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ORIGINAL ARTICLE

Five-year outcomes in liver transplant patients receiving everolimus with or without a calcineurin inhibitor: Results from the CERTITUDE study

Faouzi Saliba[1] | Christophe Duvoux[2] | Sébastien Dharancy[3] | Jérôme Dumortier[4] | Yvon Calmus[5] | Jean Gugenheim[6] | Nassim Kamar[7] | Ephrem Salamé[8] | Martine Neau-Cransac[9] | Claire Vanlemmens[10] | François Durand[11] | Georges-Philippe Pageaux[12] | Jean Hardwigsen[13] | Yasmina Benkhatar[14] | François Derquenne[14] | Filomena Conti[6]

[1]AP-HP, Hôpital Paul Brousse, Centre Hépato-Biliaire, INSERM Unit 1193, Université Paris Saclay, Villejuif, France

[2]AP-HP-Hopital henri Mondor, Université Paris Est, Créteil, France

[3]Service Hépatologie-Transplantation, Hôpital Huriez, CHRU Lille, Lille, France

[4]Hospices civils de Lyon, Hôpital Edouard Herriot, Université Claude Bernard Lyon 1, Lyon, France

[5]APHP, Unité Médicale de Transplantation Hépatique, service d'hépato-gastroentérologie, Hôpital Pitié Salpêtrière, Sorbonne Université, INSERM UMR S 938, Centre de recherche Saint-Antoine (CRSA), Institute of Cardiometabolisme and Nutrition (ICAN), Paris, France

[6]Department of Digestive Surgery and Liver Transplantation, Archet Hospital, Université Côte d'Azur, 151, Route de Saint-Antoine de Ginestière, Nice, France

[7]Department of Nephrology and Organ Transplantation, Toulouse University Hospital, Université Paul Sabatier, Toulouse, France

[8]Service de Chirurgie Hépato-Biliare et de Transplantation Hépatique,, Hôpital Trousseau, Chambray les Tours,, Tours, France

[9]Service de Chirurgie Hépatobiliaire et Transplantation Hépatique, Bâtiment Magellan, Hôpital Haut Lévèque, Pessac, France

[10]Service Hépatologie et Soins Intensifs Digestifs, CHU Jean Minjoz, Besançon Cedex, France

[11]AP-HP Hôpital Beaujon, Clichy, France

[12]Hôpital Saint Eloi, Montpellier, France

[13]Hôpital la Timone, Marseille, France

[14]Novartis Pharma SAS, Rueil-Malmaison, France

Correspondence
Faouzi Saliba, AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, INSERM Unit 1193, Université Paris-Saclay, Villejuif 94800, France.
Email: faouzi.saliba@aphp.fr

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Novartis Pharma SAS, Rueil-Malmaison, France

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Abstract

Background and Aims: To report 5-year outcomes of the CERTITUDE study.

Methods: An observational study in patients with liver transplantation (LTx) compared the long-term impact of immunosuppression (with/without a calcineurin inhibitor) on renal function, cancers, major cardiovascular events (MACEs) and other safety parameters. All patients completing the 6-month SIMCER study were recruited and analysed according to treatment received at randomization and actual treatment received during the follow-up.

Abbreviations: AE, adverse event; aMDRD, abbreviated Modification of Diet in Renal Disease; BPAR, biopsy-proven acute rejections; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; EVR, everolimus; HbA_{1c}, glycated haemoglobin; HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; KDOQI, kidney disease outcomes quality initiative; LDL-C, low-density lipoprotein; LTx, liver transplantation; MACE, major cardiovascular events; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; RAI, rejection activity index; SAE, serious adverse event; SD, standard deviation; TAC, tacrolimus.

Results: Of the 143 enrolled patients, 119 completed the 5-year follow-up (everolimus [EVR], $n = 55$; tacrolimus [TAC], $n = 64$). The mean absolute change in estimated glomerular filtration rate was not statistically different between both groups (TAC, −15.53 ml/min/1.73 m^2 and EVR, −14.56 ml/min/1.73 m^2). In the treatment subgroups based on actual treatment received, renal function was preserved better in the EVR subgroup compared with other subgroups ($p = .051$). Treated biopsy-proven acute rejection was higher in the EVR group (15.4% vs. 6.4%); however, the majority of events were mild in severity. MACE occurred in 9.2% vs. 14.1% of patients in the EVR and TAC groups respectively ($p = .370$). De novo cancer was reported in 14 and 5 patients in EVR and TAC groups respectively. Hepatocellular carcinoma (HCC) recurrence was observed in the TAC group alone ($n = 4$). Adverse events and treatment discontinuation owing to an adverse event were higher in the EVR group.

Conclusions: The CERTITUDE study demonstrated that EVR- and TAC-based regimens have comparable efficacy, safety and tolerability up to 5 years post-LTx.

KEYWORDS
calcineurin inhibitor, everolimus, immunosuppression/immune modulation, liver transplant, long-term outcomes

1 | INTRODUCTION

The use of calcineurin inhibitors (CNIs) in liver transplantation (LTx) patients has been associated with a significant reduction in rejection rates and graft loss.[1] CNIs continue to remain a prominent immunosuppressant used in LTx.[1,2] However, long-term treatment with CNIs is associated with several adverse events (AEs), the most common being nephrotoxicity and neurotoxicity.[1,3,4] Everolimus (EVR; Certican®, Novartis) is a mammalian target of rapamycin (mTOR) inhibitor with potent immunosuppressive and antiproliferative effects.[5] Studies have demonstrated that EVR with or without reduced CNIs is associated with significantly better renal function and comparable rejection rates up to 5 years post-LTx.[6–11] EVR-based regimens may help in the gradual reduction of CNI dose and could be potential alternatives to CNIs.[5,12,13]

SIMCER (NCT01625377, Eudract 2012-000137-39) was a 6-month, prospective, multicentre, randomized, open-label study in de novo LTx patients in France.[14] The SIMCER study demonstrated that early introduction of EVR with stepwise reduction of CNI post-LTx, supported by induction therapy and concomitant mycophenolic acid (MPA) with or without steroids, may be a preferable strategy for achieving CNI-free therapy.[14] To assess the long-term impact of immunosuppression with EVR (with or without CNI) on the main complications encountered by LTx patients, patients completing the SIMCER study were given the option to be followed up in the observational CERTITUDE study. The aim of the observational study was to monitor patients up to 5 years post-LTx to compare the impact of immunosuppression (with or

Lay summary

In the CERTITUDE study, patients receiving liver transplantation were observed over a period of 5 years. This study compared the long-term impact of immunosuppression (primarily using everolimus and tacrolimus) on renal function, cancers, major cardiovascular events and other safety parameters. The study showed that an everolimus-based regimen was able to preserve renal function up to 5 years post-liver transplantation without impacting graft survival or any safety concerns.

Key points

- CERTITUDE is the first long-term prospective observational study in liver transplantation patients that compared the impact of immunosuppression (with or without calcineurin inhibitors) on renal function, cancers, major cardiovascular events and other safety parameters.
- Renal function was preserved better in the everolimus subgroup compared with other subgroups.
- Safety and tolerability were similar in both treatment groups.
- Patients in the everolimus group experienced fewer major cardiovascular events and no hepatocellular carcinoma recurrence.

without CNI) on renal function, cancers, major cardiovascular events (MACE) and other safety parameters. The 2-year interim results of the study have been reported previously,[15] and the 5-year results are reported here.

2 | PATIENTS AND METHODS

The detailed methods, including the study design, endpoints and data analysis, have been reported previously.[15] The key information is summarized below.

2.1 | Study design and population

CERTITUDE was a prospective, multicentre, observational follow-up study conducted at 13 centres in France that participated in the SIMCER study[14] (NCT01625377; Eudract 2012-000137-39; Figure S1). Patients with de novo LTx who attended the end-of-study visit or the 6-month post-LTx follow-up visit in the randomized clinical study (SIMCER) and received EVR or tacrolimus (TAC) were eligible for inclusion in the CERTITUDE study. The study was conducted in accordance with good epidemiological practices (Law No. 2012-300 of 5 March 2012) specified by the French Public Health Regulations and according to Novartis Pharma standard operating procedures designed to ensure compliance with the texts and recommendations.

2.2 | Immunosuppression

During the follow-up, patients continued to receive the assigned treatment they were receiving at enrollment. The physicians were allowed to modify the immunosuppressive treatments at any time during the follow-up. Similar to the SIMCER study, patients continued to receive enteric-coated mycophenolate sodium with or without steroids (administered according to local practice) until the end of the study.[14,15]

2.3 | Endpoints and assessment

The primary endpoint (renal function measured by abbreviated Modification of Diet in Renal Disease [aMDRD] formula), key secondary endpoints and safety endpoints were evaluated up to 5-year post-LTx. Clinical parameters including cancers, renal function, treatment failure and MACE were evaluated at 6, 12, 18, 24, 36, 48 and 60 months post-LTx. The incidence of MACE included death from cardiovascular reasons, non-fatal myocardial infarction, hospitalization for the acute coronary syndrome, hospitalization for heart failure, non-fatal stroke and surgery for peripheral arteriopathy. Safety outcomes included AEs, serious AEs, AEs leading to treatment discontinuation and some AEs of special interest (de novo cancer, MACE, diabetes, dyslipidemia and deaths) over the 5-year duration.

2.4 | Data analysis

The main analyses in the study were conducted by treatment groups corresponding to the treatment received at randomization in the SIMCER study—TAC or EVR. During the follow-up, patients could switch to a different immunosuppressant at the physicians' discretion. Therefore, during the 5-year follow-up, some patients might have received a different treatment or a different sequence of treatment. With this due consideration, complementary analyses were conducted based on actual treatment received at each study visit up to month 60:

- Remained on EVR as randomized without TAC: (EVR)
- Switched from EVR to TAC: (EVR-TAC)
- Remained on TAC as randomized without EVR: (TAC)
- Switched from TAC to EVR: (TAC-EVR)

Descriptive statistics were computed for all characteristics. Statistical analyses were performed using SAS, version 9.2 (SAS Institute).

3 | RESULTS

3.1 | Demographics and baseline characteristics

Of the 188 patients randomized in the SIMCER study, 159 completed the study and 143 were included in the CERTITUDE study (TAC, $n = 78$; EVR, $n = 65$; Figure 1). Details of patients completing the SIMCER study but not included in the CERTITUDE study are provided in Figure 1. Demographics and baseline characteristics of patients entering the CERTITUDE study have been reported previously.[15] Overall, the baseline and demographics were balanced between the treatment groups except for the reason for LTx (Table S1). Overall, baseline characteristics were comparable between SIMCER study patients included and not included in the CERTITUDE study. Patients included in the CERTITUDE study had slightly less favourable characteristics regarding infections than patients not included in the study (Table S2).

3.2 | Immunosuppression therapies at month 60 post-LTx

In the TAC group, the proportion of patients receiving EVR increased from 3.8% at month 6 to 31.1% at month 60 while the use of CNI therapy progressively decreased from 100% to 77% (Figure S2). In the EVR group, the proportion of patients receiving EVR decreased from 92.3% at month 6 to about 59% from

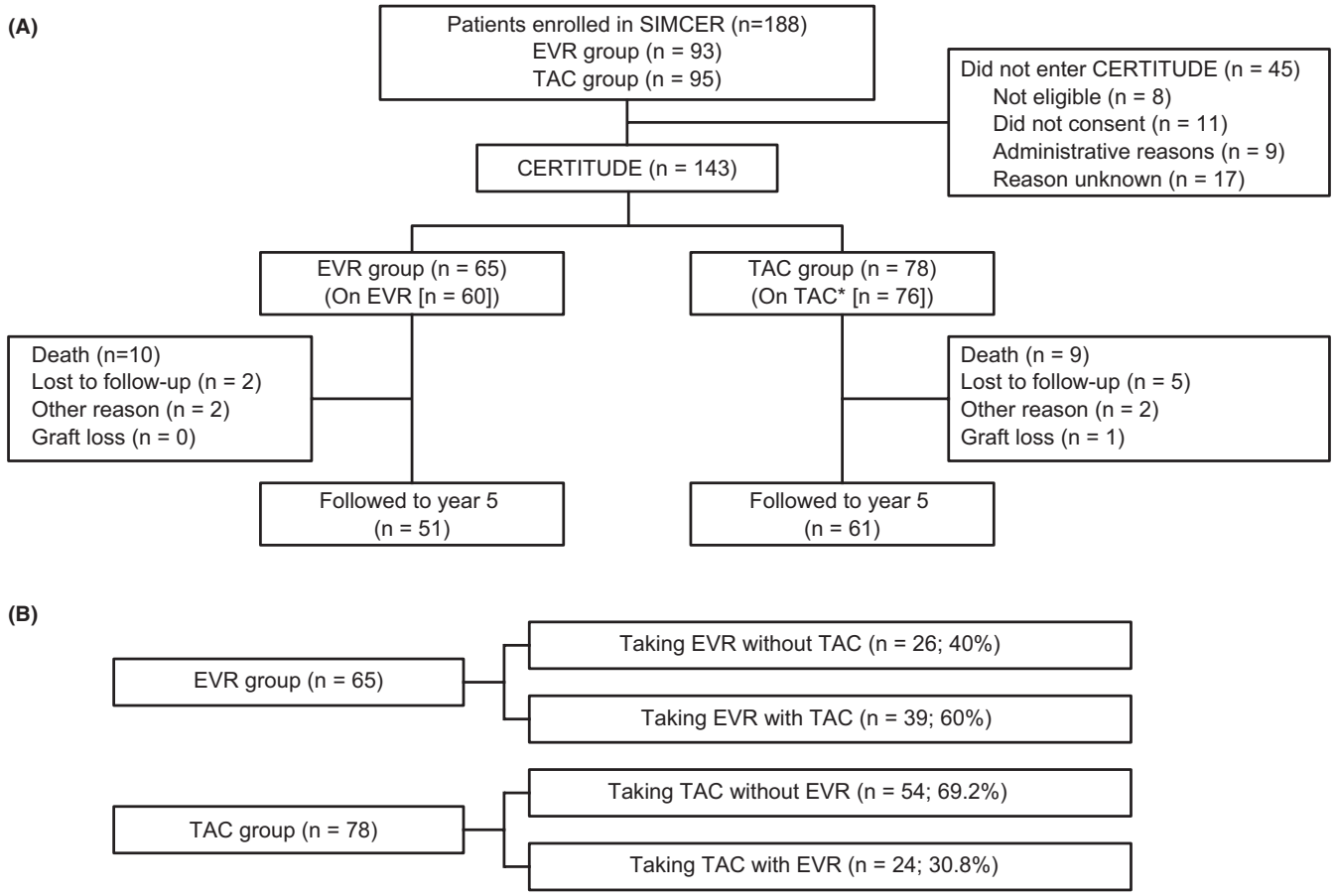

FIGURE 1 (A) Patient disposition and (B) Patient subgroups according to immunosuppression at month 60 after transplant. *One patient was receiving cyclosporine A. EVR, everolimus; *n*, number of patients; TAC, tacrolimus

month 24 onwards. The proportion of patients receiving CNI therapy increased from 23.1% at month 6 to up to 51% at month 60 (Figure S2). The proportion of patients receiving MPA decreased over time in both treatment groups (month 6: TAC, 87.2% and EVR, 81.5% vs. month 60: TAC, 62.3%; EVR, 54.9%). Similarly, the proportion of patients receiving corticosteroids also decreased over time (month 6: TAC, 52.6%; EVR, 56.9% vs. month 60: TAC: 21.3%; EVR, 29.4%; Figure S2).

3.3 | Trough levels

In the TAC group, trough levels (C_0) of both treatments remained near or below the lower limit of the target range (6–10 ng/ml) at each visit. In the EVR group, although the C_0 for EVR was within the target range at each dosage, TAC C_0 was at the lower limit or below (Figure 2).

3.4 | Renal function

In both treatment groups, estimated glomerular filtration rate (eGFR) decreased significantly over time with a mean absolute change in eGFR (±standard deviation [SD]) of −15.5 (36.18) ml/min/1.73 m^2 (p = .001) and − 14.6 (38.57) ml/min/1.73 m^2 (p = .016) at month 60 in the TAC and EVR groups respectively. At month 60, 43% and 36% of patients in the TAC and EVR groups, respectively, had eGFR values below 60 ml/min/1.73 m^2. Neither group showed any statistical difference in absolute change in eGFR between randomization and month 60 (p = .884). According to treatment received during the follow-up, the absolute change in mean eGFR (using the aMDRD formula) between randomization and month 60 was −20.1, −7.3, −6.3 and −21.81 ml/min/1.73 m^2 for the TAC, TAC-EVR, EVR and EVR-TAC subgroups respectively. The reduction in the mean eGFR from randomization to month 60 was statistically significant only for the TAC and EVR-TAC subgroups (p < .05) with no statistical difference observed between the four treatment subgroups. The mean eGFR was numerically higher in the EVR group at all time points until month 60 compared with the TAC group (Figure 3A). Observed mean eGFR (±SD) at month 60 was 75.9 (25.96) ml/min/1.73 m^2 with EVR versus 70.5 (26.71) ml/min/1.73 m^2 with TAC (p = .263). The mean eGFR decreased for the four treatment subgroups during the 5-year period post-LTx. According to the treatment received during the follow-up, mean eGFR (±SD) was 84.9 (21.88) with EVR versus 70.4 (28.45), 70.8 (23.98) and

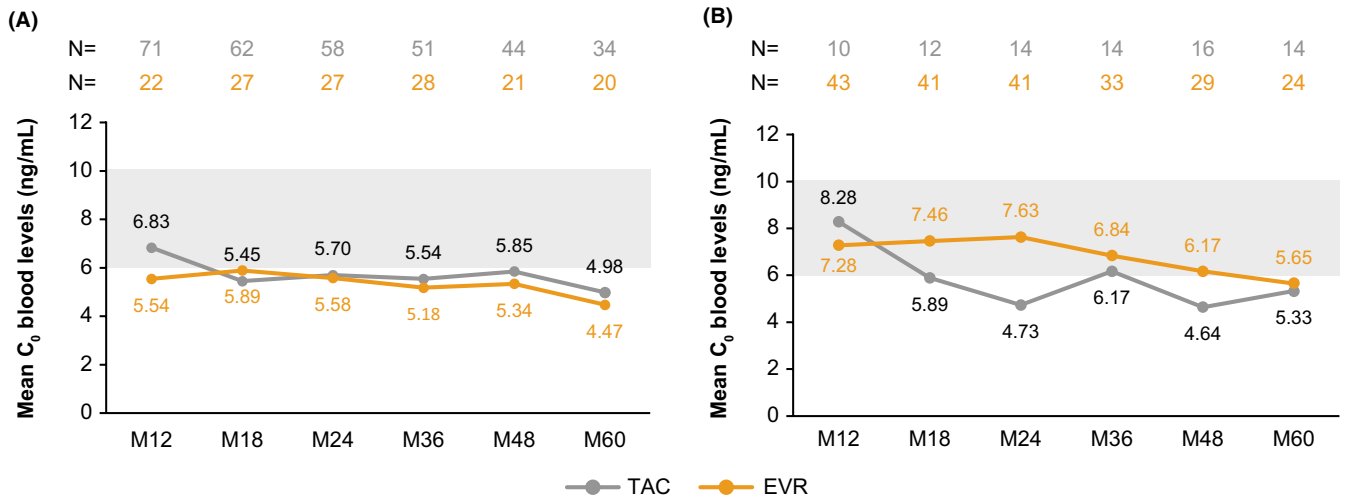

FIGURE 2 Median trough concentration in blood at each visit (A) TAC group (B) EVR group. C_0, trough levels; EVR, everolimus; M, month; *N*, number of patients; TAC, tacrolimus

68.1 (27.09) ml/min/1.73m^2 with TAC, TAC-EVR and EVR-TAC subgroups respectively (Figure 3B). The maximum difference in mean eGFR was 16.8 ml/min/1.73 m^2 between the EVR and the EVR-TAC subgroups, inclining towards EVR (p = .051). The proportion of patients with a decline of ≥10%, 20% or 30% eGFR between baseline and month 60 was not statistically different between the TAC and EVR groups. Overall, 58% of the patients presented a ≥10% decrease in eGFR and 27% had a ≥30% decrease in eGFR. The highest proportion of patients with a ≥30% decrease in GFR was observed in the TAC and EVR-TAC subgroups (33.3% and 40.0% respectively; Table S3).

3.5 | Other renal functions

The absolute change in mean (±SD) creatinine level between baseline and month 60 was 26.0 (8.02) and 5.7 (8.90) for the TAC and EVR groups respectively (p = .09). The absolute change in mean creatinine clearance between baseline and month 60, estimated by the Cockroft-Gault and chronic kidney disease epidemiology (CKD-EPI) formula was not significant in either group (p = .565 and p = .194, respectively). The proportion of patients with proteinuria above 0.5 g/L at baseline was higher in the TAC group compared with the EVR group (11.7 vs. 6.8%). At month 60, 25.1% and 9.1% of patients had proteinuria above 0.5 g/L in the TAC and EVR groups respectively.

The median urine protein/creatinine ratio (UPCR) was stable and comparable in both groups (10 mg/mmol) during the follow-up (Figure S3). The summary of patient distribution according to their CKD stage at month 60 using the KDOQI classification is presented in Figure 4. At baseline, approximately 83% of patients in both groups had stage 1 or stage 2 CKD. In the TAC group, 57.1% of patients were at stage 1 or stage 2, whereas 42.9% had stage 3 or more at month 60. In the EVR group, 63.8% were at stage 1 or stage 2 and 36.2% at stage 3. However, between-group differences were not statistically significant (p = .729). A major proportion of patients in the EVR group with CKD stage 3 were those who switched to TAC (Figure 4B).

3.6 | Efficacy endpoints

Throughout the 5-year follow-up, more treatment failures (defined as treated biopsy-proven acute rejection [tBPAR] with rejection activity index [RAI] score >3, graft loss or death) were observed in the EVR group 30.8% (n = 20) compared with the TAC group 17.9% (n = 14), although the difference was not statistically significant (p = .073, Table 1). The main reasons for treatment failure were deaths and tBPAR in both groups. Up to month 60, tBPAR was reported in 15.4% (10/65) of patients in the EVR group versus 6.4% (5/78) in the TAC group. Most of the tBPAR events were reported during the first 12 months post-LTx. The majority of tBPAR events in the EVR group were mild (80%), whereas the majority of events were severe in the TAC group (60%). From randomization until month 60, treatment failure was statistically different in all four treatment subgroups (p = .007). The highest proportion of patients showing treatment failure was in the EVR-TAC subgroup (43.6%), whereas the lowest proportion was in the EVR subgroup (11.5%). This difference was mainly caused by the incidence of tBPAR (p = .004; Table 1). During the 5-year follow-up, graft loss was reported in 1 patient alone in the TAC group; none of the patients in the EVR group had graft loss. Overall, 19 deaths (TAC, n = 9; EVR, n = 10) were reported with no statistically significant difference between the groups. There was no statistically significant difference between the groups when the death events were analysed by actual treatment received (p = .817).

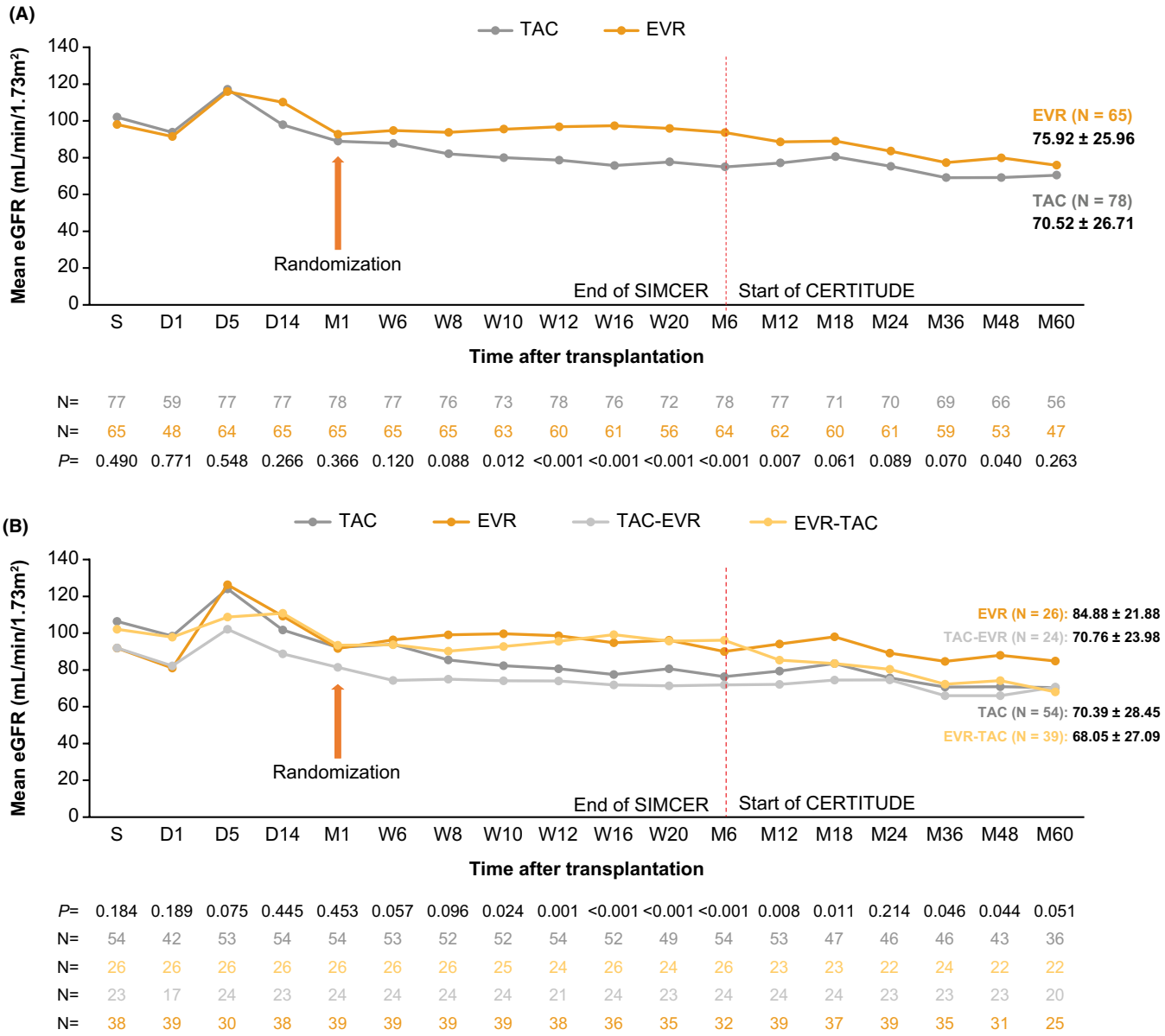

FIGURE 3 Mean eGFR (aMDRD) from randomization to month 60 after transplant according to (A) randomized treatment group (B) treatment received. aMDRD, abbreviated modification of diet in renal disease; D, day; eGFR, estimated glomerular filtration rate; EVR, everolimus; M, month; *N*, total number of patients; S, start of the study; TAC, tacrolimus; W, week

3.7 | Safety

Over the 5-year follow-up, all patients experienced ≥1 AE; throughout the CERTITUDE study (months 6–60), 98.6% of patients experienced ≥1 AE. Table 2 presents a summary of AEs reported from randomization to month 60 according to the randomized treatment groups. Compared with the TAC group, more patients in the EVR group had ≥1 AE leading to treatment discontinuation (EVR; $n = 21$, 32.3% vs. TAC; $n = 12$, 15.4%), and more patients had ≥1 serious AE (SAE; EVR; $n = 60$, 92.3% vs. TAC; $n = 61$, 78.2%). The study drug was discontinued owing to AEs in 32.3% (21/65) of patients in the EVR group vs. 15.4% (12/78) in the TAC group.

3.7.1 | Incidence of cancer

Overall, de novo cancer was reported in 14 and 5 patients in the EVR and TAC groups, respectively ($p = .008$), over 60 months. When analysed by a sequence of treatment, de novo cancer was reported in 9, 5, 2 and 3 patients in the EVR-TAC, EVR, TAC-EVR and TAC groups respectively. The difference between the four subgroups was not statistically significant ($p = .055$). De novo skin cancers (basal cell carcinoma, squamous-cell carcinoma and verrucous carcinoma) were diagnosed in 3 and 1 patient(s) in EVR and TAC groups respectively. Recurrence of hepatocellular carcinoma (HCC) was only reported in the TAC group (4 patients).

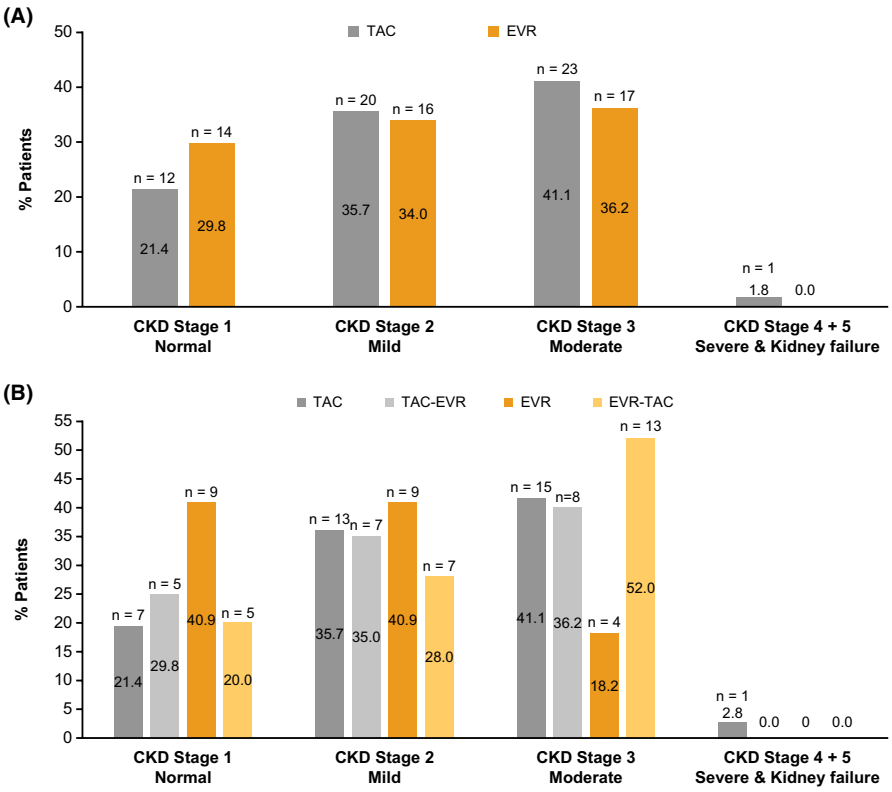

FIGURE 4 Distribution of patients according to their CKD stage at month 60 using the KDOQI classification (A) randomized treatment group (B) treatment received. CKD, chronic kidney disease; EVR, everolimus; KDOQI, kidney disease outcomes quality initiative; *n*, number of patients; TAC, tacrolimus

3.7.2 | Incidence of MACE

MACE were reported in 9.2% (6/65) and 14.1% (11/78) of patients in the EVR and TAC groups respectively; this difference between treatment groups was not statistically significant ($p = .370$). One death was reported in the TAC group owing to a cardiovascular event.

3.8 | Comorbidities and concomitant medication at baseline and during the follow-up

3.8.1 | Arterial hypertension

Before LTx and throughout the study, the proportion of patients with arterial hypertension was higher in the TAC group compared with the EVR group. During the 5-year follow-up, the proportion of patients with arterial hypertension increased in both groups.

3.8.2 | Glycemia, glycated haemoglobin (HbA_{1c})

At month 60, mean fasting glycemia did not change in the TAC group, whereas an increase of 0.31 mmol/L was observed in the EVR group. HbA_{1c} (1.2%) and total cholesterol level (0.40 mmol/L) increase from baseline were similar in both groups.

3.8.3 | Concomitant medication

Throughout the study, the proportion of patients receiving antihypertensive, lipid-lowering or hypoglycemic drugs was higher in the EVR group compared with the TAC group (Table S4).

3.9 | Lipid levels

Low-density lipoprotein cholesterol (LDL-C) level increased in the TAC group (0.41 mmol/L), whereas it decreased in the EVR group (−0.13 mmol/L). At baseline, the proportion of patients with LDL-C levels above the normal range was 11% and 13% between the TAC and EVR groups respectively; 17% and 9% of patients had LDL-C levels above the normal range at month 60 in TAC and ECR groups, respectively. A two-fold increase in high-density lipoprotein cholesterol (HDL-C) level was observed in the TAC group compared with the EVR group (0.25 mmol/L vs. 0.13 mmol/L respectively). Triglycerides increase was lower in the TAC group compared with the EVR group (0.18 mmol/L vs. 0.57 mmol/L). An increase in total cholesterol level (0.40 mmol/L) from baseline was similar in both groups. Throughout the follow-up, more patients in the EVR group were receiving lipid-lowering drugs (Table S4).

3.10 | Diabetes

The incidence of de novo diabetes 5 years post-LTx was 24% in the TAC group and 33% in the EVR group. The difference between time

TABLE 1 Efficacy parameters from randomization to month 60—cumulated cases (A) randomized treatment group (B) treatment received

(A)			
	TAC (*N* = 78)	EVR (*N* = 65)	*p* value
Treatment failure[a]	14 (17.9%)	20 (30.8%)	.073
≥1 BPAR treated, *n* (%) (RAI score >3 or indeterminate)	5 (6.4%)	10 (15.4%)	.081
Severity assessed by RAI score (maximum) for treated BPAR			
Mild acute (RAI score, 4/5)	2 (40.0%)	8 (80.0%)	.077
Moderate acute (RAI score, 6/7)	3 (60.0%)	1 (10.0%)	
Indeterminate	0 (0.0%)	1 (10.0%)	
Graft loss, *n* (%)	1 (1.3%)	0 (0.0%)	1.000
Death	9 (11.5%)	10 (15.4%)	.500

(B)					
	TAC (*N* = 54)	TAC-EVR (*N* = 24)	EVR (*N* = 26)	EVR-TAC (*N* = 39)	*p* value
Treatment failure[a]	10 (18.5%)	4 (16.7%)	3 (11.5%)	17 (43.6%)	.007
≥1 BPAR treated, *n* (%) (RAI score >3 or indeterminate)	4 (7.4%)	1 (4.2%)	0 (0.0%)	10 (25.6%)	.004
Severity assessed by RAI score (maximum) for treated BPAR					
Mild acute (RAI score, 4/5)	1 (25.0%)	1 (100.0%)		8 (80.0%)	.073
Moderate acute (RAI score, 6/7)	3 (75.0%)	0 (0.0%)		1 (10.0%)	
Indeterminate	0 (0.0%)	0 (0.0%)		1 (10.0%)	
Graft loss, *n* (%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Death	6 (11.1%)	3 (12.5%)	3 (11.5%)	7 (17.9%)	.807

Abbreviations: BPAR, biopsy-proven acute rejection; EVR, everolimus; *N*, total number of patients; *n*, number of patients; RAI, rejection activity index; TAC, tacrolimus.

[a]BPAR treated (RAI score >3), graft loss or death.

to de novo diabetes between the groups (TAC vs. EVR) was not significant ($p = .255$; Table S5). Approximately 31% of patients in the TAC group and 47% of patients in the EVR group were receiving hypoglycemic drugs.

4 | DISCUSSION

The long-term results of the observational CERTITUDE study further substantiated the efficacy, safety and tolerability of EVR compared with the TAC-based regimens. EVR-based regimen seems to be better at preserving renal function up to 5 years post-LTx without any significant impact on graft loss or safety concerns.

Compared with approximately 70% of patients who were CNI-free at month 24,[15] 59% of patients were still receiving EVR and 49% remained CNI-free at month 60. The mean eGFR significantly decreased in both groups ($p < .002$); however, there was no statistical difference in the mean absolute change in eGFR between the two groups. When analysed by the actual treatment received during follow-up, the EVR subgroup showed better maintenance of eGFR over time compared with the other three subgroups and had numerically higher mean eGFR values. The proportion of patients with a deterioration of renal function (decrease in eGFR by ≥30%) was highest in the EVR-TAC and TAC subgroups versus lowest in the EVR subgroup (40.0% and 33.3% vs. 9.1%). At month 60, the EVR group had a higher proportion of patients with normal renal function and patients were at stage 1 or stage 2 CKD, whereas more patients in the TAC group had stage 3 CKD. However, this difference between the groups was not statistically significant. When analysed by actual treatment received during the follow-up, while adding EVR to TAC showed lower deterioration of renal function, adding TAC to EVR led to severe deterioration. These results may support the rationale for adding EVR to TAC in patients with poorer kidney function. Moreover, it seems that even late introduction (>6 months post-LTx) of TAC into the immunosuppressive regimen might be deleterious to renal function when it is introduced early.

The proportion of patients experiencing BPAR was numerically higher in the EVR group; however, the severity was mild. The lower severity may less suggest a certain benefit of EVR than the fact that TAC may have been reintroduced to the treatment regimen in addition to EVR owing to signs of acute rejection. However, as the rationale for treatment adjustments was not documented, it was difficult to interpret the results. According to the CERTITUDE study protocol, episodes of acute rejection were to be reported whether they were treated (corticosteroid bolus or increased non-steroidal drug at the discretion of the clinician) or non-treated. However, as this was a

TABLE 2 AEs and SAEs reported according to randomized treatment groups

n (%)	TAC (*N* = 78)	EVR (*N* = 65)
Between randomization and month 60		
≥1 AE	78 (100.0)	65 (100.0)
≥1 AE related to EVR	12 (15.4)	47 (72.3)
≥1 AE leading to treatment discontinuation	12 (15.4)	21 (32.3)
≥1 SAE	61 (78.2)	60 (92.3)
Between months 6 and 60		
≥1 AE	76 (97.4)	65 (100.0)
≥1 SAE	56 (71.8)	57 (87.7)
AEs reported in >10% of patients in at least one group between randomization and month 60		
Cholestasis	32 (41.0)	27 (41.5)
Diarrhoea	26 (33.3)	19 (29.2)
Peripheral oedema	20 (25.6)	19 (29.2)
Hepatocellular injury	11 (14.1)	22 (33.8)
Anaemia	16 (20.5)	20 (30.8)
Hypertension	23 (29.5)	20 (30.8)
Renal failure	21 (26.9)	18 (27.7)
Hyperkalaemia	14 (17.9)	8 (12.3)
Abdominal pain	19 (24.4)	14 (21.5)
Urinary tract infection	16 (20.5)	7 (10.8)
Neutropenia	13 (16.7)	12 (18.5)
Pyrexia	9 (11.5)	10 (15.4)
Bronchitis	10 (12.8)	14 (21.5)
Dyslipidemia	8 (10.3)	18 (27.7)
Hypercholesterolaemia	11 (14.1)	15 (23.1)
Weight increased	12 (15.4)	10 (15.4)
Asthenia	12 (15.4)	11 (16.9)
Hypertriglyceridemia	11 (14.1)	13 (20.0)
Thrombocytopenia	15 (19.2)	11 (16.9)
Biliary anastomosis complication	9 (11.5)	9 (13.8)
Leukopenia	8 (10.3)	13 (20.0)
Hepatic steatosis	11 (14.1)	10 (15.4)
Cholangitis	8 (10.3)	6 (9.2)
Vitamin D deficiency	12 (15.4)	8 (12.3)
Hypokalaemia	7 (9.0)	11 (16.9)
Acute kidney injury	14 (17.9)	8 (12.3)
Hyperglycemia	9 (11.5)	7 (10.8)
Cough	9 (11.5)	11 (16.9)
Weight decreased	11 (14.1)	9 (13.8)
Back pain	12 (15.4)	7 (10.8)
Gamma-glutamyltransferase increased	10 (12.8)	5 (7.7)
Vomiting	9 (11.5)	8 (12.3)
Dyspnoea	9 (11.5)	8 (12.3)
Insomnia	8 (10.3)	7 (10.8)
Overdose	6 (7.7)	9 (13.8)
Constipation	5 (6.4)	8 (12.3)
General physical health deterioration	9 (11.5)	4 (6.2)
Depression	8 (10.3)	7 (10.8)
Cytomegalovirus infection	11 (14.1)	3 (4.6)
Diabetes mellitus	8 (10.3)	6 (9.2)
Abdominal pain upper	6 (7.7)	8 (12.3)
Pancytopenia	3 (3.8)	10 (15.4)
Pruritus	9 (11.5)	5 (7.7)
Liver transplant rejection	8 (10.3)	14 (21.5)
Proteinuria	10 (12.8)	2 (3.1)
Headache	2 (2.6)	7 (10.8)
Influenza	2 (2.6)	7 (10.8)

Abbreviations: AE, adverse event; EVR, everolimus; *N*, total number of patients; *n*, number of patients; SAE, serious AE; TAC, tacrolimus.

non-interventional study that aimed to observe and describe patient progression and occurrence of events, the proportion of patients treated with steroid boluses or increase in immunosuppressant dosage was not captured.

Treatment failures in this study, especially acute rejection post-LTx, were numerically higher in the EVR group compared with the TAC group; however, the difference was not significant. Acute rejections in the EVR group mainly occurred during the first year post-LTx and most of them were of Grade I. There were no late rejections in any of the groups. During the 5-year follow-up, 19 deaths were reported with no statistically significant difference in the time to death between the two groups ($p = .547$).

The safety profiles of both treatments in this study were in line with the previous studies and with those described in the respective summary of product characteristics of treatments taken during the study. The incidence of AEs, SAEs and AEs leading to premature discontinuation was higher in patients treated with EVR than in those treated with TAC alone.

In the PROTECT and H2304 studies, incidence of de novo cancers was lower in the EVR group compared with the CNI group.[8,10] On the contrary, the incidence of de novo cancers in his study was numerically higher in the EVR group compared with the TAC group. The reasons for this contradictory outcome remain unknown. However, the fatality rate of patients with de novo cancer was higher in the TAC group compared with EVR (67% vs. 43%). Recurrence of HCC was reported only in the TAC group (4 patients); however, it should be noted that the proportion of patients with HCC at baseline was higher in the TAC group (29.5% vs. 18.5%).

Similar to the H2304 study,[8] in the CERTITUDE study, MACE occurred infrequently in the EVR group compared with the TAC group

(9.2% vs. 14.1%). Upon further subgroup analysis based on actual treatment received during the follow-up, it was observed that MACE was not reported in the EVR subgroup, whereas 13%–17% of patients in the other three subgroups experienced MACE. However, as the baseline cardiovascular characteristics were not available by the subgroup, these subgroup analysis results are not conclusive.

Over the 5-year follow-up, the incidence of de novo diabetes was high in both groups (TAC, 24% and EVR, 33%) and 31% and 47% of patients in the respective groups were receiving hypoglycemic drugs. The higher incidence of de novo diabetes may have some correlation with the long-term use of corticosteroids, as the proportion of patients receiving corticosteroids during the follow-up was higher (TAC, 21% and EVR, 29%). However, it was not possible to fully assess this hypothesis owing to a lack of data for the doses of corticosteroids used during the follow-up. Moreover, the impact of corticosteroids on specified characteristics was not assessed in the study. The recommendations suggest reducing exposure to corticosteroids in usual clinical practice. However, it is not clear how far the recommendations are being followed in actual practice.

LDL-C levels increased in the TAC group and decreased in the EVR group; HDL-C levels remained similar in both groups. Throughout the follow-up, more patients in the EVR group received lipid-lowering drugs.

Observational studies have some inherent limitations, and the CERTITUDE study is also prone to various biases and structural limitations. As the clinical management decisions were mainly driven by local procedures, this might have introduced a potential for unmeasured time-varying confounding factors. Patients were switched to different immunosuppressive regimens, which could attenuate any long-term effects of CNI-free treatment that could have been identified in the follow-up study. Change in treatment was at the physician's discretion and some patients could have been administered different sequences of treatment during the 5-year follow-up. However, the sequences of treatment throughout follow-up were taken into account in the complementary analyses and more accurately reflect exposure to each treatment. Owing to the relatively small number of patients in subgroup analysis, the results of these analyses should be interpreted with caution.

In conclusion, the 5-year follow-up of the CERTITUDE study in de novo LTx patients suggests that the efficacy, safety and tolerability of the EVR-based regimen without CNI were comparable with that of TAC or its combination with EVR. EVR-based regimen seems to have better renal outcomes without compromising graft survival or safety. The results corroborate with the efficacy and safety results of EVR reported in previous studies.

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ORCID

Faouzi Saliba https://orcid.org/0000-0002-2058-9217
Christophe Duvoux https://orcid.org/0000-0003-4625-4279
Sébastien Dharancy https://orcid.org/0000-0002-8262-5607
Jérôme Dumortier https://orcid.org/0000-0002-7824-5396
Yvon Calmus https://orcid.org/0000-0002-6605-3012
Jean Gugenheim https://orcid.org/0000-0002-2624-3014
Nassim Kamar https://orcid.org/0000-0003-1930-8964
Ephrem Salamé https://orcid.org/0000-0002-8508-0657
Martine Neau-Cransac https://orcid.org/0000-0001-7658-9139
Claire Vanlemmens https://orcid.org/0000-0002-2048-3324
François Durand https://orcid.org/0000-0002-0357-1090
Georges-Philippe Pageaux https://orcid.org/0000-0001-5269-8373
Filomena Conti https://orcid.org/0000-0001-6914-8204

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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