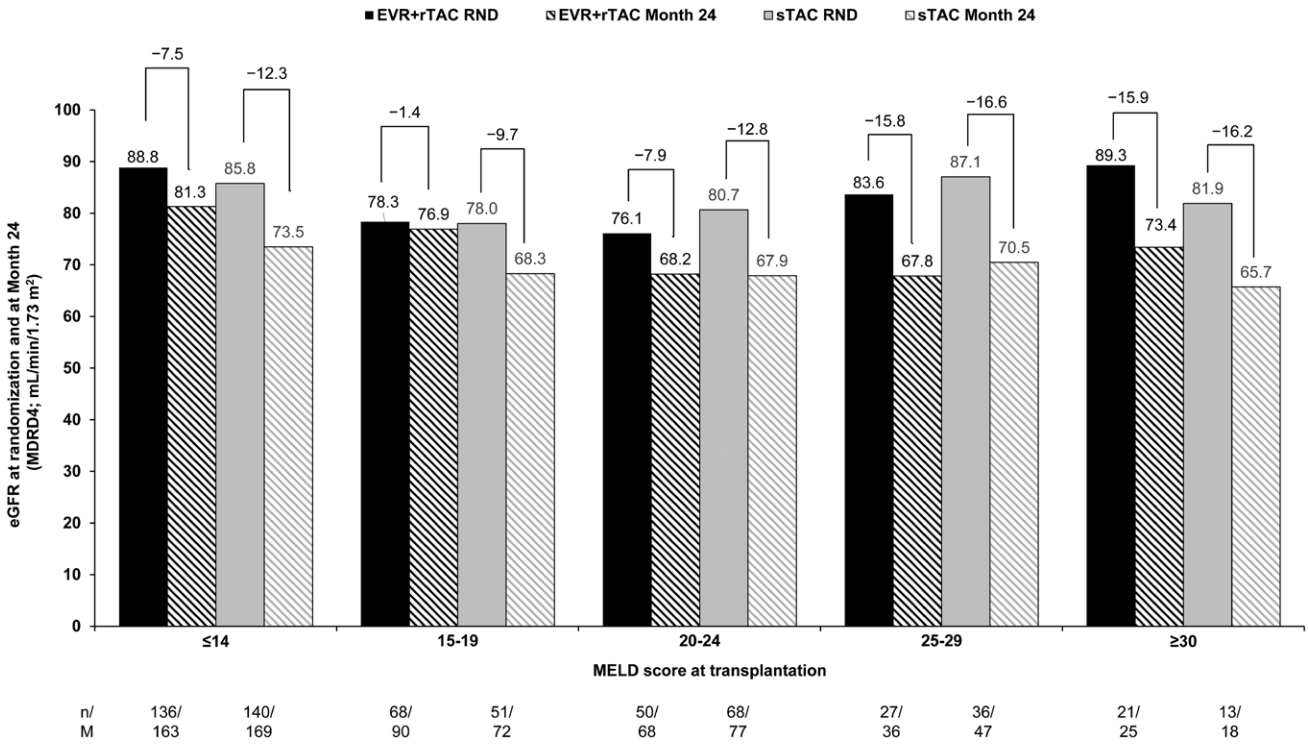


FIGURE 4. Change in eGFR from randomization to month 24 by MELD score at transplant. *P* value based on the Wilcoxon rank-sum test. Patients with assessments at both randomization and month 24 are included. eGFR, estimated glomerular filtration rate; EVR, everolimus; M, total number of patients; MDRD4, 4-variable modification of diet in renal disease formula; MELD, model for end-stage liver disease; n, number of patients evaluable; rTAC, reduced tacrolimus; sTAC, standard tacrolimus.

TABLE 4.

Shift in eGFR from randomization to month 24 by CKD stage

	Randomization		Month 24 CKD stage (eGFR range)			
	CKD stage (eGFR range)	n (%)	Stage 4/5 (<30), n (%)	Stage 3B (30–<45), n (%)	Stage 3A (45–<60), n (%)	Stage 1/2 (≥60), n (%)
EVR + rTAC (N = 387)	Stage 4/5 (<30)	4 (1.3)	1 (25.0)	2 (50.0)	0 (0.0)	1 (25.0)
	Stage 3B (30–<45)	25 (8.1)	2 (8.0)	6 (24.0)	6 (24.0)	11 (44.0)
	Stage 3A (45–<60)	49 (16.0)	5 (10.2)	10 (20.4)	9 (18.4)	25 (51.0)
	Stage 1/2 (≥60)	229 (74.6)	2 (0.9)	6 (2.6)	32 (14.0)	189 (82.5)
sTAC (N = 385)	Stage 4/5 (<30)	2 (0.6)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)
	Stage 3B (30–<45)	19 (6.1)	1 (5.3)	9 (47.4)	5 (26.3)	4 (21.1)
	Stage 3A (45–<60)	48 (15.5)	1 (2.1)	11 (22.9)	25 (52.1)	11 (22.9)
	Stage 1/2 (≥60)	241 (77.7)	3 (1.2)	11 (4.6)	43 (17.8)	184 (76.3)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EVR, everolimus; rTAC, reduced tacrolimus; sTAC, standard tacrolimus.

DISCUSSION

The 24-month results from this pooled analysis of H2304 and H2307 trials involving 772 liver transplant recipients showed that EVR + rTAC versus sTAC regimen provides comparable efficacy with a balanced safety profile. Further, EVR + rTAC treatment was associated with improved renal function, particularly in patients who had normal or mildly decreased renal function (CKD stage 1/2) at randomization, and a trend toward numerically lower HCC recurrence compared with sTAC in patients with large HCC beyond Milan at transplantation.

In the pooled analysis, EVR + rTAC was comparable to sTAC in terms of composite efficacy failure (tBPAR, graft loss, or death), which is consistent with the individual studies.[19,21] The incidence of tBPAR was numerically lower in the EVR + rTAC group compared with sTAC group, while the incidence of graft loss was comparable. With regard to safety, 20 deaths were reported in the EVR + rTAC group in comparison to 14 deaths in the sTAC group. However, on-treatment analysis demonstrated a more balanced event rate—on-treatment deaths were reported in 9 patients in the EVR + rTAC group versus 11 patients in the sTAC group. Based on the multivariate analysis, diabetes at baseline and MELD score ≥15 among the patients receiving EVR + rTAC regimen were associated with significantly higher incidences of composite efficacy failure.

In terms of renal outcomes, the mean eGFR at month 24 was significantly higher in the EVR + rTAC group versus sTAC group. Superior renal function with EVR + rTAC was evident starting from week 4 posttransplantation and was sustained to month 24. Similar results were seen in a subset of patients who remained on randomized study treatment.

TABLE 5.

Multivariate ANCOVA model for on-treatment eGFR (MDRD4) from randomization to month 24 (full analysis set)

	EVR + rTAC		TAC control	
Parameters	**Estimate (SE)**	***P***	**Estimate (SE)**	***P***
Transplant				
LDLT vs DDLT	−2.1 (5.00)	0.6702	6.4 (3.70)	0.0838
ESDCAT				
Hepatitis B vs alcoholic cirrhosis	−4.6 (5.63)	0.4200	4.2 (4.20)	0.3214
Hepatitis C vs alcoholic cirrhosis	4.6 (4.85)	0.3429	6.6 (3.53)	0.0615
Hepatocellular carcinoma vs alcoholic cirrhosis	5 (4.17)	0.2281	2.9 (3.33)	0.3860
Others vs alcoholic cirrhosis	2.7 (4.25)	0.5257	7.6 (3.13)	0.0155
Donor sex				
Male vs female	0.6 (2.99)	0.8383	1.6 (2.12)	0.4552
Recipient sex				
Male vs female	2.9 (3.44)	0.3931	9.6 (2.54)	0.0002
Diabetic				
Yes vs no	−6.7 (3.12)	0.0322	−0.9 (2.20)	0.6669
MELD score at RND				
≥15 vs ≤14	−11.2 (3.07)	0.0003	−3.0 (2.24)	0.1764
Race				
Caucasian vs Asian	−4.7 (5.00)	0.3452	2.2 (3.78)	0.5667
Other vs Asian	−3.8 (7.48)	0.6137	0.3 (5.06)	0.9483
Donor age	0.2 (0.10)	0.0616	0.04 (0.07)	0.5570
Recipient age	−0.9 (0.17)	<0.0001	−0.6 (0.13)	<0.0001
Recipient eGFR	−0.7 (0.04)	<0.0001	−0.6 (0.04)	<0.0001

ANCOVA, analysis of covariance; DDLT, deceased donor liver transplant; eGFR, estimated glomerular filtration rate; ESDCAT, end-stage disease condition at transplant; EVR, everolimus; LDLT, living donor liver transplant; MDRD4, 4-variable modification of diet in renal disease formula; MELD, model end-stage liver disease; RND, randomization; rTAC, reduced-exposure tacrolimus; TAC, tacrolimus.

TABLE 6.

HCC history at transplant and recurrence at month 24

	EVR + rTAC, N = 387	sTAC, N = 383	Risk difference (95% CI)	*P*
Patients with HCC at transplant, n (%)	123 (31.8)	128 (33.4)	–	–
Milan criteria, n (%)				
Within Milan	102 (82.9)	96 (75.0)	–	–
Beyond Milan	17 (13.8)	26 (20.3)	–	–
Missing	4 (3.3)	6 (4.7)	–	–
AFP level, µg/L, n (%)				
<400	90 (73.2)	104 (81.3)	–	–
≥400	5 (4.1)	3 (2.3)	–	–
Missing	28 (22.8)	21 (16.4)	–	–
Number of lesions, mean (SD)	2.0 (2.42)	2.0 (1.70)	–	–
Diameter of largest tumor, cm, mean (SD)	2.6 (1.54)	3.0 (3.20)	–	–
Total tumor diameter, cm, mean (SD)	4.0 (3.57)	4.7 (5.62)	–	–
HCC recurrence at month 24, n/m (%)	4/123 (3.3)	8/128 (6.3)	−3.0 (−15.4 to 9.4)	0.377
HCC recurrence by Milan criteria, n/m (%)				
Within Milan	3/102 (2.9)	2/96 (2.1)	0.9 (−13.2 to 14.8)	1.000
Beyond Milan	1/17 (5.9)	6/26 (23.1)	−17.2 (−45.6 to 13.0)	0.215
Missing	0/4	0/6	–	–
HCC recurrence by AFP level (µg/L) prior to transplant, n/m (%)				
<400	2/90 (2.2)	5/104 (4.8)	−2.6 (−16.6 to 11.5)	0.453
≥400	1/5 (20.0)	2/3 (66.7)	−46.7 (−92.3 to 30.1)	0.464
Missing	1/28 (3.6)	1/21 (4.8)	−1.2 (−29.4 to 27.1)	1.000

AFP, alpha-fetoprotein; CI, confidence interval; EVR, everolimus; HCC, hepatocellular carcinoma; m, total number of patients who had HCC at transplant in the given criteria; n, number of patients with HCC event; rTAC, reduced tacrolimus; sTAC, standard tacrolimus.

TABLE 7.
Adverse events

Event, n (%)	EVR + rTAC, N = 387	sTAC, N = 383	Risk ratio (95% CI)	*P*
Any AE/infection	376 (97.2)	373 (97.4)	1.00 (0.97-1.02)	0.8437
Any SAE/infection	221 (57.1)	209 (54.6)	1.05 (0.92-1.19)	0.4785
AEs leading to study drug discontinuation	94 (24.3)	70 (18.3)	1.33 (1.01-1.75)	0.0416
Death	20 (5.2)	14 (3.7)	1.41 (0.72-2.76)	0.3070
AEs ≥10% in any group				
Diarrhea	92 (23.8)	79 (20.6)	1.15 (0.88-1.50)	0.2937
Hypertension	81 (20.9)	67 (17.5)	1.20 (0.89-1.60)	0.2262
Headache	72 (18.6)	70 (18.3)	1.02 (0.76-1.37)	0.9066
Pyrexia	70 (18.1)	54 (14.1)	1.28 (0.93-1.78)	0.1322
Peripheral edema	63 (16.3)	37 (9.7)	1.69 (1.15-2.47)	0.0063
Abdominal pain	61 (15.8)	44 (11.5)	1.37 (0.96-1.97)	0.0840
Hypercholesterolemia	49 (12.7)	11 (2.9)	4.41 (2.33-8.35)	<0.0001
Leukopenia	48 (12.4)	19 (5.0)	2.50 (1.50-4.17)	0.0002
Nausea	44 (11.4)	42 (11.0)	1.04 (0.70-1.54)	0.8589
Nasopharyngitis	44 (11.4)	41 (10.7)	1.06 (0.71-1.59)	0.7686
Anemia	44 (11.4)	39 (10.2)	1.12 (0.74-1.68)	0.5955
Insomnia	43 (11.1)	38 (9.9)	1.12 (0.74-1.69)	0.5907
Hyperlipidemia	43 (11.1)	13 (3.4)	3.27 (1.79-5.99)	<0.0001
Hepatitis C	40 (10.3)	29 (7.6)	1.37 (0.86-2.16)	0.1794
Tremor	29 (7.5)	48 (12.5)	0.60 (0.39-0.93)	0.0198
Renal failure	29 (7.5)	40 (10.4)	0.72 (0.45-1.13)	0.1518
Back pain	29 (7.5)	39 (10.2)	0.74 (0.46-1.17)	0.1885
AEs leading to study drug discontinuation in ≥1% of patients in any group				
Proteinuria	11 (2.8)	1 (0.3)	10.89 (1.41-83.91)	0.0060
Hepatitis C	6 (1.6)	5 (1.3)	1.19 (0.37-3.86)	0.7746
Renal failure	3 (0.8)	8 (2.1)	0.37 (0.10-1.39)	0.1413
Renal impairment	2 (0.5)	7 (1.8)	0.28 (0.06-1.35)	0.1058
Blood creatinine increased	0 (0.0)	7 (1.8)	0.00	0.0073
Hepatocellular carcinoma	0 (0.0)	5 (1.3)	0.00	0.0300

P values are provided for descriptive purpose only.
AE, adverse event; CI, confidence interval; EVR, everolimus; rTAC, reduced tacrolimus; SAE, serious adverse event; sTAC, standard tacrolimus.

Comparatively higher mean MELD score and lower mean eGFR at randomization were reported in the H2304 study than in the H2307 study. Despite the differences in MELD score and eGFR at randomization, better renal function outcomes were observed in both studies with EVR + rTAC group versus sTAC group at month 24, which is similar to this pooled analysis.[19,21] Given that eGFR at the time of transplantation was close to normal in this analysis, the preservation of renal function is clinically relevant because two-thirds of deaths occur after the first year of liver transplantation, with renal insufficiency being the strongest predictor of late mortality following liver transplantation.[23] In this pooled analysis, patient survival was ≈95%, which is higher than the reported ≈80% patient survival at 2 years following liver transplantation.[1] To note, this analysis does not capture the further renal function benefit seen with EVR + rTAC regimen up to month 36 from the extension of the H2304 trial, as the H2307 trial was concluded at month 24.[18,21] Nevertheless, minimization of immunosuppressant-related renal complications early after transplantation is pivotal as the proportion of patients with high MELD score at liver transplantation has almost tripled (medical urgency status as MELD score ≥35 in 2002 was 7.0% compared with 22.9% in 2016) since the adoption of MELD score for organ allocation, particularly in the DDLT setting.[1,24] In our study, a subgroup analysis of eGFR by MELD score at transplantation showed that patients with low MELD score (≤14, 15–19, and 20–24) benefited the most with EVR + rTAC treatment compared with patients with high MELD score (25–29, and ≥30). Further, an analysis by CKD stage at randomization showed comparable renal outcomes with EVR + rTAC treatment for patients with CKD stage 4/5, stage 3B, and stage 3A, while significant benefit was seen in patients with CKD stage 1/2. These findings reiterate the benefit of EVR before irreversible kidney damage has developed. The multivariate analysis showed that diabetes at baseline and MELD score ≥15 among the patients receiving EVR + rTAC regimen were significantly associated with the lower renal function outcome up to month 24. Irrespective of immunosuppression regimen, recipient's age and eGFR at randomization were significantly associated with renal function outcomes.

HCC is the most frequent indication for liver transplantation in Asian countries and accounts for >60% of HCC cases reported globally.[3,25] To maximize the HCC patient pool who might be benefitted from liver transplantation, many transplant centers apply more liberal criteria for the

selection of HCC patients that include, but are not limited to, University of California San Francisco (UCSF) criteria, Asan criteria, Tokyo criteria, Kyoto criteria, Shanghai Fudan criteria, and Hangzhou criteria.[26-31] Similar outcomes have been reported, with these expanded criteria compared with Milan criteria following LDLT.[32-35] In this analysis, data from both HCC patients within (H2304 and H2307) and outside (H2307) Milan criteria were pooled. Overall HCC recurrence was numerically low in the EVR + rTAC versus sTAC group, despite the TAC trough level in the EVR + rTAC group was mostly beyond the upper threshold, including HCC subgroup. It is noteworthy to highlight that the H2307 trial involving LDLT recipients included HCC patients exceeding Milan criteria, provided there was no extrahepatic spread or macrovascular invasion of tumor. In this subanalysis, recurrence of HCC was numerically lower, although not statistically significant, in patients transplanted beyond Milan with EVR + rTAC compared with sTAC (5.9% versus 23.1%, $P = 0.215$). The results from this subanalysis are in line with the meta-analyses by Cholongitas et al[36] and Tarantino et al[37] who reported encouraging results with the use of mTORis in terms of prevention and treatment of HCC recurrence in patients undergoing liver transplantation for HCC.

Recently, the SiLVER trial, a large, prospective, randomized trial involving 525 liver transplant recipients with HCC, compared recurrence-free survival and overall survival for mTORi-based (sirolimus) versus mTORi-free immunosuppression therapy.[38] At 8 years, recurrence-free survival (70% versus 65%) and overall survival (75% versus 68%) were numerically higher in patients receiving mTORis; however, the difference was not statistically significant, and the primary endpoint of the study was not met. A planned analysis by yearly interval showed a significant benefit in terms of recurrence-free survival with sirolimus (81% versus 72%, $P = 0.0499$) for the first 3 years after transplantation, with significantly improved overall survival up to 5 years (79% versus 70%, $P = 0.0479$). Furthermore, a subgroup analysis showed that younger patients (aged ≤60 years), patients within Milan criteria, and patients receiving sirolimus monotherapy benefited the most. Interestingly, in our analysis, the high-risk patients (outside Milan criteria) appear to benefit the most with EVR + rTAC therapy. The HCC patients from H2307 study is being followed for additional 3 years in an observational study (H2406) to confirm these findings.

The incidence of AEs/SAEs was similar between both treatment groups. Nearly, 50% of the recipients experienced SAEs in both the groups. AEs leading to study treatment discontinuation were more frequent in the EVR + rTAC group compared with sTAC group. Proteinuria was more common in the EVR + rTAC group and led to study treatment discontinuation for 11 patients compared with 1 patient in the sTAC. Renal failure and renal impairment were more common in sTAC group, leading to study treatment discontinuation for 8 and 7 patients, compared with 3 and 2 patients in the EVR + rTAC group, respectively. After discontinuation of randomized study medications, majority of the patients in the EVR + rTAC group started receiving TAC, corticosteroids, and/or mycophenolic acid, and few patients also switched to cyclosporine. On the contrary, among patients who were discontinued from randomized study medication from the sTAC group, majority of patients received TAC and/or corticosteroids. Some of these patients also switched to mTORi (eg, sirolimus or EVR). Overall, the safety profile of EVR was consistent with the known class effect of mTORis, and no new or unexpected safety signals were identified in either trial.[39-41]

The main limitation of this study lies in the post hoc nature of the analysis. However, the main strength of the analysis is the similar study design of the H2304 and H2307 trials that enabled data pooling to achieve a large sample size, with a distinct patient population in terms of etiology, transplant setting, race, and geographical region.

In conclusion, the introduction of EVR to facilitate early TAC exposure reduction ensures similar immunosuppressive efficacy compared with the sTAC regimen at month 24 after either DDLT or LDLT, while providing better renal function and a trend toward numerically lower HCC recurrence. These findings are in line with the recently published clinical guidelines by the Asian Liver Transplant Network that recommended the use of mTORis while reducing the CNI exposure for preservation of renal function in liver transplant patients, and in patients transplanted for HCC, as well as in patients with post-transplant HCC recurrence.[42] The overall safety of EVR + rTAC therapy in this pooled analysis was in line with the known profile, and no unexpected safety concerns were identified. The trend toward numerically lower HCC recurrence seen with EVR + rTAC was more pronounced in patients outside Milan criteria, an important finding that may expand liver transplantation boundaries if confirmed by prospective studies with longer follow-up data.

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REFERENCES

1. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2016 annual data report: liver. *Am J Transplant*. 2018;18 Suppl 1:172–253. doi: 10.1111/ajt.14559.
2. Adam R, Karam V, Cailliez V, et al; all the other 126 contributing centers (www.eltr.org) and the European Liver and Intestine Transplant Association (ELITA). 2018 Annual Report of the European Liver Transplant Registry (ELTR)—50-year evolution of liver transplantation. *Transpl Int.* 2018;31(12):1293–1317. doi: 10.1111/tri.13358.
3. Chen CL, Kabiling CS, Concejero AM. Why does living donor liver transplantation flourish in Asia? *Nat Rev Gastroenterol Hepatol.* 2013;10(12):746–751. doi: 10.1038/nrgastro.2013.194.
4. Shukla A, Vadeyar H, Rela M, et al. Liver transplantation: east versus west. *J Clin Exp Hepatol.* 2013;3(3):243–253. doi: 10.1016/j.jceh.2013.08.004.
5. Trotter JF. Liver transplantation around the world. *Curr Opin Organ Transplant.* 2017;22(2):123–127. doi: 10.1097/MOT.0000000000000392.
6. de Villa V, Lo CM. Liver transplantation for hepatocellular carcinoma in Asia. *Oncologist.* 2007;12(11):1321–1331. doi: 10.1634/theoncologist.12-11-1321
7. Kwak BJ, Kim DG, Han JH, et al. Clinical outcome of 1,000 consecutive cases of liver transplantation: a single center experience. *Ann Surg Treat Res.* 2018;95(5):267–277.

8. Chen CL, Fan ST, Lee SG, et al. Living-donor liver transplantation: 12 years of experience in Asia. *Transplantation*. 2003;75(3 Suppl):S6–S11. doi: 10.1097/01.TP.0000046533.93621.C7.
9. Ahn CS, Hwang S, Kim KH, et al. Long-term outcome of living donor liver transplantation for patients with alcoholic liver disease. *Transplant Proc.* 2014;46(3):761–766. doi: 10.1016/j.transproceed.2013.12.032
10. Chan SC, Cheung TT, Chan AC, et al. New insights after the first 1000 liver transplantations at The University of Hong Kong. *Asian J Surg.* 2016;39(4):202–210. doi: 10.1016/j.asjsur.2015.03.018.
11. Meier-Kriesche HU, Li S, Gruessner RW, et al. Immunosuppression: evolution in practice and trends, 1994–2004. *Am J Transplant.* 2006;6(5 Pt 2):1111–1131. doi: 10.1111/j.1600-6143.2006.01270.x.
12. Mihatsch MJ, Kyo M, Morozumi K, et al. The side-effects of ciclosporine-A and tacrolimus. *Clin Nephrol.* 1998;49(6):356–363.
13. Nankivell BJ, Borrows RJ, Fung CL, et al. Calcineurin inhibitor nephrotoxicity: longitudinal assessment by protocol histology. *Transplantation.* 2004;78(4):557–565. doi: 10.1097/01.tp.0000128636.70499.6e.
14. Vivarelli M, Cucchetti A, La Barba G, et al. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. *Ann Surg.* 2008;248(5):857–862.
15. Schuler W, Sedrani R, Cottens S, et al. SDZ RAD, a new rapamycin derivative: pharmacological properties in vitro and in vivo. *Transplantation.* 1997;64(1):36–42. doi: 10.1097/00007890-199707150-00008.
16. AFINITOR [prescribing information]. *East Hannover*, New Jersey: Novartis Pharmaceuticals Corporation; 2018.
17. De Simone P, Nevens F, De Carlis L, et al. Everolimus with reduced tacrolimus improves renal function in de novo liver transplant recipients: a randomized controlled trial. *Am J Transplant.* 2012;12(11):3008–3020. doi: 10.1111/j.1600-6143.2012.04212.x.
18. Fischer L, Saliba F, Kaiser GM, et al. Three-year outcomes in de novo liver transplant patients receiving everolimus with reduced tacrolimus: follow-up results from a randomized, multicenter study. *Transplantation.* 2015;99(7):1455–1462.
19. Saliba F, De Simone P, Nevens F, et al. Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. *Am J Transplant.* 2013;13(7):1734–1745. doi: 10.1111/ajt.12280.
20. Jeng LB, Lee SG, Soin AS, et al. Efficacy and safety of everolimus with reduced tacrolimus in living-donor liver transplant recipients: 12-month results of a randomized multicenter study. *Am J Transplant.* 2018;18(6):1435–1446. doi: 10.1111/ajt.14623.
21. Suh KS, Jeng L-B, Soin AS, et al. Renal function outcomes with everolimus plus reduced-exposure tacrolimus in de novo living donor liver transplantation: 24-month results from the H2307 study. *Transplantation*. 2018;102:S21–S22.
22. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1–150.
23. 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(6):1420–1427. doi: 10.1111/j.1600-6143.2010.03126.x.
24. Kim WR, Smith JM, Skeans MA, et al. OPTN/SRTR 2012 annual data report: liver. *Am J Transplant.* 2014;14 Suppl 1:69–96. doi: 10.1111/ajt.12581.
25. Zhu RX, Seto WK, Lai CL, et al. Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. *Gut Liver.* 2016;10(3):332–339. doi: 10.5009/gnl15257.
26. Yao FY. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma. *Hepatol Res.* 2007;37 Suppl 2:S267–S274. doi: 10.1111/j.1872-034X.2007.00195.x.
27. Lee SG, Hwang S, Moon DB, et al. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. *Liver Transpl.* 2008;14(7):935–945. doi: 10.1002/lt.21445.
28. Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. *Dig Dis.* 2007;25(4):310–312. doi: 10.1159/000106910.
29. Takada Y, Uemoto S. Liver transplantation for hepatocellular carcinoma: the Kyoto experience. *J Hepatobiliary Pancreat Sci.* 2010;17(5):527–532. doi: 10.1007/s00534-009-0162-y.
30. Fan J, Yang GS, Fu ZR, et al. Liver transplantation outcomes in 1,078 hepatocellular carcinoma patients: a multi-center experience in Shanghai, China. *J Cancer Res Clin Oncol.* 2009;135(10):1403–1412. doi: 10.1007/s00432-009-0584-6.
31. Zheng SS, Xu X, Wu J, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. *Transplantation.* 2008;85(12):1726–1732. doi: 10.1097/TP.0b013e31816b67e4.
32. Togashi J, Akamastu N, Kokudo N. Living donor liver transplantation for hepatocellular carcinoma at the University of Tokyo Hospital. *Hepatobiliary Surg Nutr.* 2016;5(5):399–407. doi: 10.21037/hbsn.2016.08.05.
33. Lee KW, Yi NJ, Suh KS. Section 5. Further expanding the criteria for HCC in living donor liver transplantation: when not to transplant: SNUH experience. *Transplantation.* 2014;97(suppl 8):S20–S23. doi: 10.1097/01.tp.0000446269.20934.d3.
34. Lai Q, Nudo F, Mennini G, et al. Expanded criteria for hepatocellular carcinoma after liver transplantation: a 20-year evolution. *Hepatogastroenterology.* 2013;60(128):2039–2041.
35. Bonadio I, Colle I, Geerts A, et al. Liver transplantation for hepatocellular carcinoma comparing the Milan, UCSF, and Asan criteria: long-term follow-up of a western single institutional experience. *Clin Transplant.* 2015;29(5):425–433. doi: 10.1111/ctr.12534
36. Cholongitas E, Mamou C, Rodríguez-Castro KI, et al. Mammalian target of rapamycin inhibitors are associated with lower rates of hepatocellular carcinoma recurrence after liver transplantation: a systematic review. *Transpl Int.* 2014;27(10):1039–1049.
37. Tarantino G, Magistri P, Ballarin R, et al. Oncological impact of M-Tor inhibitor immunosuppressive therapy after liver transplantation for hepatocellular carcinoma: review of the literature. *Front Pharmacol.* 2016;7:387.
38. Geissler EK, Schnitzbauer AA, Zulke C, et al. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized, multicenter, open-label phase 3 trial. *Transplantation.* 2016;100(1):116–125. doi: 10.1097/TP.0000000000000965.
39. *CERTICAN/ZORTRESS [prescribing information]*. East Hannover, New Jersey: Novartis Pharmaceuticals Corporation; 2018.
40. Kaplan B, Qazi Y, Wellen JR. Strategies for the management of adverse events associated with mTOR inhibitors. *Transplant Rev (Orlando).* 2014;28(3):126–133. doi: 10.1016/j.trre.2014.03.002.
41. Ventura-Aguiar P, Campistol JM, Diekmann F. Safety of mTOR inhibitors in adult solid organ transplantation. *Expert Opin Drug Saf.* 2016;15(3):303–319. doi: 10.1517/14740338.2016.1132698.
42. Tan PS, Muthiah MD, Koh T, et al. Asian Liver Transplant Network Clinical Guidelines on immunosuppression in liver transplantation. *Transplantation.* 2019;103(3):470–480.