Annals of Gastroenterology (2018) **31,** 1-8

Everolimus with or without mycophenolate mofetil in a liver transplantation setting: a single-center experience

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Abstract

Background This study evaluated the efficacy, safety, and impact on renal function of everolimus in patients after liver transplantation (LT) with or without mycophenolate mofetil (MMF).

Methods We evaluated LT recipients with calcineurin inhibitor (CNI)-related renal dysfunction after everolimus initiation. Laboratory data, including evaluation of renal function based on glomerular filtration rate (GFR) at baseline (i.e., everolimus initiation) and at the end of follow up, were analyzed.

Results Fifty consecutive patients started taking everolimus at 30 months post-LT (range: 1-240), 6 as monotherapy and 44 in combination with MMF. After 30.5 months (range: 6-112), all patients were alive, without any biochemical evidence of a rejection episode or recurrence of hepatocellular carcinoma. The mean GFR, based on the Modification of Diet in Renal Disease equation, was 53±13 mL/min at baseline and 59±12 mL/min at the end of follow up (P=0.031). Eleven (22%) of the patients had GFR <60 mL/min at baseline but returned to GFR >60 mL/min by the end of follow up. In multivariate analysis, the time between the development of renal dysfunction and everolimus initiation was the only factor independently associated with GFR improvement (odds ratio [OR] 0.85, 95% confidence interval [95%CI] 0.76-0.96; P=0.007). Everolimus was stopped in 11 patients (22%) at the end of follow up because of adverse events.

Conclusion A CNI-free everolimus-based regimen was effective in LT recipients with renal dysfunction and was associated with an improvement in GFR.

Keywords Everolimus, liver transplantation, mammalian target of rapamycin inhibitor, renal function, hepatocellular carcinoma

Ann Gastroenterol 2018; 31 (4): 1-8

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Conflict of Interest: None

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Received 5 January 2018; accepted 11 April 2018; published online 25 May 2018

DOI: https://doi.org/10.20524/aog.2018.0278

Introduction

Patients' outcomes after liver transplantation (LT) have improved significantly during the last decades, since the use of calcineurin inhibitors (CNIs) has led to lower rates of cellular rejection and improvements in graft and patient survival post-LT [1]. However, CNIs have several limitations, including a dose-dependent increase in the risk of recurrence of hepatocellular carcinoma (HCC) and the development of renal dysfunction [2,3]. The latter is considered the most common long-term complication after LT and is responsible for increased morbidity and mortality. It is estimated that 8% of LT recipients develop chronic kidney disease at 12 months post-LT [4]. Thus, the use of CNI-free immunosuppressive protocols in the LT setting is urgently needed in order to reduce the risk of renal dysfunction without increasing the risk of rejection episodes or graft loss.

Inhibitors of the mechanistic target of rapamycin (mTOR) (sirolimus and everolimus) seem to exhibit both immunosuppressive and nephroprotective properties [5]. Several studies have investigated the impact of CNI reduction or conversion to everolimus in patients with deterioration of renal function or established renal impairment, showing that an everolimus-based immunosuppressive regimen was associated with improvement in renal function. In a large prospective, multicenter, open-label study published recently [6], a clinically relevant renal benefit in the "everolimus with reduced-dose of tacrolimus" group was found with sufficient efficacy regarding rejection episodes and graft failure. However, the arm of patients with everolimus monotherapy (tacrolimus elimination group) was terminated early because of an increase in the number of rejection episodes. Thus, there is still a concern regarding the immunosuppressive efficacy of CNI-free everolimus-based therapy.

The combination of everolimus plus mycophenolate mofetil (MMF), without CNIs, could be an alternative option in order to maintain the immunosuppressive potency without any adverse effect on renal function. Only a few studies have evaluated this nephroprotective combination in the LT setting. In a recently published randomized study [7], liver transplant recipients were randomized at week 4 post-LT to everolimus plus MMF or tacrolimus-based immunosuppressive therapy. The authors found that the everolimus-based therapy was superior as regards the change in GFR from randomization to month 6 post-LT (mean change: +1.1 vs. -13.3 mL/min, P<0.001). However, biopsy-proven acute rejection (BPAR) was observed more frequently for everolimus- than for tacrolimus-based immunosuppression (10.0% vs. 2.2%, P=0.026).

The aim of the present study was to evaluate the safety and efficacy of the CNI-free administration of everolimus, with or without MMF, in daily clinical practice and its impact on renal function in liver transplant recipients who develop CNI-related renal dysfunction.

Patients and methods

We retrospectively included all consecutive adult patients under a CNI-based immunosuppression regimen after LT, switched to everolimus administration, with or without MMF, between January 2006 and November 2014, having as indication for immunosuppressive changes the presence of renal dysfunction (defined as serum creatinine ≥1.5 mg/dL and/or Modification of Diet in Renal Disease (MDRD)-based GFR <60 mL/min), and who survived for more than 3 months after LT. All patients gave informed consent and the protocol was approved by the local ethics committee. Everolimus (Certican, Novartis Pharma AG, Basel, Switzerland) was

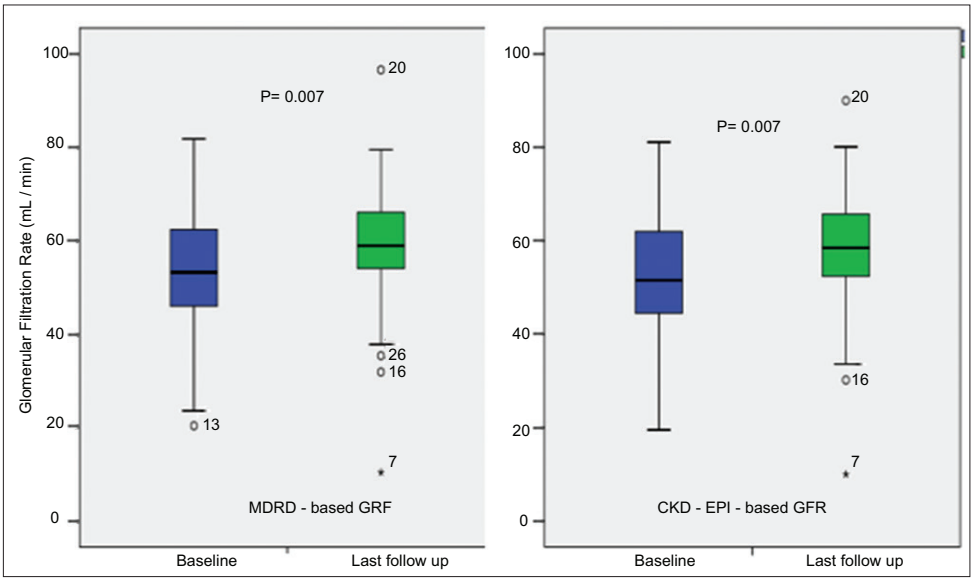

Figure 1 Evolution of glomerular filtration rate (GFR) in 50 liver transplant recipients under everolimus plus mycophenolate mofetil between baseline and end of follow up, based on the Modification of the Diet in Renal Disease (MDRD) formula and the chronic kidney disease–epidemiology (CKD-EPI) formula

started at 0.75-1.5 mg b.i.d., aiming to achieve trough levels of 3-8 ng/mL. CNIs were reduced by 50% of their initial dosages after everolimus initiation (i.e., at baseline) and were stopped when everolimus trough levels reached ≥3 ng/mL. Methylprednisolone was given in a 1 g intravenous bolus intraoperatively and then reduced to 200 mg/day (day 1), 160 mg/day (day 2), 120 mg/day (day 3), 80 mg/day (day 4), 40 mg/day (day 5), and 20 mg/day (day 6), and was stopped 3-6 months after LT.

At baseline (i.e., everolimus initiation) the following variables were recorded prospectively: age, sex, cause of liver disease before LT, concomitant diseases and medications (including diabetes mellitus and coronary artery disease) pre- or post-LT. The diagnosis of HCC pre-LT was based on the current standard criteria. Laboratory tests recorded the following: hematocrit, hemoglobin, white blood cell count, platelet count, serum creatinine (sCr), urea, uric acid, sodium, potassium, calcium, phosphate, magnesium, lactate dehydrogenase, creatine phosphokinase, aminotransferases, alkaline phosphatase, γ-glutamyltransferase, bilirubin (total and direct), protein, albumin, ferritin, lipidemic profile, α-fetoprotein, and clotting profile (prothrombin time, international normalized ration, activated partial thromboplastin time). In addition, proteinuria was evaluated via 24-h urine collection.

After baseline, the patients were closely followed up with clinical and laboratory evaluation until November 2014 and their status was recorded (alive or not or discontinuation of everolimus). Changes in immunosuppressive therapy were recorded, including the dosage and trough levels of everolimus. Liver biopsies were performed based on clinical findings and laboratory tests. Patients were converted to CNI-based immunosuppression, with or without MMF, when rejection occurred or when everolimus was discontinued because of adverse events.

Renal function was evaluated at baseline (i.e., the day of everolimus initiation) and at the end of follow up. Estimated GFR (eGFR) was assessed using: a) the creatinine-based 4-variable MDRD formula, $186 \times (sCr)^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times (1.210$ if black) [8]; and b) the chronic kidney disease-epidemiology (CKD-EPI) sCr-based formula $= 141 \times \min(sCr/\kappa,1)^{\alpha} \times \max(sCr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black] (κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of sCr/κ or 1, and max indicates the maximum of sCr/κ or 1) [9]. Finally, in a subgroup of patients, "true" GFR was assessed with ^{51}Cr-EDTA by sampling blood, after intravenous injection of tracer, at 2, 4, and 6 h. "True" GFR was calculated using the slope-intercept technique, correcting for body surface area, and the fast exponential curve recommended by the British Nuclear Medicine Society's guidelines [10]. The presence of eGFR <60 mL/min was used to define renal dysfunction, based on the National Kidney Foundation's Kidney Disease Quality Outcome Initiative guidelines [11].

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and it was not supported by an external institution or agency.

Statistical analysis

The statistical package SPSS (version 23.0 SPSS Inc., Chicago, IL) was used for the statistical analysis. The χ^2 test was used for comparing qualitative variables and the Student's *t*-test and Mann-Whitney *U* test for comparing quantitative continuous variables, while the paired *t*-test was also used for comparisons between baseline and end of follow up eGFRs. Quantitative variables normally distributed were expressed as mean values ± one standard deviation and those non-normally distributed were expressed as median values (range). Multivariable logistic regression analysis was performed to identify admission factors independently associated with changes in renal function between baseline and end of follow up. A P-value ≤0.05 was considered statistically significant.

Results

Two hundred thirty-five patients underwent LT during the study period. Of these, 50 (21.3%) were started on everolimus (with or without MMF), after CNIs were stopped because of renal dysfunction, and fulfilled the inclusion criteria. Thirty-seven (74%) patients were men and the mean age was 58±10 years. The median time from LT to everolimus initiation was 30 months (range: 1-240), while the median follow-up duration after everolimus conversion was 30.5 months (range: 6-112). Forty-two (84%) patients did not have HCC before LT, while in 8 (16%) patients everolimus was also given for prevention of HCC recurrence (Table 1). The time from LT to baseline (i.e., everolimus initiation) differed significantly between those with and those without HCC pre-LT: median 2 (range 1-144) vs. 36 (1-240) months, P=0.018. The indications for LT are presented in Table 1. At baseline (i.e., everolimus initiation), most of the patients were under a combination of cyclosporine with or without MMF (Table 1).

Efficacy

Everolimus was initially given at a dose of 2 mg/day (range: 1.5-3.0). After 30.5 months (range: 6-112) of follow up, the median dose of everolimus was 2 mg/day (range: 0.75-3.0) with median trough levels of 4.8 ng/mL (range: 3.2-9.5). In addition, the median dose of MMF was 1.5 g/day (range: 0.5-2). Six (12%) patients received everolimus monotherapy and 44 (88%) patients received everolimus plus MMF. The dose of everolimus at baseline, as well as the trough levels at 15 days and at the end of follow up, were similar between the 2 groups. All patients were alive at the end of follow up, while no biochemical evidence of a rejection episode was observed during the follow-up period. In addition, none of the 8 patients with HCC pre-LT had HCC recurrence at the end of follow up.

Table 1 Clinical and laboratory characteristics of liver transplant (LT) recipients in our cohort

Variable (unit)	Patients, n=50
Age (years)	58±10
Sex, male n, (%)	37 (74)
Indication for LT n, (%)	
Viral hepatitis	31 (62)
Alcohol	10 (20)
NASH/cryptogenic	3 (6)
Other	6 (12)
MELD score at LT	17±5
Immunosuppression before everolimus initiation, n (%)	
Cyclosporine plus MMF	45 (90)
Tacrolimus plus MMF	5 (10)
Indication for everolimus initiation	
Renal dysfunction without HCC, n (%)	42 (84)
Renal dysfunction plus prevention of HCC recurrence, n (%)	8 (16)
Immunosuppression after everolimus initiation, n (%)	
Everolimus monotherapy	6 (12)
Everolimus plus MMF	44 (88)

NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; MMF, mycophenolate mofetil; MELD, model for end-stage liver disease

Renal function

For all patients together, the mean eGFRs at baseline and end of follow up were as follows: MDRD-based GFR 53±13 mL/min vs. 59±12 mL/min (paired *t*-test: P=0.007) and CKD-EPI GFR 52±14 mL/min vs. 58±13mL/min (paired *t*-test: P=0.007), respectively (Fig. 1). In the subgroup of patients (n=28) where "true" GFR was evaluated, the respective levels were 49±11 mL/min vs. 57±13mL/min (paired *t*-test: P=0.005). Based on MDRD-based GFR, the median change in GFR was 5.6 mL/min (range: -48.2 to 51 mL/min); 24 (48%) of the patients had GFR >60 mL/min at the end of follow up, while 11 (22%) of the patients with GFR <60 mL/min at baseline returned to GFR >60 mL/min by the end of follow up. In addition, 9 (75%) of 12 patients with GFR <45 mL/min (i.e., chronic kidney disease stage 3b-5) had an improved GFR at the end of follow up, compared to 31 (81.5%) of 38 patients with GFR ≥45 mL/min at baseline (P=0.62).

At baseline, the patients who showed an improvement in renal function (change in GFR >0) (n=40), compared to those with no change or deterioration (change in GFR ≤0) (n=10), were less likely to have hyperlipidemia (20% [8/40] vs. 60% [6/10], P=0.007), had lower serum urea (36±16 vs. 56±24 mg/dL, P=0.023) and had a significantly shorter period between the development of renal dysfunction and everolimus initiation (median: 6.5 [1-29] vs. 18 [5-96] months, P=0.001) (Table 2). However, neither sCr nor eGFR levels (MDRD or CKD-EPI) at baseline were significantly associated with GFR improvement (Table 2). At the end of follow up, the patients with GFR >0, compared to those with GFR ≤0, were less likely to have arterial hypertension (40% [16/40] vs. 80% [8/10], P=0.012) and were receiving a higher dose of everolimus (1.6±0.5 vs. 1.2±0.4 mg/day, P=0.034). However, trough levels of everolimus and the dosage of MMF at the end of follow up did not differ between those with and those without GFR improvement. In multivariate analysis, the time between the development of renal dysfunction and everolimus initiation was the only factor independently associated with GFR improvement at the end of follow up (odds ratio 0.85, 95% confidence interval 0.76-0.96; P=0.007).

Safety

None of the patients had proteinuria at the baseline, while during the follow-up period no major complications, such as hepatic artery thrombosis/stenosis and bacterial or fungal infections, were recorded. In addition, no significant changes were observed between baseline and end of follow up in the proportion of patients with diabetes mellitus (22% vs. 22%), or in levels of cholesterol (178 vs. 176 mg/dL) or triglycerides (105 vs. 121 mg/dL), although 14 (28%) patients received additional prescription of anti-hyperlipidemic treatment after everolimus conversion. Regarding hematological events, median hematocrit and platelet counts were similar between baseline and end of follow up (38% vs. 40% and 182×10^9/L vs. 187×10^9/L; P>0.05). In addition, white blood cells were 5.5×10^9/L at baseline and 5.8×10^9/L at the end of follow up (P>0.05). These findings did not differ between the patients (n=6) under everolimus monotherapy and those (n=44) under a combination of everolimus plus MMF. However, in 11 patients (22%) everolimus was discontinued because of hyperlipidemia not well controlled under anti-lipidemic drugs (n=2), mouth ulcers (n=2), lower limb edema/proteinuria (n=4), possible allergic reaction (n=1) and unknown reason (n=2) after 26.7±12 months under everolimus-based immunosuppression therapy. These 11 patients, compared to those (n=39) who did not have everolimus discontinued, were significantly more likely to have diabetes mellitus (45% [5/11] vs. 15.5% [6/39], P=0.035) or arterial hypertension (72% [8/11] vs. 33% [13/39], P=0.023) at baseline (Table 3).

Discussion

The use of CNIs (cyclosporine or tacrolimus) has improved the outcomes of patients after LT, but has also been associated with several drawbacks, including an increased risk of renal dysfunction [12]. The mTOR inhibitors (sirolimus and everolimus) exhibit both immunosuppressive and nephroprotective properties [13]. However, mTORs are considered to have less immunosuppressive potency compared to CNIs and their use may lead to higher rates of rejection episodes. This was clearly shown in a recent large randomized multicenter study [6]: although the patients who received everolimus-based immunosuppressive therapy

Table 2 Baseline characteristics of liver transplant (LT) recipients (n=40) with an improvement in renal function (GFR >0) and those (n=10) without improvement (GFR ≤0) between baseline (i.e., everolimus initiation) and the end of follow up

Variable (unit)	Patients with change in GFR >0 (n=40, 80%)	Patients with change in GFR ≤0 (n=10, 20%)	P-value
Age (years)	58±7	57±5	0.90
Sex, male n, (%)	31 (77)	6 (60)	0.25
Comorbidities, n (%)			
Diabetes mellitus	8 (20)	3 (30)	0.49
Arterial hypertension	15 (37)	6 (60)	0.19
Hyperlipidemia	8 (20)	6 (60)	0.007
Laboratory			
Hematocrit, (mean±SD, %)	38±7	37±6	0.95
WBC (mean±SD, $\times 10^9$/L)	5.7±2.3	5.1±2.1	0.49
PLT (mean±SD, $\times 10^9$/L)	189±85	148±68	0.14
Sodium (mean±SD, mmol/L)	137±12	138±15	0.32
Potassium (mean±SD, mmol/L)	4.5±0.4	4.4±1.6	0.74
Calcium (mean±SD, mg/dL)	10.2±1.7	8.5±3.7	0.26
Phosphorus (mean±SD, mg/dL)	4.1±0.7	3.6±0.9	0.25
Creatinine (mean±SD, mg/dL)	1.5±0.3	1.4±0.3	0.41
Urea (mean±SD, mg/dL)	36±16	56±24	0.023
MDRD-based GFR (mean±SD, mL/min)	52±10	58±20	0.24
CKD-EPI-based GFR (mean±SD, mL/min)	51±11	59±18	0.22
ALT (mean±SD, IU/L)	28±12	24±11	0.42
ALP (mean±SD, IU/L)	138±45	124±39	0.38
Protein (mean±SD, g/dL)	7.1±1.3	7.2±1.9	0.91
Albumin (mean±SD, g/dL)	4.1±0.9	3.9±1.1	0.35
Bilirubin (mean±SD, mg//dL)	1.1±0.2	1.0±0.2	0.45
Cholesterol (mean±SD, mg/dL)	168±80	139±70	0.32
Triglycerides (mean±SD, mg/dL)	95±48	88±41	0.77
Immunosuppression, n (%)			0.82
Everolimus monotherapy	5 (12.5)	1 (10)	
Everolimus+MMF	35 (87.5)	9 (90)	
Time from LT to everolimus initiation, median (range), months	48 (24-240)	18 (1-204)	0.09
Time from renal dysfunction to everolimus initiation, median (range), months	6.5 (1-29)	18 (5-96)	0.001
Follow-up period after everolimus initiation, median (range), months	31 (9-112)	28.5 (6-108)	0.97

SD, standard deviation; WBC, white blood cell count, PLT, platelets; GFR, glomerular filtration rate; MDRD, Modification of the Diet in Renal Disease equation; CKD-EPI, chronic kidney disease–epidemiology equation; MMF, mycophenolate mofetil

(as monotherapy or with reduced-exposure tacrolimus) had improved GFR, in the arm of everolimus monotherapy higher risk of rejection episodes were observed.

The combination of everolimus plus MMF without CNIs could be an alternative option for maintaining the immunosuppressive potency without an adverse effect on renal function. In a recent multicenter trial, the SIMCER study [7], in which basiliximab induction and enteric-coated mycophenolate, with or without steroids, was given to LT recipients and at week 4 post-LT, the patients were randomized to everolimus plus MMF (after low-exposure tacrolimus discontinued by month 4) or tacrolimus-based therapy. Although the incidence of treatment failure (BPAR, graft loss or death) was similar in both groups (everolimus vs. tacrolimus: 10% vs. 4.3%, P=0.134), BPAR was observed at significantly higher rates in the everolimus group (10% vs. 2.2%, P=0.026). It is better to delete this as we mentioned before the main findings of SIMCER study. In our study, none of the 50 patients

Table 3 Baselines characteristics of liver transplant (LT) recipients with discontinuation (n=11) of everolimus because of adverse events and those (n=39) without discontinuation of everolimus

Variable (unit)	Patients with everolimus discontinuation due to adverse events (n=11, 22%)	Patients without everolimus discontinuation due to adverse events (n=39, 88%)	P value
Age (years)	63±8	62±6	0.73
Sex, male n, (%)	9 (82)	28 (72)	0.50
Cormobidities at baseline, n (%)			
Diabetes mellitus	5 (45)	6 (15.5)	0.035
Arterial hypertension	8 (72)	13 (33)	0.023
Hyperlipidemia	5 (45)	9 (24)	0.15
Laboratory at baseline			
Hematocrit (mean±SD, %)	37±13	37±7	0.88
WBC (mean±SD, $\times 10^9$/L)	6.4±3	5.3±2.1	0.27
PLT (mean±SD, $\times 10^9$/L)	182±74	179±86	0.91
Sodium (mean±SD, mmol/L)	137±14	139±12	0.55
Potassium (mean±SD, mmol/L)	4.2±1.3	4.6±0.5	0.44
Calcium (mean±SD, mg/dL)	9.2±1.4	9.4±017	0.25
Phosphorus (mean±SD, mg/dL)	3.4±1.9	3.8±1.6	0.76
Creatinine (mean±SD, mg/dL)	1.5±0.3	1.5±0.4	0.92
Urea (mean±SD, mg/dL)	43±22	54±19	0.16
MDRD-based GFR	54±14	53±12	0.89
ALT (mean±SD, IU/L)	25±11	24±10	0.63
ALP (mean±SD, IU/L)	122±56	134±39	0.72
Protein (mean±SD, g/dL)	7.2±1.5	7.1±1.2	0.85
Albumin (mean±SD, g/dL)	4.1±1.4	4.1±1.3	0.98
Bilirubin (mean±SD, mg//dL)	0.9±0.2	1.1±0.2	0.41
At the end of follow up			
Levels of immunosuppression			0.63
Everolimus (mean±SD, ng/mL)	5.7±2.6	5.3±2.7	
Immunosuppression, n (%)			0.19
Everolimus monotherapy	0 (0)	6 (15)	
Everolimus+MMF	11 (100)	33 (85)	
Time from renal dysfunction to everolimus initiation, median (range), months	9 (1-48)	12 (1-96)	0.46
Follow-up period after everolimus initiation, mean±SD, months	43±12	38±15	0.58

SD, standard deviation; WBC, white blood cell count, PLT, platelets; GFR, glomerular filtration rate; MDRD, Modification of the Diet in Renal Disease equation; CKD-EPI, chronic kidney disease–epidemiology equation; MMF, mycophenolate mofetil

who converted to everolimus—with (n=44) or without (n=6) MMF—had any clinical or laboratory evidence of rejection during the follow-up period (30.5 months [range: 6-112]), demonstrating the efficacy of this immunosuppressive protocol in our patients. However, it should be mentioned that we did not perform protocol liver biopsies, the median time from LT to the introduction of everolimus was 30 months (range: 1-240 months) and only 9 (18%) of the patients converted to everolimus during the first 4 months post-LT.

Immunosuppression after LT for HCC is associated with a higher risk for tumor recurrence, but mTOR inhibitors may also exert an antineoplastic effect, as has been shown in a recently published meta-analysis [14]. After a median 30.5 months (range: 6-112) of follow up, no HCC recurrence was observed. However, the number of patients was extremely small for final conclusions.

Nevertheless, the main endpoint of our study was the change in renal function after the introduction of everolimus (with or without MMF). Several studies have shown that mTORs have a beneficial effect on renal function [15,16]. However, only very few small observational studies [17-19] and two randomized trials [6,7] have evaluated the CNI-free combination of

everolimus plus MMF, and they confirmed that early introduction of everolimus during the first month after LT was associated with a significant long-term benefit for renal function. For example, in the SIMCER study [7], the authors found that the change in MDRD-based GFR was superior under an everolimus- vs. a tacrolimus-based regimen (+1.1 vs. -13.3 mL/min, P<0.001) at 24 weeks after randomization. In our study, the indication for CNI-free everolimus-based administration was renal dysfunction (defined as the presence of serum creatinine ≥1.5 mg/dL and/or MDRD-based GFR <60 mL/min) and there was a significant improvement in renal function (i.e., GFR) between baseline and the end of follow up (53±13 vs. 59±12 mL/min, P=0.031). Interestingly, in our study, although the median time from LT to the introduction of everolimus was 30 months, the median GFR improvement was 5.6 mL/min after 30.5 months' follow up, compared to only 1.1 mL/min after 6 months follow up in the SIMCER study [7]. This may be because the baseline GFR (i.e., everolimus initiation) in the SIMCER study [7] was normal (mean: 91.4 mL/min) and it would have been difficult to observe further improvement.

In our study, we found that the time between the development of renal dysfunction and everolimus initiation was the only factor independently associated with GFR improvement (OR 0.85, 95%CI 0.76-0.96; P=0.007). In fact, the patients who showed an improvement in GFR, compared to those with no change or a deterioration, had a significantly shorter period between the diagnosis of renal dysfunction post-LT and the initiation of everolimus (with or without MMF): median: 6.5 (1-29) vs. 18 (5-96) months, P=0.001. Thus, although the number of patients was small, we were able to confirm the finding of previous studies, that prompt initiation of everolimus was associated with a greater improvement in renal function [6,7]. In addition, based on our findings, it could be suggested that conversion to CNI-free everolimus-based immunosuppression might represent an alternative option for LT recipients who develop renal dysfunction after short or long-term CNI administration, provided that everolimus is started early after GFR impairment. However, larger studies will be needed to confirm these findings.

In our study, everolimus was not associated with a higher risk for a new appearance of diabetes mellitus or arterial hypertension, while no significant hematological adverse events were recorded (with no difference between everolimus monotherapy and its combination with MMF). However, it should be mentioned that mTOR inhibitors are not devoid of side effects: in our cohort, 11 patients (22%) discontinued everolimus because of several adverse events, including 2 patients with uncontrolled hyperlipidemia, although 14 (28%) of the 50 patients started on anti-hyperlipidemic treatment after everolimus conversion.

The present study has some limitations. First, it was a small single-center retrospective study without protocol liver biopsies. Hence, larger, randomized controlled studies should be performed in order to safely address the use of everolimus with MMF in patients after LT with renal dysfunction linked to CNI administration. However, our aim was to evaluate the effect of everolimus in daily clinical practice, focusing mainly on CNI-related renal dysfunction after LT.

In conclusion, this study showed that, although a relatively high proportion of patients discontinued everolimus because of adverse events, it was very effective in LT recipients, whether given as monotherapy or in combination with MMF, and its early administration after the development of renal dysfunction was associated with a beneficial effect on GFR.

Summary Box

What is already known:

- Calcineurin inhibitors (CNIs) can achieve a significant reduction in the rates of rejection episodes and can increase graft and patient survival after liver transplantation (LT). However, they are not without drawbacks, including the development of renal dysfunction
- The mTOR inhibitors, such as sirolimus and everolimus, seem to represent an alternative immunosuppressive regimen, since they exhibit both immunosuppressive and nephroprotective properties
- The administration of everolimus, with or without mycophenolate mofetil (MMF), could be an alternative option as immunosuppressive therapy. Only few studies have evaluated this nephroprotective combination in the LT setting

What the new findings are:

- Everolimus was effective as immunosuppressive therapy in LT recipients, whether given as monotherapy or in combination with MMF
- The time between the development of CNI-related renal dysfunction and everolimus initiation was the only factor independently associated with glomerular filtration rate (GFR) improvement during follow up
- This study shows for the first time that everolimus-based immunosuppression has a beneficial effect on GFR, irrespectively of the time interval from LT, providing that is given early after the development of renal dysfunction

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