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EXPERT REVIEW

The Role of Everolimus in Lung and Liver Transplantation

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Abstract: Everolimus (ERL) is a recently developed mTOR inhibitor. This rapamycin analog is used to prevent acute rejection during kidney and heart transplantation. We review here published clinical trials and experiences concerning potential applications of ERL in liver and lung transplantation. Most of the data concern conversion for rescue situations, but a small number of studies have been conducted in de novo patients. In most cases, everolimus was used to spare renal function and to minimize calcineurine inhibitor use, but also, due to the antiproliferative properties of the drugs of this class, to control malignancy. Safety issues are an important consideration when deciding whether to maintain a patient on treatment. Therapeutic drug monitoring is strongly recommended, to achieve a mean whole-blood trough concentration of 6 ng/mL, with doses of 0.5 to 1.5 mg administered twice daily. There is solid evidence that ERL is a feasible and effective treatment, for a selected subset of patients, in the contexts of liver and lung transplantation.

Keywords: everolimus, mTOR inhibitors, liver transplantation, lung transplantation

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Introduction

Everolimus (ERL) is a recently developed immunosuppressive drug marketed for the prevention of acute rejection, in combination with steroids and cyclosporine, in kidney and heart transplantation in Europe. In this review, we address the possible role of everolimus in liver and lung transplantation, two potential areas of application for this drug in the field of solid organ transplantation.

Methods

This review was based on a Pubmed search with the following keywords: "everolimus AND liver (hepatic) transplantation"; "everolimus AND lung (pulmonary) transplantation". Selected studies presenting original data from clinical studies were analyzed and classified according to whether ERL was used in conversion or de novo. The number of patients (n) is based on effective ERL drug intake (intention-to-treat analysis).

General Considerations

Structure, physical chemical properties, classification

Everolimus (ERL) is a macrolide developed as an immunosuppressant. It is the second proliferation signal inhibitor or mammalian target of rapamycin (mTOR) inhibitor to be described, after sirolimus (SRL). ERL is the 40-hydroxy-derivative (SDZ RAD) of the natural rapamycin (sirolimus)[1] and has more hydrophilic properties than the natural molecule, with implications for solubility and stability and, therefore, for pharmacokinetics.

Pharmacodynamics

The immunosuppressive action of these compounds is mediated by the formation of an FKBP12 complex that inhibits mTOR. This complex blocks signal 3 in the activation cascade of antigen-activated T cells, by preventing interleukin 2 cytokine (IL2) receptors from activating the cell cycle. This mechanism is different from that of calcineurin inhibitors (CNI): mTOR inhibitors act at a later stage, blocking T-cell proliferation at the G1stage.[2]

These inhibitors also have antiproliferative, vascular properties (role in remodeling)[3] likely to decrease graft vasculopathy in heart transplantation, consistent with expectations that they might be able to prevent the emergence of signs of "chronic rejection". Moreover, the mTOR pathway not only targets alloimmune reactivity, by blocking IL2 signaling in T cells, but also controls cell growth, that may result in antineoplastic activity.[4–6]

The *indications* of this class of drugs already reflect their diverse pharmacodynamic properties, with clinical applications in organ transplantation, oncology and cardiology.[7–9] ERL has been registered for use in the prevention of acute rejection during kidney and heart transplantation in Europe since 2004, as part of a combination including steroids and cyclosporine (CsA), at a dose of 0.75 mg BID.[10] However, nephrotoxicity tends to limit the use of a full-dose CsA regimen in combination with ERL. As part of a different formulation, ERL is indicated for the treatment of metastatic renal carcinoma, at a dose of 5 to 10 mg QD. The use of everolimus as a second-generation drug-eluting coronary stent has also been proposed.

Pharmacokinetics

ERL is an orally active drug with linear pharmacokinetics (PK), displaying rapid absorption, with peak concentration reached in 1.5 to 2 hours. The bioavailability of ERL is greater than that of SRL, but remains low, at about 14% in the presence of CsA and steroids. This drug should be administered consistently with or without food. ERL has a broad distribution in the body, with high levels of incorporation into red blood cells, justifying the use of whole-blood rather than plasma determinations. ERL is eliminated by intensive metabolism, by CYP3A4 and, to a lesser extent, 2C8.[11] Everolimus is substrate of both the efflux pump P-glycoprotein and cytochrome P450, and this may result in variability and intensive drug-drug interactions resulting in a metabolic profile similar to that described for CNI. The half-life of ERL is about half that of SRL, but remains long, at about 30 h. Steady-state levels are, therefore, generally achieved within seven days.[12]

The impairment of liver function has a major effect on ERL pharmacokinetics and dose reduction should be proposed, with careful monitoring, in patients with such impairment.[13]

Safety

The safety profiles of the two mTOR inhibitors are similar, with the following adverse drug events and toxicities reported:[14] hematotoxicity (leukopenia,

thrombocytopenia and anemia), lipid changes (high triglycerides and cholesterol levels, requiring specific treatment, with statins, for example) and gastrointestinal disorders (eg, diarrhea). Renal endpoints are important and the precise contributions of CNI and mTOR inhibitors to the development of nephrotoxicity remain a matter of debate: mTOR inhibitors have been shown to act in synergy with CNI, thereby increasing CNI nephrotoxicity and making it necessary to decrease the CNI dose (ERL) or to withdraw the CNI (SRL) in maintenance treatments. Proteinuria has also been reported with mTOR inhibitors, resulting in the issuing of a specific warning. Podocyte damage is clearly emerging as a factor in this dual contribution to changes in creatinine levels.[15] Edema and mouth ulcers are common and may reflect overexposure to the drug. Impaired wound healing has been reported,[16] probably due to the antiproliferative effects of the drug, raising questions about its de novo introduction in patients undergoing complex surgery, such as liver or lung transplantation.

Pulmonary toxicity, presenting as drug-induced interstitial pneumonitis, has been described with these compounds and must be considered in the differential diagnosis of non infectious pneumonitis.[17]

Drug-drug interactions

The two mTOR inhibitors have the same drug-to-drug interaction (DDI) profile, dominated by the P-glycoprotein and CYP3A4 metabolism system, as for CNI. Theoretically, higher doses are required to maintain a given ERL concentration in the absence of CsA, because drug metabolism is not inhibited in these conditions. However, when ERL is administered in combination with tacrolimus (TRL), which is a very potent CNI immunosuppressive drug, the tapering of TRL is particularly important for the correct management of ERL dose adjustment.

DDI are very frequent and may involved both the PD and PK mechanisms. Most of the PK DDI encountered with ERL involve the inhibition or induction of metabolism by anti-infectious drugs, such as macrolides or azoles (both of which inhibit metabolism) and rifamycin (which induces metabolism). It is important to consider quantitative aspects.[18] Overexposure to ERL may cause not only the exacerbation of specific toxicities, but also excessive immunosuppression likely to affect control of the infection, whereas very low levels of exposure may result in rejection. DDI are a major source of variability and must be controlled by careful monitoring.[19]

Therapeutic drug monitoring

Therapeutic drug monitoring (TDM), based on the analytical determination of whole-blood trough ERL concentration is particularly important, due to the many sources of variability in drug exposure.[10,20] Indicative targets in the range of 3–8 ng/mL,[21,22] assessed by a specific liquid chromatographic assay with ultraviolet or mass spectrometry detection, have been proposed. Immunoassays are also available, but the antibodies used are not specific, and about 25% cross-reactivity should be expected.[23]

Sirolimus/everolimus comparison

The two mTOR inhibitors have very similar pharmacodynamic profiles, resulting in identical side effects and activities. The main difference between them is that ERL is more soluble, this higher solubility leading to other pharmacokinetic differences. The half-life of ERL is half that of SRL, facilitating management, particularly in cases of adjustment to PK drug-drug interactions.

Rationale for the Use of ERL in Liver and Lung Transplantation

In the domain of solid organ transplantation, the use of ERL for liver and lung transplantation has been evaluated over the last 10 years. The rationale underlying this development is based on the points outlined below and concerns either the early introduction of ERL or a switch to this drug in maintenance immunosuppressive therapy.

CNI minimization to spare renal function

Benefits associated with the minimization of exposure to CNI are actively sought. Indeed, these nephrotoxic drugs[24,25] have been strongly implicated in renal impairment and end-stage renal failure after long periods of maintenance therapy. There are currently two options, the choice of which depends on the time elapsed since the introduction of ERL after transplantation:

- Switch to ERL after the onset of renal impairment[26]
- De novo introduction to preserve kidney function in patients with a high risk of renal failure.[27]

The minimization of CNI use may vary from the use of a full dose followed by early withdrawal to the use of very low doses or of no CNI at all. In cases of delayed ERL introduction, some studies have reported the need to introduce the mTOR inhibitor soon enough after transplantation to maintain all the expected potential benefits of this therapeutic intervention. In cases of de novo use, attention must be paid to the risk of impaired wound healing associated with the antiproliferative properties of the drug. This is of particular importance in the context of liver or lung surgery, in which the early introduction of steroids is already limited. The risk of insufficiently high levels of immunosuppression must therefore by countered by the use of induction therapies and careful TDM for the remaining immunosuppressant drugs.

Cancers

The antineoplastic properties of this class of drugs strongly suggest a potential use in case of cancers. Such an approach is likely to be justified in two particular situations:[28,29]

- De novo use of the antiproliferative anticancer properties of the drug to prevent the relapse of primary cancers, such as cellular hepatocarcinoma, after liver transplantation[30]
- Switch in cases of the development of a de novo cancer after transplantation.[31]

The rationale of the mTOR inhibitor strategy is based not only on the intrinsic anticancer activity of ERL, but also on controlling the risk of excessive immunosuppression due to the strength of CNI. It may be necessary to increase the dose of ERL to achieve a mean concentration of more than 8–12 ng/mL and to counterbalance the lack of metabolic inhibition due to the use of little or no CsA.

It is important to consider of the risk of increasing overall immunosuppression in cases of ERL use in combination with full doses of other powerful immunosuppressive drugs. This higher level of immunosuppression may result in an excessive rate of opportunistic infections and lymphoma.[32,33]

Late graft dysfunction

Investigations of the mTOR pathway and preclinical studies have raised hopes that it might be possible to prevent "chronic rejection" or late graft dysfunctions, such as cardiac vasculopathy. It is difficult to assess such long-term endpoints in classically designed

Table 1a. De novo use in liver transplantation.

Ref	Background	n ERL	Objectives study design	Post Tx delay at ERL	ERL duration
Levy[34]	PK, safety Phase I	26	4 groups: focusing on mode and timing of administration	W1 or W5–6	Single doses
Levy[35]	Efficacy/ safety Phase II	119	ERL + CSA, steroids Prospective randomized controlled double-blind ERL vs. placebo	D1	12 mo 20% ↕ > surgical technical complications
Masetti[36]	CNI early withdrawal	78	ERL monotherapy Sparing RF Prospective randomized 3 arms: CSA, CSA(30D) + ERL, ERL	D10 after CSA	12 mo

clinical trials, but this remains a possible objective for the drugs of this class. Again, there are several lines of evidence suggesting that the potential benefits of treatment require early introduction of the drug, within the first few months of transplantation.

Reported Experiences with the Use of ERL in Liver and Lung Transplantation

The available data are reported in Table 1a and 1b, as the use of ERL de novo[34–36] and for conversion[37–50] in liver transplantation (LiT), and in Table 2 for the use of ERL in lung transplantation (LuTx).[51–59]

Liver transplantation

Most experience in the use of ERL for liver transplantation relates to the conversion situation for rescue indications.[37–50] Most of the studies reported were retrospective evaluations, consistently demonstrating the feasibility of treatment for cancers and for sparing renal function. The most recent results obtained are highly representative, due to the size of the study and its multicenter design[50] or an interesting design based on the time of introduction and renal function at the time of transplantation.[48]

Very few studies of de novo ERL use have been carried out for LiTx: a phase I PK and safety study,[34] a phase II study versus placebo[35,60] and a recent study investigating early CNI withdrawal.[36]

Lung transplantation

Few data are available concerning ERL use in LuTx. The most important studies to date have been a phase III study versus azathioprine,[52] and the PK/PD phase II-related substudy.[53] The most representative study concerned a 12-month extension in the conversion use of ERL.[55,56] Global approaches to ERL use in LuTx are broadly similarly to those in LiTx, focusing on the preservation of renal function and the minimization of CNI treatment,[55,56] and the control of new cancers[57] and bronchiolitis obliterans syndrome (BOS).[54,57]

Special Features

Pediatrics

Few specific data are available, but children generally display higher rates of drug clearance. Careful TDM is therefore useful, to control variability.

Cystic fibrosis

Cystic fibrosis is a frequent background condition in patients undergoing LuTx and, to a lesser extent, LiTx. Few specific reports are available concerning ERL use in patients with this disease.[51] Cystic fibrosis

Dose mg	C0 ng/mL	Maintenance on ERL	Acute Rx	Safety	Conclusions
7.5 CSA steroids				Acceptable	Bile diversion affects Cmax, not AUC No effect of naso vs. nasoduod route Time W1–W5: no effect
0.5 BID 1 BID 2 BID placebo	3–6	12–36 mo 50% ↕ after 1 yr (safety)	NS trend towards fewer treated AR with increasing ERL dose and C0	More problems with an ERL dose of 4 mg ClCr= Infection=	Acceptable efficacy/safety C0 > 3 ng/mL (Eff) Confirmed in LiTx Acceptable tolerance Discontinuation increases with dose
1 BID	6–10, 10, then 8 (Innofluor)	22 mo 10% ↕ 1 yr 6†, NS	NS	ClCr 87 mL/mn ERL vs. 60 CSA	Early withdrawal of CNI improves RF outcome without increase in AR or complications

Table Ib. Liver transplantation conversion.

Ref	Background	n	Objectives study design	Timing of ERL introduction post Tx	ERL duration
Gomez-Camarero[37]	K, rescue	10	Safety, survival + AK therapy Prospective Case vs. historical cohort		12.7 mo
De Simone[38]	RI	40	CNI withdrawal (4 weeks) Renal function Prospective	45 mo	12 mo
Rubio[39]	HCC	1	Metastatic adrenal tumor Case report		
Alamo[40]	CNI rescue √ K, RI, CRx	22	Improvement 7 HCC, 5 de novo K, 4 RI, 4 CRx, 2 ARx		13 mo
Bilbao[41]	HCC, K CNI side effects	25	Rescue, all situations 10 HCC, 6 de novo K, 3 CRx, 3, CNI toxicity, 3 other Retrospective	40 mo	10 mo
De Simone[42]	CNI minimization	72	Sparing RF Prospective, randomized multicenter (n = 145 patients)	>3 yrs	6 + 6 mo
Castroagudin[43]	CNI minimization	21	Sparing RF Prospective	62.4 mo	19.8 mo
Martinez[44]	CNI rescue √ K, RI, CRx cf 88	28	Safety, efficacy 8 HCC, 7 de novo K, 6 RI, 3 CRx, 3 Arx, 1 other		11.2 mo
Valdivieso[45]	HCC recurrence	2	HCC rescue case series (n = 23) Retrospective	23.4 mo	
Bhoori[46]	HCC recurrence	1	Case report	11 yrs	6 mo
Waidmann[47]		3	Personalized molecular targeted therapy		
Schleicher[48]	RI at Tx	57	Efficacy on RI √ time of conversion Retrospective	4 groups: 2 early < 3 mo 2 late with or without RI at Tx	

Dose mg/d	C0 ng/mL	Maintenance on ERL	Acute Rx	Safety	Conclusions
0.5–1.5 bid 8/10 monotherapy	3–8	21.3 mo > historical 3† (2 non K)	None	Acceptable	Safe in LiTx with ≠ K after Tx May improve short-term survival
0.75 mg bid 30/40 ERL monother	3–8	75% success 10 failures	4 AR 3 HCV	Pruritis, oral ulcerations	3/4 stabilization to improvement of RF ClCr + 4 mL/min
Surgery + ERL		>24 mo			Survival
mTOR	ERL 3–5 SRL 8–12			Considered as OK or manageable by dose reduction	K recurrence 16.7% RF improved in 25% Feasible and manageable
Rejection: 0.5 mg bid Cancer: 0.5 qd	5 <3	4†		Usual (lipids)	Efficacy in 60% with RI and 75% with CRxEarly refractory Rx, HCC recurrence Late serious CNI side effects De novo K Supportive second-line IS in LiTx
1.5 mg bid 80% CNI minimization	3–8 /CNI 6–12 no CNI	5↕ study 18↕ (14 side effects)	None		No benefits in terms of RF: try to introduce ERL earlier Possible to stop CNI without graft loss
0.75 mg bid ↕ CNI in 20/21	3–8 ↕ CNI when targeted	ClCr+10 mL/ min (54 → 64)	None	Acceptable 1↕ for hematotox	Possible to stop CNI and sustained gain in terms of RF normalization (30%–50%) Early ERL to achieve best results
mTOR	8–12	60 mo	2 AR	Usual (lipids, hematotox)	No additional value Cf 88
Surgery + ERL					
ERL 1.5 bid + sorafenib	↕CSA	8 mo		1 hemorragic problem temporary ↕	Multikinase mTOR combination. proof of concept of role of mTOR signaling in HCC in selected patients
mTOR	SRL 5–10 ERL 3–8	1 yr		Early: surgery complications	Early: better outcome in RF, √ initial renal status 1 proteinuria CNI conversion feasible

(*Continued*)

Table Ib. (*Continued*)

Ref	Background	n	Objectives study design	Timing of ERL introduction post Tx	ERL duration
Vallin[49]	√ conversion	94	Tolerability Retrospective	5 yrs	12 mo
Saliba[50]	√ conversion Retrospective multicenter	240	Chronic RF (50%) HCC recurrence (18% + 16%) De novo K (14%)	4.9 yrs	15.3 mo

Abbreviations: ARx, Acute rejection; RF, renal function; RI, Renal insufficiency; K, cancer; HCC, Hepatocellular carcinoma; CRx, Chronic rejection; √, all.

may decrease drug absorption, and this, together with the higher levels of drug clearance in young patients, may increase the risk of low levels of exposure to the drug. Cystic fibrosis should therefore be considered as an additional factor contributing to PK variability. Moreover, cystic fibrosis patients present a large number of comorbidities, such as colonizations (CMV, aspergillus), necessitating the use of several forms of prophylaxis and increasing the risk of DDI. Anti-infectious drugs, in particular, have been implicated in the development of many PD (nephrotoxicity, hematotoxicity, hepatotoxicity) and PK (CYP3A4 metabolic inhibition or induction) interactions. TDM is therefore essential in cystic fibrosis patients treated with ERL.

HIV in liver transplantation

Particular attention should be paid to the high frequency of HCV-HIV co-infection. Increasing numbers of patients with a stable HIV viral load but end-stage cirrhosis are undergoing liver transplantation. Preliminary data have provided support for a direct role for mTOR inhibitors in controlling HIV replication, possibly via downregulation of the expression of the HIV fusion coreceptor CCR5. These findings support recommendations for the use of this class of drug after liver transplantation.[61,62] The use of mTOR inhibitors is subject to the same constraints as CNI regarding the control of metabolic drug-drug interactions,[63] particularly if ritonavir is also administered, and careful TDM is therefore necessary.

Interstitial pneumonitis

Pneumopathies related to drug class have also been described in these patients.[64,65]

Analysis of Findings to Date

ERL appears to be a promising alternative for use in immunosuppressive drug regimens in a selected subsets of patients. Confirmed rationales for the use of ERL are the sparing of renal function and CNI minimization in all forms of solid organ transplantation and the management of cancers, particularly in terms of controlling the recurrence of hepatocellular carcinoma in LiTx patients and reasonable hopes for the treatment of de novo cancers occurring after transplantation.

Efficacy and immunosuppressant drug combination

As expected from previous findings, there is good evidence to suggest that ERL is an effective immunosuppressive drug for preventing acute rejection, as part of a maintenance therapy after LuTx or LiTx.[50,56] The proof-of-concept for such an approach overlaps largely with that for SRL, but the similar pharmacodynamics of these two mTOR inhibitors are consistent with the extrapolation of findings from SRL to ERL.

Early conversion or de novo use (31%) have been reported, as has late conversion (69%).[55–57] ERL is most commonly administered with steroids and CNI but, in some situation, including maintenance treatment after LiTx, ERL monotherapy may be proposed.[37,38,43,50] The need to decrease CNI dose in the presence of ERL is a constraint common to all

Dose mg/d	C0 ng/mL	Maintenance on ERL	Acute Rx	Safety	Conclusions
0.75–1.5 mg bid CNI minimization	6	At least 1 side effect in 70%	9%	16% ↕ due to side effects	Expected safety profile 70% at least one AR Dose reduction or ↕ in >15%
2 mg (2.4 ± 0.8 mg)	7–8	Survival 95% 2 yrs after conversion 14† (6HCC)	1.6%	19.6% ↕ due to side effects 24.5% ↘ dose	61.6% CNI free, MPA 26.7% free Few Rx Acceptable safety Over 12 mo: Cr 149 ± 69 to134 ± 69 μM Gain mostly when RI

types of solid organ transplantation,[56] due to the risk of additional nephrotoxicity and of the recent demonstration that excessive overall immunosuppression increases the frequency of infection. Standards of care in LiTx were recently assessed by evaluating decreases in the TRL dose associated with mycophenolic acid and steroids,[66] confirming the feasibility and the beneficial effects of limiting CNI exposure.

Geographic differences in the strength of initial marketing for renal and cardiac transplantation have resulted in differences in drug availability and limited evaluations of the use of ERL in LuTx and LiTx. Therefore, only a small number of centers have shared their experience in the potential use of ERL in these two types of organ transplantation.

Overall, about 1120 patients exposed to ERL in LiTx (69%) and LuTx (31%) have been described. Several different situations were reported, confirming the rationale underlying expectations for ERL treatment (see Fig. 1).

Sparing renal function from CNI-nephropathy

The use of ERL makes it possible to minimize CNI levels, even, possibly, to the extent of using a CNI-free immunosuppressive regimen in LiTx.[37,38,43,50] Beneficial effects are anticipated particularly in situations associated with a high risk of renal failure at transplantation ("CNI holidays")[48] and/or in cases of early intervention after transplantation.[42] The kidney seems to have functional reserves that can be called upon to reverse CNI damage, provided that tissue destruction has not already progressed too far.[38,40,43,67] Some caution is required when evaluating the observed gain, depending on the initial levels of renal function parameters.[43,50] Late interventions have been found to be of little benefit, but may nonetheless be associated with sustained renal function. These drugs have a complex effect on renal function. Indeed, mTOR inhibitors present specific risks in terms of renal injury: their use is not recommended in cases of proteinuria (>0.8 to 1 g per day), particularly in patients with nephritic syndrome. A direct and synergic role of ERL in CNI nephropathy should be considered. The effects of podocyte change on renal function, more recently described, are of increasing concern. An increase in creatinine clearance cannot currently be considered to reflect an improvement in renal function, if the decrease in serum creatinine concentration is accompanied by proteinuria. Nephropathies in transplant recipients are favored by comorbidities, such as diabetes, hypertension and immunosuppressants. The main objective is to control the progression of fibrosis.

Antiproliferative effects and cancers

The dual properties of the drugs of this class are consistent with the use of ERL to prevent hepatocellular carcinoma recurrence or new cancers after transplantation, and such a use of ERL is supported by all reported experiences of the use of ERL in conversion situations of this type.[39–41,44,45,49,50] Furthermore, two studies have recently addressed the role of mTOR

Table 2. Lung transplantation.

Ref	Background	n	Objectives study design	Timing of ERL intro post Tx	ERL duration
Doyle[51]	PK	20 8 CF	Phase I 2 doses Randomized Cross-over	>3 mo	2 single doses
Snell[52]	Maintenance Efficacy/safety	101	ERL vs. AZA Maintenance + CSA steroids Randomized, double-blind multicenter	14.1 mo	12–24 mo
Kovarik[53]	PK/PD maintenance substudy	89/101	Safety, efficacy concentration target range randomized, double-blind	14.1 mo	3 yrs
Snell[54]	PD study IL17 Prospective randomized Cf ERL vs. AZA	19	IL17 endobronchial biopsy and BOS	3–36 mo (307 d)	3 yr (266 d)
Gullestad[55]	Conversion	Thoracic 140 46 LuTx	Late conversion Reduced CNI Sparing RF Multicenter randomized controlled trial	>1 yr (52 mo)	12 mo
Gullestad[56]	Conversion	Thoracic 108 39 LuTx	CNI minim° Sparing RF Follow-up Extension	>1 yr	12–24 mo
Parada[57]	Conversion	8	Retrospective Case series 3 CNI nephro 4 BOS 1 lymphoma		2 yrs
Bresci[58]	Case report with H1N1	1			4 yrs
Lovric[59]	Case series retrospective	67/126	Switch ERL vs. MMF	W4	105 days in HUS cases

inhibitors in the management of hepatocarcinoma in the absence of transplantation.[68,69]

A potential role in the prevention of "chronic rejection" was an important expectation from in vitro and animal studies. Few data are available concerning the possible delay in progression to late graft dysfunction.[42] Late intervention, more than six months or one year after transplantation, is unlikely to be beneficial.[50] The small number of data available support the use of ERL for preventing chronic rejection, but few large prospective studies have been carried out.[70]

Therapeutic drug monitoring

ERL is considered to have a narrow therapeutic index, justifying the use of TDM to personalize dose adaptation. TDM is based on whole-blood trough concentration determinations. Intra-individual variability is generally thought to be lower than that for CNI in the absence of PK DDI, but inter-individual variability is high. In the absence of significant changes in biological and clinical findings and coprescription, the frequency of TDM may be lower than that for CNI.

The primary endpoint concerns efficacy. A low rate of rejection has consistently been linked to exposure

Dose mg/d	C0 ng/mL	Maintenance on ERL	Acute Rx	Safety	Conclusions
2.5 7.5	tlag 0.5 h $t_{1/2}$ CF 2.5 h non CF2.8 h tmax 1.5h	NA	NA	Changes in laboratory test results	No PK differences in CF patients (but 32-yr-old weighing 64 kg)
3 then 2.4	6.6	59 12 mo 39 24 mo 14† vs. 15 AZA		62%↕ at 24 mo Infections Increase Cr	Better outcome in delaying BOS progression at 12 mo, less evident at 24 mo Subset of patients do not tolerate and discontinue treatment
3 then 2.4	6.6			Lipids Hematotox Azole DDI	C0 3–12 ng/mL, with CSA and steroids
3 (1.8)					No specific role for IL17 in BOS progression, √ AZA or ERL
1.6–1.2	3–8	12 mo	3	At least 1 side effect in almost 100%	Significant improvement in renal function Greater benefits in early conversion and HeTx
1	5	12–24 mo	5.6%	+3.2 mL/min ERL vs. –2.4 control	50% CNI reduction Improvement in RF without loss of efficacy in maintenance thoracic Tx
	4.2 TRL 5.5	1† 11 mo after conversion in lymphoma	none	1↕ due to side effects	Effective for reversing renal dysfunction, possibly retarding BOS
					Good control of IS under careful TDM during flu episode and treatment
	6.6	6 mo after diagnostic		↕ 5 HUS	Rare but 2 renal failure and HD, 1†

to the drug. A minimal exposure threshold of 3 ng/mL has been reported for the prevention of rejection and has been confirmed for both LiTx[42] and LuTx.[53]

The safety profile is identical in all type of patients and appears to be similar to that previously reported for kidney and heart transplantation. A clinical upper limit of 8 ng/mL has been extrapolated from these findings. Prolonged maintenance therapy, with ERL overexposure, results in high rates of treatment cessation, due to adverse reactions, with no additional benefits in terms of the prevention of acute rejection.

However, in some situations, such as the early post-transplantation period, the transplantation of organs with a high risk of rejection (LuTx) and monotherapy for cancer, ERL may make a major contribution to immunosuppression. In these situations, whole-blood concentration targets of 8–12 ng/mL may be proposed.[36,53]

The doses required to achieve trough ERL concentration objectives depend on the presence or absence of CsA (which inhibits ERL metabolism) and steroids. The 0.75 mg BID scheme with reduced CsA plus steroids established for renal transplantation was converted to a mean of 0.5 to 1.5 mg BID, to achieve

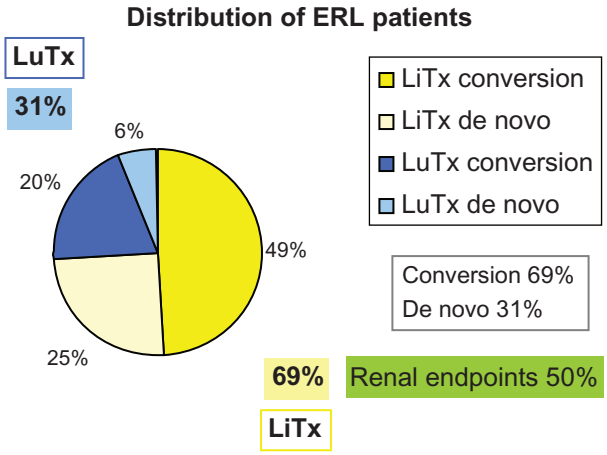

Figure 1. In total, 1120 transplanted patients treated with everolimus (ERL) in the contexts considered have been reported, with liver transplants (LiTx) accounting for 69% of these patients, and lung (LuTx) transplants for 31%. Similarly, conversion treatments accounted for 69% of the patients and de novo treatments for 31%. Renal function endpoints were of concern in half the cases.

whole-blood trough concentrations of 6 ng/mL in most of the reported experiences for both LiTx and LuTx.[49,50,55]

Safety issues

Pharmacodynamics analyses showed the safety profiles for the two mTOR inhibitors to be superimposable, and reports for LiTx and LuTx fit the expected profile established in other categories of patients. There is increasing evidence to suggest that the possibilities for increasing the dose are limited. In addition to hyperlipidemia and hematotoxicity,[41,44,53,71] mouth ulcers, mucositis and ulcerations are also strong limitations to drug tolerance. The objective of sparing renal function is thus counterbalanced by limitations due to direct nephrotoxicity, and proteinuria in particular, or post-transplant hemolytic uremic syndrome.[59,72]

Safety profiles are identical for all types of organ transplantation and affect the time for which the patient can be kept on ERL treatment. Increases in lipid levels are controlled by specific treatment and hematotoxicity is moderate but may be increased by concomitant treatment with other hematotoxic drugs (ganciclovir, mycophenolic acid).

Impaired liver function is likely to increase exposure to the drug.[13] This effect may be of particular importance after LiTx. The use of ERL should be avoided in cases of severe impairment of liver function, whereas moderate impairment should lead to careful TDM in cases of ERL treatment.

Non infectious pneumonitis is a rare adverse reaction to the drugs of this class. However, it is regularly reported in all categories of patients and must be considered as a possible differential diagnosis when mTOR inhibitors are prescribed. Specific reports concerning the use of ERL in both LiTx[64,65] and LuTx are available (personal data as case reports in the French Drug Safety Database). Clinical symptoms generally resolve after drug withdrawal. In some cases, the reintroduction of an alternative mTOR inhibitor has proved successful.[61]

Drug-drug interactions

ERL and SRL are well metabolized by CYP3A4 and are also substrates of Pgp. The expected profile for PK DDI, with strong metabolism of the drug, has already been confirmed in the first case reports published.[73] TDM plays a crucial role in the monitoring of changes in ERL concentration. PK differences between ERL and SRL favor the adaptation of ERL doses during DDI management.

Timing of ERL introduction after transplantation

The early use of ERL is reported less frequently than conversion to this drug. Protocols exploring the de novo use of ERL have suggested that it may be best to delay the introduction of this drug until 10 days after transplantation, and to withdraw CNI early.[35,36] However, when introducing ERL early, it is important to take into account the antiproliferative properties of the drug, which may impair wound healing or aggravate surgical complications, such as dehiscence, in patients undergoing such complex surgery.

Conclusion

Most of the published experience relating to the use of ERL in both LiTx and LuTx is based on rescue, observational and retrospective studies, together with a relatively small number of prospective trials. Formal demonstrations, of long-term benefit in particular, are still required.

However, there is a substantial body of evidence to justify the rational use of ERL in the following situations:

– Patients with a high risk of renal failure, de novo cancers, recurrence of hepatocellular carcinoma and as a second-line treatment in cases of CNI withdrawal,

- Early introduction after the intervention, with a view to sparing renal function and, perhaps, preventing chronic rejection, in particular. The introduction of the drug should be delayed until day 10 after transplantation, to prevent impaired wound healing and complications of surgery,
- Patients with late graft dysfunction, although it is difficult to demonstrate the attainment of long-term objectives.

A consistent finding of studies in this field is that the outcomes of a *selected* subset of patients is improved by ERL and that this treatment is therefore likely to be beneficial to these patients. This is in keeping with the trend towards *personalized* therapy and monitoring in transplanted patients.

The criteria for identifying patients likely to benefit from ERL treatment have not yet been clearly established and the optimal timing of ERL introduction remains a matter of debate. There are arguments in favor of ERL monotherapy in maintenance LiTx, for the treatment of cancers and in patients with a high risk of renal impairment at the time of transplantation, in the absence of proteinuria and nephritic syndrome. The criteria for ERL withdrawal include renal function and proteinuria. It is important to limit overall immunosuppression, so the minimization of CNI treatment is necessary when used in combination with ERL. However, poly-immunosuppressive reduced therapies may be favored over a dedicated free class scheme in the future.

Doses are established upon steroid or CNI reduction, to moderate immunosuppression in cases of cancer or infection and to control renal function: when ERL is prescribed without CsA, but with steroids, the dose of ERL should not exceed 1.5 mg BID. The primary endpoint is a whole-blood trough ERL concentration (C0) above 3 ng/mL, with concentrations in the range of 6–8 ng/mL, measured by a specific assay (LCMS), targeted, as for other indications. A C0 above 8 ng/mL is associated with efficacy for the prevention of rejection, but the use of such concentrations is limited by safety issues. Theoretically, higher concentrations should be targeted in patients with cancers, to maximize the effects against the tumor, but this should be balanced by a decrease in the overall level of immunosuppression.

It is difficult to determine the place of this new class drug of mTOR inhibitors in treatment, because effective alternative treatments giving good results for several post-transplantation endpoints already exist. Active compounds are associated with adverse events and toxicities, and it is difficult to demonstrate long-term benefits in patient samples of limited size, particularly for LuTx.

In this context, attempts to achieve the best possible result may compromise the good results already achieved. The entirely valid objective of improving long-term outcome should not be achieved at the expense of the good short-term performances already achieved with classical immunosuppressive regimens. The role of ERL in the immunosuppressive therapeutic arsenal is governed by paradoxical factors. More than ever, immunosuppression should be considered as a compromise rather than an optimization or a balance between rejection and infection, cancer and specific drug-related toxicities. Overall immunosuppression must be carefully controlled in the context of increasingly potent associations.

There is an increasing body of evidence confirming the potential benefits of ERL in selected series of patients after LiTx and LuTx. Large-scale multicenter prospective studies should make it possible to evaluate long-term benefits and to identify the optimal immunosuppressive strategy incorporating ERL for LiTx and LuTx.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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