Review

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Mammalian Target of Rapamycin Inhibitors and Kidney Function After Thoracic Transplantation: A Systematic Review and Recommendations for Management of Lung Transplant Recipients

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Background. Chronic kidney disease (CKD) after lung transplantation is common and limits the survival of transplant recipients. The calcineurin inhibitors (CNI), cyclosporine A, and tacrolimus being the cornerstone of immunosuppression are key mediators of nephrotoxicity. The mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, are increasingly used in combination with reduced CNI dosage after lung transplantation. **Methods.** This systematic review examined the efficacy and safety of mTOR inhibitors after lung transplantation and explored their effect on kidney function. **Results.** mTOR inhibitors are often introduced to preserve kidney function. Several clinical trials have demonstrated improved kidney function and efficacy of mTOR inhibitors. The potential for kidney function improvement and preservation increases with early initiation of mTOR inhibitors and low target levels for both mTOR inhibitors and CNI. No defined stage of CKD for mTOR inhibitor initiation exists, nor does severe CKD preclude the improvement of kidney function under mTOR inhibitors. Baseline proteinuria may negatively predict the preservation and improvement of kidney function. Discontinuation rates of mTOR inhibitors due to adverse effects increase with higher target levels. **Conclusions.** More evidence is needed to define the optimal immunosuppressive regimen incorporating mTOR inhibitors after lung transplantation. Not only the indication criteria for the introduction of mTOR inhibitors are needed, but also the best timing, target levels, and possibly discontinuation criteria must be defined more clearly. Current evidence supports the notion of nephroprotective potential under certain conditions.

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INTRODUCTION

Chronic kidney disease (CKD) is a common complication after nonrenal–solid-organ transplantation, with a risk of severely decreased kidney function (defined as a glomerular filtration rate [GFR] of <30 mL/min/1.73 m^2 of body surface area) in 16% of patients 5 y after lung transplantation, and is associated with an increased risk of death (relative risk of death 4.6 for patients with nonrenal transplantation).[1,2]

There are several combinations of immunosuppressants following lung transplantation with calcineurin inhibitors (CNI), cyclosporine A (CsA), and tacrolimus (Tac), which are still the cornerstone of immunosuppression in combination with antimetabolites and corticosteroids. CNI-mediated nephrotoxicity, which is based on vascular, glomerular, and tubulointerstitial damage, is considered a key component of posttransplant kidney dysfunction, along with diabetes, hypertension, infections, and perioperative acute kidney injury (Figure 1).[2-4]

The mammalian target of rapamycin (mTOR) inhibitors, sirolimus (SRL) and everolimus (EVL), exert their immunosuppressive action by binding to the cytosolic FK506 binding protein 12 complex and blocking the activity of the

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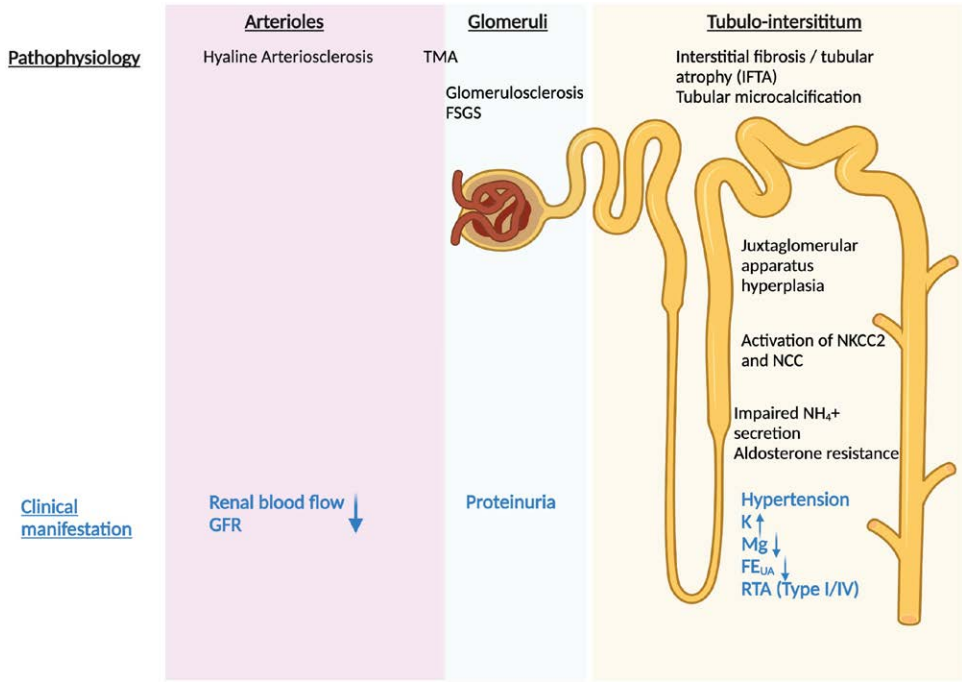

FIGURE 1. Pathophysiology and clinical manifestation of calcineurin inhibitor nephropathy. Figure created with Biorender.com. FE_{UA}, fractional excretion of uric acid; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; K, potassium; Mg, magnesium; NCC, sodium-chloride symporter; NKCC2, sodium-potassium-chloride cotransporter; RTA, renal tubular acidosis; TMA, thrombotic microangiopathy.

serine-threonine kinase mTOR, ultimately inhibiting the proliferation of lymphocytes and fibroblasts and the expression of proliferative cytokines.[5,6] EVL has a shorter half-life and improved bioavailability compared to SRL.[7] The inhibition of fibroblasts is assumed to negatively affect wound healing so that mTOR inhibitors are usually withheld at the time of transplantation and in the early posttransplant phase.

The use of mTOR inhibitors increases with time after lung transplantation and is part of maintenance immunosuppression in 16% of patients 5 y after transplantation.[8] Although the use of mTOR inhibitors in kidney and heart transplantation recipients has been well studied,[9-11] there is a growing body of evidence supporting the role of mTOR inhibitors in reducing nephrotoxic CNI exposure in lung transplant recipients (LTR) with chronic lung allograft dysfunction, cytomegalovirus, and Epstein-Barr virus infection or reactivation, malignancy, and CKD.[12-14]

However, the above-mentioned kidney-related adverse effects of CNI are also described in patients receiving mTOR inhibitors. These include proteinuria, focal segmental glomerulosclerosis, thrombotic microangiopathy, and acute tubular necrosis.[15-18] Most of the patients on mTOR inhibitors have previously been treated with a CNI, which poses a dilemma regarding the main culprit compound leading to deterioration of renal function. The lack of pathognomonic histomorphological changes precludes the differentiation between synergistic and sequential nephrotoxicity.[19]

Uncertainty regarding the optimal indication and immunosuppressive regimen using mTOR inhibitors in lung transplantation persists because of the narrow therapeutic index, considerable number of drug interactions, and high discontinuation rates. Common adverse events are impaired wound healing, infections, gastrointestinal symptoms, stomatitis, pneumonitis, progressive proteinuria, and hematologic side effects.[20-23]

This article reviews the recent evidence of mTOR inhibitors in thoracic organ transplantation with a special focus on kidney function and provides recommendations for the use of mTOR inhibitors in patients with lung transplantation.

SOURCES AND SELECTION CRITERIA

A systematic literature search was performed from September 26, 2021, to January 19, 2022, using the following databases: MEDLINE, EMBASE, Cochrane Library, and Google Scholar. Medical subject headings terms included "sirolimus," "everolimus," or "mTOR serine-threonine kinases"; "heart lung transplantation," "lung transplantation," or "heart transplantation"; and "drug-related side effects and adverse reactions," "glomerular filtration rate," "kidney function test," or "drug toxicity." The search was filtered for adults older than 18 y.

The reference lists of identified articles were searched for additional relevant studies. Eligible studies had to meet the following inclusion criteria: (1) immunosuppressive regimen containing mTOR inhibitor after transplantation, (2) provide data on lung transplant or combined heart/LTR and kidney function, and (3) full text available in English. Articles on both heart and lung recipients were included in the subgroup analysis of lung recipients. Therefore, we included prospective and retrospective trials, and no other restrictions were applied. A total of 320 articles were screened, 38 were selected for a complete review to assess eligibility, and 20 were included in this review (Figure 2). Twelve articles on prospective trials were identified, with a total of 1027 participants, of whom 201 were heart transplant recipients (Table 1). A total of 645 patients participated in 8 retrospective trials, of whom 137 underwent heart transplantation (Table 1). Several articles have been published from the same study population, namely the

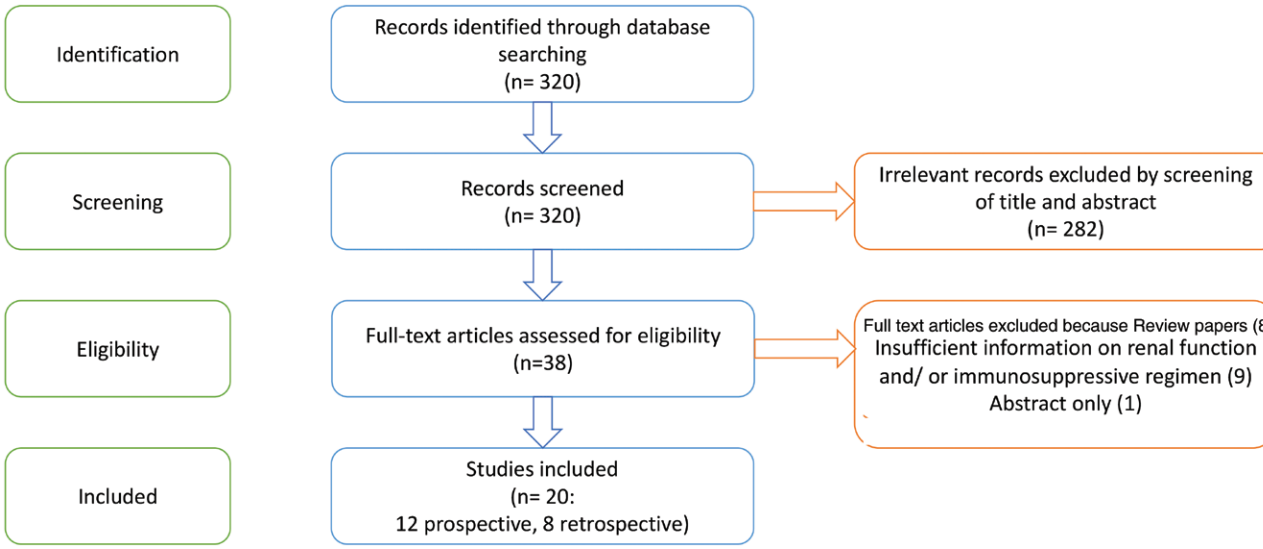

FIGURE 2. Flowchart of the process of systematic literature search.

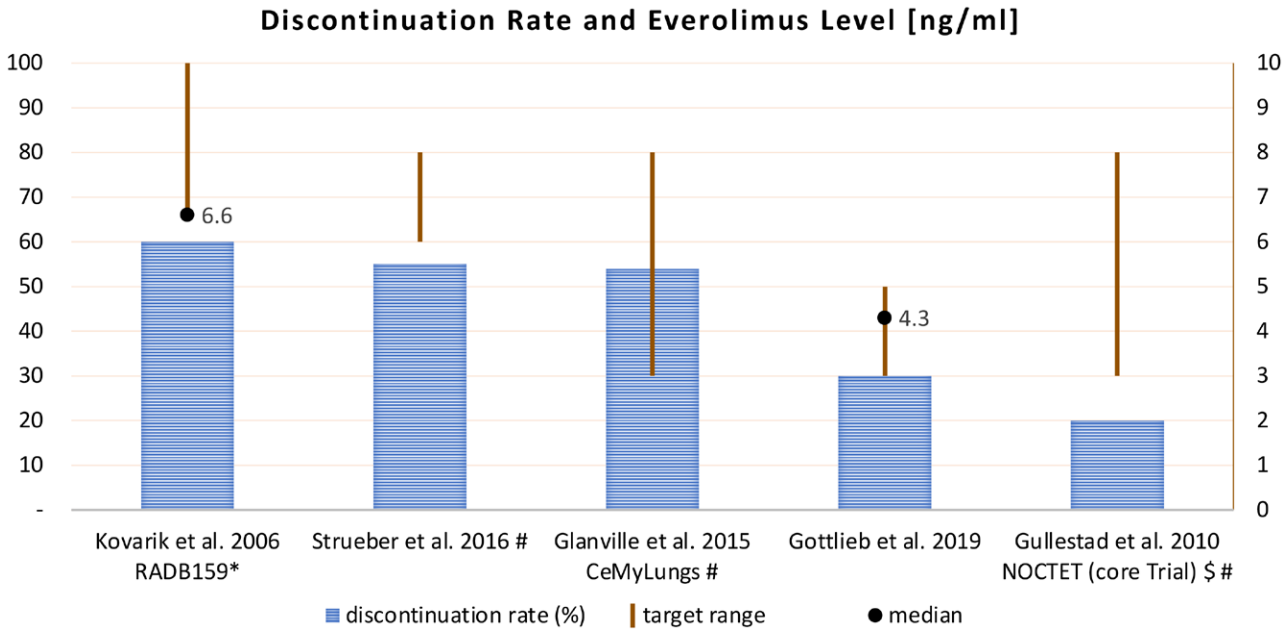

FIGURE 3. Everolimus (EVL) discontinuation rate and EVL level in prospective studies in thoracic organ transplantation. The x-axis on the left represents the EVL discontinuation rate (%), and EVL levels (ng/mL) are on the right. *Lower target level unknown. # No median level reported. $Because of the significant increase in infections in the EVL arm, target levels were lowered to 3–6 ng/mL after the initial phase. NOCTET, Nordic Certican Trial in HEart and lung transplantation.

NOrdic Certican Trial in Heart and Lung Transplantation (NOCTET)[24-26] and the Chilean lung transplantation cohort,[27,28] of which participants from the core study were considered only for study population description.

IMMUNOSUPPRESSIVE REGIMENS

Maintenance immunosuppression after lung transplantation traditionally consists of a CNI (Tac or CsA), antimetabolite, and corticosteroids. The immune response to lung allografts poses a pharmacological challenge to ensure graft function and immunosuppression tolerability.[6] CNI-containing regimens are the mainstay in lung transplantation, and CNI-free immunosuppressive combinations are rarely used in very selected situations. This fact and lack of evidence of other immunosuppressive combinations may explain clinicians' caution towards CNI discontinuation, leading to combinations of mTOR inhibitors with reduced-dose CNI drugs in most cases.[23-34] Only in 115/1672 (6.9%) of study participants the CNI was completely stopped.[12,35-41] Tac and CsA administration was reported in 24% and 76% of cases, respectively, before reduction occurred in the intervention groups.

EVL was administered to 642 lung transplantation cases (78%), whereas SRL was used in 178 LTR (22%). The preference for EVL over SRL in recent years is likely related to the better bioavailability and shorter half-life of EVL.[5]

A majority of participants took antimetabolites (derivates of mycophenolic acid [MPA], mostly mycophenolate

TABLE 1.

Trials assessing renal function under mTOR inhibitors in lung and/or heart transplantation included in review

Author (y), study group	Organ other than lung	n, mTORi/ Total	mTORi, time for initiation, target and/or measured level after conversion[a]	Study design	Treatment, CNI, n baseline/total, time for conversion, target or measured level after conversion[a], n stop	Treatment, antimetabolites, n baseline/Total, modulation after start mTORi	Inclusion	Primary endpoint/ follow up
Venuta et al (2004)		15	SRL, target 4–12 with CNI, target 12–20 SRL only	Prospective observational	CsA 8/15, 3 mo, 8/8 Stop after gradual reduction FK506 7/15	AZA 15/15, immediately reduced to 25%–50% of baseline	Persistent drug nephrotoxicity, serum Cr steadily ≥1.8 mg/dL 8/15 also BOS	Renal and lung graft function and clinical status after 1, 3, 6, and 12 mo
Groetzner et al (2006)	5 heart lung Tx	11	SRL, 3 wk, target first year post-Tx 10–14, afterwards 8–12, measured 10.6 ± 1.8	Prospective, observational	Tac 6/11, 3 wk, 6/6 stop CsA 5/11, 3 wk, 5/5 stop	MMF 11/11, continued	Reduction in pulmonary function of >20% (FEV1, MEF, PEF, a.o.) due to ongoing BOS-associated respiratory failure.	Self-determined pulmonary function tests, microbiological screening, chest radiographs, and laboratory studies
Shitrit et al (2005)		8/16	SRL, 31 ± 1.2 mo, target 4–8, measured 4.5	RCT	Tac, 6/8, 2.7 ± 0.9 mo, measured 6.8 CsA 2/8, 2.7 ± 0.9 mo, measured 94	AZA 6/8 MMF 2/8	Posttransplantation renal dysfunction CrCl below 50 mL/min in two 24 h urine collections	Renal function Graft function
			CRL		Tac, 8/8, target 8–12	Standard MMF		
Lischke et al (2006)		10	SRL, 5 d, target 12–18 without Tac, 6–12 in combination with Tac	Prospective observational	Tac, 10/10, immediate, 10/10 Stop, possibility to reintroduce in patients with BOS target 5–7	MMF 10/10	Persistent drug nephrotoxicity stable serum Cr-level of≥ 180 µmol/L 4/10 also BOS	Renal function Graft function Clinical status
Kovarik et al (2006), RADB159		89/189	EVL, 2 mo for DOWN-Titration, target first 2 mo 10, afterwards reduction, 6.6 median	RCT	CsA, 89/89, 157 ± 103		Maintenance lung transplant recipients, free of BOS	Tolerated and efficacious range of EVL

Renal outcome	Mortality n/total	Rejection n/total	mTORi discontinuation n/total	Male/female	Age (y)[e]	Time from Tx (mo)[e]	Length of follow-up (mo)[e]	Reason for lung Tx
Significant Cr decrease after 6 mo of treatment ($P < 0.02$)	3/15 related to BOS 1 related to laryngeal carcinoma.	0/15	1/15 after being referred to other centers.	10/5	38.9 ± 13.6	34.8 ± 19.7	19.7 ± 9.4	Cystic fibrosis > COPD/ emphysema > pulmonary fibrosis
Renal function improved after conversion. Mean creatinine values decreased significantly from 2.6 ± 0.9 mg/dl to 2.0 ± 0.8 mg/dl during follow-up period.	2/11 progressive BOS awaiting retransplantation	2/11	0/11	8/3	37 ± 13 (17–62)	35 ± 13 (11–96)	14.8 ± 1.4	NR
SRL group: significant improvement in GFR (42.6 mL/min versus 32.5 mL/min, $P = 0.05$)	NR	2/8	0/8	6/2	60.5 ± 6 (51–66)	51.5 ± 28 (15–96)	18	COPD/emphysema > pulmonary fibrosis = other
CRL group: significant reduction (32.3 mL/min versus 40.3 mL/min, $P = 0.02$) The difference between the groups was statistically significant ($P < 0.0001$).	NR	1/8	n.a.	7/1	56.3 ± 15	61.3 ± 36	18	COPD/ emphysema > pulmonary fibrosis = other
significant decrease of Cr after 1 wk, initial serum Cr level 240.6 ± 108.9 µmol/L, at 12 mo 138.8 ± 42.0 µmol/L. ($P = 0.011$)	1/10 related to BOS	0/10	0/10	7/3	43 ± 2.4	20.1 ± 13.2	22.1 ± 9.4	Pulmonary fibrosis > COPD/ emphysema > cystic fibrosis
Creatinine baseline: 141 ± 48 µmol/l, 226 ± 48 µmol/l after 12 mo	13/101[b]	12/101[b] BPAR	62/101[b] after 2 y	54/35	45.7 ± 13.5	14.1 (3–36)	24	23% cystic fibrosis

continued

TABLE 1.
continued

Author (y), study group	Organ other than lung	n, mTORi/ Total	mTORi, time for initiation, target and/or measured level after conversiona	Study design	Treatment, CNI, n baseline/total, time for conversion, target or measured level after conversiona, n stop	Treatment, antimetabolites, n baseline/Total, modulation after start mTORi	Inclusion	Primary endpoint/ follow up
Gullestad et al (2010), NOCTET, core Trial	EVL: 94 heart Tx	140/282	EVL, immediate, initial target 3–8, afterwards 3–6	RCT	Tac, 22/140, target <4 CsA 118/140, immediate, target <75	AZA 49/140 MPA 86/140, recommendation to reduce by 25%–50% within 1 wk when combined with CsA	maintenance thoracic transplant patients (GFR≥ 20 and <90). If GFR≥ and <90, at least 1 posttransplant GFR value >10% below baseline GFR was required.	Mean change in mGFR
	CRL: 96 heart Tx		CRL		Tac, 18/142, 8.6 ± 2.6 CsA, 124/142, 112 ± 47	AZA 62/142 MPA 76/142		
Gullestad et al (2010), NOCTET, Extension	EVL: 69 heart Tx	108/235	EVL, initial target 3–8, afterwards 3–6, 4.5 ± 1.4	RCT	Tac, 10/39 Lung Tx, 5.0 ± 1.4 overall CsA, 29/39 lung Tx, 59 ± 45 overall	AZA 16/39 Lung Tx MPA 22/39 Lung Tx, reduced in Combination with CsA	See above, extension of follow-up to 24 mo	Mean change in mGFR
	CRL: 86 heart Tx		CRL		Tac, 8/41 Lung Tx, 8.7 ± 3.6 overall CsA, 33/41 Lung Tx, 110 ± 39 overall	AZA 39/41 Lung Tx MPA 19/41 Lung Tx		
Arora et al (2012), NOCTET, Core substudy	see core trial	Total: 249 mGFR 60–89 (n = 35/55): mGFR 30–59 (n = 93/173): mGFR 20–29 (n = 12/21)	EVL, initial target 3–8, afterwards 3–6 4.8 ± 1.4 5.2 ± 2.1 5.1 ± 1.5	RCT	Tac, 5/35,4.4 ±1.7 Tac, 12/93, 4.3±1.8 Tac, 1/12, 3.0 CsA, 30/35, 53±21 CsA, 81/93, 55±35 CsA, 11/12, 59. ± 18	AZA 8/35 AZA 35/93 AZA 7/12 MMF 26/35 MMF 56/93 MMF 4/12	See above Baseline mGFR 67.4 ± 7.0 43.9 ± 9.1 23.4 ± 3.4	Assessment of EVL in advanced renal function

Renal outcome	Mortality n/total	Rejection n/total	mTORi discontinuation n/total	Male/female	Age (y)[e]	Time from Tx (mo)[e]	Length of follow-up (mo)[e]	Reason for lung Tx
mean change in mGFR after 12 mo EVL: +4.6 mL/min EVL patients in the lowest tertile for time posttransplant: + 7.8 mL/min (heart Tx) and +4.9 mL/min, (lung Tx). Lung Tx baseline mGFR: 43.8 ± 14.2, after 12 mo 46.2 ± 13.3	3/140 (sudden death, cardiac arrest, and heart failure)	6/140 BPAR 29/140 episodes of rejection of any type (heart Tx: 14 grade IA, 4 grade IB, 2 grade 2 and 5, grade 3A; lung Tx 3 grade AI and 1 grade A2)	28/140 (18 adverse events, 3 deaths, 5 withdrew consent, 1 administrative reason, 1 other).	37/103	All: 59.2 ± 9.5, heart Tx: 60.2 ± 9.3	All: 61.3 ± 44.4, heart Tx: 68.4 ± 48.2	12	NR
Mean change in mGFR after 12 mo CRL: −0.5 mL/min ($P = 0.0001$). Lung Tx baseline mGFR: 43.1 ± 12.4, after 12 mo 41.8 ± 16.3	0/142	4/142 BPAR, 30/142 episodes of rejection of any type (heart Tx: 19 grade IA, 4 grade IB, 2 grade 2, and 5 grade 3A; 0 in lung Tx).	9/142 (2 adverse events, 2 withdrew consent, 1 administrative reason, 4 other)	40/102	All: 56.4 ± 10.7, heart Tx: 55.3 ± 12	All: 74.6 ± 54.3, heart Tx: 83.1 ± 57.5	12	NR
After 24 mo EVL group: mGFR + 3.2 ± 12.3.	1/108 autopsy: BOS, chronic rejection, and unspecified inflammation	6/108 BPAR (5 Grade 1A/2 and 1 Grade 3A)	Since 12 mo follow-up: 10/108 (8 adverse events, 1 death, 1 laboratory abnormality)	17/22 lung Tx	57.3 ± 8.4 lung Tx	50 ± 31 lung Tx	24	NR
After 24 mo CRL group: −2.4 ± 9.0 mL/min ($P = 0.001$), significance also for subpopulations	1/127 complications of a left lower leg amputation	5/127 BPAR (4 Grade 1A and 1 Grade 3A)	Since 12 mo follow-up: 4/127 (1 death, 3 other)	21/20 lung Tx	58.8 ± 7.0 lung Tx	57 ± 42 lung Tx	24	NR
Mean change in mGFR after 12 mo EVL: + 2.4 ± 8.5 EVL: + 5.1 ± 11.1 EVL: + 6.7 ± 9.0	See above	See above	See above	29/6 28/65 3/9	56.5 ± 10.1 59.7 ± 8.4 63.2 ± 8.	4.3 ± 2.7 5.2 ± 4.0 6.9 ± 3.6	12	NR

continued

TABLE 1.
continued

Author (y), study group	Organ other than lung	n, mTORi/ Total	mTORi, time for initiation, target and/or measured level after conversiona	Study design	Treatment, CNI, n baseline/total, time for conversion, target or measured level after conversiona, n stop	Treatment, antimetabolites, n baseline/Total, modulation after start mTORi	Inclusion	Primary endpoint/ follow up
Glanville et al (2015), CeMyLungs		84/184	EVL, target 3–8	RCT	CsA, 84/84, C2 target initially 700 to 1000 ng/ml (days 31–60), reduction to 300 to 500 ng/ml after 1 y.		De novo lung Tx, confirmation of anastomotic healing, stratified for CsAtic fibrosis	Prevention of BOS or death after lung Tx
			CRL		CsA, 80/80, >800 by day 2, >1200 by day 7	Ec-MPS 80/80		
Strueber et al (2016)		95/190	EVL, target 6–8	RCT	CsA, 95/95, 12 mo, target 100–150		De novo lung Tx	Freedom from BOS
			CRL		CsA, 95/95, target 150–200	MMF 95/95		

Renal outcome	Mortality n/total	Rejection n/total	mTORi discontinuation n/total	Male/female	Age (y)[e]	Time from Tx (mo)[e]	Length of follow-up (mo)[e]	Reason for lung Tx
Creatinine at 3 y EVL: 152 ± 98 µmol/L no information on baseline Creatinine	13/84	43/84	46/84 (Adverse event (18) Patient death (13) Drug discontinuation (10) Investigator withdrew patient (2) Graft loss (2) Lost to follow up (1).)	42/42	49.7 ± 13.6 (20–66)	(1–3) De novo	36	COPD/ emphysema > other> Cystic fibrosis > Pulmonary fibrosis
Creatinine at 3 y Ec-MPS: 160 ± 112 µmol/L (P = 0.67).	6/80	34/80	34/80: Drug discontinuation (16) Adverse event (6) Patient death (6) Investigator withdrew patient (2) Graft loss (1) Lost to follow up (1) Other (2).	41/39	48.9 ± 11.3 (20–63)	De novo	36	COPD/ emphysema > other> Cystic fibrosis > Pulmonary fibrosis
GFR decreased in both groups about 50% within 6 mo EVL: Baseline GFR 103, after 24 mo 52	10/95 (most frequent causes: sepsis [n = 4], respiratory failure due to CLAD [n = 3], cardiovascular failure [n = 1])	19/95	52/95 (rejection n = 19, BOS n = 2, thrombotic angiopathy n = 4, severe pneumonia n = 3, other infection n = 6, wound healing disorder n = 8, Death n = 8, intolerance/ side effects n = 6, other N = 6)	53/42	56 (45–62)	1 De novo	24	COPD/ emphysema > pulmonary fibrosis > cystic fibrosis > other
CRL: Baseline GFR 96, after 24 mo 56	12/95 (most frequent causes: sepsis [n = 6], respiratory failure due to CLAD [n = 8], cardiovascular failure [n = 3] and malignancy [n = 2]).	15/95	41/95 (rejection n = 15, BOS n = 10, other infection n = 2, death n = 8, other N = 6)	56/39	60 (47–64)	De novo	24	COPD/ emphysema > cystic fibrosis > pulmonary fibrosis > other

continued

TABLE 1.
continued

Author (y), study group	Organ other than lung	n, mTORi/ Total	mTORi, time for initiation, target and/or measured level after conversiona	Study design	Treatment, CNI, n baseline/total, time for conversion, target or measured level after conversiona, n stop	Treatment, antimetabolites, n baseline/Total, modulation after start mTORi	Inclusion	Primary endpoint/ follow up
			CRL 13/91 switched to EVL, target 3–8, 5.2 ± 2.4		Tac 10/91, 7.2 ± 2.0 CsA, 71/91, 94 ± 32	NR		
Gottlieb et al (2019)		67/130	EVL, 24 h, target 3–5, 4.3 ± 1.1	RCT	45/67, immediate, measured 5.1 ± 1.6 CsA, 22/67, immediate, target 25–75	AZA 2/67 MMF 63/67 EC-MMF 2/67	eGFR ≥50 and ≤90 Severe renal impairment excluded	
			CRL		Tac, 45/63, measured 10 CsA, 18/63, measured 105	AZA 4/63 MMF 58/63 EC-MMF 1/63		eGFR after 12 mo
Snell et al (2002)	5 heart Tx	25	SRL, 10 to 40 µg/L[c] and 5–13 µg/L[d]	Retrospective, observational	Tac 4/25, 2.5 (1–5), 2/4 stop CsA 19/25, 48 (25–80)	AZA 16/25, dose reduction MMF 8/25, dose reduction	>90 posttransplantation days chronic renal impairment: 20 elevated serum Cr, mean 0.29 ± 0.12 mmol/L (minimum 0.20 mmol/L) 5 acutely dialysis-dependent (for a mean of 8.6 wk) Despite modification in immunosuppressive therapy Other indications present simultaneously – difficult-to-control acute rejection (n = 5) – progressive BOS (n = 2).	Review of clinical outcomes after selected use of SRL
Stephany et al 2009	56/169	SRL, target 15-25	Retrospective, observational	Tac, 28/56, 2.5 ± 2.5 CsA, 10/56, 100 ± 100 10/56 CNI Stop	10/56 Antimetabolite (replacement for CNI)	eGFR <60ml/min/1.73m3	Investigation of independent predictors for renal improvement after SRL conversion	Baseline eGFR 35 ± 14, after 1 month + 8 ± 14 (p=0.01) absence of proteinuria as positive predictive factor, odds ratio = 3.3 (95% confidence interval 1.0 to 12.5,p=0.05).

Renal outcome	Mortality n/total	Rejection n/total	mTORi discontinuation n/total	Male/female	Age (y)[e]	Time from Tx (mo)[e]	Length of follow-up (mo)[e]	Reason for lung Tx
Last follow-up: CRL:mGFR 42.9 ± 14.7 in lung Tx (20/87)	Since 24 mo follow-up: 23/123	2 in heart transplant recipient	Since 24 mo follow-up: 32/123 (23 death, 7 lack of consent, 2 other)	NR	NR	NR	5.5 y	NR
eGFR after 12 mo better in EVL quadruple low CNI regimen: 64.5 mL/min versus	3/67 (1 CLAD, 2 septic shock, and hemorrhagic shock [after study drug discontinuation])	6 episodes of BPAR (n = 5 grade A1, n = 1 grade A2. (New-onset CLAD n = 5)	20/67 (17 adverse events, 1 abnormal laboratory value, 1 protocol violation, 1withdrew consent)	40/27	58 [49, 61] median [25th, 75th quartiles]	10.9 [6.5, 14.4] median [25th, 75th quartiles]	12	COPD/emphysema > pulmonary fibrosis > other > cystic fibrosis
eGFR after 12 mo CRL: 54.6 (least squares mean, ANCOVA; $P < 0.001$).	1/63 (CLAD)	6 episodes of BPAR (n = 5 grade A1, n = 1 grade A2). (New-onset CLAD n = 5)	6/63 (4 adverse events, 2 protocol violation)	41/22	56 [50, 60] median [25th, 75th quartiles]	8.7 [6.5, 12.4] median [25th, 75th quartiles]	12	COPD/emphysema > pulmonary fibrosis > other > cystic fibrosis
After 30 d, 4 of 5 dialyzed patients ceased dialysis and 15 of 20 patients with an elevated serum creatinine (Cr) (mean Cr 0.29 mmol/L ±0.12) improved their Cr. The direction of change in Cr at 30 d predicted longer-term Cr. Creatinine pre-SRL, 30 d after start and current: Dialysis at baseline (n = 5) 0.60, 0.15, 0.19. Progress to dialysis (n = 4) 0.34, 0.37, 0.55. Never dialysis (n = 16) 0.28, 0.21, 0.21	7/25 (3 pulmonary sepsis, 3 progressive renal failure, and 1 progressive BOS)	2/25	10/25: toxicity concerns (n = 2); death (n = 5); and lack of efficacy (n = 3).	12/13	43 ± 15	1185-d median (120–3840)	307-d duration of therapy median (range 26–834).	NR
7/56	1 episode, acute rejection	NR	27/29	50 ± 13 (19, 65) (minimum, maximum)	27/29 50 ± 13 (19, 65) (minimum, maximum)	28.8 (9.6, 62.4) median (10th, 90th percentile)	1-18	NR

continued

TABLE 1.
continued

Author (y), study group	Organ other than lung	n, mTORi/ Total	mTORi, time for initiation, target and/or measured level after conversiona	Study design	Treatment, CNI, n baseline/total, time for conversion, target or measured level after conversiona, n stop	Treatment, antimetabolites, n baseline/Total, modulation after start mTORi	Inclusion	Primary endpoint/ follow up
			CRL		CNI-based, rates NR	NR		
Demirjian et al (2009)	SRL only: 17 heart	25/186	SRL only, target 10–15 (heart Tx), and 15–25 (lung Tx)	Retrospective, observational	Tac, Stop CsA Stop	MMF overall 38/186	Progressive CKD, recent acute renal failure, BOS (lung recipients), and adverse allograft events (ie, acute or chronic rejections)	Comparison of renal function in CNI-free versus reduced CNI–SRL regimens Comparison of renal function in Tac versus CsA-regimen
	62 heart Tx	67/186	SRL, target 3–8 (heart Tx) and 10–15 (lung Tx)		CsA, 67/67, 168 ± 139	MMF overall 38/186		
	53 heart Tx	94/186	SRL target 3–8 (heart Tx) and 10–15 (lung Tx)		Tac, 94/94, 8.1 ± 2.5	MMF overall 38/186		
Parada et al (2010)		8	EVL, 4.2	Retrospective, observational	Tac, 8/8, 5.5	AZA/ MMF 8/8 stopped	Nephropathy 3, BOS 4, lymphoma 1	Characterization of EVL-treated patients
Parada et al (2011) Long-term outcomes		10	EVL, 3.9	Retrospective, observational	Tac, 10/10, 6.6	NR	CNI-associated renal damage; n = 4), BOS (n = 4), lymphoma (n = 1), and graft fibrosis (n = 1).	Efficacy and safety of longer-term EVL use

Renal outcome	Mortality n/total	Rejection n/total	mTORi discontinuation n/total	Male/female	Age (y)[e]	Time from Tx (mo)[e]	Length of follow-up (mo)[e]	Reason for lung Tx
	NR	NR	NR	60/53	52 ± 11 (23, 67) (minimum, maximum)	NR	NR	NR
Considering confounders, in all 3 groups similar renal outcome (P = 0.40) When at least trace proteinuria at baseline fared worse than those with no proteinuria (Kaplan–Meier log-rank test for overall difference, P = 0.032).	56/186 overall	NR	NR	18/7	59 ± 10	81 ± 60	18 median	NR
	NR	NR	NR	49/18	59 ± 10	77 ± 51	18 median	NR
	NR	NR	NR	51/43	53 ± 13	31 ± 26	18 median	NR
In patients with renal dysfunction Serum Cr increased from 1.1 to 1.8 mg/dL, but at 3 mo, after EVL conversion, returned to baseline values maintaining that level for at least 2-y follow-up	1/8 (progressive lymphoma/multiple myeloma)	0/8	1/8 intolerance	5/3	48.5	NR	24	Pulmonary fibrosis = cystic fibrosis > emphysema > other
In patients with renal dysfunction after mean follow-up of 25 mo (range = 3–60) Renal function remained stable Baseline of 42.7 mL/min vs final CrCl of 45.7 mL/min	2/10 (multiple myeloma, BOS)	0/10	1/10 intolerance	7/3	51.9 (31–65)	25 (3–60)	Mean follow-up of 25 mo (range = 3–60)	Pulmonary fibrosis = cystic fibrosis > emphysema > other

continued

TABLE 1.
continued

Author (y), study group	Organ other than lung	n, mTORi/ Total	mTORi, time for initiation, target and/or measured level after conversiona	Study design	Treatment, CNI, n baseline/total, time for conversion, target or measured level after conversiona, n stop	Treatment, antimetabolites, n baseline/Total, modulation after start mTORi	Inclusion	Primary endpoint/ follow up
Schneer et al (2014)		41	EVL, 3–8	Retrospective, observational	Tac, target 3–5 CsA, target 150–175	MMF	>3 mo after Tx and stable graft function 30/41 rise in Cr to 1.5 mg/dL for male and 1.4 mg/dL for female with serum Cr increase in >15% in 2 consecutive measurements 1 mo apart. 10/41 malignancies 1 recurrent pulmonary lymphangioleiomyomatosis (LAM)	Renal function Pulmonary function
Bos et al (2021)		149	144 EVL, target initial 3–8, later 3–5, 4.74, 4 SRL, 1 sequential 4 SRL	Retrospective, observational	CNI 60/149, 36/60 Stop	AZA 38/149 MMF 59/149	104 renal insufficiency: median eGFR of 30 33 malignancies (10 lung carcinoma, 4 nonmelanoma skin cancer, 4 posttransplant lymphoproliferative disorder, 15 various other malignancies), 13 CNI-related adverse events 5 other	Indication to stop mTORi, duration of treatment

[a]In ng/mL, mean ± SD (range) if not otherwise specified.
[b]Total refers to core RAD B159 study group.
[c]Microparticle Enzyme Immuno-Assay (Abbott, Laboratories, Abbott Park, IL) before November 1999.
[d]High-performance liquid chromatography–tandem mass spectrometry thereafter.
[e]Mean ±SD (range) if not specified otherwise.
AZA, azathioprine; BOS, bronchiolitis obliterans syndrome; BPAR, biopsy proofed acute rejection; CKD, chronic kidney disease; CLAD, chronic lung allograft dysfunction; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CRL, control; CsA, cyclosporine A; ec-MPS, enteric-coated mycophenolate sodium; eGFR, estimated glomerular filtration rate in mL/min/1.73m^2; EVL, everolimus; IQR, interquartile range; mGFR, measured glomerular filtration rate in mL/min/1.73m^2; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; NOCTET, Nordic Certican Trial in HEart and lung transplantation; SRL, sirolimus; Tac, tacrolimus; Tx, transplantation.

Renal outcome	Mortality n/total	Rejection n/total	mTORi discontinuation n/total	Male/female	Age (y)[e]	Time from Tx (mo)[e]	Length of follow-up (mo)[e]	Reason for lung Tx
Improvement in renal function especially before proteinuria develops Renal function improvement as reflected by CrCl was statistically significant at 1, 3, and 6 mo but lost statistical significance by 12 mo, probably due to small size sample	1/41	No increase in graft rejection	20/41 (renal failure n = 5, diarrhea 4, edema 7, pruritus 1, tumor 2, death 1)	23/18	(28–74)	NR >3	Min 12	COPD/emphysema > pulmonary fibrosis > cystic fibrosis > other
13% received mTORi, significant increase in eGFR mTORi for >6 mo, ESKD excluded (n = 4): Significant increase in eGFR after 6 mo, in both, subgroup with renal insufficiency (n = 58, $P = <0.0001$, median eGFR from 30 to 37), and overall (n = 85, $P = 0.0001$, median eGFR from 32 to 39) Subanalysis renal insufficiency: significant increase when eGFR ≤ 29 (n = 29, $P = <0.0001$, median eGFR from 24 to 33), but not with eGFR 30–44 (n = 26, $P = 0.1032$, median eGFR from 36 to 42)	28/149 mTORi unrelated death	9/149 (7/9 biopsy-proven)	105/149 (28 death, 77 adverse events or drug intolerance)	79/70	59 (50–62) median (IQR)	1324 (459–2727), median d (IQR)	Min 6	COPD/emphysema > pulmonary fibrosis > cystic fibrosis > other

TABLE 2.
Adverse effects of mTOR inhibitors

Adverse effects	Frequency (%)
Dyslipidemia	
Hypercholesteremia	78%–82%
Hypertriglyceridemia	68%–90%
Infections	
Bacterial pneumonia	35%
Viral	30%
Fungal	28%
Hematological alterations	
Anemia	7%–14%
Thrombocytopenia	10%–13%
Leukopenia	11%–23%
PTLD	2%
TMA	5%
VTE	NA
Dermatological alterations	
Edema	8%–41%
Wound healing	NA
Mucocutaneous disorders/stomatitis	5%–26%
Pneumonitis	13%
Kidney disorders	
Kidney failure	12%
Proteinuria	42%
Digestive disorders	
Nausea	26%
Diarrhea	16%
Neoplasia	6%–13%

mTOR, mammalian target of rapamycin; NA, not available; PTLD, posttransplant lymphoproliferative disorder; TMA, thrombotic microangiopathy; VTE, venous thromboembolism.

mofetil [MMF] more often than azathioprine [AZA]), and almost all patients received corticosteroids.

According to previous recommendations, mTOR inhibitors should preferably be introduced in the first year and no later than 5 y after transplantation.[42] The average introduction time within 5 y after transplantation was met in all reported trials, except for the prospective study by Demirjian et al (81 ± 60 mo)[40] and the overall study population of NOCTET (61.3 ± 44.4 mo). Nevertheless, the subpopulation of LTR in the NOCTET study cohort was switched to EVL within 5 y of transplantation (50 ± 31 mo).[25,26]

De novo administration of EVL, meaning EVL started within 1–3 mo after transplantation, once wound healing had occurred, was investigated in 2 trials: no effect on preservation of lung function and prevention of bronchiolitis obliterans syndrome (BOS) (primary endpoints) was seen. Before EVL start, primary anastomotic healing had to be established and verified visually at bronchoscopy, since wound healing complications have been reported previously in thoracic transplantation (delayed healing, etc). The observed high mTOR discontinuation rates (52/95 and 46/84, respectively) preclude solid conclusions regarding the effect of mTOR inhibitors on kidney function in de novo LTR.[23,32]

Two more trials initiated EVL at a median time of <1 y after transplantation.[33,41] EVL-based quadruple therapy in LTR with baseline estimated GFR (eGFR) 50–90 mL/min/1.73 m^2 resulted in significantly improved kidney function compared to standard triple immunosuppressive therapy.[33]

In the reviewed articles, there was an intention for long-term mTOR inhibitor use. Temporary introduction of mTOR inhibitors, for instance in the setting of kidney rescue treatments, were not reported.

Monitoring the drug level of mTOR inhibitors is pivotal because of their narrow therapeutic index. De Pablo et al suggested EVL trough blood levels between 4 and 8 ng/mL after lung transplantation in line with reported target levels.[42] The reviewed studies revealed higher target levels when mTOR inhibitors were administered without CNI.[35-41] The highest target level of EVL was 10ng/ml, sought in the first 2 mo after combination with cyclosporine in the RADB159 study group before down-titration. Accordingly, the median measured EVL level was the highest at 6.6 ng/mL.[29] The lowest target level was set at 3–5 ng/mL by Gottlieb et al after combination therapy with a reduced dose of Tac or CsA (Table 1; Figure 3).[33]

- The most common mTOR inhibitor-based immunosuppression regimen consisted of everolimus in combination with reduced CNI (CsA > Tac), corticosteroids with or without antimetabolites (quadruple or triple therapy, respectively). The introduction of mTOR inhibitors took place between 1 mo and 5 y after transplantation. For de novo EVL initiation wound healing of bronchial anastomosis was verified in advance. Target drug levels varied from 3–5 ng/mL to 10 ng/mL.

THE EFFECT OF MTOR INHIBITORS ON KIDNEY FUNCTION

Assessment of Kidney Function

The GFR was measured (mGFR) in the NOCTET study group, in contrast to the eGFR used in most other trials. The following equations were used in descending order of frequency to estimate GFR: CKD–Epidemiology Collaboration, Modification of Diet in Renal Disease, and Cockcroft-Gault. Proteinuria was assessed only in the retrospective analyses.[34,39,40] The main challenge in the assessment of kidney function with mTOR inhibitors is the distinction between a variety of nephrotoxic factors throughout the transplantation procedure. For instance, proteinuria, as a surrogate marker for assessing kidney function, can also be a side effect of mTOR inhibitors without relevant kidney impairment.[43] Acute kidney injury (AKI) perioperatively and the subsequent development of CKD are common and are not only a consequence of immunosuppressive regimens but also of comorbidities in the LTR, such as hypertension, dyslipidemia, and diabetes.[2] Finally, interpreting the effect of mTOR inhibitors on kidney function is challenging because it encompasses a whole set of immunosuppressive agents, which complicates the comparability of different trials with different levels of comedications, especially relating to CNI use.

Effect of mTOR Inhibitors on GFR

Seven of the 20 reviewed articles showed no significant benefit to kidney function after mTOR inhibitor initiation.[23,25,27-29,32,34] Initially, 4 small studies of SRL-based regimens after lung transplantation showed promising results, with a significant decrease in creatinine[35-37] and an increase in eGFR.[30]

However, in 2006 a large trial introducing EVL for immunosuppression after lung transplantation showed differing results with deterioration of kidney function after introduction; Snell et al on behalf of the RAD B159 Study Group[44] compared prospectively EVL versus AZA with reduced CNI and found significant slowing of lung function loss in LTR. Nevertheless, high serum creatinine levels have been reported more often with EVL. To review the renal deterioration of the RAD B159 study group in detail, Kovarik et al published an article on EVL pharmacokinetics and exposure-response relationships. Indeed, creatinine increased more in the EVL group than in the AZA group: creatinine at baseline was 141 ± 48 μmol/L and 226 ± 48 μmol/L after 12 mo for EVL, and the creatinine at baseline for AZA was 149 ± 51 μmol/L and increased slightly to 186 ± 57 μmol/L after 12 mo; the difference was not significant in this exposure-response relationship evaluation.

The relevant increase in creatinine in this study was probably related to the long time needed for CsA reduction, up to 12 mo, until the target levels were reached. High EVL dosing during the first 2 mo could aggravate CNI-related nephrotoxicity.

The potential improvement in kidney function was supported by the NOCTET trial.[24-26,31] To evaluate renal function assessed by mean change in mGFR, 94 heart transplant recipients and 46 LTR received EVL and reduced CNI (CsA was administered more often than Tac [CsA > Tac]) with antimetabolites as adjunct (more patients had MPA with reduced dose, fewer patients had AZA [reduced MPA < AZA]) after 1:1 randomization, whereas the control (CRL) group received CNI and antimetabolites. The primary outcome (improved mGFR) was met after 12 mo core study follow-up (21) for both the heart transplantation and the lung transplantation subpopulations: the mean change in mGFR of heart and lung transplantation patients had improved after 12 mo of EVL by +4.6 mL/min and CRL was reduced by −0.5 mL/min.[26] The change in mGFR was most pronounced in those with the shortest time interval since the transplantation was documented. Arora et al[24] provided detailed information on renal function 12 mo after introduction of mTOR inhibitor according to baseline mGFR, with the largest change in mGFR for participants with moderate kidney disease (mGFR 30–59 mL/min/1.73 m^2; mean change in mGFR after 12 mo EVL: +5.1 ± 11.1, CRL: −0.5 ± 8.8, $P < 0.01$). However, renal improvement was limited to conversion to EVL within 5 y after transplantation. In the 2 y extension study with 235 of the 282 initial patients included,[31] renal improvement was assessed as the mean change in mGFR after 24 mo in the EVL group compared with the CRL group remained significantly positive.

Finally, the long-term outcomes were published in 2016[25] after an average follow-up of 5.7 y. Evaluation of 163 of 282 initial study participants indicated a neutralized renal effect in LTR when comparing EVL versus CRL. Importantly mean intervals since lung transplantation to EVL-switch were relatively long (4.2 ± 2.6 y), this may have diminished the potential for kidney function improvement.

In summary, the NOCTET study showed that introduction of EVL in combination with reduced CNI dosing several years after lung transplantation led to a higher mGFR after 12 and 24 mo compared with continued CNI standard treatment, but no significant changes were observed after a follow-up of 5 y.

Kidney function stabilization without significant improvement in renal function was confirmed in 2011, when Roman et al published a retrospective 12 mo study of conversion to EVL in LTR with data from the EVERODATA registry in Spain.[41] At the clinician's discretion, 65 patients were converted to EVL with reduced or, in some instances, stopped CNI. Half of the patients were also treated with antimetabolites. The reason for treatment modification was mostly bronchiolitis obliterans syndrome, in which a slight decrease in eGFR was observed, whereas renal function in the subgroup with renal impairment before treatment modification remained stable.

Two small retrospective studies by Parada et al characterized EVL after lung transplantation in Chile. The creatinine level increased in the first 3 mo after the addition of EVL and reduction of Tac dosing before spontaneous return to baseline in the first study.[27] In the second study,[28] eGFR remained stable, making EVL in combination with low-dose CNIs a safe and effective maintenance treatment option after lung transplantation.

Effect of mTOR Inhibitors on Renal Function According to Baseline GFR

In 104 patients with renal insufficiency with a median eGFR of 30 mL/min/1.73 m^2, Bos et al[12] retrospectively evaluated the differences in the decrease in eGFR after conversion to mTOR inhibitors (predominantly EVL-treated LTR) and reduced CNI dosing according to baseline eGFR. Subanalysis indicated improvement in renal function for eGFR ≤29 mL/min (median eGFR from 24 to 33 mL/min, n = 29, $P < 0.0001$), but not for eGFR 30–44 mL/min (median eGFR from 36 to 42 mL/min, n = 26, $P = 0.1032$). This contradicts the findings of the NOCTET study, as reported by Arora et al[24] with biggest improvement of mGFR in moderate CKD (mGFR 30–59 mL/min/1.73 m^2), more so than in severe CKD (mGFR < 30 mL/min), whereas no significant change for mGFR 60–89 mL/min was observed. In the retrospective analysis of Schneer et al,[34] evaluating 41 patients with increased serum Cr, no correlation between baseline GFR and improvement in renal function could be demonstrated (Table 1).

Effect of mTOR Inhibitors on Renal Function in De Novo LTR

Glanville[23] (CeMyLungs study group) and Strueber[32] introduced EVL in the early stage after lung transplantation "de novo" 1–3 mo after transplantation, once wound healing was established early posttransplant. Eighty-four and 95 patients received EVL and CsA, respectively, whereas CRL received MMF in combination with CsA in the triple immunosuppressive regimen. For the primary endpoint prevention of freedom from BOS, no significant difference was demonstrated. Glanville et al found the mean creatinine level at 3 y to be 152 ± 98 μmol/L in the EVL group versus 160 ± 112 μmol/L in the MMF group ($P = 0.67$). The data of Strueber et al indicated a decrease of eGFR in both groups of approximately 50% within 6 mo with comparable eGFR after 24 mo (baseline eGFR 103 mL/min, 52 mL/min after 24 mo in the EVL group versus baseline eGFR 96 mL/min, 56 mL/min after 24 mo in the MMF group).

A high incidence of AKI in the perioperative period has been previously reported in several studies and is a risk factor for CKD development.[2] A relevant deterioration of

kidney function early after lung transplantation occurs frequently and could explain the progressive kidney disease independent of EVL in these 2 trials.

Effect of mTOR Inhibitors on Renal Function With CNI Discontinuation

Whether the beneficial effect of CNI sparing can be improved by drug discontinuation was investigated retrospectively in 131 heart transplants and 55 LTR by Demirjian et al in 2009.[40] There was no significant difference in kidney function between the 3 groups. In the SRL-only and SRL + Tac/+CsA groups, similar initial improvement with subsequent slow decline in eGFR was observed. Considering the results from other CNI-free trials,[12,35-41] we agree with De Pablo and Fine[5,42] that evidence and expected renal benefits of CNI discontinuation are scarce.

Proteinuria for Prediction of mTOR Inhibitor Response

In the SRL-based retrospective study by Stephany et al, an increase in eGFR of 8 ± 14 mL/min from baseline was observed during the follow-up period of 1–18 mo in 56 patients with kidney impairment after switching to SRL and reduced/partially stopped CNI (Tac > CsA).[39,40] Proteinuria was identified as a negative predictor of a favorable kidney response after conversion. The absence of proteinuria led to a distinct improvement in renal function. This concurs with findings from Demirjian et al, in which patients with at least trace proteinuria at baseline had a worse renal outcome, especially in combination with eGFR <60 mL/min, in line with the findings of Schneer et al.[34,40]

Recently, proteinuria in heart transplant recipients converted to mTOR inhibitors has been associated with higher all-cause mortality.[45] Therefore, mTOR inhibitors should be used with caution in patients with advanced CKD or proteinuria after lung transplantation.

- The effect of mTOR inhibitors on kidney function should be interpreted in the context of the patient's comorbidities and comedication to assess confounders such as perioperative AKI, diabetes, and CNI dose (reduction) after mTOR Inhibitor introduction. A majority of the reviewed articles showed improvement or stabilization of kidney function. However, especially with high EVL levels and lack of CNI reduction, deterioration of kidney function occurred. More evidence is needed to define GFR-based indication criteria for EVL use. Early EVL introduction increases the potential benefit on kidney function. However, in "de novo" EVL introduction, especially wound healing and the high incidence of perioperative AKI must be considered. Limited evidence supports CNI discontinuation after mTOR inhibitor introduction and this regimen raises concerns about insufficient immunosuppression. In patients with preexisting proteinuria, mTOR inhibitors should be used with caution.

EFFICACY AND SAFETY OF MTOR INHIBITORS IN LUNG TRANSPLANTATION

Allograft Function and Overall Survival

The reviewed studies revealed mTOR inhibitors to be efficacious in preserving lung function and mortality, and rejection episodes were comparable to those in CRL groups.[12,23,25,27-30,32-38,41] Snell et al reported even fewer allograft rejection episodes with EVL than with AZA after 12 and 24 mo.[44,46]

Several studies hypothesized a better outcome in BOS[29,32,36,44] or longer freedom of BOS with mTOR inhibitors; however, they failed to demonstrate a significant difference.

Safety and Tolerability of mTOR Inhibitors in Lung Transplantation

The commonly reported adverse effects of mTOR inhibitors are presented in Table 2 with dyslipidemia, infections, hematological and mucocutaneous disorders, edema, and proteinuria being the most common.[12,32,41-43,47-49]

The discontinuation rate of EVL varies considerably. High discontinuation rates of 50–71% were reported in 4 studies.[12,23,32,34] The measured EVL levels and EVL target levels were high in these trials (4.74, 3–8, 6–8, and 3–8 ng/mL, respectively). Discontinuation rates and EVL levels from prospective studies are illustrated in Figure 3.[23,26,29,32,33] The highest discontinuation rate was found in 2006 during the first trial of this type on behalf of the RADB159 study group using the highest EVL target level of 10 ng/mL during the first 2 mo after initiation before down-titration.[44] Lower EVL target levels seemed to improve tolerability with decreased discontinuation rates. Notably, the EVL target level was lowered during the NOCTET trial from 3–8 ng/mL to 3–6 ng/ml because of a significant increase in infections in the EVL arm.[24,26]

It is unclear from the study reports whether clinicians tend to discontinue EVL instead of treating adverse effects. Bos et al reported that mTOR inhibitor discontinuation was mostly due to infection (19%) (bacterial > fungal > viral) and edema (14%).[12] Glanville et al found in the CRL group (enteric-coated Mycophenolate sodium) higher rates of biopsy-proven acute rejection, leukopenia, diarrhea, and CMV infection, whereas in the EVL group venous thromboembolism was more frequent.[23] Decreased rates of cytomegalovirus infection under SRL have also been described in the literature, probably due to improved T-cell fitness and thus better virus control.[50,51]

The immunosuppressive protocols after failed mTOR inhibitor use were not reported in detail in the reviewed articles. We assume reconversion to prior administered regimens occurred.

- mTOR inhibitor-based regimens provide adequate immunosuppression to preserve allograft function with comparable survival rates. Nevertheless, adverse effects are common and lead to discontinuation, especially when high EVL target levels are applied.

AREAS OF UNCERTAINTY AND FUTURE DIRECTIONS

Despite the growing body of literature on mTOR inhibitors and their effects on kidney function after transplantation, more evidence is needed to define the optimal indication, timing and immunosuppressive regimen for LTR.

The regimen reported by Gottlieb et al,[33] initiated early after lung transplantation (median 10.9 mo), may be a promising strategy for future trials. It is the most recent prospective trial published to date that compared patients

with mild to moderate kidney impairment randomly assigned to EVL-based quadruple therapy versus standard triple therapy after lung transplantation (CNI [Tac > CsA] + antimetabolite [MMF > AZA] + corticosteroids). In the quadruple regimen, EVL levels were immediately established, and CNI was immediately reduced. Notably, the low CsA target level after conversion of 25–75 ng/L was the lowest target level reported in all the reviewed articles (except for CNI discontinuation). Likewise, the mean EVL level of 4.2 ng/mL (target 3–5 ng/mL) was in the lower range compared with other trials and was stable at 12 mo after conversion. They found significantly improved kidney function, with similar immunosuppressive activity and rejection rates. Notably, in contrast to the high discontinuation rates reported in previous studies, adverse effects seemed to be manageable (ie, by dose reduction) and led to less EVL discontinuation.

From a historical perspective, the drug target levels have declined over the years and with this the (dose-dependent) drug tolerability for EVL has improved. Defining the most appropriate drug target levels for EVL possibly tailored to the overall immunosuppressive strategy (dual, triple, or quadruple immunosuppressive regimen) is likely going to improve the risk-benefit ratio of the compound and thus may improve its nephroprotective potential.

Possibly future drug target levels for EVL will be lower than those used in most studies cited here and it will be interesting to see whether, even at these lower doses and with improved tolerability, the nephroprotective effects are retained and sustainable over longer periods of time. With the advent of more recent strategies for measuring overall immunosuppression for example by biological markers such as cytological or cytokine patterns or levels of virological markers (eg, torque teno virus load) the more personalized approach will allow for lower dosing regimens.

Future research should focus on biomarkers to predict renal recovery after mTOR inhibitor administration in CKD and perioperative AKI. In addition to assessing GFR and proteinuria, there is insufficient data regarding complications of CKD, such as hypertension, dyselectrolytemia, and metabolic acidosis, in the context of mTOR inhibitors after lung transplantation. Future studies should also address the nephroprotective potential of sodium-glucose cotransporter-2 inhibitors and the nonsteroidal mineralocorticoid antagonist Finerenone in solid organ transplantation.

Belatacept, a US Food and Drug Administration–approved, non-CNI–based immunosuppressive compound, is used in combination with mycophenolate and corticosteroids in kidney transplant recipients. It inhibits CD28-mediated T-cell costimulation by binding to CD80 and CD86 on the surfaces of antigen-presenting cells.[52,53] Belatacept use was associated with superior kidney function and lower rates of hypertension, posttransplant diabetes, and hyperlipidemia. However, higher rates of acute rejection were noted in studies of kidney transplant recipients.[54,55]

In LTR, only scarce data from retrospective series using belatacept to reduce CNI exposure are available with conflicting safety results.[56,57] A recently published pilot randomized controlled trial of de novo belatacept-based immunosuppression in lung transplantation was prematurely stopped because of increased mortality rates in the belatacept-treated patients.[58]

Future research should focus on CNI conversion regimens to belatacept instead of de novo belatacept-based regimens, which may avoid early acute rejection and help preserve kidney function in the long term.

- To improve immunosuppression regimens in lung TPL recipients with impaired kidney function, more research is needed addressing what to expect from EVL introduction and at what time, dose and baseline eGFR should this be considered. Predictive markers such as time since transplantation and baseline proteinuria may be helpful in selecting patients who will benefit most from the introduction of mTOR inhibitors. Optimal combinations and target levels of EVL, CNI, and antimetabolites should be defined. Nephroprotective drugs may further influence the benefit of EVL on kidney function. Currently, there is insufficient data to support the use of belatacept after lung transplantation.

CONCLUSION AND RECOMMENDATIONS FOR MANAGEMENT

mTOR inhibitors are relatively safe and efficacious immunosuppressants for lung transplantation and have the potential to improve or preserve kidney function, especially if the following are considered:

1. mTOR inhibitors should be initiated early in the development of CKD, preferably in the first year, and no later than 5 y after transplantation.
2. For de novo mTOR inhibitor use, once wound healing of bronchial anastomosis is verified, further studies are needed because evidence of its beneficial effects is scarce.
3. Medication regimens containing CNI remain the cornerstone of immunosuppression in lung transplantation. The lowest effective drug levels of CNI and mTOR inhibitors should be sought, and the ideal target levels still need to be defined.
4. mTOR inhibitors are used with a long-term intention. Whether mTOR inhibitors could serve as temporary "rescue" medication to improve kidney function and how to proceed after reconversion has not been reported.
5. There is no clearly defined stage of CKD for mTOR inhibitor indication, nor does severe CKD preclude the improvement of kidney function under mTOR inhibitors.
6. Baseline proteinuria may be a negative predictor of favorable kidney response after the introduction of an mTOR inhibitor.
7. Common adverse effects are impaired wound healing, infections, gastrointestinal symptoms, stomatitis, pneumonitis, progressive proteinuria, and hematologic side effects that appear to be dose-dependent.

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