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et al

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Effect of Early Everolimus-Facilitated Reduction of Tacrolimus on Efficacy and Renal Function in De Novo Liver Transplant Recipients: 24-Month Results for the North American Subpopulation

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Background. A recent randomized phase III study of 719 de novo liver transplant recipients showed that early everolimus plus reduced-dose tacrolimus (EVR + rTAC) led to significantly better kidney function than standard TAC (TAC-C), without compromising efficacy. In that study, patients from North America (n = 211) had increased risk factors for posttransplant renal insufficiency at study start, relative to patients from Europe and rest of world (eg, worse renal function, more diabetes, older age). **Methods.** A post hoc analysis was performed to assess whether these regional disparities affected study outcomes in North American patients. **Results.** In this subpopulation, estimated glomerular filtration rates at randomization were higher in TAC-C over EVR + rTAC (76.4 vs 69.3 mL/min per 1.73 m^2). Mean changes in estimated glomerular filtration rate values (mL/min per 1.73 m^2) favored EVR + rTAC over TAC-C at months 12 (+3.7 vs −4.5; $P = 0.032$), 24 (+2.7 vs −6.6; $P = 0.042$), and 36 (+4.3 vs −8.1; $P = 0.059$). The composite efficacy endpoint of treated biopsy-proven acute rejection, graft loss, or death was 10.9%, 14.1%, and 14.1% for EVR + rTAC and 13.1%, 17.2%, and 19.3% for TAC-C at months 12, 24, and 36, respectively. **Conclusions.** Although the North American cohort had more comorbidities, results were consistent with the overall population for efficacy and renal function.

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Liver transplantation has become a standard-of-care treatment modality for end-stage liver disease, with excellent overall 5-year survival rates of around 70% or greater.[1] However, one of the persistent challenges in the posttransplant period has been management of renal complications associated with chronic immunosuppression therapy required to prevent rejection of the transplanted graft. In the United States, it is estimated that the 5-year incidence of chronic renal failure after liver transplantation is 18.1%.[2] Moreover, patients developing chronic renal failure have an increased mortality risk that is estimated to be more than 4 times greater than those not developing chronic renal failure.[2,3] The vast majority of patients who undergo liver transplantation are currently placed on a calcineurin inhibitor (CNI)-based immunosuppressive regimen, and this is a factor associated with an increased risk of renal dysfunction.[4]

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Strategies to reduce CNI-related nephrotoxicity by early CNI minimization/elimination are of particular interest in the field of liver transplantation. Recently, in a 24-month international, randomized, controlled study (H2304) in de novo liver transplant recipients, it was shown that early everolimus (EVR)-facilitated tacrolimus (TAC) dose reduction led to significantly better kidney function versus standard TAC (TAC-C) without compromising efficacy.[5,6] The adjusted change (via an analysis of covariance model) from randomization in estimated glomerular filtration rate (eGFR), based on the Modification of Diet in Renal Disease-4 variables (MDRD4) formula,[7] favored EVR + reduced TAC (rTAC) over TAC-C by 8.5 mL/min per 1.73 m^2 ($P < 0.001$) at month 12 and 6.7 mL/min per 1.73 m^2 ($P = 0.002$) at month 24.[5,6]

There are notable differences in patients undergoing liver transplantation in North America compared with other regions in the world. For example, in the H2304 study, more participants from North America compared with Europe and rest of world (ROW) had hepatitis C virus (HCV) infection.[8] This difference is not surprising because previous reports have recognized that HCV infection is known to be the most common cause of liver transplantation in the United States.[9] In addition, North American participants from Study H2304 had lower eGFR values, and higher model for end-stage liver disease (MELD) scores at time of transplantation, than those from other regions.[10] They also had a higher incidence of diabetes and were older when compared with individuals from Europe and ROW.[8] These factors are known to be associated with an increased risk of chronic kidney disease or acute kidney injury.[11,12] Regional variation in patient characteristics after liver transplantation have also previously been reported in the literature.[13] Because geographical disparities in risk factors for posttransplant renal insufficiency could have an impact on study outcomes, it is important to analyze data for specific subpopulations to assess results in comparison to the overall study population. Here we report a post hoc analysis of efficacy, renal function, and adverse event (AE) results for the H2304 North American subpopulation.

MATERIALS AND METHODS

Methods for Study H2304 were previously published in detail[5] and are briefly summarized here.

Study Design

This 24-month international, randomized, controlled study in de novo liver transplant recipients compared 3 open-label treatments (Figure 1). An initial 30-day (±5 days) posttransplantation run-in period with TAC (± mycophenolate mofetil [MMF]) was stratified by pretransplant HCV status and eGFR (MDRD4). Participants were then randomized (1:1:1) into the treatment groups: EVR (trough concentration [C0] 3-8 ng/mL) plus rTAC (C0 3-5 ng/mL) ("EVR + rTAC"); EVR (C0 3–8 ng/mL to month 4, then 6–10 ng/mL) plus TAC (C0 3-5 ng/mL), with TAC withdrawal by month 4 (TAC-WD); and standard TAC (C0 8-12 ng/mL to month 4, then 6-10 ng/mL) ("TAC-C"). EVR was initiated at a dose of 1 mg twice daily, with dose adjustment to achieve the target C0. All patients received corticosteroids for a minimum of 180 days. Enrollment in the TAC-WD arm was prematurely terminated, at the recommendation of the independent data monitoring committee, due to higher rejection rates. Thereafter, eligible patients completing the run-in period were randomized 1:1 to EVR + rTAC or TAC-C. Patients who had already been randomized to the TAC-WD arm converted to local standard treatment if ≤ 180 days after randomization, or either continued on their assigned treatment or converted to local standard treatment if longer than 180 days after randomization.

Study Endpoints

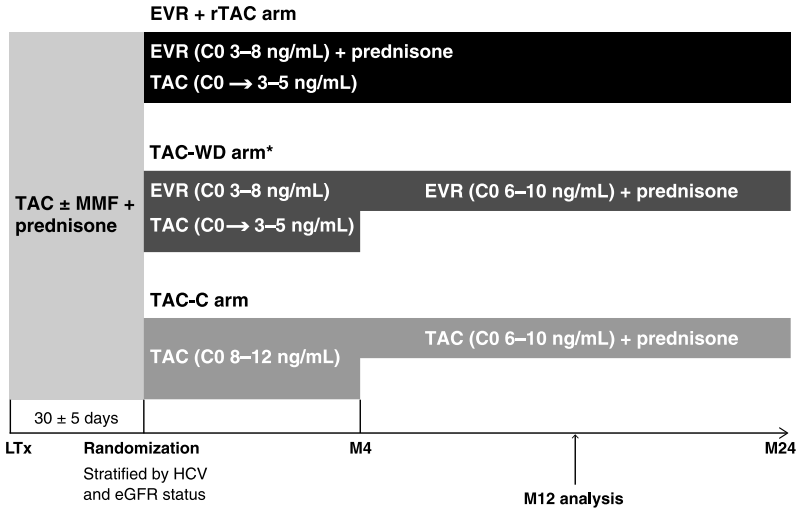
The original protocol endpoints were noninferiority of composite efficacy failure rate of death, graft loss, or loss to follow-up (primary endpoint) and superior renal function (coprimary endpoint), as assessed by eGFR (MDRD4), at month 12. After implementation of the protocol amendment to discontinue enrollment in the TAC-WD arm and to implement the European Medicines Agency guideline on clinical investigation of immunosuppressants for solid organ transplantation,[14] the primary and coprimary endpoints were separated into noninferior composite efficacy failure rate of (a) treated biopsy-proven acute rejection (tBPAR) (defined as an acute rejection with a locally confirmed rejection activity index of 3 or greater according to Banff 1997 criteria[15] treated with antirejection therapy), (b) graft loss, or (c) death at month 12 (primary endpoint, noninferiority margin = 12%), and noninferior renal function as measured by change in eGFR (MDRD4) from randomization to month 12 (key secondary endpoint, noninferiority margin = –6 mL/min per 1.73 m^2).

Patients

Briefly, patients were adult (18-70 years of age) recipients of a primary liver transplant from a deceased donor and had received an immunosuppressive regimen containing corticosteroids and TAC 3 to 7 days after liver transplantation, with 1 or more TAC C0 values of 8 ng/mL or greater in the week before randomization. The eGFR (MDRD4) at randomization was 30 mL/min per 1.73 m^2 or greater. Patients were excluded for the following reasons: recipients of multiple solid-organ or islet-cell transplants, recipients of a liver from a living donor or a split liver, history of malignancy of any organ system within the past 5 years (except nonmetastatic basal or squamous cell carcinoma of the skin or hepatocellular carcinoma), hepatocellular carcinoma not meeting Milan criteria[16,17] at the time of transplantation and any antibody induction therapy. AEs were summarized for the safety population, which included all randomized patients who received 1 dose or more of study medication. The majority of discontinuations in the EVR + rTAC and TAC-C groups were due to AEs; see Results section for further details.

Statistical Analysis

Efficacy and renal function (eGFR) analyses were performed using the intent-to-treat population, which included all randomized patients. eGFR values and changes from randomization to each visit were compared between the EVR + rTAC and TAC-C groups using the Wilcoxon Rank-sum test. Data are primarily presented for the North American subpopulation; results for the European and ROW subpopulations are also described for context. However, it is important to note that the study was not designed to compare subpopulations from the various



*Enrollment into the TAC-WD arm was stopped due to higher rejection rates and the protocol was subsequently amended.

C0, trough concentration; eGFR, estimated glomerular filration rate; EVR + rTAC, everolimus + reduced tacrolimus; HCV, Hepatitis C virus; LTx, liver transplantation; M, month; MMF, mycophenolate mofetil; TAC-C, standard tacrolimus; TAC-WD, tacrolimus withdrawal by month 4.

FIGURE 1. H2304 study design.

regions or to assess outcomes with respect to individual risk factors. As this was an ad hoc analysis, no formal statistical test was performed.

RESULTS

The following sections focus on the EVR + rTAC and TAC-C treatment groups; results for the terminated TAC-WD arm are shown in the tables and figures and briefly summarized within the text.

Patients

Of the 719 randomized patients in the overall population, 211 were from North America (EVR + rTAC [n = 65], TAC-WD [n = 68], and TAC-C [n = 78]); 419 were from Europe (EVR + rTAC [n = 149], TAC-WD [n = 138], and TAC-C [n = 132]); and 89 were from ROW (EVR + rTAC [n = 31], TAC-WD [n = 25], and TAC-C [n = 33]). Patient disposition for the North American subpopulation is shown in Figure 2.

Demographic and baseline characteristics for the overall population and the North American subpopulation were generally similar across the 3 treatment groups (Table 1). In the North American subpopulation, mean and median eGFR values at randomization were lower in the EVR + rTAC group (69.3 and 66.1 mL/min per 1.73 m^2, respectively) than in the TAC-WD (82.2 and 76.1 mL/min per 1.73 m^2) and TAC-C (76.4 and 73.1 mL/min per 1.73 m^2) treatment arms. As mentioned previously, several other differences were apparent between North American participants and those from Europe and ROW: mean age (54.8 vs 53.8 and 51.4 years, respectively); diabetes (44% vs 29% and 34%), HCV infection (49% vs 21% and 37%), mean eGFR values (76.1 vs 78.6 and 83.7 mL/min per 1.73 m^2), body mass index (26.1 vs 24.4 and 25.2 kg/m^2), and MELD scores (22.7 vs 17.6 and 18.5).

Immunosuppression

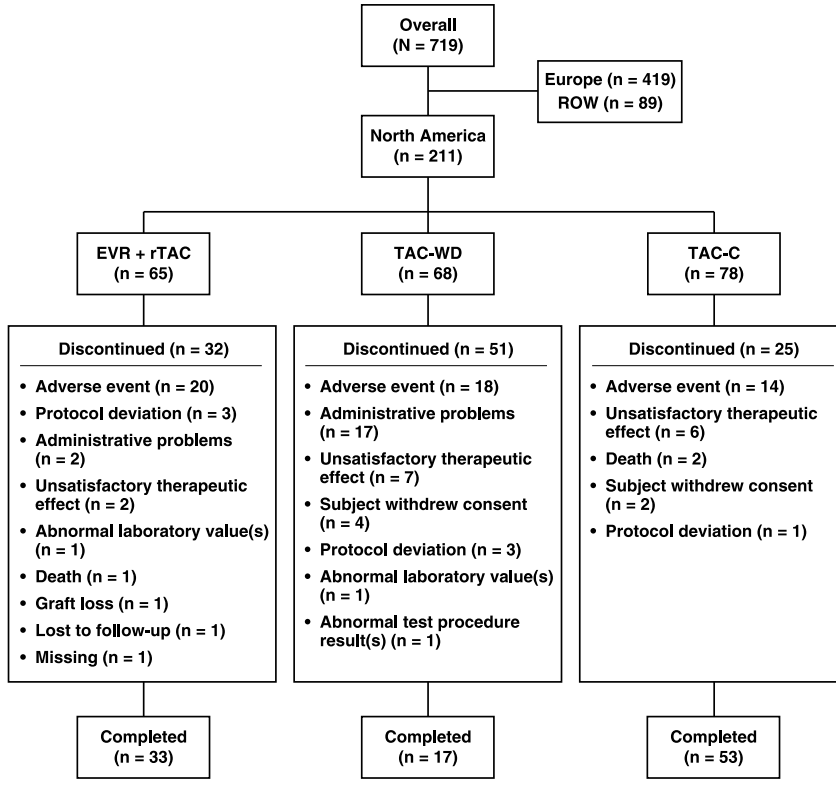
At randomization, mean trough levels of TAC were 10.3 ng/mL in the EVR + rTAC group and 9.8 ng/mL in the TAC-C group (Table 2). At months 12 and 24, mean trough levels of TAC were within the target ranges both in the EVR + rTAC group (4.5 and 3.6 ng/mL, respectively; target, 3-5 ng/mL) and TAC-C group (7.7 and 6.7 ng/mL, respectively; target, 6-10 ng/mL). At months 12 and 24, mean trough levels of EVR were within the target range in the EVR + rTAC group (5.8 and 6.1 ng/mL, respectively; target, 3-8 ng/mL). Results in Europe were similar to those in North America; sample sizes in ROW were too limited for meaningful comparison.

Renal Function

There was an imbalance in renal function at time of randomization with lower values for North America compared with Europe, as well as within the North American subgroup, thus favoring the TAC-C group with a higher eGFR at time of randomization. However, at most visits after randomization in North America, treatment with EVR + rTAC was associated with greater mean eGFR values (Figure 3) and mean increases in eGFR values (Figure 4), versus TAC-C treatment, with most mean increases being statistically significant ($p < 0.05$).

In North America, despite having lower eGFR at randomization, mean eGFR values in the EVR + rTAC group increased after randomization and were significantly higher at month 3 versus the TAC-C group (Figure 3). At month 12, mean eGFR values were 71.5 versus 70.5 mL/min per 1.73 m^2 ($P = 0.549$), respectively. Corresponding results at month 24 were 68.4 versus 68.0 mL/min per 1.73 m^2 ($P = 0.747$).

In contrast to mean eGFR values, mean changes in eGFR values were observed from randomization to each visit in the EVR + rTAC group, with statistically significant ($P < 0.05$) differences favoring EVR + rTAC versus TAC-C at all visits except week 5 (data not shown) and months 9 and 18 (Figure 4). At month 12, mean changes in eGFR values were +3.7 versus –4.5 mL/min per 1.73 m^2 (P = 0.032)



EVR + rTAC, everolimus + reduced tacrolimus; ROW, Rest of World; TAC-C, standard tacrolimus; TAC-WD, tacrolimus withdrawal by month 4.

FIGURE 2. Patient disposition for North American subpopulation.

for EVR + rTAC and TAC-C, respectively; corresponding median changes were –0.2 versus –6.1 mL/min per 1.73 m^2. At month 24, mean changes in eGFR values were +2.7 versus –6.6 mL/min per 1.73 m^2 (P = 0.042), respectively; corresponding median changes were +1.4 and –9.4 mL/min per 1.73 m^2.

The terminated TAC-WD arm had the highest mean eGFR values throughout the study (82.2, 81.7, and 75.0 mL/min per 1.73 m^2 at randomization, month 12, and month 24, respectively). Mean reductions in eGFR values were observed from randomization to months 12 and 24 (–3.0 and –10.0 mL/min per 1.73 m^2, respectively); corresponding median changes were –0.2 and –0.6 mL/min per 1.73 m^2.

Alternative measures (MDRD6, CKD-EPI, serum creatinine, Nankivell, Cockcroft-Gault, and cystatin C) to calculate eGFR were also assessed. The results were similar to those reported with MDRD4, that is, significantly better mean eGFR changes versus TAC-C in almost all cases (data not shown).

Efficacy

Efficacy results are summarized in Table 3 and Figure 5. In North America, the Kaplan-Meier incidence rate of the primary composite efficacy endpoint of tBPAR, graft loss, or death for EVR + rTAC at month 12 and month 24 were 10.9% and 14.1%, respectively, and for TAC-C were 13.1% and 17.2% (Table 3 and Figure 5A).

tBPAR occurred in 4 (6.2%) of 65 patients in the EVR + rTAC group and 9 (11.5%) of 78 patients in the TAC-C group at month 12. At month 24, the Kaplan-Meier incidence rate of tBPAR was 8.1% for EVR + rTAC and 13.2% for TAC-C (Table 3 and Figure 5B).

The terminated TAC-WD arm was associated with the highest event rate of the primary composite efficacy endpoint, primarily driven by a higher tBPAR rate within 3 months of withdrawal of TAC. The primary composite efficacy endpoint, for example, had Kaplan-Meier incidence rates of 24.6% and 25.9% at months 12 and 24, respectively.

In Europe and ROW, comparability between the EVR + rTAC and TAC-C arms was also shown for the above endpoints.

Adverse Events

The most common AEs reported in the North American subpopulation are shown in Table 4. Throughout the study, the majority of the most common AEs were reported at a similar incidence in the EVR + rTAC and TAC-C groups. Incidence of specific AEs of interest in the EVR + rTAC and TAC-C groups were as follows: hypertension (26.2% vs 14.1%, respectively), leukopenia (20.0% vs 7.7%), abdominal pain (12.3% vs 20.5%), nausea (15.4% vs 21.8%), vomiting (9.2% vs 15.4%), insomnia (6.2% vs 17.9%), and hyperkalemia (7.7% vs 20.5%). The vast majority of AEs occurred during the initial year of therapy (Table 4).

AEs affecting the cardiovascular system were reported in 11 (16.9%) patients in the EVR + rTAC group and 14 (17.9%) patients in the TAC-C group. AEs reported by more than 1 patient in either group (EVR + rTAC vs TAC-C, respectively) included: angina pectoris (2 [3.1%], 4 [5.1%]), tachycardia (3 [4.6%], 3 [3.8%]), atrial fibrillation (2 [3.1%], 1 [1.3%]), coronary artery disease (2 [3.1%], 1 [1.3%]), myocardial ischemia (0, 3 [3.8%]), acute myocardial infarction (0, 2 [2.6%]), and cardiomegaly (2 [3.1%], 0). Diabetes mellitus was reported as an AE in 5 (7.7%) patients in the EVR + rTAC

TABLE 1.

Demographic and baseline characteristics of intent-to-treat in the overall H2304 population and the North American subpopulation

	North American subpopulation			Total H2304 population		
Characteristics	**EVR + rTAC (n = 65)**	**TAC-WD (n = 68)**	**TAC-C (n = 78)**	**EVR + rTAC (N = 245)**	**TAC-WD (N = 231)**	**TAC-C (N = 243)**
Age: mean ± SD, y	54.2 ± 8.3	55.5 ± 8.5	54.7 ± 7.3	53.6 ± 9.2	53.2 ± 10.8	54.5 ± 8.7
Sex, n (%)						
Male	47 (72.3)	51 (75.0)	55 (70.5)	180 (73.5)	164 (71.0)	179 (73.7)
Female	18 (27.7)	17 (25.0)	23 (29.5)	65 (26.5)	67 (29.0)	64 (26.3)
Race, n (%)						
White	56 (86.2)	54 (79.4)	64 (82.1)	211 (86.1)	196 (84.8)	195 (80.2)
Black	4 (6.2)	5 (7.4)	8 (10.3)	4 (1.6)	6 (2.6)	9 (3.7)
Other	5 (7.7)	9 (13.2)	6 (7.7)	30 (12.2)	29 (12.6)	39 (16.0)
BMI: mean ± SD, kg/m^2	26.5 ± 4.5	26.6 ± 4.5	25.4 ± 4.8	25.2 ± 4.2	25.3 ± 4.3	24.5 ± 4.2
HCV positive status, n (%)	31 (47.7)	32 (47.1)	41 (52.6)	79 (32.2)	72 (31.2)	76 (31.3)
eGFR (MDRD4) at randomization, mL/min per 1.73 m^2						
Mean ± SD	69.3 ± 26.1	82.2 ± 39.9	76.4 ± 24.4	81.3 ± 33.3	82.9 ± 37.2	78.8 ± 27.7
Median	66.1	76.1	73.1	75.7	75.7	77.4
Diabetic at randomization, n (%)	28 (43.1)	30 (44.1)	39 (50.0)	87 (35.5)	79 (34.2)	97 (39.9)
Primary disease leading to liver transplantation, n (%)						
Hepatitis C	29 (44.6)	27 (39.7)	36 (46.2)	61 (24.9)	55 (23.8)	56 (23.0)
Alcoholic cirrhosis	13 (20.0)	12 (17.6)	4 (5.1)	70 (28.6)	49 (21.2)	51 (21.0)
Hepatocellular carcinoma	4 (6.2)	8 (11.8)	6 (7.7)	44 (18.0)	32 (13.9)	36 (14.8)
Cryptogenic cirrhosis	5 (7.7)	2 (2.9)	7 (9.0)	7 (2.9)	11 (4.8)	18 (7.4)
Primary biliary cirrhosis	5 (7.7)	3 (4.4)	3 (3.8)	8 (3.3)	11 (4.8)	8 (3.3)
Sclerosing cholangitis	0	5 (7.4)	5 (6.4)	8 (3.3)	20 (8.7)	12 (4.9)
Hepatitis B	2 (3.1)	3 (4.4)	2 (2.6)	16 (6.5)	17 (7.4)	15 (6.2)
Autoimmune liver hepatitis	1 (1.5)	0	2 (2.6)	4 (1.6)	7 (3.0)	6 (2.5)
Other	6 (9.2)	8 (11.8)	13 (16.7)	27 (11.0)	29 (12.6)	41 (16.9)
MELD score, mean ± SD	22.8 ± 10.8	22.6 ± 6.4	22.6 ± 6.2	19.2 ± 9.0	19.6 ± 7.5	19.0 ± 7.6
Donor age, mean ± SD	42.2 ± 16.2	42.3 ± 17.0	40.8 ± 15.2	48.8 ± 18.2	50.0 ± 18.2	48.7 ± 17.4
Cold ischemia time: mean ± SD, h	7.4 ± 4.3[1]	6.4 ± 2.3[2]	6.5 ± 2.2[3]	7.9 ± 4.4	7.1 ± 2.8	7.6 ± 5.2

[a] n = 63, [b] n = 67, [c] n = 77.
BMI, body mass index.

group and 4 (5.1%) patients in the TAC-C group. AEs of lipid metabolism in the EVR + rTAC and TAC-C groups, respectively, included hypercholesterolemia (5 [7.7%], 2 [2.6%]), hyperlipidemia (5 [7.7%], 2 [2.6%]), and hypertriglyceridemia (5 [7.7%], 1 [1.3%]).

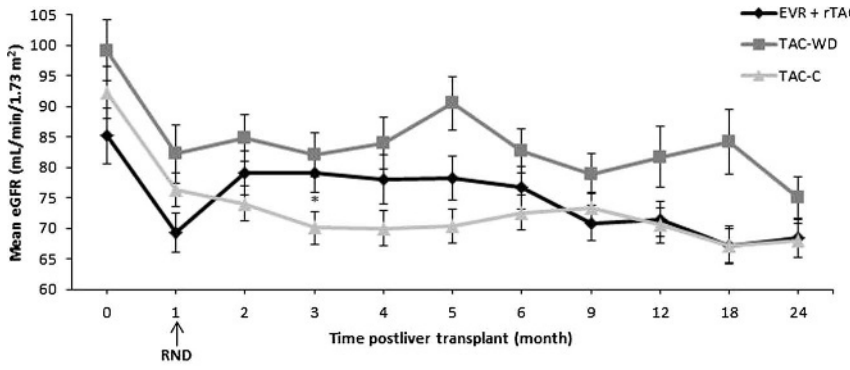
Wound infections were infrequent during the study, with only 2 (3.1%) AE reports in the EVR + rTAC group compared with 0 in the other treatment groups. Proteinuria was also uncommon: 0 with EVR + rTAC treatment and 1 (1.3%) with TAC-C treatment. A single case of stomatitis was reported in the EVR + rTAC group. AEs of infections/infestations occurred at a similar rate between treatments, with the most common being HCV (23.1% vs 20.5% in the EVR + rTAC vs TAC-C groups, respectively).

Throughout the study, AEs resulted in the discontinuation of study medication for 20 (30.8%) patients in the EVR + rTAC group and 14 (17.9%) patients in the TAC-C group (Figure 2). The only AEs that led to the discontinuation of more than 1 patient in these treatment groups were hepatitis C infection/acute hepatitis (n = 2) in the EVR + rTAC group and renal failure (n = 3), hepatitis C infection (n = 2), and increased blood creatinine (n = 2) in the TAC-C group. Most discontinuations resulting from AEs occurred within 6 months of randomization.

TABLE 2.

Tacrolimus trough levels at randomization, month 12 and month 24 in the overall H2304 population and the North American subpopulation

		North American subpopulation		Total H2304 population	
Visit	**Statistic**	**EVR + rTAC (n = 65)**	**TAC-C (n = 78)**	**EVR + rTAC (N = 245)**	**TAC-C (N = 243)**
Randomization/week 4	n	57	73	205	211
	Mean (SD)	10.3 (4.5)	9.8 (3.3)	10.5 (4.2)	10.0 (3.1)
Month 12	n	32	50	135	148
	Mean (SD)	4.5 (1.8)	7.7 (2.8)	4.9 (2.1)	7.7 (2.8)
Month 24	n	22	41	109	128
	Mean (SD)	3.6 (1.5)	6.7 (2.6)	4.0 (1.7)	7.0 (2.5)



*p = 0.024 vs TAC-C.
EVR + rTAC, everolimus + reduced tacrolimus; RND, randomization; TAC-C, standard tacrolimus; TAC-WD, tacrolimus withdrawal by month 4.

FIGURE 3. Mean eGFR values (MDRD4 formula) over time in the intent-to-treat North American subpopulation.

In the terminated TAC-WD arm, AEs were reported in 91.2% of North American patients over the course of the study, the most common of which were diarrhea (25.0%), abnormal liver function tests (23.5%), abdominal pain (22.1%), peripheral edema (19.1%), and pyrexia (19.1%).

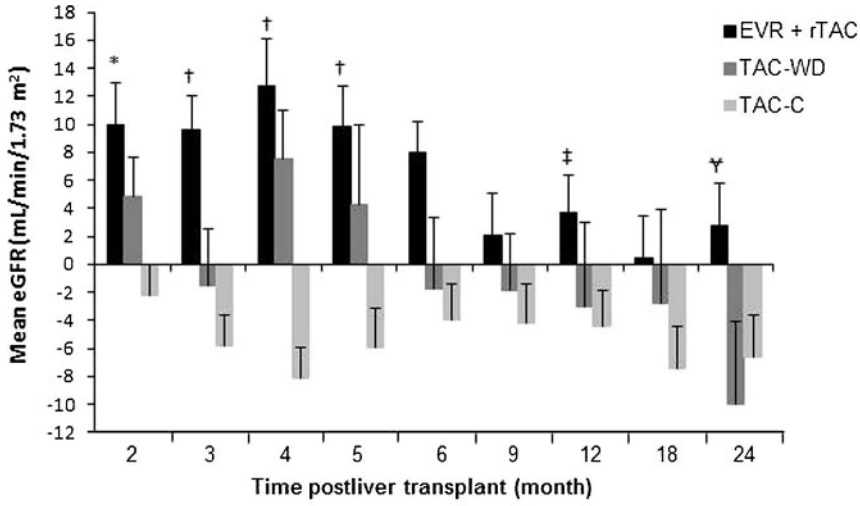
In Europe and ROW, overall AE and discontinuation rates were similar to those in North America. The differences in individual AE rates mentioned above were not seen in Europe, with the exception of a higher incidence of leukopenia in the EVR + rTAC group compared with the TAC-C group (8.1% vs 1.5%).

3-Year Results

After the 24-month core study, patients who completed 24-month treatment were offered enrollment into the extension study. After informed consent, in the North American subpopulation, 22 patients in the EVR + rTAC group, 15 patients in the TAC-WD group, and 42 patients in the TAC-C group were followed up until month 36; 14 patients in the EVR + rTAC group and 14 patients in the TAC-WD group were followed up to month 48. The mean change in eGFR from randomization to month 36 was +4.3 versus −8.1 mL/min per 1.73 m^2 ($P = 0.059$) in the EVR + rTAC and TAC-C groups, respectively. Over the same time period, the primary composite efficacy failure occurred in 14.1% of patients in the EVR + rTAC group and 19.3% of patients in the TAC-C group (P = 0.42). Between months 24 and 36, AEs were reported in 90.9% and 78.6% of patients and SAEs were reported in 31.8% and 28.6% of patients, respectively.

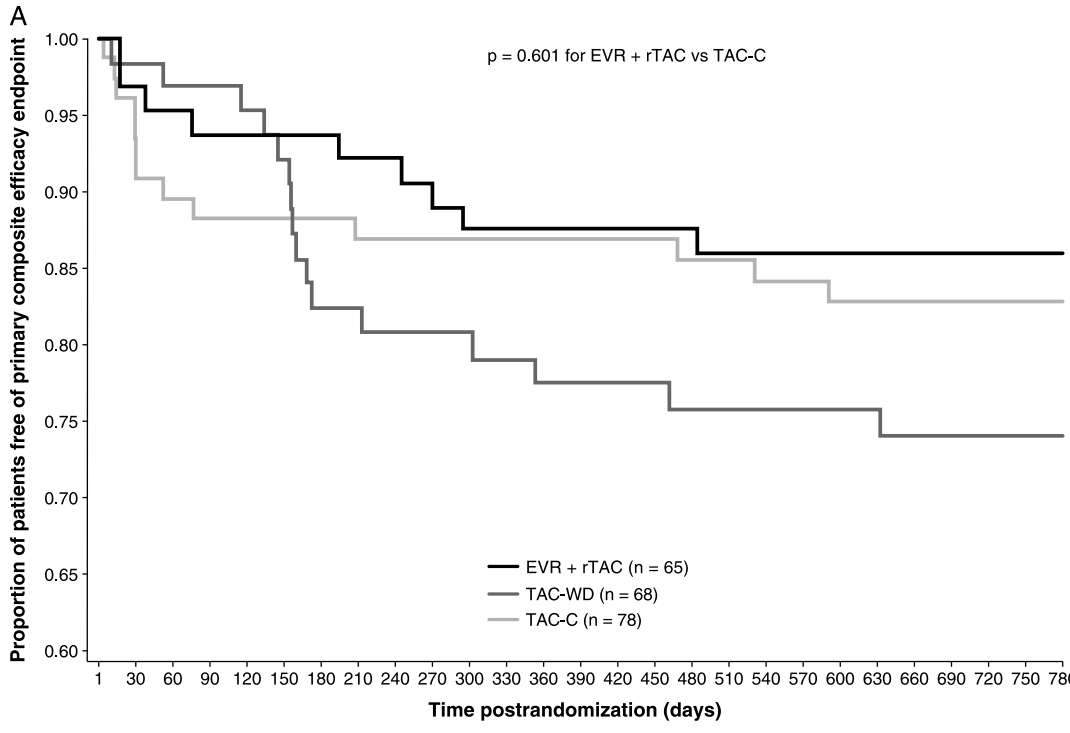
DISCUSSION

This report presents important subset analysis data on patients from North America participating in the H2304 randomized trial investigating the role and benefit of EVR for TAC dose reduction compared with standard-dose TAC immunosuppression. The use of EVR with TAC allowed for substantial and safe TAC reduction with resulting comparable efficacy and improved eGFR at month 12

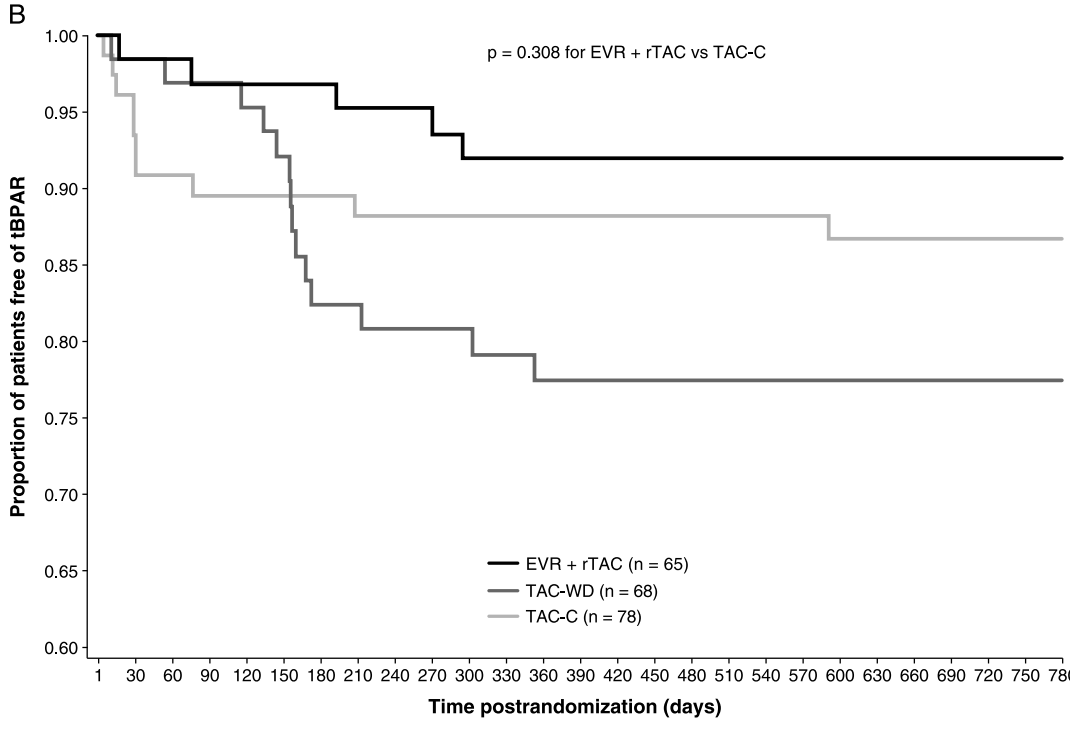


All comparisons vs TAC-C. *p = 0.002; †p < 0.001; ‡p = 0.032; ϒp = 0.042.
EVR + rTAC, everolimus + reduced tacrolimus; TAC-C, standard tacrolimus; TAC-WD, tacrolimus withdrawal by month 4.

FIGURE 4. Mean change in eGFR values (MDRD4 formula) from randomization over time in the intent-to-treat North American subpopulation.



EVR + rTAC, everolimus + reduced tacrolimus; TAC-C, standard tacrolimus; TAC-WD, tacrolimus withdrawal by month 4.



EVR + rTAC, everolimus + reduced tacrolimus; TAC-C, standard tacrolimus; TAC-WD, tacrolimus withdrawal by month 4.

FIGURE 5. Kaplan-Meier plot of the proportion of patients free from (a) the primary composite efficacy endpoint of tBPAR, graft loss, or death and (b) tBPAR in the intent-to-treat North American subpopulation.

compared with patients treated in the standard TAC control arm. Importantly, the improvement in eGFR was preserved at month 24 and month 36 (albeit the sample size was limited at this latter time point) with EVR + rTAC, in comparison to TAC-C. Thus, North American patients exposed to EVR + rTAC, despite having worse renal function and higher MELD scores at study start, had findings that were consistent with those of European patients and the previously reported overall population.[5,6]

North American patients enrolled in the current study had slightly worse renal function for those randomized to EVR + rTAC compared with the control TAC arm (eGFR:

TABLE 3.

Summary of efficacy results at months 12 and 24 in the intent-to-treat North American subpopulation

	Month 12				Month 24[a]			
Efficacy parameter, n (%)	EVR + rTAC (n = 65)	TAC-WD (n = 68)	TAC-C (n = 78)	Risk Difference: EVR + rTAC vs TAC-C (95% CI)	EVR + rTAC (n = 65)	TAC-WD (n = 68)	TAC-C (n = 78)	Risk Difference of EVR + rTAC vs TAC-C (95% CI)
tBPAR, graft loss, or death (primary endpoint)	7 (10.9)[a]	14 (24.6)[a]	10 (13.1)[a]	–2.1 (–12.9 to 8.6)	9 (14.1)	16 (25.9)	13 (17.2)	–3.0 (–15.1 to 9.0)
tBPAR	4 (6.2)	14 (20.6)	9 (11.5)	–5.4 (–14.6 to 3.8)	5 (8.1)	14 (22.5)	10 (13.2)	–5.1 (–15.4 to 5.1)
Graft loss or death	4 (6.3)[a]	0 (0.0)[a]	1 (1.3)[a]	4.9 (–1.5 to 11.4)	5 (7.9)	3 (5.1)	4 (5.4)	2.5 (–5.9 to 10.9)
Graft loss, death, or loss to follow-up	5 (7.7)	7 (10.3)	6 (7.7)	0.0 (–8.8 to 8.8)	11 (16.9)	12 (17.7)	8 (10.3)	6.7 (–4.7 to 18.0)
tBPAR, graft loss, death, or loss to follow-up	8 (12.3)	21 (30.9)	14 (17.9)	–5.6 (–17.3 to 6.0)	15 (23.1)	24 (35.3)	17 (21.8)	1.3 (–12.5 to 15.0)

[a] Kaplan-Meier incidence rate is shown.

69.3 vs 76.4 mL/min per 1.73 m^2). These differences can be attributed to this study being a post hoc analysis on a subgroup of the H2304 study, and so the randomization of subjects was not controlled for the North American cohort. Our therapeutic drug monitoring data showed that at month 24 mean trough levels of TAC were 3.6 ng/mL in the EVR + rTAC arm versus 6.7 ng/mL in the TAC-C arm (slightly lower than in the overall population: ~4.0 and ~7.0 ng/mL, respectively).[6] This finding indicates that use of EVR was successful in decreasing CNI exposure. Although the TAC-WD arm was prematurely terminated in this study, it should be noted that PROTECT, a separate long-term study assessing the effect of EVR treatment and TAC elimination on renal outcomes in de novo liver transplant recipients, was successfully continued for up to 60 months, and reported significantly better renal function and comparable patient and graft outcomes vs CNI-based immunosuppression.[18]

An important goal of the H2304 study was to establish that EVR for CNI exposure reduction was safe to use after liver transplantation. In this trial, the primary composite efficacy failure rate of tBPAR, graft loss, or death was noninferior with EVR + rTAC versus TAC-C at month 12 (6.7% vs 9.7%) and month 24 (10.3% vs 12.5%).[5,6] The United States Prescribing Information (USPI) states a slightly different composite efficacy failure endpoint in its evaluation of this study (ie, tBPAR, graft loss, death, or loss to follow-up), which also showed noninferiority between the 2 treatment groups (9.0% EVR + rTAC vs 13.6% TAC-C at month 12).[19] In the USPI analysis of the composite efficacy failure endpoint of tBPAR, graft loss, death, or loss to follow-up,[19] deaths that occurred after study discontinuation or study drug discontinuation were also included in the data analysis. Although this approach was not taken in our intent-to-treat analysis, there were no North American patients who died after study or study drug discontinuation and, thus, our results for this endpoint were identical to those using the USPI definition. A previous study found that the incidence of BPAR was significantly greater with MMF and sirolimus (12.2%) versus MMF and TAC (4.1%) at 12 months posttransplant, and that sirolimus was poorly tolerated.[20] In the current

TABLE 4.

Patients reporting most common (≥10%) adverse events in safety North American subpopulation

	Month 12			Month 24		
Adverse events, n (%)	EVR + rTAC (n = 65)	TAC-WD (n = 68)	TAC-C (n = 78)	EVR + rTAC (n = 65)	TAC-WD (n = 68)	TAC-C (n = 78)
Any adverse event	63 (96.9)	63 (92.6)	74 (94.9)	64 (98.5)	62 (91.2)	77 (98.7)
Diarrhea	11 (16.9)	16 (23.5)	17 (21.8)	14 (21.5)	17 (25.0)	20 (25.6)
Headache	14 (21.5)	9 (13.2)	18 (23.1)	16 (24.6)	10 (14.7)	21 (26.9)
Hepatitis C	13 (20.0)	11 (16.2)	13 (16.7)	15 (23.1)	12 (17.6)	16 (20.5)
Fatigue	12 (18.5)	8 (11.8)	16 (20.5)	15 (23.1)	10 (14.7)	16 (20.5)
Abdominal pain	8 (12.3)	11 (16.2)	12 (15.4)	8 (12.3)	15 (22.1)	16 (20.5)
Hypertension	14 (21.5)	9 (13.2)	10 (12.8)	17 (26.2)	10 (14.7)	11 (14.1)
Abnormal liver function test	9 (13.8)	15 (22.1)	11 (14.1)	10 (15.4)	16 (23.5)	11 (14.1)
Nausea	9 (13.8)	10 (14.7)	15 (19.2)	10 (15.4)	10 (14.7)	17 (21.8)
Pyrexia	5 (7.7)	11 (16.2)	11 (14.1)	11 (16.9)	13 (19.1)	12 (15.4)
Increased hepatic enzyme	9 (13.8)	11 (16.2)	9 (11.5)	10 (15.4)	12 (17.6)	12 (15.4)
Peripheral edema	10 (15.4)	12 (17.6)	7 (9.0)	11 (16.9)	13 (19.1)	10 (12.8)
Tremor	9 (13.8)	5 (7.4)	12 (15.4)	10 (15.4)	5 (7.4)	15 (19.2)
Vomiting	4 (6.2)	6 (8.8)	11 (14.1)	6 (9.2)	7 (10.3)	12 (15.4)
Insomnia	4 (6.2)	5 (7.4)	9 (11.5)	4 (6.2)	6 (8.8)	14 (17.9)
Leukopenia	13 (20.0)	4 (5.9)	6 (7.7)	13 (20.0)	4 (5.9)	6 (7.7)
Back pain	5 (7.7)	5 (7.4)	11 (14.1)	7 (10.8)	4 (5.9)	11 (14.1)
Hyperkalemia	5 (7.7)	1 (1.5)	16 (20.5)	5 (7.7)	1 (1.5)	16 (20.5)
Nasopharyngitis	8 (12.3)	4 (5.9)	6 (7.7)	9 (13.8)	5 (7.4)	8 (10.3)

Adverse events shown are those reported in ≥ 10% of patients at either month 12 or month 24. Adverse events are sorted by overall frequency of occurrence at month 24.

analysis, EVR was well tolerated and tBPAR incidence at month 12 was lower with EVR + rTAC (6.2%) than with TAC-C (11.5%).

Important demographic differences were identified in North American patients when compared with European and ROW patients. As mentioned previously, patients were older, had higher body mass index and higher MELD scores at transplant, and had higher rates of diabetes and HCV infection associated with their chronic liver disease. Given that the North American patients had higher rates of these comorbidities, it is reassuring that the use of EVR + rTAC allowed for improved renal preservation in this cohort compared with the TAC-C arm of the study.

There are limitations to the current study. First, the H2304 study was developed as an international trial with no a priori plan to compare results across regions as well as between treatment arms within a given region. Second, the small sample sizes of subpopulations limit the ability to demonstrate significant differences in some of the outcomes; hence, the data are presented for the North American population as a whole. However, this study does demonstrate excellent immunosuppression and renal function outcomes for North American patients, despite the differences in study cohorts that existed at baseline. A follow-up study on a larger cohort of North American patients is warranted. Third, EVR + rTAC is the only approved regimen to lower TAC exposure in liver transplant recipients. Other immunosuppressive regimens are sometimes used to decrease CNI exposure in this population, including TAC + mycophenolic acid; however, the regimen of TAC + mycophenolic acid is not approved in liver transplantation and so was not investigated as part of the current study. The use of EVR with mycophenolic acid derivatives without CNIs may be another renal-protective strategy used in liver transplant recipients.[21] Fourth, there were high rates of discontinuation in both the EVR + rTAC and TAC-C groups (49.2% vs 32.1%). The higher discontinuation rate in the EVR + rTAC arm might be attributable to the fact that this is the experimental arm and so clinicians would have been less familiar with this treatment in comparison to the standard treatment.

CONCLUSIONS

In summary, this report demonstrates that North American patients enrolled in the H2304 international trial investigating use of EVR to facilitate rTAC for immunosuppression after liver transplant had improved renal function at months 12 and 24 after study enrollment. The North American cohort had higher MELD scores at transplant and higher comorbidities with increased rates of diabetes, HCV, obesity, and MELD score at time of transplant compared with patients enrolled in Europe and ROW. In addition, patients randomized to the EVR + rTAC arm of the trial in North America had worse renal function at baseline compared with patients in the TAC-C arm of the trial. Nevertheless, North American patients randomized to EVR + rTAC maintained significantly better renal function (ie, improved mean change from baseline in eGFR) at month 12 and 24 compared with patients in the standard TAC dosing arm of the trial. Improvement in renal function was maintained at month 36. We believe this treatment strategy may allow for excellent immunosuppression with reduced risks of renal insufficiency after liver transplantation.

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