Everolimus and Enteric-Coated Mycophenolate Sodium Ab Initio after Liver Transplantation: Midterm Results

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ABSTRACT

Background and aim. Everolimus (EVR) use in liver transplantation (OLT) has been prescribed with calcineurin inhibitors (CNIs), steroids, and monoclonal antibodies. The aim of our study was to evaluate the safety, feasibility, and impact on renal function of EVR ab initio, in combination with enteric-coated mycophenolate sodium (EC-MPS) without the use of induction treatment, steroids, or CNIs.

Patients and methods. We retrospective analyzed nine consecutive patients who underwent OLT at our institution. The initial dose of EVR (1.5 mg/d) was adjusted to achieve trough levels of 8 to 12 ng/mL. EC-MPS introduced at 1080 mg/d was maintained at the same dose over time.

Results. At a mean follow-up of 21.48 (standard deviation [SD] 1.4) months from OLT, 7/9 recipients were alive with stable graft function. The 2-year patient and graft survivals were 77%. One recipient died due to cerebral hemorrhage and one, lung failure. No clinical evidence of an acute rejection episode was observed. Mean estimated glomerular filtration rate value, according to the Modification of Diet in Renal Disease formula increased from 59.5 (SD 9.89) mL/min/1.73 m^2 at OLT to 100.2 (SD 47.5) mL/min/1.73 m^2 ($P = .03$) after 12 months and 98.71 (SD 33.74) mL/min/1.73 m^2 ($P = .03$) after 24 months' follow-up.

Conclusion. A double immunosuppression therapy with EVR and EC-MPS ab initio seemed to be efficacions and safe, representing a valid alternative to CNIs to prevent renal failure after OLT.

IMMUNOSUPPRESSIVE THERAPY based on calcineurin inhibitors (CNIs) in liver transplantation (OLT) reduces the risk of rejection but is associated with side effects including renal failure, neurotoxicity, cardiovascular complications, hypertension, and diabetes mellitus.[1] Chronic renal dysfunction (CRD) among OLT recipients shows a cumulative incidence of 20% within 3 years and a fourfold increased risk of death.[2–4] CRD among OLT recipients has multifactorial origins: female sex, renal disease pretransplantation, primary graft dysfunction, perioperative acute renal damage, recipient age, hepatitis C, hypertension, diabetes mellitus. The prescription of CNIs seems to be the only modifiable risk factor.[5]

CNIs lead to acute nephropathy by renal arteriolar vasoconstriction and tubular vacuolization; pathological findings can be reversed by CNI withdrawal. In contrast, the chronic CNI-induced nephrotoxicity, which is characterized by arteriolopathy and tubulointerstitial fibrosis, develops irreversible structural damage.[6] CNI therapy is also responsible for new-onset diabetes and hypertension, important risk factors for CRD.[7]

The current clinical challenge is therefore to develop regimens that maintain high rates of efficacy while minimizing side effects. Everolimus (EVR; Certican; Novartis, Basel, Switzerland), a proliferation signal inhibitor (PSI),[8] seems to not increase the risk of renal dysfunction while maintaining excellent efficacy as an immunosuppressant. A few studies have shown the safety and efficacy of PSI in midterm results[9,10]; however, there was no renal functional

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improvement after PSI introduction,[9,11] possibly due to the onset of irreversible renal "stigmata" from chronic CNI use. Thus, it seems reasonable to introduce EVR earlier with CNI avoidance immediately after OLT to minimize the risk of renal dysfunction particularly among patients at high risk of renal failure. Based on the dogma of "earlier is better," the aim of our study was to evaluate the safety, feasibility, and renal functional impact of EVR ab initio, as the main drug in OLT, in combination with enteric-coated mycophenolate sodium (EC-MPS) without the use of induction antibody treatment, steroids and CNIs.

PATIENTS AND METHODS

We retrospective analyzed nine patients who consecutively underwent OLT between September 2009 and February 2010. The regimen consisted of EVR and EC-MPS ab initio. No patients received an induction therapy (basiliximab or daclizumab) and/or steroids. The initial EVR dose was 1.5 mg/d, seeking to achieve a C_0 level of 8 to 12 ng/mL within 7 postoperative days (POD). The EVR dose was then modified to achieve an EVR target trough level of 6 to 10 ng/mL. EC-MPS was introduced and maintained at 1080 mg per day. EC-MPS and/or EVR administration was modified in the presence of side effects and/or the need for more intense immunosuppression.

The primary endpoint of the study was to evaluate the safety and efficacy of a CNI-free regimen without induction or steroid in de novo OLT recipients. The second aim was to assess renal function expressed as estimated glomerular filtration rate (EGFR) using the Modification of Diet in Renal Disease (MDRD) formula in OLT recipients who received EVR and EC-MPS ab initio.

Clinical and laboratory data were prospectively recorded at baseline as well as at months 3, 12, and 24 after OLT. The collected data included hematology and biochemistry tests and EVR trough levels.

EVR was assayed on aTDxFLx analyzer (Abbott Diagnostic, Ill, USA) using a Certican homogeneous fluorescence polarization immunoassay system.

Data were retrieved from a prospective database (Microsoft Access 2.0, Microsoft Corporation, USA). Categorical metrics were analysed using Fisher exact test for simple cross tables; continuous data of normal distribution, by the parametric Student *t* test using mean values ± standard deviations (SD). A *P* value of <.05 was considered significant. Graft and patient survival were evaluated using the Kaplan-Meier method.

RESULTS

Demographics Characteristics of the Study Population

Nine consecutive patients (eight male, one female) who underwent OLT at our institution between September 2009 and February 2010 received EVR and EC-MPS ab initio. Their indications for OLT are reported in Table 1. At the time of OLT the mean age was 48.6 ± 5.7 years and mean Model for End-stage Liver Disease (MELD) score was 22 (SD 6.4). Three recipients (33.3%) were hospitalized before OLT. The mean eGRF value according to MDRD was 59.5 (SD 9.89) mL/min/1.73 m^2 and 2 patients (22.2%) required dialysis for hepatorenal syndrome. None of the recipients had a significant additional medical history such as leukopenia, diabetes or dyslipidemia. All OLT were performed

Table 1. Demographic Characteristics of the Study Population

Patient	Gender/Age	Primary Diagnosis	MELD pre-OLT	Donor Gender/Age	Follow-up from OLT (mon)	Status	Cause of Death	eGFR pre-OLT* (mL/min/1.73 m^2)	eGFR post-OLT*,† (mL/min/1.73 m^2)	Graft Function† ALT (UI/L)	Graft Function† GGT (UI/L)	Therapy	Complication
1	M/32	GSD + HCC	22	M/32	24	Alive	—	90	153	28	242	EVR + EC-MPS	Lower limb and eyelid edema
2	M/56	HCV	32	F/26	35 d	Dead	Respiratory failure	Dialysis	Dialysis	15	35	EVR + EC-MPS	Pneumonia
3	F/62	Alcohol	22	M/66	4 d	Dead	Cerebral hemorrhage	Dialysis	Dialysis	182	107	EVR + EC-MPS	
4	M/48	Alcohol	19	F/66	23	Alive	—	39	59	136	301	EVR + EC-MPS (EVR monotherapy from 15 mo)	Leukopenia, wound dehiscence, incisional hernia
5	M/49	Wilson's disease	32	M/60	22	Alive	—	40	84	24	45	EVR + EC-MPS	
6	M/51	HBV	17	F/18	21	Alive	—	66	71	40	45	EVR + EC-MPS	
7	M/45	HCV	18	M/59	21	Alive	—	129	134	42	35	EVR + EC-MPS	Pneumonia
8	M/47	HCC	22	M/62	19	Alive	—	54	90	122	211	EVR + EC-MPS	Thrombosis of the inferior vena cava
9	M/47	PSC	16	F/29	20	Alive	—	104	100	35	50	EVR + EC-MPS	Wound dehiscence, incisional hernia

GSD, glycogen storage disease; HCC, hepatocellular carcinoma; PSC, primary sclerosing cholangitis; MELD, model for End-stage Liver Disease; OLT, orthotopic liver transplantation; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; GGT, gamma-glutamyl-transferase; HCV, hepatitis C virus; EVR, everolimus; EC-MPS, enteric-coated mycophenolate sodium; HBV, hepatitis B virus;
*According to Modification of Diet in Renal Disease formula.
†Value at last follow-up.

using the venovenous bypass and all of them, a whole organ graft, except one who received a right split liver from a compatible group donor. The mean donor age was 46.4 (SD 19.8) years and the mean cold and warm ischemic times were 402.4 ± 58.1 and 40.8 ± 7.7 minutes respectively.

Safety and Tolerability

After a mean of 21.4 (SD 1.4) months from OLT, 7/9 recipients (77.7%) were alive with stable graft function. One recipient died due to a cerebral hemorrhage and one, to lung failure after 4 and 35 days, respectively; both of them experienced pre-OLT dialysis due to renal failure.

Regimen and Graft Function

Within the 6 months, the mean EVR trough levels were between 8 and 12 ng/mL initially trending to < 10 ng/mL. No patients required EVR therapy discontinuation during the follow-up. EC-MPS was maintained at 1080 mg per day. Neither graft lost nor clinical evidence of an acute rejection episode or, liver dysfunction was observed at any of the considered times. At 24 months' follow-up, alanine aminotransferase and gamma-glutamyl-transferase were 61 (SD 66.46) UI/L and 100 (SD 21.9) UI/L respectively.

Renal Function

At OLT, two patients presented severe renal impairment requiring replacement therapy; both continued dialysis after OLT. In the early posttransplant period one patient with severe hepatorenal syndrome before OLT (eGFR = 36 mL/min/1.73 m^2) developed acute renal dysfunction (eGFR = 19.41 mL/min/1.73 m^2) that resolved after 30 days (eGFR of 68 mL/min/1.73 m^2) without requiring any dialysis. At 22 months' follow-up the patient was in good clinical condition with stable renal function (eGFR = 84 mL/min/1.73 m^2). The overall mean eGRF value increased from 59.5 (SD 9.89) mL/min/1.73 m^2 at OLT to 113.63 (SD 63.5) mL/min/1.73 m^2 ($P = .04$) at 3 months, remaining stable during the follow-up: eGFR = 100.2 ± 47.5 mL/min/1.73 m^2 (P = NS) at 12 months and 98.71 ± 33.74 mL/min/1.73 m^2 (P = NS) at 24 months.

Adverse Events

In the early posttransplant period, one patient developed a inferior vena cava thrombosis, that resolved with anticoagulant therapy. One patient required EC-MPS withdrawal after 9 months for severe leukopenia (white blood cell count < 2000/μL) but remained under EVR monotherapy with stable graft function.

Two patients developed pneumonia immediately after OLT that resolved with antibiotic therapy; there was no other infection including that due to cytomegalovirus. One patient presented severe lower limb and eyelid edema, but no evidence of mucositis/oral ulcer or dermatitis. Two recipients (22.2%) experienced a surgical wound dehiscence, developing an incisional hernia. No gastrointestinal side effects such as nausea, diarrhea, or abdominal pain were observed. Dyslipidemia requiring medical therapy was reported in three cases.

DISCUSSION

PSI acts at a later stage in the cell cycle blocking the proliferation signal provided by growth factors, thereby preventing cells from entering the S phase. The antiproliferative effects of PSI are not limited to the immune system but also to nonhematopoietic elements including vascular smooth muscle cells. The safety and efficacy of EVR have been demonstrated in renal[11] and heart[12] transplant recipients. It is currently used in these patients to reduce CNI toxicity and/or prevent CRD. There are few data concerning the use of EVR in OLT recipients. Levy et al reported no significant changes in laboratory parameters, infection rates and an acceptable safety and toxicity profile of EVR in combination with cyclosporine.[13,14] Preliminary studies of PSI for a maintenance regimen in OLT recipients have mainly focused on sirolimus (SRL) to treat patients with CNI-related CRD.[15,16]

These experiences have demonstrated that CNI minimization associated with SRL or conversion from a CNI to SRL-based regimen was feasible. This strategy was associated with 5% to 15% risk of acute rejection with a variable degree of improvement in renal function according to the baseline creatinine clearance,[17–20] CNI-related renal disease, and time from OLT.[21] Nevertheless, more recent data have suggested the efficacy of SRL-based regimens on long-term renal function post OLT.[22–25]

CNI produces acute nephropathy characterized by vasoconstriction of renal arterioles, as manifested clinically by reduced glomerular filtration, hyperkalemia, hypertension, increased sodium reabsorption, and oliguria.[6] The CNI-induced chronic renal damage is characterized by the development of arteriolopathy and tubulointerstitial fibrosis, which is irreversible and may lead to end-stage nephropathy.[6] The toxicity may be reversed when CNI therapy is reduced or withdrawn. Therefore, benefit from PSI therapy may be expected only for early CNI minimization/withdrawal or avoidance ab initio, namely while pathological changes are still reversible. In OLT, most series have reported EVR used as maintenance therapy seeking to improve renal function but not CRD prevention.[5,7,12,26]

In this scenario, the purpose of our study was to evaluate whether a CNI-free regimen using EVR and EC-MPS as the main drugs ab initio without induction or steroids was safe and effective and ensured preservation of renal function among OLT recipients. Our data showed PSI use ab initio to be safe in terms of patients and graft survival and acute cellular rejection rate. Furthermore no patients with baseline normal renal function developed post-OLT renal dysfunction that required kidney replacement therapy. Only one patient with hepatorenal syndrome before OLT developed severe renal impairment immediately there after, which never required dialysis and recovered within 30 POD.

These results suggested that EVR and EC-MPS ab initio may be used to prevent renal dysfunction especially among patients who showed renal impairment before surgery.

As reported by Masetti[23] and Sanchez Fructuoso,[24] hematologic side effects of the antimetabolite in association of PSI were rare. In our cohort only one patient who developed leukopenia after 9 months completely recovered after EC-MPS withdrawal, suggesting the hematotoxicity was rare and easily managed. A few patients experienced other side effects,[27–33] including dyslipidemia (n = 3), wound healing (n = 2), and lower limb edema (n = 1), that completely recovered after dose adjustment and conservative management.

In conclusion, this series explores EVR associated with EC-MPS without CNI, induction therapy, or steroid in de novo OLT recipients. Our data suggested that this feasible and safe regimen was a valid alternative for patients who require a CNI-free protocol due to renal dysfunction before transplantation.

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