Original Article

mTOR inhibitors after lung transplantation: a real-life experience

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Background: The mammalian target of rapamycin (mTOR) inhibitors in combination with calcineurin inhibitors (CNIs), antimetabolites and corticosteroids for immunosuppression after lung transplantation (TPL) have gained importance in patients with chronic kidney disease (CKD). The goal of this study was to characterize lung transplant recipients (LTR) treated with mTOR inhibitors, with a special focus on kidney function.

Methods: LTR transplanted at the University Hospital Zurich between December 1992 and April 2022 were analyzed. Demographics, estimated glomerular filtration rate (eGFR) before and after mTOR initiation, TPL circumstances, immunosuppressive regimens, and allograft function were recorded. We used linear regression to calculate the Mitch curves and a linear mixed-effects model to compare the eGFR.

Results: Of all LTR, 70/593 (12%) received mTOR inhibitors. Intolerance or adverse events of antimetabolites were the most common indications for mTOR inhibitor introduction. Discontinuation in 34/70 (49%) was often related to planned or urgent surgery to prevent impaired wound healing. The majority of patients had a preserved baseline eGFR at mTOR inhibitor introduction with CKD Kidney Disease Improving Global Outcomes (KDIGO) stage G1 or 2. The mean annual eGFR decline changed significantly from −16.19 mL/min/1.73 m^2/year [95% confidence interval (CI): −22.27 to −10.11] 12 months before to −6.16 mL/min/1.73 m^2/year (95% CI: −13.37 to 1.05) 12 months after mTOR initiation (P=0.009) showing better outcomes with earlier mTOR inhibitor initiation after lung TPL.

Conclusions: This retrospective study suggests stabilization of kidney function after mTOR inhibitor initiation in LTR documented by a slower eGFR decline after mTOR inhibitor introduction with better outcomes early after lung TPL. Intolerance or adverse events of antimetabolites are important indications for the introduction of mTOR inhibitors. A relatively high discontinuation rate (49%) can be explained by planned discontinuation of mTOR inhibitors prior to surgery to avoid impaired wound healing.

Keywords: Kidney function; mammalian target of rapamycin inhibitors (mTOR inhibitors); lung transplantation (lung TPL); immunosuppression; everolimus (EVL)

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Introduction

Clinicians face a challenging task in managing immunosuppression after lung transplantation (TPL) because of the need to balance the level of immunosuppression with the risk of rejection, tolerability of the immunosuppressive regimen and imminent infection (1). After lung TPL, a triple immunosuppressive regimen consisting of a calcineurin inhibitor (CNI), an antimetabolite, and a corticosteroid, continues to be the cornerstone of treatment.

Chronic kidney disease (CKD) is common in non-renal solid organ TPL. Five years after TPL, 16% of patients had a glomerular filtration rate (GFR) lower than 30 mL/min/1.73 m^2 and an increased risk of death (4.6 times the relative risk of death for patients with non-renal TPL) (2,3). CNI-mediated nephrotoxicity is a critical component of post-transplant kidney dysfunction along with diabetes mellitus, arterial hypertension, infections, and perioperative kidney injury (3-5).

Mammalian target of rapamycin (mTOR) inhibitors are increasingly being used for immunosuppression after lung TPL because of their beneficial effects on renal function and preserved efficacy of allograft function (6-10). However, clear criteria for indication, patient selection, timing, and optimized target doses of mTOR inhibitors remain unknown (6).

Recent evidence indicates that initiating mTOR inhibitors early after lung TPL and optimizing drug levels for both mTOR inhibitors and CNI may improve or maintain kidney function (9). Lower mTOR inhibitor target levels appear to reduce common adverse effects (impaired wound healing, infections, gastrointestinal symptoms, stomatitis, pneumonitis, progressive proteinuria, and hematologic side effects) and may therefore reduce discontinuation rates. It is unclear whether CKD stage and proteinuria at the start of mTOR inhibitor treatment predict kidney outcomes (6).

This retrospective study aimed to evaluate the use of mTOR inhibitors, patient characteristics, and outcomes after lung TPL in patients who received mTOR inhibitors, with a particular focus on kidney function. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1623/rc).

Highlight box

Key findings

- A stabilization of kidney function in lung transplant recipients (LTR) was shown by a significantly slower estimated glomerular filtration rate decline after mammalian target of rapamycin (mTOR) inhibitor initiation and reduction of calcineurin inhibitors.
- Intolerance and adverse events of antimetabolites are important indications for mTOR inhibitor introduction.

What is known and what is new?

- The beneficial effect on kidney function has been described previously for mTOR inhibitors after lung transplantation. However, clear indication criteria, optimal timing, and target levels are lacking.
- We provide real-life experience and our approach to immunosuppressive regimens including mTOR inhibitors.

What is the implication, and what should change now?

- mTOR inhibitors appear to be beneficial for kidney function in LTR even when renal function was not the primary indication for its use but antimetabolite intolerance. However, more prospective studies are needed to recommend mTOR inhibitors with clearly defined indication criteria, including baseline glomerular filtration rate and proteinuria, defined drug target levels, and a systematic approach to dealing with mTOR inhibitor adverse effects.
- The role of nephroprotective drugs such as SGLT2 inhibitors or non-steroidal mineralocorticoid antagonists should be explored in future trials.

Methods

Study design

In this retrospective observational study, electronic medical records of all lung transplant recipients (LTR) transplanted at the University Hospital Zurich since the inception of the lung TPL cohort from December 1992 to April 2022 were reviewed. We included all patients who had received mTOR inhibitors during the follow-up period. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the regional ethics committee of Kanton Zurich (BASEC No. 2022-01015). All patients provided written general informed consent for further use of patient data and samples for research purposes prior to lung TPL.

The primary outcome was the evaluation of kidney function before and after the initiation of mTOR inhibitors. Furthermore, we assessed demographics, TPL circumstances, immunosuppressive regimens, and allograft function.

Data collection and definitions

The lung transplant team conducts regular follow-up appointments with all patients, addressing both ongoing

health concerns and immediate medical issues through frequent evaluations of clinical and laboratory data. Data for analysis were retrieved at pre-specified time points from TPL (at 0, 1, 2, 3, 6, 12, 18, 24, 30, 36 months) and from mTOR inhibitor introduction (at –12, –6, –3, 0, 1, 2, 3, 6, 12, 18, 24, 30, 36 months, and yearly thereafter) until death or the end of follow-up in April 2022.

To increase the reliability of the reported indications and causes of discontinuation, they were independently confirmed by two investigators.

Extracorporeal photopheresis (ECP) is additionally used with standard triple immunosuppressive regimens in patients with allograft dysfunction. Changes in the immunosuppressive regimen, including the initiation of mTOR inhibitors, were based on the consensus of experienced TPL physicians, except the CeMyLung study participants, who received mTOR inhibitors fairly early after lung TPL (11). To monitor immunosuppression, clinical markers, and therapeutic drug monitoring, as well as white blood cell counts, particularly lymphocytes and eosinophils, are considered (12). We noted that mTOR inhibitors lead to cytopenic adverse reactions to a lesser extent and less frequently than MMF and therefore consider them as alternative medications (12).

Kidney function was assessed using the estimated GFR (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and using representative creatinine values within pre-specified time ranges. We selected manually creatinine levels at above mentioned time points that were assumed steady states, rather than creatinine values, during acute health problems such as infection to calculate eGFR values.

Target drug levels for everolimus (EVL) were lowered over time, beginning at 5–8 ng/mL in the early era (until 2013) later to 4–6 ng/mL (era 2014–2019), and then 3–5 ng/mL (era 2020 onwards) bearing drug tolerability in mind. CNI drug levels were reduced by 20–30% at the time of introduction. For example, the target drug level for tacrolimus combined with EVL was 3–5 ng/mL for both compounds (12). Measured drug levels were not included in this study.

Evaluation of allograft function consisted of clinical and laboratory as well as lung function measurements and radiologic work-up. Based on clinical discretion, additional examinations were added to the routine evaluation. We used the updated definition from the consensus paper on the definition of chronic lung allograft dysfunction (CLAD) published by Verleden *et al.* (13). CLAD phenotypes include bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), mixed type, and undefined (13).

Statistical analysis

Descriptive statistics were performed using IBM SPSS Statistics Version 28 (IBM, Armonk, NY, USA). The association between eGFR decline before and after mTOR initiation was analyzed using STATA version 17.1. Quantitative data are presented as the mean ± standard deviation (SD) or median [interquartile range (IQR)], as appropriate. Either a Student's *t*-test or a Mann-Whitney *U* test were employed, contingent upon the distribution of the data. For longitudinal comparisons within patients, to accommodate the data dependency, either a paired *t*-test or a Wilcoxon signed-rank test were utilized. Categorical variables were expressed as counts (n) and percentages (%).

We hypothesized that eGFR declines linearly with age but with different slopes before and after mTOR treatment initiation. This model assumed that each patient had a piecewise linear spline eGFR decline with a knot at time 0 (treatment initiation with mTOR inhibitor).

A linear regression model was used to calculate the average Mitch curves. For the primary outcome, a linear mixed-effects model was used to compare changes before and after initiation of the mTOR inhibitor. Furthermore, a dynamic difference-in-difference model was used to display overall changes in the primary outcome.

We truncated the dataset of eGFR values to before and after (–/+) 12 months of mTOR inhibitor initiation because we assume that changes during this period correlate best with the effect of mTOR inhibitors on kidney function by reflecting steady states and baring bias due to the multifarious reasons for kidney deterioration after lung TPL in mind. In addition, we provide results from the entire follow-up period to show the overall trend.

Results

Patient characteristics

Five hundred and ninety-three patients underwent lung TPL. Seventy LTR (12%) received mTOR inhibitors. *Table 1* shows the key characteristics of LTR treated with mTOR inhibitors.

Most patients were male (63%) and underwent their first lung TPL at a median age of 42.8 (IQR, 24.3–57.5) years with a median body mass index (BMI) of 19.8 (IQR, 17.1–25.5) kg/m^2.

Table 1 Patient characteristics and follow-up (n=70)

Characteristics	Data
Patients ever taking mTOR inhibitors/all LTR USZ	70/593 [12]
Female/male	26 [37]/44 [63]
Alive/deceased at end of follow-up	36 [51]/34 [49]
Bilateral/single lung TPL	69 [99]/1 [1]
Re-lung TPL	4 [6]
Year of first lung TPL	2009 [2005–2015]
Age at first lung TPL (years)	42.8 [24.3–57.5]
BMI at first lung TPL (kg/m^2)	19.8 [17.1–25.5]
Lung TPL indications	
CF	32 [46]
COPD/emphysema	16 [23]
ILD	16 [23]
Other	6 [9]
mTOR inhibitors	
EVL/SRL	68 [97]/2 [3]
Follow-up total from first TPL (years)	8.2 [4.3–11.9]
Follow-up total from first mTOR inhibitor introduction (months)	34.8 [12.9–62.8]
Survival from first TPL (years)	6.7 [3.7–10.6]

Data are presented as n/N [%], n [%] or median [IQR]. mTOR, mammalian target of rapamycin; LTR lung transplant recipients; USZ, University Hospital of Zurich; TPL, transplantation; BMI, body mass index; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; EVL, everolimus; SRL, sirolimus; IQR, interquartile range.

Age and BMI distribution reflects the considerable number of 32 cystic fibrosis (CF) patients (46%) who underwent TPL at a significantly younger median age of 24.3 (IQR, 21.2–30.3) years (P<0.001) with a significantly lower median BMI of 17.1 (IQR, 15.8–18.7) kg/m^2 (P<0.001).

The median follow-up time after lung TPL was 8.2 (IQR, 4.3–11.9) years. The median survival time after lung TPL was 6.7 (IQR, 3.7–10.6) years. At the end of follow-up 36 LTR were alive. *Table 2* shows the causes of death. Only one patient was lost to follow-up after 9 years because of the transfer to another center.

CF was the most prevalent disease leading to lung TPL in 32/70 patients (46%) treated with an mTOR inhibitor, followed by chronic obstructive pulmonary disease (COPD)/emphysema, and interstitial lung disease (ILD). Serostatus of cytomegalovirus (CMV), Epstein-Barr virus (EBV), and toxoplasmosis before lung TPL were assessed and are presented in Table S1.

Table 2 Cause of death (n=70)

Causes	N [%]
Respiratory failure	14 [20]
Best supportive care (patient wish)	7 [10]
Multiorgan failure due to sepsis	6 [9]
Cardiac failure	4 [6]
Hepatic failure	1 [1]
Pancreatic cancer	1 [1]
Hemorrhagic shock	1 [1]

Immunosuppressive regimens

mTOR inhibitor introduction

All patients in our cohort except two were treated with the mTOR inhibitor EVL (Certican®) due to better bioavailability and shorter half-life compared to sirolimus (SRL) (14). The mTOR inhibitor introduction times are shown in *Table 3*.

Twenty-four patients (34%) received mTOR inhibitors within 1 year of lung TPL and 51 (73%) within the first 5 years. *De novo* introduction, defined as introduction 1–3 months after lung TPL (after established wound healing), was implemented in 4 (6%) patients participating in the CeMyLung study, earliest at 2.3 months after lung TPL.

mTOR inhibitor indication

The most common reason for mTOR inhibitor initiation was intolerance or adverse events of antimetabolites in 36 patients (51%), such as suspected or confirmed mycophenolate mofetil/ mycophenolic acid colitis in 18 patients. Seven patients received mTOR inhibitors for cytopenia. Cytopenia had previously occurred in three patients, which is why antimetabolites were withheld. The other eight patients experienced a variety of antimetabolite adverse events, including gastrointestinal adverse events other than colitis (n=4), cholestatic hepatitis (n=1), dermatologic side effects (n=1), allergic alveolitis (n=1), and joint pain (n=1).

Table 3 Patient outcomes: mTOR inhibitor duration and introduction time, ESKD, and allograft dysfunction of the lung TPL cohort treated with mTOR inhibitors

Outcomes	Data
Total mTOR inhibitor duration (months)	23.2 [6.2–49.6]
Year of first mTOR inhibitor introduction	2017 [2008–2019]
Interval between first lung TPL and first mTOR inhibitor introduction (years)	1.6 [0.7–5.3]
First mTOR inhibitor duration when discontinued (n=34) (months)	4.8 [1.4–18.4]
Second mTOR inhibitor duration when discontinued (n=4) (months)	29.6 [14.0–38.3]
mTOR inhibitor discontinuation	34 [49]
Re-introduction of mTOR inhibitor after discontinuation	10 [14]
ESKD	17 [24]
Interval first TPL to ESKD (years)	5.8 [3.7–8.3]
Interval first mTOR inhibitor initiation to ESKD (years)	3.4 [2.4–6.6]
Dialysis	11 [16]
Interval first TPL to dialysis (years)	6.3 [3.7–8.6]
Interval first mTOR inhibitor initiation to dialysis (years)	4.6 [3.3–7.6]
Kidney TPL	6 [9]
Interval first TPL to kidney TPL (years)	9.0 [5.7–13.0]
Interval first mTOR inhibitor initiation to kidney TPL (years)	4.9 [1.3–10.6]
Year of kidney TPL	2016 [2010–2021]
Rejection any type	46 [66]
CLAD any type	40 [57]
CLAD BOS	29 [41]
CLAD RAS	1 [1]
CLAD mixed	4 [6]
CLAD not otherwise specified	6 [9]
Acute lung allograft dysfunction	1 [1]
Antibody-mediated rejection	2 [3]
Subclinical antibody-mediated rejection	3 [4]
ECP anytime	32 [46]

Data are presented as median [IQR] or n [%]. mTOR, mammalian target of rapamycin; ESKD, end-stage kidney disease; TPL, transplantation; CLAD, chronic lung allograft dysfunction; BOS, bronchiolitis obliterans syndrome; RAS, restrictive allograft syndrome; ECP, extracorporeal photopheresis; IQR, interquartile range.

mTOR inhibitors were introduced in 17 patients (24%) because of allograft dysfunction and, surprisingly, only in 13 LTR (19%) because of kidney disease. Seven patients (10%) were enrolled in the CeMyLung trial. Viral infection and malignancy were indications in 4 (6%) and 3 (4%) patients, respectively. One patient had CNI intolerance and four patients had other indications. Of note, 12 patients had more than one indication for mTOR inhibitor introduction.

mTOR inhibitor discontinuation reason

Thirty-four patients (49%) discontinued mTOR inhibitors, mainly because of imminent or performed surgery (n=16; 23%). Only 8 patients (11%) experienced mTOR inhibitor adverse effects, leading to discontinuation. Some patients had cytopenia or nausea due to EVL. There have been single cases of hemolytic uremic syndrome (HUS), possibly due to EVL, autoimmune hemolytic anemia with warm antibodies, kidney disease, other anemia, malignancy, ulcerative gingivitis, and cholestatic hepatitis. Two patients discontinued mTOR inhibitor treatment because of suspected EVL pneumonitis. Other reasons for discontinuation were impaired kidney function and malignancy [1 patient each (1%)], other (n=5; 7%), and unknown (n=4; 6%). Again, three patients had combined causes of mTOR inhibitor discontinuation.

In 10/34 cases, mTOR inhibitor re-exposure was attempted and successfully established in 6/10 patients.

mTOR inhibitor duration

The median duration of mTOR inhibitor administration until discontinuation, death, or the end of follow-up was 23.2 (IQR, 6.2–49.6) months (*Table 3*). In the subgroup of patients with antimetabolite intolerance or adverse events leading to mTOR inhibitor introduction, the median total duration of mTOR inhibitor administration was significantly longer at 35.3 (IQR, 7.0–57.5) *vs.* 28.8 (IQR, 4.5–35.7) months (P=0.043), while the discontinuation rate was comparable at 16/36 (44%, P=0.48). Discontinued mTOR inhibitors resulted in a significantly shorter median total duration of 11.4 (IQR, 4.2–41.7) months, compared to mTOR inhibitor duration limited by death or end of follow-up of 33.9 (IQR, 11.2–57.5) months (P=0.02).

Adjustment of other immunosuppressive agents

Cyclosporine was administered more frequently than tacrolimus (Prograf®) for standard initial immunosuppression after lung TPL; 40 (57%) and 26 (37%) patients continued cyclosporine or tacrolimus respectively after mTOR

Table 4 CKD KDIGO stage at mTOR inhibitor introduction

Stage	N (%)	Cumulative (%)
1	11 (15.7)	15.7
2	28 (40.0)	55.7
3a	14 (20.0)	75.7
3b	10 (14.3)	90.0
4	6 (8.6)	98.6
5	1 (1.4)	100.0
Total	70 (100.0)	–

CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Global Outcomes; mTOR, mammalian target of rapamycin.

Table 5 CKD KDIGO stage at second mTOR inhibitor introduction

Stage	N (%)	Cumulative (%)
NA	60 (85.7)	85.7
1	1 (1.4)	87.1
2	2 (2.9)	90.0
3a	2 (2.9)	92.9
3b	3 (4.3)	97.1
4	2 (2.9)	100.0
Total	70 (100.0)	–

CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Global Outcomes; mTOR, mammalian target of rapamycin; NA, not applicable (no renal failure).

inhibitor introduction. Four patients (6%) were switched from cyclosporine to tacrolimus. Cyclosporine was our first choice CNI until end of 2022 because it was the first CNI to be introduced, the longstanding experience with it even in the context of polymedication, and we were satisfied with the results obtained (12).

Antimetabolites consisted of mycophenolate mofetil (CellCept®) or mycophenolic acid (Myfortic®), and only a few patients were treated with azathioprine (n=2) at the time of mTOR inhibitor introduction. Azathioprine was the first antimetabolite used from 1992 to 1998 after which it was replaced by mycophenolate mofetil which continues to be the antimetabolite of choice. mTOR inhibitor introduction allowed cessation of antimetabolites in 40 patients (57%; 19 mycophenolate mofetil and 21 mycophenolic acid). Antimetabolites were continued in 17 patients (24%). In 12 patients (17%), antimetabolites were stopped or withheld before mTOR inhibitor introduction (e.g., due to documented cytopenia).

Lung allograft function

The majority of patients had CLAD, and a very small number had clinical or subclinical antibody-mediated rejection or acute lung allograft dysfunction (*Table 3*).

Kidney function and mTOR inhibitor

Comorbidities and co-medication concerning kidney function

Twenty-nine patients (41%) received insulin treatment for diabetes mellitus at the initiation of mTOR inhibitor treatment. CF patients had significantly more frequent insulin treatment for diabetes mellitus 24/32 (75%, P<0.001). Co-medication with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) was administered to 24 patients (34%) at mTOR inhibitor initiation. In the CF subgroup, renin-angiotensin-aldosterone system (RAAS) blockage was prescribed to 9/31 (29%, P=0.32) of CF patients.

End-stage kidney disease (ESKD) and proteinuria

ESKD occurred in 17 patients (24%) at the end of the follow-up (*Table 3*). Insufficient data on proteinuria were available: Twenty LTR (19%) had protein-positive urine dipsticks a few months before or after mTOR inhibitor introduction. Of these 10/20 had either a trace or a 1+ positive result.

eGFR at mTOR inhibitor initiation

The median baseline eGFR at mTOR initiation was 63.4 (IQR, 44.8–85.7) and 46.9 (IQR, 29.9–74.3) mL/min when administered a second time, respectively. *Tables 4,5* lists the corresponding Kidney Disease Improving Global Outcomes (KDIGO) classification. The KDIGO stages did not significantly differ between patients with CF and others (P=0.10).

Association of eGFR-decline before and after mTOR initiation

The distribution of the observations [n=1,465; median 19 (IQR, 16–25) observations per interval] over time reflects the predefined time points predominantly around mTOR inhibitor introduction (see statistical feature, kernel density estimates are shown in Figure S1).

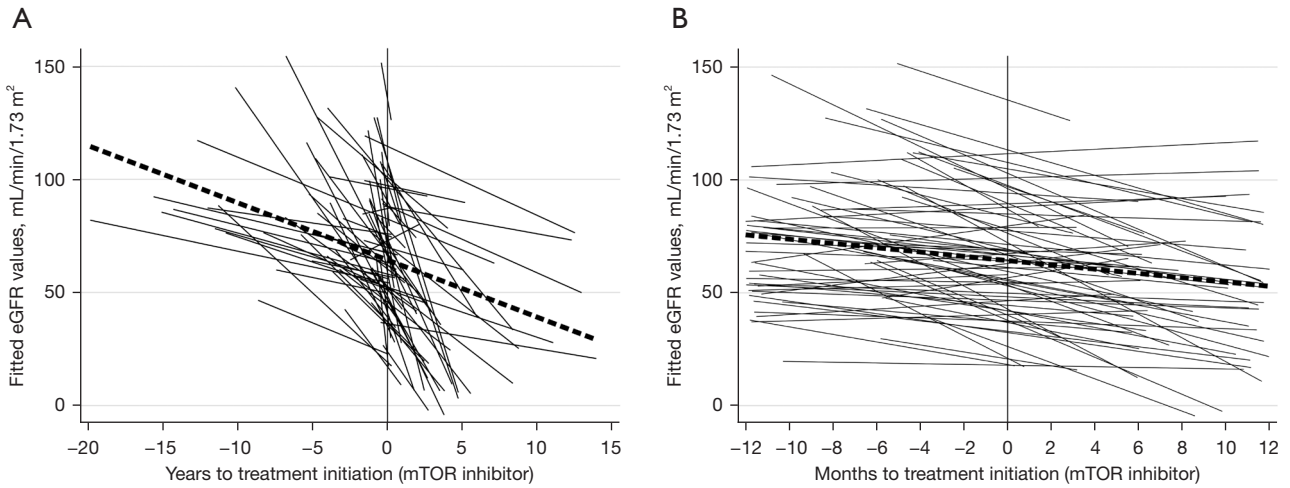

Figure 1 eGFR changes for all 80 intervals (individual linear regression slopes) for (A) the whole group and (B) truncated to –/+ 12 months. eGFR, estimated glomerular filtration rate; mTOR, mammalian target of rapamycin; –/+, before and after.

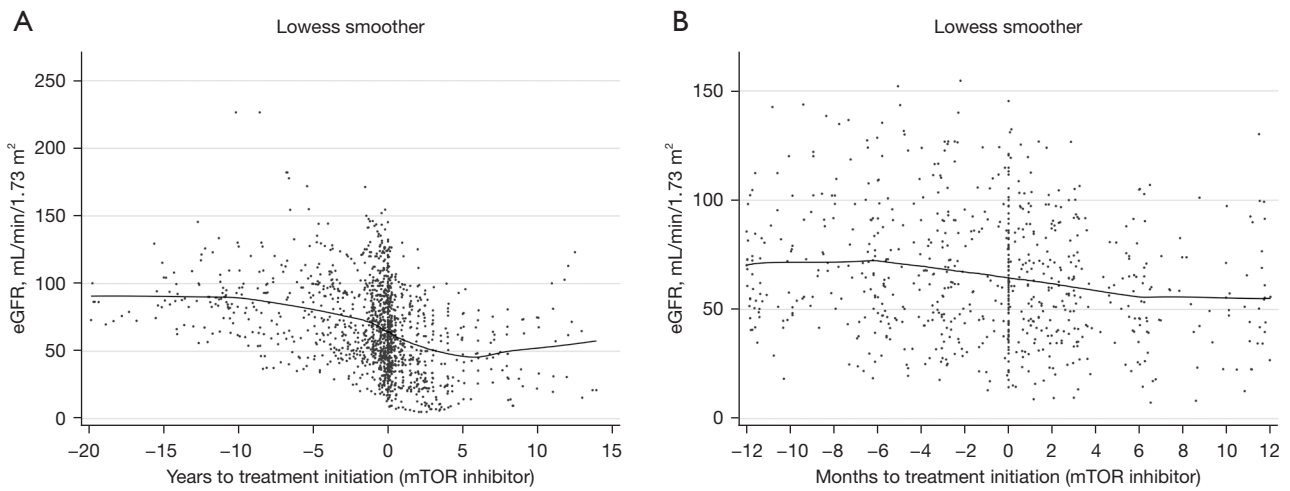

Figure 2 Locally weighted scatter-plots (bandwidth =0.8) from all observations (n=1,465) combined from the predicted values from the linear regression and the use of the tricube weighting function for (A) the whole group and (B) truncated to –/+ 12 months. eGFR, estimated glomerular filtration rate; mTOR, mammalian target of rapamycin; –/+, before and after.

The primary outcome for all data

The individual linear regression slopes (Mitch curves) over the entire follow-up period are shown in *Figure 1*. *Figure 2* shows the locally weighted scatter plots combined with the predicted values from the linear regression. Over the whole follow-up period we observed a declining eGFR slope {overall –6.30 mL/min/1.73 m^2/year [95% confidence interval (CI): –7.87 to –4.73]} before initiation of an mTOR inhibitor, whereas, under treatment, an increase in eGFR was observed [average increase of 3.46 mL/min/1.73 m^2/year (95% CI: 0.91 to 3.78; P<0.001)]. This finding was confirmed after truncating for –/+12 months (722 observations in 70 subjects): the mean annual eGFR decline differs significantly with –16.19 mL/min/1.73 m^2/year (95% CI: –22.27 to –10.11) before and –6.16 mL/min/1.73 m^2/year (95% CI: –13.37 to 1.05; level 0.05; P=0.009) after mTOR initiation. This main finding is shown in the dynamic difference-in-differences graph (*Figure 3*).

The estimated variance of annual eGFR decline is 27, indicating substantial variability from patient to patient

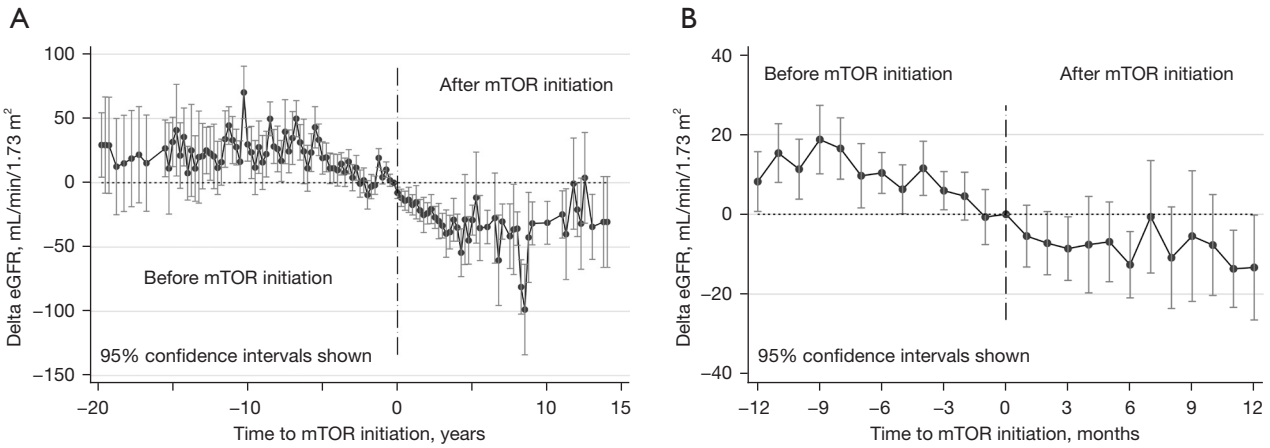

Figure 3 Dynamic difference-in-differences graph (two-way fixed effects event study regressions) on (A) the whole group (rounded for quarters) and (B) truncated to –/+ 12 months (rounded for months). eGFR, estimated glomerular filtration rate; mTOR, mammalian target of rapamycin; –/+, before and after.

Table 6 Estimated regression coefficients (mixed-effects model) for a multivariable analysis and standard errors for the eGFR

Parameters	Estimate	Standard error	Z	P value
Intercept for eGFR (mL/min/1.73 m^2)	83.81	12.49	6.71	<0.001
Time (change per year)	−16.19	3.11	−5.22	<0.001
mTOR inhibitor (0= no, 1= yes)	−1.59	1.55	−1.03	0.30
Annual eGFR change × mTOR inhibitor	10.03	3.83	2.62	0.009
Time since lung TPL (years)	−0.02	0.01	−5.82	<0.001
Sex (0= female, 1= male)	−0.98	6.97	−0.14	0.89
Baseline eGFR (mL/min/1.73 m^2)	−0.43	0.13	−0.34	0.74
RAAS drug (0= no, 1= yes)	−5.04	7.17	−0.70	0.48
Insulin (0= no, 1= yes)	0.12	8.74	0.01	0.99
Reason for lung TPL (ref = COPD)				
CF	−4.31	10.73	−0.4	0.69
Other reason	−9.28	9.21	−1.01	0.31

eGFR (mL/min/1.73 m^2) was calculated using the CKD-EPI formula for 70 patients (722 observations). eGFR, estimated glomerular filtration rate; mTOR, mammalian target of rapamycin; TPL, transplantation; RAAS, renin-angiotensin-aldosterone system; ref, reference; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

in rates of eGFR slope during the observation period (i.e., 95% of patients had annual changes in eGFR slopes between +3.38 and −16.48 mL/min/1.73 m^2). In the multivariable analysis (*Table 6*), approximately 30% of the variability could be explained by the variable "years after TPL". Baseline eGFR, as well as other parameters in *Table 6*, were not significantly related to change in eGFR after mTOR inhibitor introduction.

Discussion

In this retrospective study of mTOR inhibitor use in LTR, stabilization of kidney function was shown by a significantly slower eGFR decline after mTOR inhibitor initiation, as documented by comparison of Mitch curves of each individual calculated for 12 months before and after mTOR inhibitor introduction. In addition, multivariable analysis

suggested that earlier mTOR inhibitor introduction was associated with better kidney outcomes. This was observed in a cohort in which the indication for mTOR inhibitors was predominately based on intolerance or adverse events of antimetabolites. The high discontinuation rate of mTOR inhibitors was mainly related to surgery to avoid delayed wound healing.

The majority of patients had a preserved baseline eGFR at mTOR inhibitor introduction with CKD KDIGO stage G1 or 2. In the mixed effects model after truncating the intervals to –/+12 months the mean annual eGFR decline before and after mTOR initiation was –16.19 (95% CI: –22.27 to –10.11) and –6.16 mL/min/1.73 m^2/year (95% CI -13.37 to 1.05) (P=0.009), respectively. Looking at the overall follow-up period, the trend toward kidney function stabilization persists. Although this retrospective study cannot establish causality, the observed improvement in kidney function suggests a potential nephroprotective benefit of mTOR inhibitors. This finding is in line with the results of Gottlieb *et al.* (9), who compared patients with mild to moderate kidney impairment randomly assigned to EVL-based quadruple therapy *vs.* standard triple therapy after lung TPL and found significantly improved kidney function after 12 months. Furthermore, the NOCTET trial showed the nephroprotective potential of mTOR inhibitor use in LTR 12 and 24 months after EVL introduction in combination with reduced CNI dosing (7,8,10). However, in 163 of the initial 282 LTR enrolled in the NOCTET trial, 5 years after EVL introduction the effect on kidney function was neutralized compared to controls (15).

A better kidney outcome with earlier initiation is consistent with previous research, which has prompted recommendations to begin mTOR inhibitor therapy no later than 5 years after TPL (16). Lower CNI exposure may pathophysiologically explain the benefits of early mTOR inhibitor initiation.

Kidney disease is an uncommon indication for mTOR inhibitor administration in our setting, which makes the stabilization of kidney function a side effect of mTOR inhibitor administration in most cases. Unexpectedly, the indication for mTOR inhibitors is predominately based on intolerance or adverse events of antimetabolites.

High mTOR inhibitor discontinuation rates of 50–71% are well known and correlate with target drug levels and measured drug levels in other studies (6,11,17-19). The high discontinuation rate in this study was related to imminent or performed surgery in many cases. Wound healing problems are a concern in the context of mTOR inhibitors (20). Therefore, in clinical practice, mTOR inhibitors are often discontinued for prevention, and only in a minority of 8 (11%) patients, symptomatic adverse events due to mTOR inhibitors were suspected.

Sixty-six patients (94%) continued CNI with reduced target levels after mTOR inhibitor introduction, whereas others switched between agents. Reduction in CNI is assumed to be the key to diminishing nephrotoxicity and has been documented in several previous studies (7-11,15,17,19,21-24). In our cohort, the lowest drug levels were sought but were not analyzed in detail. Notably, CNI minimization appears to be more favorable than CNI elimination in terms of survival, according to a recent study (25).

Acute and chronic rejection are common problems after lung TPL. The high prevalence of BOS and poor survival was described by Kulkarni *et al.* (26) in 2019, who found that only 40% of bilateral lung TPL recipients remained alive and free from BOS 5 years after TPL. In our cohort, 46/70 patients (66%) had acute lung allograft dysfunction or CLAD during follow-up, of whom 29/70 (41%) had CLAD BOS. According to a recent study by Ivulich *et al.* (27), EVL introduction did not increase the risk of death or the progression to CLAD compared to CNI-based immunosuppression.

The retrospective study design has apparent limitations, mainly missing data and a potential selection bias introduced by the treating physician. Overall, mTOR inhibitors are used only in a small proportion of LTR and mainly in recent years. In our cohort almost half of LTR had CF. Even if the change in eGFR was comparable to that of patients with other reasons for lung TPL according to the multivariable analysis, younger age and specific comorbidities are particular in this subgroup. The CF subgroup in international cohorts is smaller accounting for around 15% of lung TPL (28).

Assessing kidney function is challenging due to many confounders, we carefully selected data reflecting steady states of eGFR to increase reliability. There is a relevant deterioration in kidney function in the months around the modification of the immunosuppressive regimen, possibly due to confounders that were not covered by our analysis. LTR are highly vulnerable to acute and chronic kidney dysfunction due to polypharmacy and comorbidities, such as diabetes mellitus, arterial hypertension, and atherosclerosis.

These confounders were minimized by close follow-

up and the consequent management of comorbidities and medications. This approach is implemented by our team and is considered key for the long-term preservation of kidney function. Detailed medical data and consistent follow-up are the strengths of this study and allowed manual selection of eGFR values to reflect steady states, rather than eGFR values, during acute health problems such as infection. The reliability of the indication and discontinuation information was supported by the two investigators.

Detailed information on drug levels before and after mTOR inhibitor initiation is essential for understanding nephrotoxic effects. Furthermore, they are assumed to be of concern for discontinuation rates and should be addressed in further studies. To date, nephroprotective drugs such as SGLT2 inhibitors or non-steroidal mineralocorticoid antagonists (i.e., finerenone and esaxerenone) have not been administered in this cohort and need to be explored in future trials. For the preservation of kidney function, more prospective studies are needed to establish a clearer recommendation of mTOR inhibitors. Clearly defined indication criteria, including baseline GFR and proteinuria, defined drug target levels, and a systematic approach to deal with mTOR inhibitor adverse effects, could help clinicians to further optimize immunosuppressive regimens after lung TPL.

Conclusions

In conclusion, this study provides an overview of a real-life experience with a particular focus on kidney function in LTR treated with mTOR inhibitors. We found stabilization of kidney function with a slower eGFR decline after mTOR inhibitor initiation when comparing the Mitch curves of each individual before and after mTOR inhibitor introduction in patients who mainly received mTOR inhibitors due to antimetabolite adverse events or intolerance. High discontinuation rates were observed and led to a limited duration of mTOR inhibitor administration; however, discontinuation was predominantly related to surgical interventions to avoid wound healing problems and not caused by experienced mTOR inhibitor adverse events.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1623/coif). R.H. participated as symposium presenter at Lunge Zürich, further, and he has presented for OM Pharma and Vertex. R.H. is a board member of CMV Board Takeda Pharma. S.U. reports grants or contracts from Swiss National Science Foundation, Swiss Lung Foundation, MSD SA, and Orpha Swiss. Further, she declares consulting fees, payment or honoraria, and support for attending meetings/travel from Janssen SA, Actelion SA, MSD SA, and Orpha Swiss. She participates on a Data Safety Monitoring Board or Advisory Board from Janssen SA, Actelion SA, and MSD SA. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the regional ethics committee of Kanton Zurich (BASEC No. 2022-01015). All patients provided written general informed consent for further use of patient data and samples for research purposes prior to lung TPL.

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Supplementary

Table S1 Serostatus at lung TPL (n=70)

Serostatus	N (%)
CMV r/d	
–/–	22 (31.4)
–/?	1 (1.4)
–/+	14 (20.0)
?/+	1 (1.4)
+/–	11 (15.7)
+/?	7 (10.0)
+/+	14 (20.0)
EBV r/d	
–/–	2 (2.9)
–/?	2 (2.9)
–/+	9 (12.9)
?/–	1 (1.4)
?/?	1 (1.4)
?/+	2 (2.9)
+/–	3 (4.3)
+/?	16 (22.9)
+/+	34 (48.6)
Toxoplasmosis r/d	
–/–	11 (15.7)
–/?	12 (17.1)
–/+	12 (17.1)
?/ –	3 (4.3)
?/?	3 (4.3)
?/+	2 (2.9)
+/–	9 (12.9)
+/?	12 (17.1)
+/+	5 (7.1)
+/border-line	1 (1.4)

TPL, transplantation; CMV, cytomegalovirus; r, recipient; d, donor; –, negative; ?, unknown; +, positive; EBV, Epstein-Barr virus.

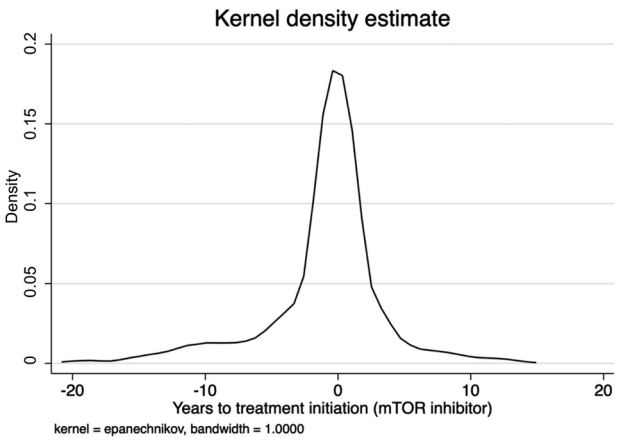

Figure S1 Epanechnikov kernel density estimate on observations before and after treatment initiation. mTOR, mammalian target of rapamycin.

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