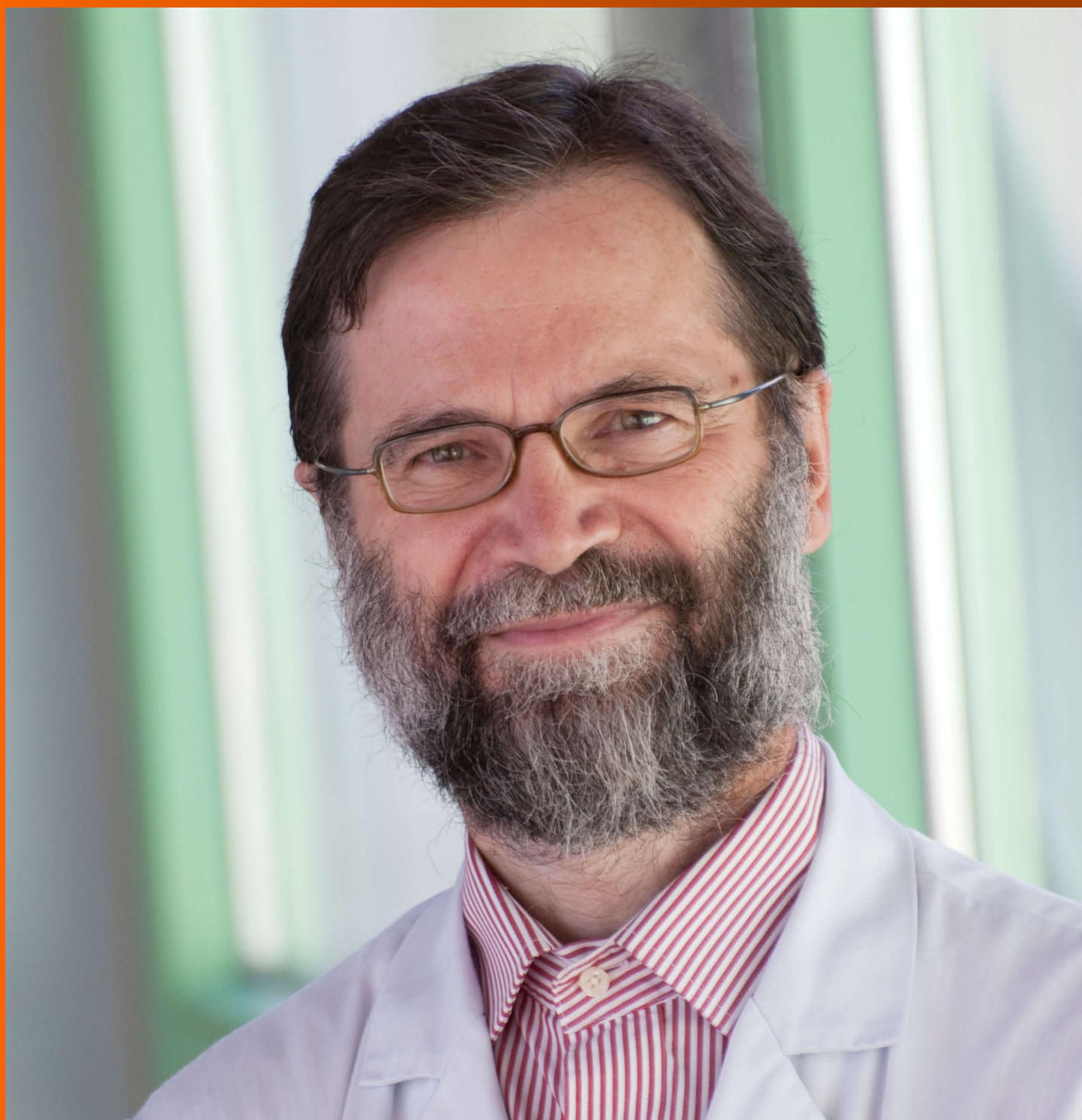


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# Systemic meta-analysis assessing the short term applicability of early conversion to mammalian target of rapamycin inhibitors in kidney transplant

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**Author contributions:** Kumar J and Halawa A designed study; Kumar J and Reccia I collected data; Kumar J, Reccia I, Kusano T and Julie BM analyzed data; Kumar J, Sharma A and Halawa A wrote paper.

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## Abstract

### AIM

To consolidate the present evidence of effectiveness in renal functioning and graft survival following early introduction of mammalian target of rapamycin (mTOR) inhibitors with or without calcineurin inhibitors (CNIs) in renal transplant recipients.

### METHODS

We analysed the current literature following PROSPERO approval describing the role of immunosuppressive agent, mTOR inhibitors as an alternative to CNI within six months of renal transplant by searching the PubMed, EMBASE, Cochrane, Crossref, and Scopus using MeSH terms.

### RESULTS

Six articles of early withdrawal of CNI and introduction of mTOR-inhibitors within six months of renal transplantation were sought. Glomerular filtration rate (GFR) and serum creatinine were significantly better in mTOR inhibitor group with equivalent survival at 12 mo, even though Biopsy Proven Acute rejection was significantly higher in mTOR-inhibitor group.

### CONCLUSION

The evidence reviewed in this meta-analysis suggests



that early introduction mTOR-inhibitors substantial CNI minimization. The mTOR inhibitors such as everolimus and sirolimus, due to their complementary mechanism of action and favourable nephrotoxicity profile; better glomerular filtration, lower serum creatinine with equivalent survival. Having said that, due to the higher rejection rate, may influence the use of these regimens to patients with moderate to high immunological risk patients.

**Key words:** Adverse events; Calcineurin inhibitors; Graft failure; Kidney transplantation; Mammalian target of rapamycin inhibitors

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**Core tip:** Early calcineurin inhibitor withdrawal seems to be more pragmatic approach as it bestows better renal functioning in the low immunological risk renal transplant recipients.

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## INTRODUCTION

Inventions in medical science enhance life which has been realized in the concept of kidney transplantation and add significant amount of productive years to the patients of chronic kidney disease<sup>[1]</sup>. The calcineurin inhibitors (CNIs), cyclosporine A (CsA) and tacrolimus (Tac) were instituted in clinical practice in 1980's. and established themselves as an effective immunosuppressive agent with more than 90% one-year graft survival whilst maintaining a rejection rate of less than 20%<sup>[2]</sup>. Anyhow, the superlative results of short-term allograft survival have not been maintained for long that could be because of slow, steady decline in renal functioning as, eGFR reduced to below 50% in a span of ten years<sup>[3]</sup>. Studies have reported chronic allograft nephropathy as the most common cause of late graft loss in 40% kidney transplant patients, whilst the mortality incidence with delayed functioning graft (DFG) was reported in 43% cases. The cardiovascular diseases and malignancies are considered as the most important causes of DFG in transplant patients<sup>[4]</sup>.

The CNI induced nephrotoxicity is considered as an important cause of long-term graft failure in 96.8% of allograft biopsies by virtue of increased production of vasoconstrictors, such as thromboxane and endothelin, together with decreasing the turn-out of vasodilators, such as nitric oxide, prostaglandin E2, and

prostacyclin<sup>[5,6]</sup>. Nankivell *et al*<sup>[7]</sup> (2004) outlined that more than 50% of kidney allograft biopsies unveiled attestation of chronic CNI toxicity following ten years transplant as 79.2%-100% exhibit histological alterations as tubular atrophy, nodular arteriolar hyalinosis, tubular vacuolization, luminal narrowing, interstitial fibrosis, focal or global segmental sclerosis and micro-calcifications. Surprisingly, the reward of minimal early acute rejection has not been translated into any long term benefits. In addition, CNIs have been associated with development of various cardiovascular risk factors such as hyperlipidemia, hypertension, and new onset diabetes mellitus after transplantation<sup>[8,9]</sup>.

However, the biggest challenge with immunosuppression therapy is to maintain the balance of immunosuppression need in order to avert any rejection episode whilst keeping the check on the toxicities. The recent introduction of better and more efficient non-nephrotoxic immunosuppressive agents such as the mammalian target of rapamycin (mTOR) inhibitors, sirolimus (SRL) and everolimus (EVR), with mechanism of action similar to that of CNIs, forms the basis of use of these drugs<sup>[10,11]</sup>.

CNIs as Tacrolimus (Tac) and Cyclosporin A (CsA) attach with the intracellular proteins called FKBP and immunophilins to form complex which blocks the effect of calcineurin which normally potentiates the intracellular processes associated with the activation of T-lymphocytes. This causes decreased production of interleukin-2 and inhibit the proliferation of T-cells<sup>[12,13]</sup>.

In the similar manner mTOR inhibitors as SRL and EVR form a complex with FKBP to reduces T-cell activation by blocking growth-factor-mediated cell proliferation in the response to an alloantigen<sup>[14-17]</sup>. The distinct immunological properties with and limited nephrotoxic potential of mTOR-inhibitors have prevailed clinicians to use them as a surrogate to CNIs in renal transplantation<sup>[18-21]</sup>.

The main aim of this review is to focus on the short term benefit early conversion to mTOR-inhibitors with or without CNI in renal transplant recipients in terms of graft functioning and graft survival.

## MATERIALS AND METHODS

This meta-analysis was performed following registration in PROSPERO an international database of prospectively registered systematic reviews (CRD42017054458). An extensive search of all the published literature on the role of early conversion to mTOR inhibitors as an alternative to CNI has been made on National Library of Medicine Database (PubMed), EMBASE, Cochrane, Crossref, and Scopus databases on 30<sup>th</sup> August 2016. The search covered the period 2001 (the year of the first reported early CsA withdrawal with sirolimus in the literature) to September 30<sup>th</sup>, 2016<sup>[22]</sup>. The following medical subject headings (MeSH) terms: "Adverse events", "calcineurin inhibitors", "cyclosporin",

**Table 1** Criteria for the inclusion of early mammalian target of rapamycin inhibitor conversion studies

Study design	Prospective cohort design with a well-defined study population
Study group	Post renal transplant
Conversion time	Period of 2 wk to 6 mo post-transplant
Study size	> 30 patients
Length of follow-up	Any
Source	Peer-reviewed journals
Language	English
Outcome measure	Patient safety, exposure-response relationships, adverse events, and graft functioning and long-term survival

"everolimus", "graft rejection", "graft survival", "kidney transplantation", "mTOR inhibitors", "sirolimus", "tacrolimus" were searched.

### Study selection methodology

The original English literature articles published between 2001-September 2016 were included. Only studies which systematically and quantitatively assessed the graft functioning and graft survival of more than or equal to 12 mo following early conversion to mTORI with or without CNI in different randomised clinical studies were analysed. All kind of comparative studies, retrospective and prospective were included. We have excluded publications as editorials, reviews and letters (Table 1).

### Data extraction

Two separate physician reviewers Kumar J, Reccia I reviewed all the articles. Disagreements were resolved through discussion, whilst in scenarios were consensus could not be achieved were resolved by a third author (Ahmed Halawa). We have analysed all papers with empirical studies using a standardised quality assessment tool and pre-specified inclusion and exclusion criteria. The present meta-analysis was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines and registered in PROSPERO an international database of prospectively registered systematic reviews (Figure 1).

### Statistical analysis

The QUADAS-II (quality assessment of diagnostic accuracy studies-II) based analysis was done to assess the internal validity of pre-specified inclusion and exclusion criteria of the various studies. QUADAS-2 is an evidence-based bias assessment tool to evaluate the quality of diagnostic accuracy studies in a systematic review.

A total of six peer-reviewed multi-institutional studies were included in the present meta-analysis. We reviewed each study comprehensively, and data were extracted for the outcomes such as patient safety, exposure-response relationships, adverse events, and various shortcomings or weaknesses to improve the

graft functioning and long-term survival (Table 2).

Review Manager (RevMan) Version 5.3 was used to analyse continuous and dichotomous trial data when at least two trials reported. Odds ratios (OR) for dichotomous outcomes, mean difference (MD) for continuous outcomes including a 95%CI, heterogeneity between the trials was measured using the statistic with > 30% considered as significant. The random effects model was used in cases of significant heterogeneity by visualizing the forest plot of involved trials.

## RESULTS

The initial search yielded a total of 112 manuscripts. After careful evaluation, 98 articles were excluded on basis period of introduction was not within six months of transplantation. Eventually, a total of six articles matched the previously described inclusion criteria, *i.e.*, ZEUS trial (2011), CENTRAL trial (2012), CONCEPT trial (2009), SMART trial (2010), Spare the Nephron trial (2010)<sup>[23-27]</sup> and Heilman *et al.*<sup>[28]</sup> (2011) (Table 2). The comprehensive data of all these studies summarizing the renal functioning, Biopsy Proven Acute rejection (BPAR), survival and adverse events were included in Table 3, below we have further analyzed these studies in the time frame of 12 mo following transplantation.

### Renal function

The 12 mo estimated renal function (eGFR) was significantly better in the mTOR inhibitor group compared to CNI group (six trials, 1257 patients, mean difference 5.24 mL/min per 1.73 m<sup>2</sup>, 95%CI: 2.18 to 8.29, *P* = 0.00, *I*<sup>2</sup> = 70%) (Figure 2). Similarly, the measured serum creatinine was significantly lower in the mTOR inhibitors groups at 12 mo (six trials, 1256 patients, mean difference = -11.59 µmol/L, 95%CI: -20.08 to -3.09, *P* < 0.00, *I*<sup>2</sup> = 73%) (Figure 3).

### BPAR

The incidence of BPAR was significantly higher in mTORs groups compared to CNIs groups (six trials, 1265 patients, OR = 2.11, 95%CI: 1.43 to 3.11, *P* = 0.00, *I*<sup>2</sup> = 3%) at 12 mo (Figure 4).

### Graft survival and adverse events

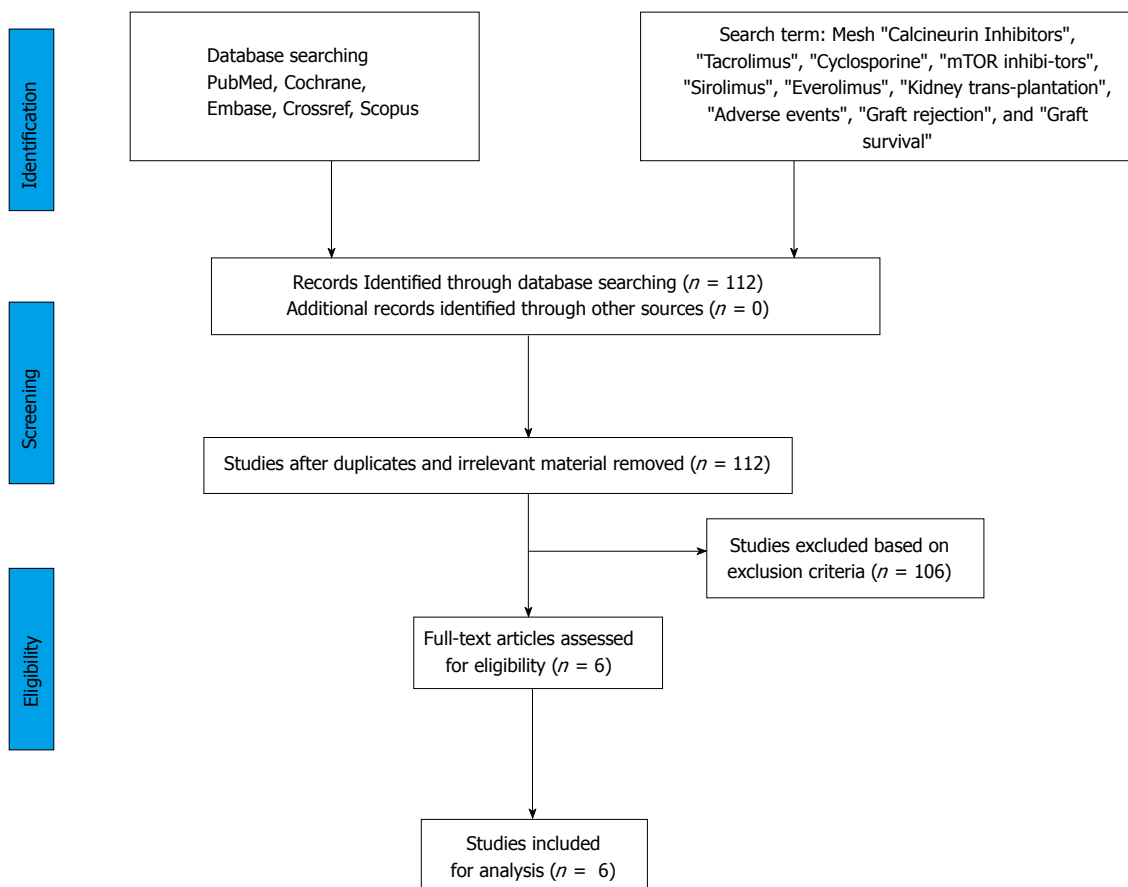
At 12 mo, the rates of graft survival were comparable for mTOR inhibitor group and the CNI groups (Table 3). There was no significant difference in the incidence of serious adverse events/infection between the mTOR inhibitors and CNI groups in majority of studies.

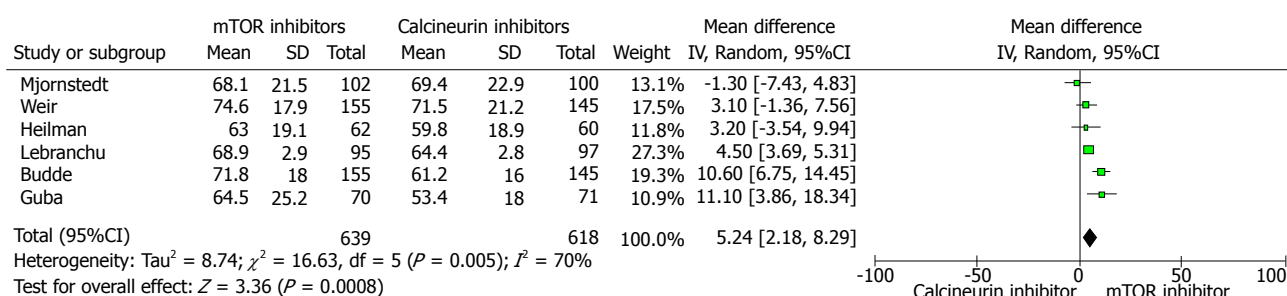
## DISCUSSION

The initiation of mTOR-inhibitors in early post-transplant period is one of the arduous decision taken by clinicians as it should be done following the period of the heightened immunological risk is over, but no evidence of CNI related toxicity evolved<sup>[29,30]</sup>. Various

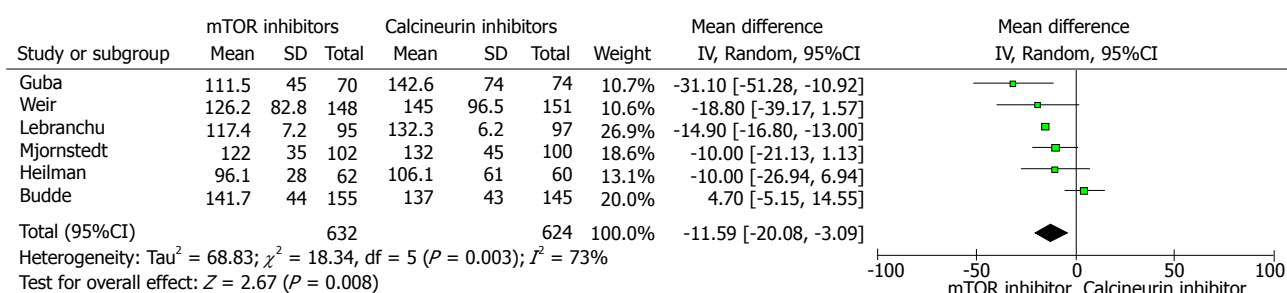
**Table 2 Summary of Different Early Conversion Clinical Trials**

Ref.	Study design	Time of conversion	Group 1	Group 2
<b>Everolimus</b>				
Budde <i>et al</i> <sup>[23]</sup> , 2011 (ZEUS Study)	Multicentre, Prospective, Randomized Study ( <i>n</i> = 300), 12 mo	4.5 <sup>th</sup> month	EVR (C0, 6-10 ng/mL) Induction: Basiliximab ( <i>n</i> = 155)	CsA (C0, 120-180 ng/mL till 4.5-6 mo then decreased to 100-150 ng/mL) Induction: Basiliximab ( <i>n</i> = 145)
Mjörnstedt <i>et al</i> <sup>[24]</sup> , 2012 (CENTRAL trial)	Multicentre, Prospective, Randomized Study, ( <i>n</i> = 269), 12 mo	7 <sup>th</sup> week	EVR (C0, 6-10 ng/mL) + MMF (1.4 g/d till 2 wk then decreased to 1.08 g/d) + S ( <i>n</i> = 92)	Low CsA (C0, 75-200 ng/mL till 2 wk then decreased to 50-150 ng/mL) + MMF (1.4 g/d) + S ( <i>n</i> = 90)
<b>Sirolimus</b>				
Lebranchu <i>et al</i> <sup>[25]</sup> , 2009 (CONCEPT Study)	Multicentre Prospective, Randomized Study, ( <i>n</i> = 193), 12 mo	3 <sup>rd</sup> month	SRL (C0, 8-15 ng/mL till 39 wk then decreased to 5-10 ng/mL) + MMF + S (Induction: Daclizumab) ( <i>n</i> = 95)	CsA (C0, 500-800 ng/mL) + MMF + S (Induction: Daclizumab) ( <i>n</i> = 97)
Guba <i>et al</i> <sup>[26]</sup> , 2010 (SMART Trial)	Multicentre Prospective, Randomized Study, ( <i>n</i> = 140), 12 mo	10-24 <sup>th</sup> day	SRL (C0, 8-12 ng/mL then decreased to 5-10 ng/mL) + MMF (1.5 g/d) + S (Induction: ATG) ( <i>n</i> = 69)	CsA (C0, 150-200 ng/mL then decreased to 100-150 ng/mL) + MMF (2 g/d) + S (Induction: ATG) ( <i>n</i> = 71)
Weir <i>et al</i> <sup>[27]</sup> , 2010 (Spare the Nephron Trial)	Multicentre, Prospective, Randomized Study, ( <i>n</i> = 299), 12 mo	Within 115 d	MMF + SRL ( <i>n</i> = 148)	MMF + CNi ( <i>n</i> = 151)
Heilman <i>et al</i> <sup>[28]</sup> , 2011	Multicentre Prospective, Randomized Study, ( <i>n</i> = 122), 12 mo	1 mo	SRL (C0, 9.8 ± 3.6 ng/mL) + MMF + S (Induction: Basiliximab) ( <i>n</i> = 62)	TAC (C0, 6.9 ± 4.6 ng/mL) + MMF + S (Induction: Basiliximab) ( <i>n</i> = 60)

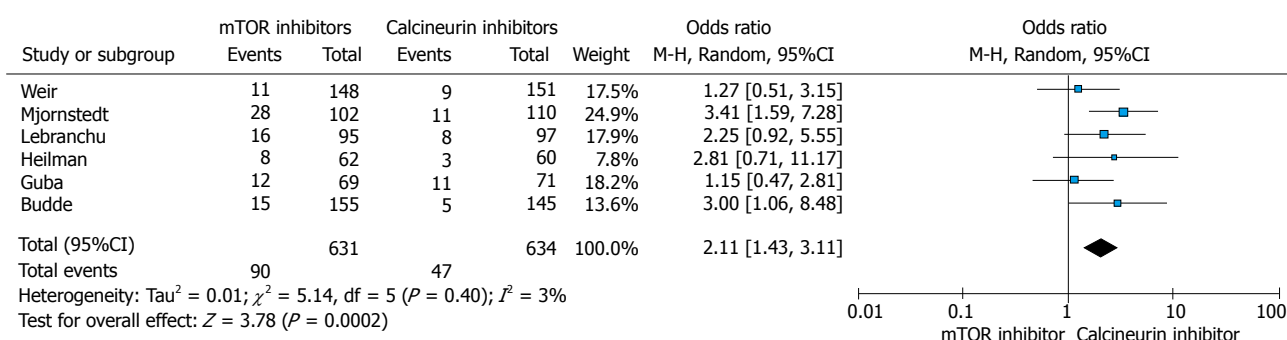
**Figure 1 Search strategy and study selection used in this systematic review as per PRISMA protocol.**



**Figure 2** Forest plot represents the glomerular filtration rate at 12 mo in kidney transplant recipients when treated with mammalian target of rapamycin inhibitor or calcineurin inhibitor therapy. Squares represent size effects of studies, comparing the weight of the study in the meta-analysis. The diamond summary effect shows significant favour towards mTOR inhibitors. 95%CI's represented in horizontal bars. mTOR: Mammalian target of rapamycin.



**Figure 3** Forest plot represents the serum creatinine at 12 mo in kidney transplant recipients when treated with mammalian target of rapamycin inhibitor or calcineurin inhibitor therapy. Squares represent size effects of studies, comparing the weight of the study in the meta-analysis. The diamond shows summary effect towards mTOR inhibitors with 95%CI's represented in horizontal bars. mTOR: Mammalian target of rapamycin.



**Figure 4** Forest plot represents the biopsy proven acute rejection at 12 mo in kidney transplant recipients when treated with mammalian target of rapamycin inhibitor or calcineurin inhibitor therapy. Squares represent size effects of studies, comparing the weight of the study in the meta-analysis. The meta-analysis significantly favours CNI, with 95%CI's represented in horizontal bars. CNI: Calcineurin inhibitor.

CNI free or reduced dosing regimens have been tried to minimize nephrotoxic adverse effect. The peril of increased risk of rejection with the denovo use of CNI free protocols, has been pared down with the early introduction mTOR inhibitors. However, data regarding optimal transmutation time to mTOR inhibitor based immunosuppression is not clear. Though, the present literatures support the notion of early conversion to mTOR inhibitors within the six months of transplant whereas the reward of conversion after month 6 is not that encouraging. The major hindrance in the expected outcome following late conversion might be because the CNI related nephrotoxicity has already settled in<sup>[23,25]</sup>.

In the present rationale, mTOR inhibitors should be introduced within a period of 2 wk to 6 mo, *i.e.*, following the period of increased risk for rejection and

wound infection has been over.

In a ZEUS study, which was multicenter randomised trial done by Budde *et al.*<sup>[23]</sup> (2011) considered early conversion from CsA to everolimus at 4.5 mo after renal transplantation. Two hundred and sixty-nine patients were randomised into two groups the first group received everolimus with MMF, while another group was maintained on gradually tapered lower dose of CsA with MMF. The group has reported a statistically significant improvement in renal functioning, *i.e.*, eGFR for the everolimus group ( $71.8 \pm 18$  mL/min vs  $61.2 \pm 16$  mL/min;  $P = 0.000$ ), at 12 mo while, BPAR was a higher in the everolimus group (13.9% vs 7.5%,  $P = 0.09$ ). Nevertheless, they heralded no difference in terms of graft and patient survival<sup>[23]</sup>.

In a CENTRAL trial by Mjornstedt *et al.*<sup>[24]</sup> (2012)



**Table 3 Summary of outcomes in Different Early Conversion Clinical Trials**

Ref.	Renal function (Gp1 vs Gp 2)	BPAR (Gp1 vs Gp 2)	Adverse event (Gp1 vs Gp 2)	Remarks
<b>Everolimus</b>				
Budde <i>et al</i> <sup>[23]</sup> , 2011, (ZEUS Study)	12 mo Sr. Cr: 141.7 ± 44 µmol/L vs 137.0 ± 43 µmol/L ( <i>P</i> = NS) eGFR: 71.8 ± 18 mL/min vs 61.2 ± 16 mL/min ( <i>P</i> = 0.000)	9.7% vs 3.4% ( <i>P</i> = 0.03)	SAE/Infection: 61% vs 59% ( <i>P</i> = NS) UTI: 57.0% vs 53% ( <i>P</i> = NS) Diarrhoea: 36% vs 27% ( <i>P</i> = NS) HPL: 14% vs 10% ( <i>P</i> = NS)	Graft survival: 100% vs 100% ( <i>P</i> = NS) Patient survival 100% vs 99% ( <i>P</i> = NS)
Mjornstedt <i>et al</i> <sup>[24]</sup> , 2012 (CENTRAL trial)	12 mo Sr. Cr: 122.0 ± 35 µmol/L vs 132.0 ± 45 µmol/L ( <i>P</i> = NS) eGFR: 68.1 ± 21.5 mL/min vs 69.4 ± 22.9 mL/min ( <i>P</i> = NS)	27.5% vs 11.0% ( <i>P</i> = 0.004)	SAE/Infection: 53.9% vs 38.0% ( <i>P</i> = 0.025) CMV infection: 8.8% vs 13.0% ( <i>P</i> = NS) Edema: 29.4% vs 21.0% ( <i>P</i> = NS) Anaemia: 16.7% vs 6.0% ( <i>P</i> = 0.02) HPL: 12.7% vs 9.0% ( <i>P</i> = NS) Proteinuria: 4.9% vs 0% ( <i>P</i> = 0.06) Acne: 12.7% vs 2.0% ( <i>P</i> = 0.006) Mouth Ulceration: 12.7% vs 2.0% ( <i>P</i> = 0.001)	Graft survival: 100% vs 100% ( <i>P</i> = NS) Patient survival 98% vs 98% ( <i>P</i> = NS)
<b>Sirolimus</b>				
Lebranchu <i>et al</i> <sup>[25]</sup> , 2009 (CONCEPT Study)	12 mo: Sr. Cr: 117.4 µmol/L vs 132.3 µmol/L ( <i>P</i> < 0.001) eGFR: 68.9 mL/min vs 64.4 mL/min ( <i>P</i> = 0.017)	16.8% vs 8.2% ( <i>P</i> = NS)	Peripheral Edema: 28.1% vs 22.6% ( <i>P</i> = NS) SAE/infection: 60% vs 44% ( <i>P</i> = 0.025) Diarrhoea: 30.2% vs 9.2% ( <i>P</i> < 0.001) Dyslipidemia: 5.20% vs 4.12% ( <i>P</i> = NS) Proteinuria: 9.3% vs 3.09% ( <i>P</i> = NS) NODAT: 3.1% vs 2.06% ( <i>P</i> = NS) Aphthous Stomatitis: 45.8% vs 5.15% ( <i>P</i> < 0.001) Wound Healing Disorder: 10.1% vs 11.3%, ( <i>P</i> = NS)	Graft Survival: 99% ( <i>P</i> = NS) Patient Survival 97% ( <i>P</i> = NS)
Guba <i>et al</i> <sup>[26]</sup> , 2010, (SMART Trial)	12 mo: Sr Cr: 111.5 ± 45 mg/dL vs 142.6 ± 74 mg/dL ( <i>P</i> = 0.004) eGFR: 64.5 ± 25.2 mL/min vs 53.4 ± 18.0 mL/min ( <i>P</i> = 0.001)	17.4% vs 15.5% ( <i>P</i> = NS)	Infection: 52.2% vs 60.6% ( <i>P</i> = NS) CMV: 7.3% vs 28.2% ( <i>P</i> < 0.001) HPL: 20.3% vs 7.0% ( <i>P</i> = 0.02) Diarrhoea: 13.0% vs 9.9% ( <i>P</i> = NS) Lymphocele: 27.5% vs 23.9% ( <i>P</i> = NS)	Graft Survival: 99% vs 97% ( <i>P</i> = NS) Patient Survival 99% vs 99% ( <i>P</i> = NS)
Weir <i>et al</i> <sup>[27]</sup> , 2010 (Spare the Nephron Trial)	12 mo Sr. Cr: 126.2 ± 82.8 µmol/L vs 145.0 ± 96.5 µmol/L ( <i>P</i> = NS) eGFR: 74.6 ± 17.9 mL/min vs 71.5 ± 21.2 mL/min ( <i>P</i> = 0.06)	7.4% vs 6.0% ( <i>P</i> = NS)	Infection: 16.2% vs 18.3% ( <i>P</i> = NS) HPL: 24.3% vs 10.5% ( <i>P</i> = 0.000) CMV: 4.7% vs 9.2% ( <i>P</i> = NS) Polyoma virus: 2% vs 4% ( <i>P</i> = NS) Diarrhoea: 29.7% vs 9.8% ( <i>P</i> = 0.001) Malignancy: 4.7% vs 6.5% ( <i>P</i> = NS) CMV: 13% vs 13% ( <i>P</i> = NS) Polyoma virus: 2% vs 4% ( <i>P</i> = NS)	Graft Survival: 98% vs 97.4% ( <i>P</i> = NS) Patient Survival 100% vs 98% ( <i>P</i> = NS)
Heilman <i>et al</i> <sup>[28]</sup> , 2011	12 mo Sr. Cr: 96.1 ± 28 µmol/L vs 106.1 ± 61 µmol/L ( <i>P</i> = NS) eGFR: 63.0 ± 19.1 mL/min vs 59.8 ± 18.9 mL/min ( <i>P</i> = NS)	13% vs 5% ( <i>P</i> = NS)		NA

eGFR: Estimated renal function; NA: Not Available; Not Significant; NODAT: New-onset diabetes after transplantation; CMV: Acute cytomegalovirus.

they studied the effect of early conversion from CsA to everolimus in the seventh week of the post-transplant. About two hundred and two patients who were randomised to receive intervention group everolimus (C0, 3-8 ng/mL) and were compared with CsA (C0, 75-200 ng/mL for two weeks then reduced, further maintained at 50-150 ng/mL) with oral steroids and MMF. They didn't report significant improvement in GFR in everolimus group (68.1 ± 21.5 mL/min vs 69.4 ± 22.9 mL/min, *P* = NS) at 12 mo, although serum creatinine was lower in mTOR inhibitor group (122.0 ± 35 µmol/L vs 132.0 ± 45 µmol/L, *P* = NS).

Though the reported incidence of BPAR was significantly higher in EVR group than in CsA group (27.5% vs 11.0%, *P* = 0.004), the survival outcomes were similar at 12 mo. The reported side effects as proteinuria, anaemia, hyperlipidemia, acne and mouth ulceration were significantly more frequent in the everolimus group<sup>[24]</sup>.

In the CONCEPT study 2009 by Lebranchu *et al*<sup>[25]</sup>, instituted Sirolimus by replacing CsA in the third month of the post-transplantation. Their literature listed significantly better eGFR (68.9 mL/min vs 64.4 mL/min) and significantly lower serum creatinine (117.4 µmol/L vs 132.3 µmol/L, *P* < 0.001) in the sirolimus group at 12 mo. The detailed BPAR was similar for entire period of observation. The side effects such as diarrhoea, SAE, aphthous stomatitis, proteinuria and new onset diabetes mellitus were either significantly higher or higher in the sirolimus group<sup>[25]</sup>.

Guba *et al*<sup>[26]</sup> (2010) carried out a multicenter randomised SMART trial, to explore the effects of very early conversion to sirolimus from CsA only 10 to 24 d after the renal transplantation. They randomised one hundred and forty-one patients were into two groups to confer sirolimus with MMF and steroid, on the other hand the second group was maintained on gradually tapered lower dose of CsA with MMF and steroid. They

reported statistically significant improvement in renal functioning, eGFR ( $64.5 \pm 25.2$  mL/min vs  $53.4 \pm 18$  mL/min;  $P = 0.001$ ) with significantly reduced serum creatinine ( $111.5 \pm 45$   $\mu$ mol/L vs  $142.6 \pm 74$   $\mu$ mol/L,  $P = 0.004$ ) for the sirolimus group at 12 mo. The detailed incidence of BPAR ( $17.4\%$  vs  $15.5\%$ ,  $P = \text{NS}$ ) was similar in both groups, likewise, the graft and patient survival were quite similar. In addition, the recipients in the sirolimus group reported a significantly higher number of adverse effects such as acne, hyperlipidemia and lower number CMV viremia with the incidence of BPAR was similar in both groups ( $20.2\%$  vs  $19.7\%$ ,  $P = \text{NS}$ )<sup>[26]</sup>.

In Spare the Nephron Trial, Weir *et al.*<sup>[27]</sup> (2010) randomized 299 kidney transplant recipients into two groups following 115 d of the transplant. The first group received sirolimus with MMF while the second group was maintained on CNI and MMF. They reported significant improvement in renal function in terms of higher eGFR ( $74.6 \pm 17.9$  mL/min vs  $71.5 \pm 21.2$  mL/min;  $P = 0.06$ ) and lower serum creatinine ( $126.2 \pm 82.8$   $\mu$ mol/L vs  $145.0 \pm 96.5$   $\mu$ mol/L,  $P = \text{NS}$ ) in the sirolimus group. They delineated the likewise patient and graft survival in both groups. However, patients in the sirolimus group reported a significantly higher number of adverse effects as hyperlipidemia and diarrhoea<sup>[27]</sup>.

In the 2011 study by Heilman *et al.*<sup>[28]</sup>, sirolimus introduced in the first month of the renal transplant. They have given the account of significant improvement in eGFR ( $63.0 \pm 19.1$  mL/min vs  $59.8 \pm 18.9$  mL/min;  $P = \text{NS}$ ) and set out lower serum creatinine in the sirolimus group at 12 mo while the reported BPAR was likewise in both groups<sup>[28]</sup>.

Publication bias is an important point to consider in a meta-analysis because all the researches which take place are not published. Studies with a significant result are more likely to be published. Studies with a significant result are more likely to be placed in a higher impact journal compared to the studies with null results. Moreover, well controlled and properly carried out studies are less likely to achieve significance.

In general, early CNI withdrawal in the wake of mTOR inhibitor based regimen institution seems a more empirical and constructive approach towards immunosuppressive management of renal transplant recipients. Nonetheless, taking into account of the high rejection rate contemplated in these studies, it will be a judicious decision of not to proffer this therapy to patients with moderate to high immunological risk though additional studies with long duration of follow-up are demanded to confirm present conjecture<sup>[29-33]</sup>.

Despite the fact that the data on the Tac minimization strategies are limited, the present evidence suggest that treatment with mTOR-inhibitors allows early and substantial CNI minimization and provides better renal functioning at the end of first year of transplantation. Thus, it is not judicious to extend these regimens to patients with moderate to high immunological risk.

However, further trials directed towards different ethnicity and geography are needed to determine further evidence.

## COMMENTS

### Background

The aim of this review is to assess the one-year effectiveness of the early introduction of mammalian target of rapamycin (mTOR) inhibitors with or without calcineurin inhibitors (CNIs) within six months of renal transplantation.

### Research frontiers

The current literature was reviewed to assess the role of immunosuppressive agent, mTOR inhibitors as an alternative to CNI within six months of renal transplant in terms of better renal functioning and survival by assessing glomerular filtration rate (GFR), serum creatinine, Biopsy Proven Acute Rejection (BPAR) and survival.

### Innovations and breakthroughs

The major advantages were observed regarding better renal functioning, GFR and serum creatinine were better in mTOR inhibitor group at 12 mo. BPAR was significantly higher in the mTOR-inhibitor group though survival was comparable.

### Application

In general, early CNI withdrawal seems to be a more empirical and constructive approach as it provides better renal functioning in the low immunological risk transplant recipients.

### Peer-review

This study is a systemic review and meta-analysis of the effect on renal function and graft survival following early conversion of CNI to mTOR inhibitors with or without CNI after kidney transplantation. The authors initially selected 112 manuscripts, and of them, only 6 papers were useful for meta-analysis. They conclude that introduction of mTOR-inhibitors allows early and substantial CNI minimization.

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