ORIGINAL PAPERS

Effects of everolimus plus minimized tacrolimus on kidney function in liver transplantation: REDUCE, a prospective, randomized controlled study

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ABSTRACT

Background and aim: reduction in calcineurin inhibitor levels is considered crucial to decrease the incidence of kidney dysfunction in liver transplant (LT) recipients. The aim of this study was to evaluate the safety and impact of everolimus plus reduced tacrolimus (EVR + rTAC) vs. mycophenolate mofetil plus tacrolimus (MMF + TAC) on kidney function in LT recipients from Spain.

Methods: the REDUCE study was a 52-week, multicenter, randomized, controlled, open-label, phase 3b study in

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de novo LT recipients. Eligible patients were randomized (1:1) 28 days post-transplantation to receive EVR + rTAC (TAC levels ≤ 5 ng/mL) or to continue with MMF + TAC (TAC levels = 6-10 ng/mL). Mean estimated glomerular filtration rate (eGFR), clinical benefit in renal function, and safety were evaluated.

Results: in the EVR + rTAC group (n = 105), eGFR increased from randomization to week 52 (82.2 [28.5] mL/min/1.73 m^2 to 86.1 [27.9] mL/min/1.73 m^2) whereas it decreased in the MMF + TAC (n = 106) group (88.4 [34.3] mL/min/1.73 m^2 to 83.2 [25.2] mL/min/1.73 m^2), with significant ($p < 0.05$) differences in eGFR throughout the study. However, both groups had a similar clinical benefit regarding renal function (improvement in 18.6 % vs. 19.1 %, and stabilization in 81.4 % vs. 80.9 % of patients in the EVR + rTAC vs. MMF + TAC groups, respectively). There were no significant differences in the incidence of acute rejection (5.7 % vs. 3.8 %), deaths (5.7 % vs. 2.8 %), and serious adverse events (51.9 % vs. 44.0 %) between the 2 groups.

Conclusion: EVR + rTAC allows a safe reduction in tacrolimus exposure in *de novo* liver transplant recipients, with a significant improvement in eGFR but without significant differences in renal clinical benefit 1 year after liver transplantation.

Keywords: Everolimus. De novo liver transplant. Renal function. eGFR. KDIGO.

INTRODUCTION

Approximately 7 % to 21 % of liver transplant (LT) recipients develop severe deterioration of renal function that may progress to end-stage chronic kidney disease (1). This is mostly due to prolonged calcineurin inhibitor (CNI) exposure (2). Mammalian target of rapamycin inhibitors (mTORi; everolimus [EVR] and sirolimus) protect against CNI-associated toxicities by facilitating CNI minimization. Several studies have shown that EVR-based CNI withdrawal (3-5) or CNI reduction regimes improve renal function (6-8). The aim of the REDUCE study was to evaluate the effect of early initiation of EVR with reduced tacrolimus (rTAC) on renal function when compared with mycophenolate mofetil (MMF) plus TAC in de novo LT recipients from Spanish transplant centers.

PATIENTS AND METHODS

Study design and conduct

The REDUCE study (EudraCT No. 2013-001191-38) was a 52-week, multicenter, randomized, controlled, open-label, phase 3b study in de novo LT recipients. Details of study design and treatment regimens are presented in figure 1. The study was performed in accordance with the principles of the Declaration of Helsinki, with an independent ethics committee and institutional review board (HCP/2013/109). Written informed consent was obtained from all participants.

Study population

LT recipients who met the inclusion criteria 28 days after liver transplantation were eligible for enrolment into the study. Adult patients receiving their first LT from a deceased donor were eligible for screening. Patients with hepatocellular carcinoma were required to meet the Milan criteria at the time of inclusion on the waiting list. Patients with a functioning allograft (aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels ≤ 4 times the upper limit of normal [ULN]; alkaline phosphatase and gamma glutamyl transpeptidase levels ≤ 5 times the ULN) and estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 were randomized.

Exclusion criteria were proteinuria ≥ 1.0 g/24 h; cholesterol levels ≥ 350 mg/dL (≥ 9 mmol/L) or triglyceride levels ≥ 750 mg/dL; platelet count ≤ 50,000/mm^3; absolute neutrophil count ≤ 1000/mm^3 or white blood cell count ≤ 2000/mm^3; renal replacement therapy within 7 days before randomization and ≥ 2 corticosteroid-sensitive acute rejection (AR) episodes.

Immunosuppression

All patients received interleukin-2 receptor antagonist + TAC (trough level [C_0] 6-10 ng/mL) + MMF (500-1000 mg/12 hour) + corticosteroids before randomization. A centralized randomization system included in the electronic case report form was used. EVR was started within

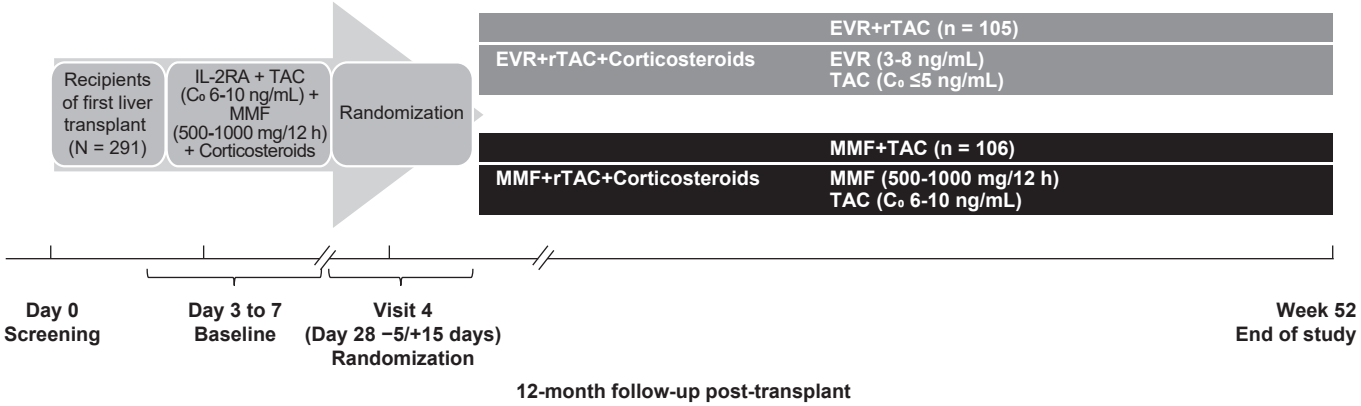

Fig. 1. *Study design. Corticosteroids were withdrawn by week 24 post-transplantation, except in patients with baseline autoimmune liver disease (EVR: everolimus; IL-2RA: interleukin-2 receptor antagonist; MMF: mycophenolate mofetil; rTAC: reduced tacrolimus; TAC: tacrolimus).*

24 hours of randomization in the EVR + rTAC group, at a dose of 1 mg twice daily and adjusted to a target C_0 of 3 to 8 ng/mL. Upon achieving the required EVR C_0, a reduction of TAC dose was initiated to achieve a target C_0 of ≤ 5 ng/mL within 4 weeks post-randomization, and these levels were maintained until week 52. In the MMF + TAC group, TAC C_0 was maintained within the range of 6 to 10 ng/mL according to the levels shown in the TAC minimization studies with MMF. TAC capsules were used according to normal clinical practice to adjust the dose of TAC until week 3 post-transplant, at the latest. Beginning at week 3, all patients had to be in treatment with prolonged release TAC capsules in order to have stable levels of TAC prior to randomization.

Study objectives

The study assessed the evolution of kidney function from randomization (week 4) to the end of the study (week 52) in the EVR + rTAC vs the MMF + TAC group. Clinical benefit in renal function was defined by either (i) an improvement in 1 or 2 ranges of eGFR at week 52 post transplantation in patients with values of 30 to < 45 (Kidney Disease: Improving Global Outcomes [KDIGO] category G3b) or 45 to < 60 mL/min/1.73 m^2 (G3a) at randomization, or (ii) stabilization of eGFR at week 52 post transplantation in patients with eGFR ≥ 60 mL/min/1.73 m^2 (G2, G1) at randomization (9). Kidney function was also assessed by evaluating the mean eGFR changes throughout the study. The study also evaluated incidence, time to rejection and severity of biopsy-proven AR (BPAR); graft loss and death; new onset of clinical events of interest and the incidence of adverse events (AEs) and serious AEs (SAEs).

Statistical analysis

In this study, the aim was to reject the null hypothesis of no difference in kidney function between the groups with a bilateral level of significance of 0.05. The plan was to recruit 250 de novo LT recipients, considering 10 % of screening failures and 20 % for patient discontinuation rate.

Fisher's exact test or the chi-squared test were used for categorical variables, and the t-test or Mann-Whitney U-test was used for treatment comparisons between continuous variables. Renal function was analyzed using an analysis of covariance (ANCOVA) model with levels of each variable at randomization as a concomitant variable.

RESULTS

Patients

From December 2013 to February 2016, patients were recruited from 20 centers across Spain. Of the 291 patients screened, 217 were randomized 4 weeks after transplantation to receive EVR + rTAC (n = 108) or MMF + TAC (n = 109). Patients prematurely discontinuing the study medication were similar in the study groups (Fig. 2). The demographic and baseline characteristics including mean eGFR were similar in the study groups, with the exception of recipient age which was significantly higher in the EVR + rTAC group (Table 1).

Immunosuppression

In the EVR + rTAC group, the mean (standard deviation, SD) everolimus C_0 was 3.6 (2.0) ng/mL at week 5, 4.7 (2.4) ng/mL at week 8, 5.7 (2.7) ng/mL at week 24, and 4.9 (1.7) ng/mL at week 52. Everolimus C_0 was within the target range in 36.2 %, 72.4 %, 67.6 %, and 60.0 % of patients at weeks 5, 8, 24 and 52, respectively.

Tacrolimus C_0 at randomization in the EVR + rTAC and MMF + TAC groups were 8.3 (3.1) ng/mL and 8.2 (2.9) ng/mL, respectively (p = NS). In the EVR + rTAC group, TAC C_0 was reduced, reaching < 6 ng/mL in 32.4 %, 64.8 %, 71.4 %, and 62.9 % of the patients at weeks 5, 8, 24 and 52, respectively. The mean TAC C_0 in this group was 6.9 (2.9) ng/mL at week 5, 5.3 (2.5) ng/mL at week 8, 4.7 (1.8) ng/mL at week 24, and 4.3 (1.9) ng/mL at week 52 (lower than the TAC levels in the MMF + TAC group at each time point) (Fig. 3). There was a 30 % reduction in the mean TAC levels in the EVR + rTAC vs MMF + TAC group as early as 2 weeks after randomization, with a 41 % reduction at week 52.

Renal function

Clinical benefit in renal function was observed in 81.9 % and 84.0 % of patients in the EVR + rTAC and MMF + TAC groups, respectively (p = NS). Improvement of renal function was seen in 18.6 % vs 19.1 %, and stabilization was achieved in 81.4 % vs 80.9 % of patients in the EVR + rTAC vs MMF + TAC group, respectively (p = NS). There were no statistical differences in the clinical benefit in renal function by eGFR stratification (Table 2).

The EVR + rTAC group had a lower (albeit not significantly different) mean eGFR value at randomization compared with the MMF + TAC group, and it improved as the study progressed. Conversely, the mean eGFR of the MMF + TAC group decreased during the subsequent study visits (Fig. 4A). A significant difference was reported in the mean change in eGFR from randomization to week 52 between the EVR + rTAC and MMF + TAC groups at all visits (p < 0.05 for all visits) (Fig. 4B). Proteinuria (> 0.5 g/day) was reported in 21 (9.95 %) patients during the study period and was more common in the EVR + rTAC group (13.3 % vs 6.6 %, p = NS).

BPAR, graft loss, and death

BPAR was reported in 6 (5.7 %) patients in the EVR + rTAC and in 4 (3.8 %) patients in the MMF + TAC group (p = NS) (Table 2). Graft loss was observed in 2 (1.9 %) patients in the EVR + rTAC and 1 (0.9 %) patient in the MMF + TAC group (p = NS). Nine deaths (6 in the EVR + rTAC group and 3 in the MMF + TAC group, p = NS) were reported between randomization and week 52. None of the deaths were related to the study drug (Table 2).

Safety

Over the 12-month study period, the overall rates of AEs and SAEs were similar between the study groups. With regard to new onset events of clinical interest, dyslipidemia

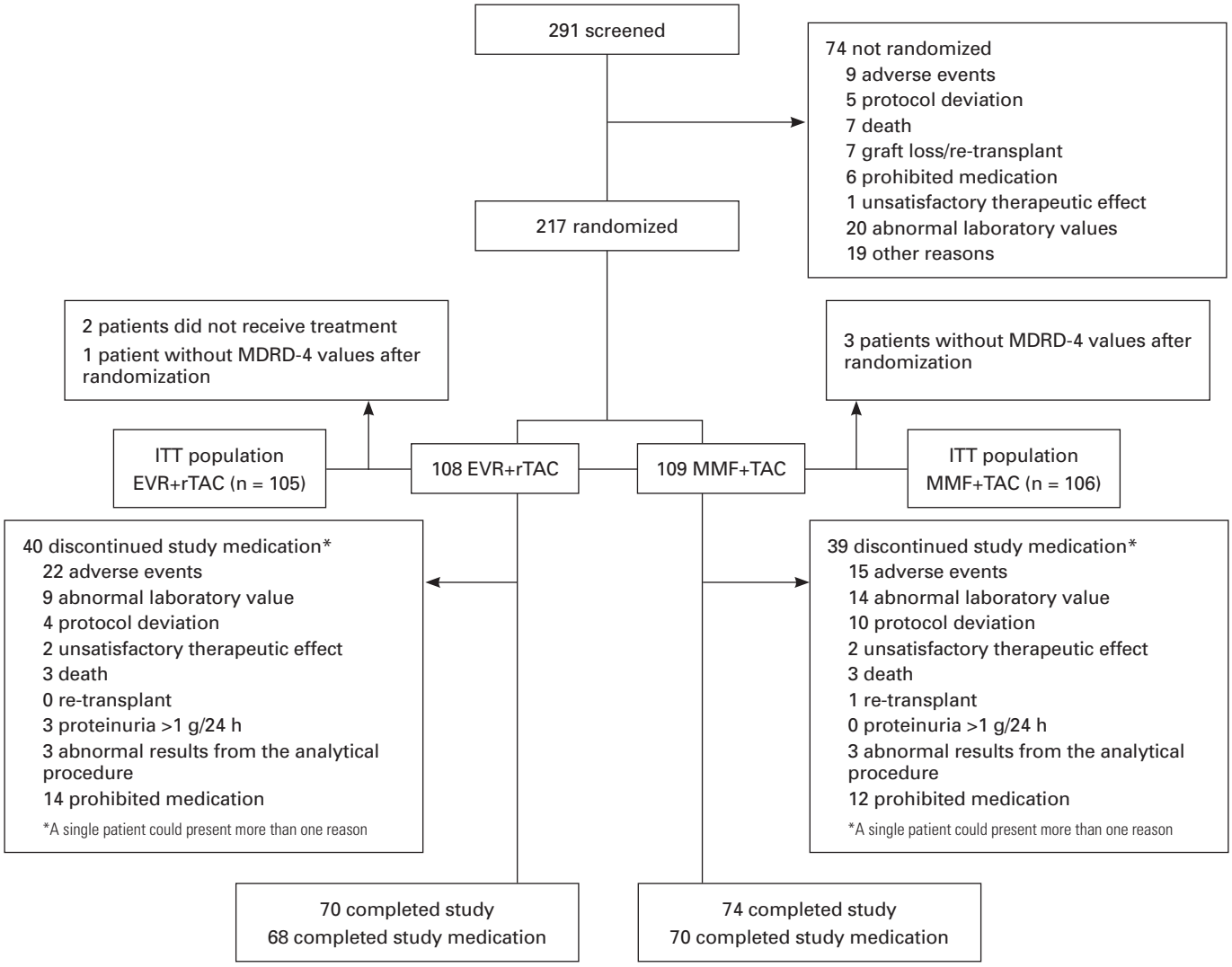

Fig. 2. *Patient disposition (EVR: everolimus; ITT: intention-to-treat; MDRD4: 4-variable modification of diet in renal disease; MMF: mycophenolate mofetil; rTAC: reduced tacrolimus; TAC: tacrolimus).*

Table 1. *Demographics and baseline characteristics (ITT population)*

		EVR + rTAC (n = 105)	MMF + TAC (n = 106)	p-value
Demographic characteristics	Age (years), mean (SD)	58.4 (6.4)	55.8 (7.5)	*0.007*
	Gender (male), n (%)	91 (86.7)	90 (84.9)	0.866
	Cytomegalovirus positive, n (%)	83 (79.1)	80 (75.5)	0.649
	Screening eGFR (MDRD4), mL/min/1.73 m^2, mean (SD)	100.2 (38.7)	99.4 (43.1)	0.890
	MELD, mean (SD)	15.0 (6.2)	15.0 (6.3)	0.999
Medical history/relevant comorbidities	Diabetes *mellitus,* n (%)	37 (35.2)	30 (28.3)	0.350
	Hypertension, n (%)	31 (29.5)	34 (32.1)	0.801
Main reasons for transplantation	Cirrhosis, n (%)	96 (91.4)	98 (92.5)	0.984
	HCC, n (%)*	46 (43.8)	53 (50.0)	0.445
Donor characteristics	Age (years), mean (SD)	60.8 (13.8)	62.4 (16.5)	0.443
	Gender (male), n (%)	64 (61.0)	58 (54.7)	0.437

*Most patients with HCC also belong to the cirrhosis group. eGFR: estimated glomerular filtration rate; EVR: everolimus; HCC: hepatocellular carcinoma; ITT: intention-to-treat; MDRD4: 4-variable modification of diet in renal disease; MELD: model for end stage liver disease; MMF: mycophenolate mofetil; rTAC: reduced tacrolimus; SD: standard deviation; TAC: tacrolimus.

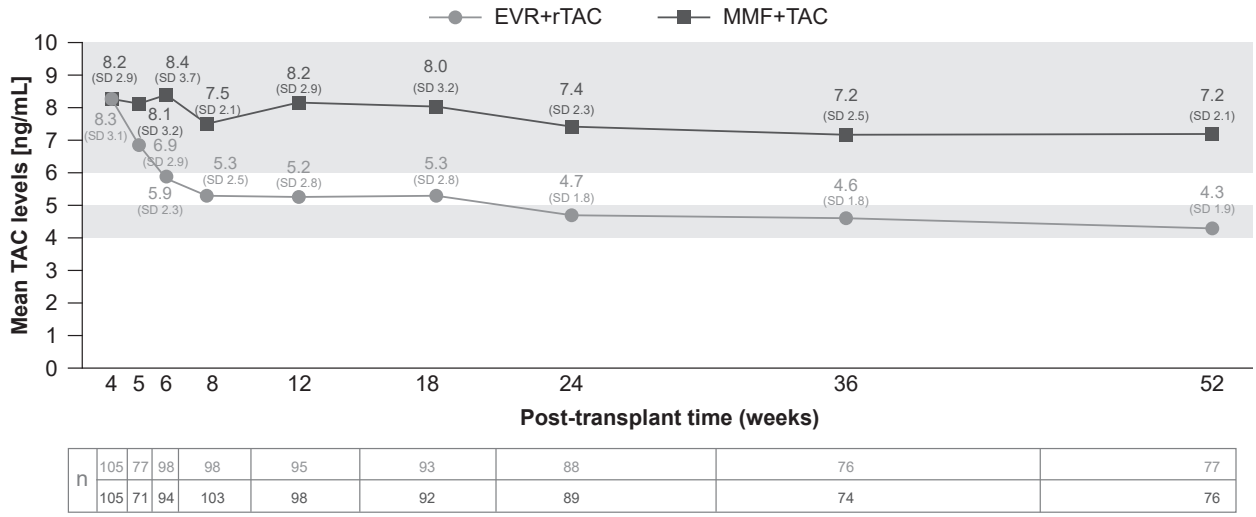

Fig. 3. *Mean tacrolimus trough levels (EVR: everolimus; MMF: mycophenolate mofetil; rTAC: reduced tacrolimus; SD: standard deviation; TAC: tacrolimus).*

Table 2. *Renal function and key efficacy endpoints (ITT population)*

	EVR + rTAC (n = 105)	MMF + TAC (n = 106)	p-value
Clinical benefit in renal function, n (%)	86 (81.9)	89 (84.0)	0.691
Improvement	16 (18.6)	17 (19.1)	0.933
Stabilization	70 (81.4)	72 (80.9)	
Clinical benefit in renal function by eGFR (mL/min/1.73 m²) stratification, n (%)			
30 to < 45	6 (85.7)	7 (70.0)	0.452
45 to < 60	10 (52.6)	10 (58.8)	0.709
≥ 60	70 (88.6)	72 (91.1)	0.598
Change in eGFR (mL/min/1.73 m²) from randomization to week 52, mean (SD)	2.6 (24.6)	–8.8 (24.4)	0.005
eGFR (MDRD4), mL/min/1.73 m², mean (SD)			
Randomization	82.2 (28.5)	88.4 (34.3)	0.154
Week 52	86.1 (27.9)	83.2 (25.2)	0.435
Clinically suspected AR, n (%)	18 (17.1)	16 (15.1)	0.686
BPAR, n (%)	6 (5.7)	4 (3.8)	0.734
tBPAR, n (%)	5 (4.8)	2 (1.9)	0.434
Time to tBPAR (months), mean (SD)	2.7 (1.5)	3.9 (5.3)	0.619
Graft loss, n (%)	2 (1.9)	1 (0.9)	0.993
Death, n (%)	6 (5.7)	3 (2.8)	0.486

AR: acute rejection; BPAR: biopsy-proven AR; eGFR: estimated glomerular filtration rate; EVR: everolimus; ITT: intention-to-treat; MDRD4: 4-variable modification of diet in renal disease; MMF: mycophenolate mofetil; rTAC: reduced tacrolimus; SD: standard deviation; TAC: tacrolimus; tBPAR: treated BPAR.

and diabetes were more common in the EVR + rTAC group. The incidence of cytomegalovirus infections was lower in the EVR + rTAC group (Table 3).

DISCUSSION

The present study shows that the concomitant administration of EVR allows the safe reduction of TAC exposure to C_0 below 6 ng/mL at month 1 after liver transplantation. As a result, a clinically significant reduction of almost 30 % of the TAC C_0 was achieved in the EVR + rTAC group as early as 2 weeks after randomization, in comparison with the TAC C_0 in the MMF + TAC group. Furthermore, this reduction increased during the study period and reached 41 % at week 52. These differences were greater than the reduction in the exposure to TAC achieved in the H2304 study (26 % to 38 % in the EVR + rTAC group) (6), and the TAC lev-

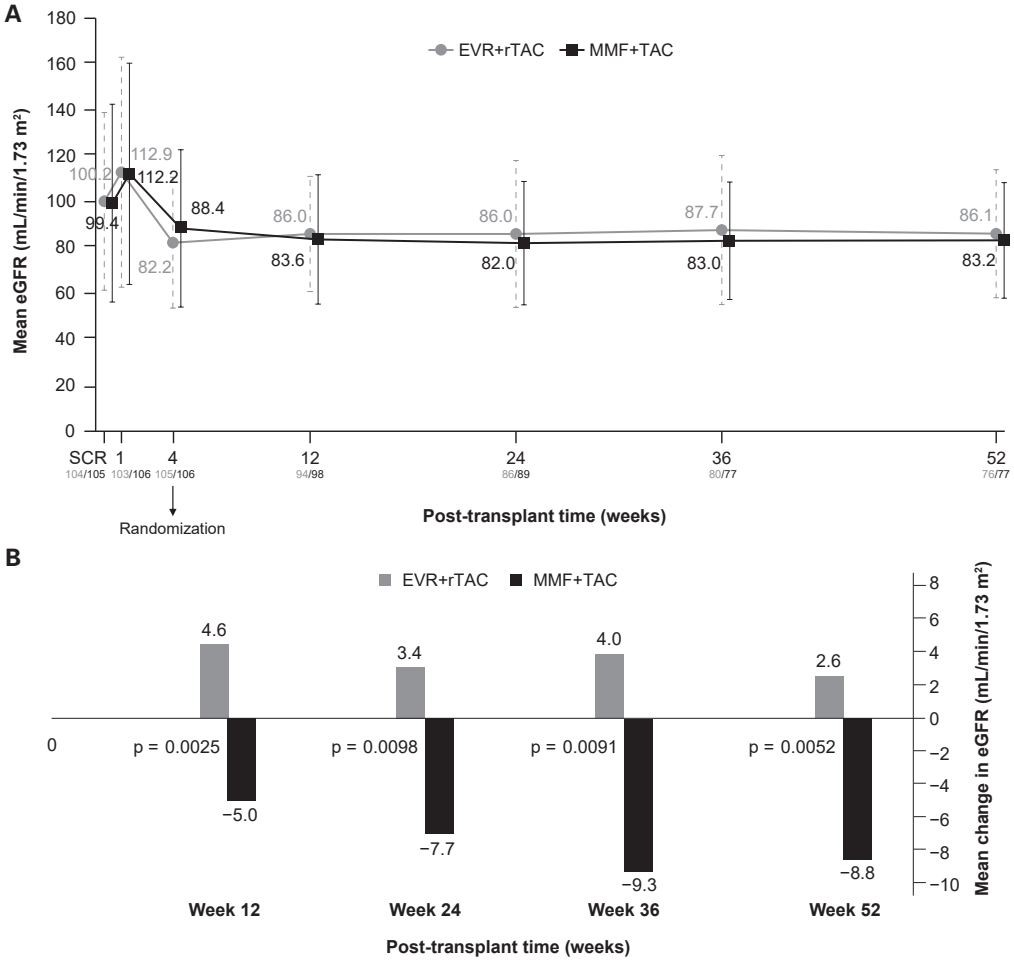

Fig. 4. *A. Evolution of renal function (eGFR, MDRD4). B. Mean change in eGFR from randomization. Vertical bars (in 4A) indicate the respective standard deviations (eGFR: estimated glomerular filtration rate; EVR: everolimus; MDRD4: 4-variable modification of diet in renal disease; MMF: mycophenolate mofetil; rTAC: reduced tacrolimus; TAC: tacrolimus).*

Table 3. *Safety evaluation (safety population)*

	EVR + rTAC (n = 106)	MMF + TAC (n = 109)	p-value
AEs, n (%)			
Patients with any AE	105 (99.1)	109 (100.0)	0.989
Patients with any SAE	55 (51.9)	48 (44.0)	0.310
Renal failure	13 (12.3)	19 (17.4)	0.287
Peripheral edema	39 (36.8)	27 (24.8)	0.056
Anemia	31 (29.3)	36 (33.0)	0.652
Leukopenia	14 (13.2)	10 (9.2)	0.348
Thrombocytopenia	25 (23.6)	22 (20.2)	0.546
Hepatic artery and portal vein thrombosis	3 (2.8)	2 (1.8)	0.680
New onset events of clinical interest			
Dyslipidemia	78 (73.6)	55 (50.5)	*0.0005*
Hypertension	66 (62.3)	59 (54.1)	0.284
Diabetes	36 (34.0)	24 (22.0)	0.051
Neoplasia	3 (2.8)	2 (1.8)	0.680
Cytomegalovirus infection	25 (23.6)	41 (37.6)	*0.026*

AE: adverse events; EVR: everolimus; MMF: mycophenolate mofetil; rTAC: reduced tacrolimus; SAE: serious adverse events; TAC: tacrolimus.

els were clearly lower than those described in randomized studies using the combination of MMF + TAC (10-14) and in those reflecting real-world experience aimed at minimization of CNI (15,16).

The results of the current study also show that despite the important and significant reduction in TAC exposure achieved in the EVR + rTAC group, clinical renal function benefits were similar with both regimens. This could due to the fact that both groups had effective TAC reduction, which reinforces the fact that this reduction is key to preserving kidney function after liver transplantation. With a more pronounced TAC reduction in the EVR + rTAC group, the mean eGFR from randomization to week 52 significantly improved. In contrast, it worsened in the MMF + TAC group from week 12 onwards, even though the patients in the EVR + rTAC group had a lower eGFR at randomization. When we consider the evolution of eGFR during the entire study period (pre, peri, and post transplantation), once the initial decrease in GFR after liver transplantation was established, the reduction in CNI exposure to maintain kidney function thereafter is mandatory. From the results of the present study, it is not clear whether the trend to improvement in kidney function in the EVR + rTAC group in contrast to the trend to stabilization or even decrease of eGFR in the MMF + TAC group, would translate to clinically significant differences in renal function with a longer follow-up.

The current study confirms the possibility of safely using TAC levels below 6 ng/mL in the relatively early post-transplant period. The EVR + rTAC group showed a similar incidence of BPAR, treated BPAR, graft loss and death as that of the MMF + TAC group. In addition, the incidence of AEs and study medication discontinuation rates were similar in both groups. Interestingly, the 19 % discontinuation rate using EVR was lower than the approximate 30 % rate reported in previous studies (3,6). Better control of EVR levels and lower target levels could probably explain the low rate of discontinuation and reinforce early EVR introduction with low TAC exposure. The incidence of proteinuria and AEs was similar in both groups, except for a higher incidence of dyslipidemia and diabetes in the EVR + rTAC group and a higher incidence of cytomegalovirus infection in the MMF + TAC group.

This study opens several lines for further exploration, namely assessing the effects of early low exposure to CNI on kidney function with a longer follow-up; evaluating whether the decreased exposure to CNI can improve the incidence of medium- and long-term cardiovascular events and assessing whether this immunosuppressive regime can reduce the incidence of de novo neoplasia.

A limitation of the REDUCE study was that the target TAC $C_0 \leq 5$ ng/mL was not achieved within 4 weeks post-randomization. Another limitation was that, due to scarce data on renal function benefit at the time of the study design, the sample size was calculated based on the benefit shown in a previous study evaluating TAC monotherapy as the control group (2). However, most patients in both groups had an eGFR > 60 mL/min/1.73 m^2 at randomization, which did not allow the assessment of whether patients with an eGFR < 60 mL/min/1.73 m^2 could have had an improvement in renal function. The distribution of the patients in the different subgroups according to the baseline renal function indicates that the sample size may be too small to provide accurate results. Future studies of superiority are needed to derive more consistent conclusions. Secondly, considering the difference in changes in eGFR between the groups, a long-term follow-up may have been better to show additional changes in renal function.

In summary, the REDUCE study shows that the early introduction of EVR allows a significant reduction in the mean TAC C_0, which in turn is associated with a significant improvement in eGFR 1 year after liver transplantation, without compromising safety. Whether this may have long-term benefits in LT recipients remains to be explored in future studies.

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