Outcome After Conversion Of Immunosuppression To mTOR Inhibitors

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- Short- and intermediate-term graft survival has improved with the introduction of calcineurin inhibitors (CNIs) in the 1980s.

- Long term CNI therapy has been identified as an important risk factor in the development of CAN/IFTA .

- In addition to graft-related complications, CNI has been associated with the development of multiple CVD risk factors including hypertension, hyperlipidemia and new onset diabetes after transplantation .

- CNI avoidance, and minimization immunosuppressive regimens have largely been disappointing as they are associated with unacceptably high rates of acute rejection .

Cyclosporine Withdrawal Improves Long-Term Graft Survival in Renal Transplantation

Martin Gallagher,[1,5] Meg Jardine,[1] Vlado Perkovic,[1] Alan Cass,[1] Stephen McDonald,[2] James Petrie,[3] and Josette Eris[4]

Background. The reduction in renal transplant rejection rates achieved over the last 20 years have not translated into a commensurate improvement in long-term graft survival. Cyclosporine has been central to immunosuppressive regimens throughout this period but its effect on long-term transplant outcomes remains unclear.
Methods. This randomized controlled trial allocated first cadaveric renal transplant recipients in seven centers around Australia to three immunosuppressive regimens: azathioprine and prednisolone (AP), long-term cyclosporine alone (Cy), or cyclosporine initiation followed by withdrawal at 3 months and azathioprine and prednisolone replacement (WDL).
Results. Between 1983 and 1986, 489 patients were randomized with 98% follow-up to a median of 20.6 years. Mean graft survival (censoring deaths) was superior in the WDL group (14.8 years) when compared with both AP (12.4 years, $P=0.01$ log-rank test) and Cy (12.5 years, $P=0.01$ log-rank test) groups by intention-to-treat. Without death censoring, graft survival with WDL was superior to AP (9.5 years vs. 6.7 years, $P=0.04$) and of borderline superiority to Cy (9.5 years vs. 8.5 years, $P=0.06$). Patient survival was not different between the three groups. Renal function was superior in AP (at 1, 10, and 15 years posttransplant) and WDL (at 1, 5, 10, 15, and 20 years) groups when compared with Cy.
Conclusion. This study illustrates superior long-term renal transplant survival and preservation of renal function with a protocol using cyclosporine withdrawal. If long-term renal transplant outcomes are to improve, we should reconsider guidelines recommending universal maintenance use of cyclosporine.

Keywords: Kidney transplantation, Cyclosporine, Graft survival.

(*Transplantation* 2009;87: 1877–1883)

Renal transplantation is the preferred treatment for end-stage kidney failure as it delivers superior patient survival

vival (*2*, *3*) making the search for treatments that reduce the burden of late chronic graft loss even more urgent.

mTOR inhibitors

- Randomized controlled trials (RCTs) evaluating the de novo use of low- or high-dose mTORi as replacement for CNIs have failed and is associated with high rates of rejection and/or graft failure.

- Subsequently, multiple RCTs have been undertaken to explore the benefit of delay introduction of mTORi following initial CNI therapy

Early conversion trials

Table 2: Summary of various parameters in different early conversion clinical trials

Authors	Study design	Time of conversion	Group 1	Group 2
A) Everolimus				
Budde, *et al*, 2011, (ZEUS Study) [23]	Multicenter randomized trial (n=300), 12 months, 36 months, 5 years	4.5th month	EVR (C0, 6–10 ng/mL) Induction: Basiliximab (n=155)	CsA (C0, 120–180 ng/mL till 4.5–6 months then decreased to 100–150 ng/mL) Induction: Basiliximab (n=145)
Mjornstedt, *et al*, 2012, (CENTRAL trial) [24]	Multicenter randomized trial (n=269), 5 years	7th week	EVR (C0, 6–10 ng/mL) + MMF (1.4 g/d till 2 weeks then decreased to 1.08 g/d) + S (n=92)	Low CsA (C0, 75–200 ng/mL till 2 weeks then decreased to 50–150 ng/mL) + MMF (1.4 g/d) + S (n=90)
B) Sirolimus				
Lebranchu, *et al*, 2009, (CONCEPT Study) [25]	Multicenter randomized trial (n=193), 12 months, 48 months	3rd month	SRL (C0, 8–15 ng/mL till 39 weeks then decreased to 5–10 ng/ mL) + MMF + S Induction: Daclizumab (n=95)	CsA (C0, 500–800 ng/mL) + MMF + S Induction: Daclizumab (n=97)
Guba, *et al*, 2010, (SMART Trial) [26]	Multicenter randomized trial (n=140), 12 and 36 months	10–24th day	SRL (C0, 8–12 ng/mL then decreased to 5–10 ng/ mL) + MMF (1.5 g/d) + S Induction: ATG (n=69)	CsA (C0, 150–200 ng/mL then decreased to 100–150 ng/ mL) + MMF (2 g/d) + S Induction: ATG (n=71)
Weir, *et al*, 2010, (Spare the Nephron Trial) [27]	Multicenter randomized trial (n=299), 2 years	Within 115 days	MMF + SRL (n=148)	MMF + CNI (n=151)
Heilman, *et al*, 2011 [28]	Multicenter randomized trial (n=122), 24 months	1 month	SRL (C0, 9.8±3.6 ng/mL) + MMF + S Induction: Basiliximab (n=62)	TAC (C0, 6.9±4.6 ng/mL) + MMF + S Induction: Basiliximab (n=60)

Randomized Controlled Trial > Am J Transplant. 2009 May;9(5):1115-23.
doi: 10.1111/j.1600-6143.2009.02615.x.

Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation: concept study

Y Lebranchu [1], A Thierry, O Toupance, P F Westeel, I Etienne, E Thervet, B Moulin, T Frouget, Y Le Meur, D Glotz, A-E Heng, C Onno, M Buchler, S Girardot-Seguin, B Hurault de Ligny

- Two hundred and thirty-five nonimmunized patients transplanted with a deceased donor kidney received induction therapy with daclizumab and tri-therapy with CsA, MMF and steroids for 3 months.
- At 3 months, 192 patients with proteinuria <1 g/day and GFR ≥40 ml/minute were randomized to either continue CsA (n = 97) or to convert to SRL (n = 95). MMF and steroids were planned to be discontinued at month 8.
- The primary endpoint, estimated renal function (creatinine clearance) at 1 year according to the Cockcroft–Gault equation, was significantly better in the SRL group (68.9 vs. 64.4 ml/minute, P = 0.017).
- Similar results were observed when the GFR was calculated according to the Modification of Diet in Renal Disease formula (61.2 vs. 53.9 ml/minute, P = 0.002) or was measured using iohexol (67.3 vs. 60.3 ml/minute, P = 0.004).
- Patient and graft survival were excellent, with no death and only one graft loss, which occurred in the CsA group.

…CONCEPT study

The incidence of BPAR episodes was not significantly higher in the SRL group (17% vs. 8%, P = 0.07), while steroids were withdrawn in 72% and 78% of patients, respectively.

Of note, most episodes of BPAR occurred just after withdrawal of steroids in the SRL group.

The incidence of adverse events (stomatitis, acne, diarrhoea, high triglyceride levels) was slightly increased in the SRL group (60% vs. 44%, P = 0.025) and more patients discontinued SRL (16% vs. 7%).

Interestingly, haemoglobin, cholesterol, and proteinuria were similar in both groups.

The number of patients with proteinuria >0.5 g/ day was also similar in both groups (12% in the SRL group vs. 9% in the CsA group).

Aortic stiff ness and biomarkers of endothelial activation were studied in 44 patients enrolled in the CONCEPT study .

One year after transplantation, the carotid-to-femoral pulse-wave velocity was significantly lower in the SRL group.

Plasma levels of endothelin-1 decreased in the SRL group during the study, suggesting a beneficial effect of SRL in preventing the development of cardiovascular complications after kidney trans plantation.

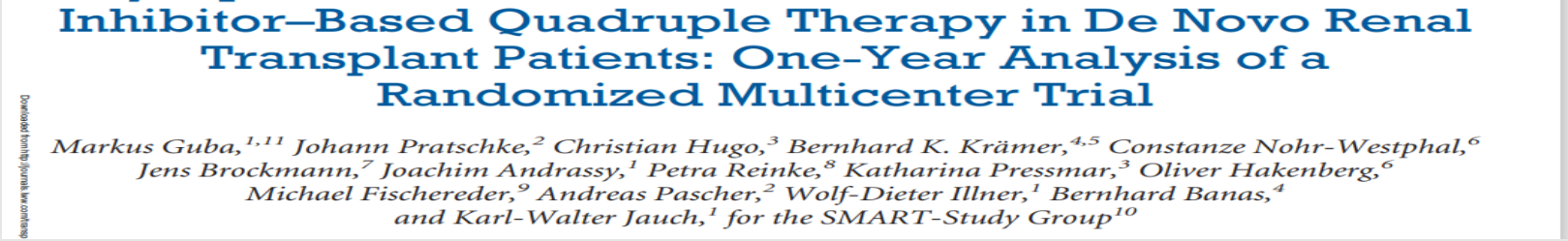
Conversion from CsA to SRL combined with MMF treatment 3 months after transplantation was therefore associated with an improvement in renal function with a good risk to-benefit ratio.

Utilizing the FDA Adverse Event Reporting System (FAERS) database from 2004 to 2018 to perform a retrospective database analysis.

The mTOR inhibitors arm had 1282 reports with 4176 adverse events (AEs), while the tacrolimus arm had a total of 7587 reports with 20 940 individual AEs.

mTOR inhibitors had significantly higher incidences of cardiovascular ,endocrine ,gastrointestinal, musculoskeletal ,pulmonary , renal, and vascular Aes.

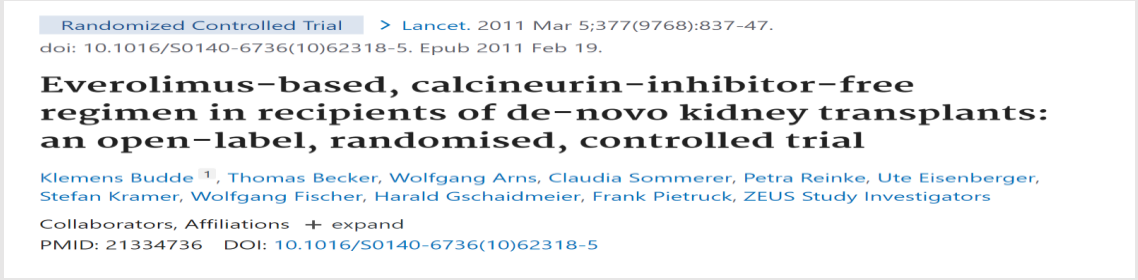
Across every organ type, mTOR inhibitors had greater cardiovascular AEs compared to tacrolimus, specifically in arteriosclerosis, heart failure, hypotension, tachycardia, chest pain, edema, and pericardial disorders.



Inhibitor–Based Quadruple Therapy in De Novo Renal Transplant Patients: One-Year Analysis of a Randomized Multicenter Trial

Markus Guba,[1,11] Johann Pratschke,[2] Christian Hugo,[3] Bernhard K. Krämer,[4,5] Constanze Nohr-Westphal,[6] Jens Brockmann,[7] Joachim Andrassy,[1] Petra Reinke,[8] Katharina Pressmar,[3] Oliver Hakenberg,[6] Michael Fischereder,[9] Andreas Pascher,[2] Wolf-Dieter Illner,[1] Bernhard Banas,[4] and Karl-Walter Jauch,[1] for the SMART-Study Group[10]

- Guba, et al, completed the multicenter randomized SMART trial, by introducing very early conversion to SRL only 10 to 24 days from CsA following the renal transplantation.
- A total of 141 patients were randomized into two groups SRL with MMF and steroid, while the second group was maintained on gradually tapered lower doses of CsA with MMF and steroid.
- They demonstrated statistically significant improvement in renal function, eGFR (64.5±25.2 vs. 53.4±18 mL/min; p=0.001) with significant reduction in serum creatinine (111.5±45 vs. 142.6±74 μmol/L; p=0.004) for the SRL group at 12 months.
- Incidence of BPAR (17.4% vs. 15.5%, p>0.05) was similar in both groups; the graft and patient survival rates were quite similar.
- The recipients in the SRL group reported a significantly higher number of adverse effects such as acne, hyperlipidemia
- CMV viremia was significantly decreased (7.3% vs. 28.2%, p=0.0016).



Randomized Controlled Trial > Lancet. 2011 Mar 5;377(9768):837-47.
doi: 10.1016/S0140-6736(10)62318-5. Epub 2011 Feb 19.

Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial

Klemens Budde [1], Thomas Becker, Wolfgang Arns, Claudia Sommerer, Petra Reinke, Ute Eisenberger, Stefan Kramer, Wolfgang Fischer, Harald Gschaidmeier, Frank Pietruck, ZEUS Study Investigators

Collaborators, Affiliations + expand
PMID: 21334736 DOI: 10.1016/S0140-6736(10)62318-5

- A multicenter randomized trial (ZEUS study) conducted by Budde, et al, reported early conversion to EVR from CsA , 4.5 months after renal transplantation.
- They randomized 269 patients into two groups.
- The first group received EVR with MMF, while another group was maintained on gradually tapered lower doses of CsA with MMF.
- They demonstrated significant improvement in GFR at 12 months following change to EVR (71.8±18 vs. 61.2±16 mL/min; $p<0.001$);
- BPAR was non-significantly higher in the EVR group (13.9% vs. 7.5%; $p=0.09$).
- No difference in terms of graft and patient survival

Lancet 2011;377:837-4

Results of a prospective randomized trial of sirolimus conversion in kidney transplant recipients on early corticosteroid withdrawal

Raymond L Heilman [1], Kerrie Younan, Hani M Wadei, Martin L Mai, Kunam S Reddy, Harini A Chakkera, Thomas A Gonwa

- In the 2011 study by Heilman, et al, SRL was instituted in the first month of the post-transplantation period.
- Sixty patients were randomized to stay on tacrolimus-MMF and 62 to sirolimus-MMF.
- Actual graft survival (including death) at 2 years was 98.4% in the sirolimus group, 96.7% in the tacrolimus group.
- Sixty-three percentage of the patients in the sirolimus group withdrew during the 2-year period of the study compared with 18% of the tacrolimus group (P<0.0001), primarily related to rejection or medication side effects.
- Rejection during the first year occurred in 5% of the tacrolimus group and 13% of the sirolimus group (P=0.15).
- Measured GFR at 1 year (mean±SD) was 57.4±20.7 mL/min/1.73 m in the sirolimus group and 62.7±26.5 mL/min/1.73 m in the tacrolimus group (95% CI of difference -3.7-14.4).
- **They conclude that conversion from tacrolimus-MMF to sirolimus-MMF at 1 month posttransplant in kidney recipients on rapid steroid withdrawal is poorly tolerated and does not improve GFR at 1 year**

Transplantation 2011;92:767- 73

TRANSPLANT INTERNATIONAL

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ORIGINAL ARTICLE

Renal function three years after early conversion from a calcineurin inhibitor to everolimus: results from a randomized trial in kidney transplantation

Lars Mjörnstedt,[1] Søren Schwartz Sørensen,[2] Bengt von zur Mühlen,[3] Bente Jespersen,[4] Jesper M. Hansen,[5] Claus Bistrup,[6] Helene Andersson,[7] Bengt Gustafsson,[1] Dag Solbu[8] and Hallvard Holdaas[9]

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- In 2012, Mjornstedt, et al, did a CENTRAL trial to study the effect of early conversion from CsA to EVR seven weeks post-transplantation.
- Two-hundred and two patients who were randomized into EVR group (C0 , 3–8 ng/mL) and CsA (C0 , 75–200 ng/mL for two weeks then reduced, further maintained at 50–150 ng/ mL) with oral steroids and MMF group.
- **They reported lower serum creatinine in mTOR inhibitor group** (122.0±35 vs. 132.0±45 μmol/L, **p>0.05**)
- There was **no significant change in GFR** in EVR group compared to CsA group (68.1±21.5 vs. 69.4±22.9 mL/min, p>0.05) at 12 months.
- During months 12–36, 13.0% and 11.1% of patients in the everolimus and control groups, respectively, experienced **BPAR** (***P* = 0.720**)
- The **survival outcomes were similar** at 12 months.
- The reported adverse effects as proteinuria, anemia, hyperlipidemia, acne, and mouth ulceration were significantly more common in the EVR group .

Late conversion studies

Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial

Francesco P Schena [1], Michael D Pascoe, Josefina Alberu, Maria del Carmen Rial, Rainer Oberbauer, Daniel C Brennan, Josep M Campistol, Lorraine Racusen, Martin S Polinsky, Robert Goldberg-Alberts, Huihua Li, Joseph Scarola, John F Neylan, Sirolimus CONVERT Trial Study Group

- In the CONVERT study, 830 patients were randomized 6 to 120 months after transplantation (mean 3.1 years) with a 2:1 ratio to either convert to SRL or to continue on a CNI (cyclosporine or tacrolimus) .
- Patients were stratified by baseline GFR: either 20 to 40 ml/minute or >40 ml/minute.
- At 2 years, SRL conversion among patients with baseline GFR more than 40 mL/min was associated with excellent patient and graft survival,
- No difference in BPAR, increased urinary protein excretion
- Lower incidence of malignancy compared with CNI continuation.
- The discontinuation rate was higher in the SRL group at 12 months but not at 24 months ,with more adverse events during the first 6 months after randomization.
- Superior renal function was observed among patients who remained on SRL through 12 to 24 months, particularly in the subgroup of patients with:

baseline GFR more than 40 mL/min and UPr/Cr less than or equal to 0.11.

Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study

Hallvard Holdaas [1], Lionel Rostaing, Daniel Serón, Edward Cole, Jeremy Chapman, Bengt Fellstrøm, Erik H Strom, Alan Jardine, Karsten Midtvedt, Uwe Machein, Bettina Ulbricht, Alexander Karpov, Philip J O'Connell, ASCERTAIN Investigators

In the ASCERTAIN study, 398 patients were randomized to continue CNIs (cyclosporine or tacrolimus), to minimize CNI therapy with the addition of EVL or to convert to EVL.

The mean measured GFR at 24 months, the primary endpoint, was not significantly different between the three groups, while proteinuria was significantly higher in the EVL group at 12 months.

A post-hoc analysis in patients with better baseline graft function (defined by GFR >50 ml/minute) and who remained on the randomized treatment regimen has shown that the **increase in GFR from baseline to month 24 was significantly greater in the CNI elimination group** than in control patients.

Adverse events resulted in discontinuation for 28.3% of patients ($P < 0.001$ vs. CNI-free patients) in the CNI elimination group, for 16.7% of patients in the CNI minimization group ($P = 0.02$ vs. CNI-free patients) and for only 4% of patients who continued on a CNI-based regimen.

The incidence of malignancies was not different

Conversion to everolimus with CNI elimination or minimization a mean of 5.6 years after kidney transplantation had **no overall renal benefit** and was associated with more frequent adverse events and discontinuations.

Patients with Cr Cl more than 50 mL/min may benefit from a change in therapy more than 6 months after renal transplantation.

These data suggest that the renal benefit of a late conversion, 1 year or more after transplantation, is limited, except in patients with good renal function and without proteinuria.

Renal biopsy prior to conversion is useful to select patients without mild to severe chronic renal allograft damage in whom conversion from CNIs to mTOR inhibitors can be accomplished safely and effectively.

SYSTEMIC REVIEWS

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A Systematic Review of Conversion From Calcineurin Inhibitor to Mammalian Target of Rapamycin Inhibitors for Maintenance Immunosuppression in Kidney Transplant Recipients

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This was a systematic review of randomized controlled trials comparing delayed conversion of mammalian target of rapamycin inhibitors (mTORi) for calcineurin

Abbreviations: BPAR, biopsy-proven acute rejection; CAN, chronic allograft nephropathy; CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CVD, cardiovascular disease; df, degree of freedom; DFG, death with functioning graft; IFTA, interstitial fibrosis and tubular atrophy; ITT, intention to treat; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; NODAT, new-onset diabetes after transplantation; OT, on-treatment; RCT, randomized controlled trial; RR, risk ratio; WMD, weighted mean difference

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Introduction

Kidney transplantation confers a significant survival advantage in patients with end-stage kidney disease (1). Although short- and intermediate-term graft survival has improved with the introduction of calcineurin inhibitors (CNIs) in the 1980s, the rate of graft failure beyond 10 years posttrans-

Up to 1 year posttransplant

Patients converted to mTORi showed a significantly higher GFR compared with those remaining on CNIs

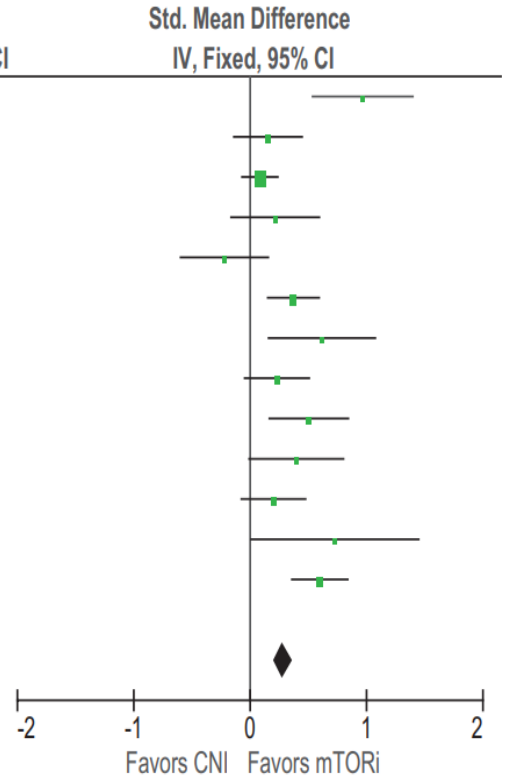
($p < 0.001$).

Table 1A: Mammalian target of rapamycin inhibitor (mTORi) versus calcineurin inhibitor (CNI); mean GFR up to 1 year posttransplant (intention-to-treat analysis)

	mTORi			CNI				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
APOLLO	62.9	3.69	46	59.3	3.69	47	3.4%	0.97 [0.54, 1.40]
Baboolal	37.3	13.6	116	35	16.7	74	7.3%	0.15 [-0.14, 0.45]
CONVERT	59	15.4	497	57.7	15.4	246	26.8%	0.08 [-0.07, 0.24]
ERIC	57.3	18	54	53.4	18	54	4.4%	0.22 [-0.16, 0.59]
Heilman	57.4	20.7	54	62.7	26.5	55	4.4%	-0.22 [-0.60, 0.16]
HERAKLES	69	16.2	163	63	16	159	12.9%	0.37 [0.15, 0.59]
MECANO	55	20	38	44	15	39	3.0%	0.62 [0.16, 1.07]
Mjornstedt	51.2	14.1	102	47.8	15.4	100	8.2%	0.23 [-0.05, 0.51]
SMART	64.5	25.2	69	53.4	18	70	5.5%	0.50 [0.17, 0.84]
SOCRATES	72.3	2.5	49	71.3	2.5	47	3.8%	0.40 [-0.01, 0.80]
Tedesco/Pestana	74.8	25.7	110	70.2	19.1	95	8.3%	0.20 [-0.07, 0.48]
Watson	46.3	14.8	17	31.8	23.6	15	1.2%	0.73 [0.01, 1.45]
ZEUS	7[illegible]8	18.5	143	61.2	16.7	137	10.9%	0.60 [0.36, 0.84]
Total (95% CI)			**1458**			**1138**	**100.0%**	**0.28 [0.21, 0.36]**

Heterogeneity: $Chi^2 = 37.23$, $df = 12$ ($P = 0.0002$); $I^2 = 68\%$

Test for overall effect: $Z = 7.06$ ($P < 0.00001$)



American Journal of Transplantation 2014; 14: 2106–2119 **2109**

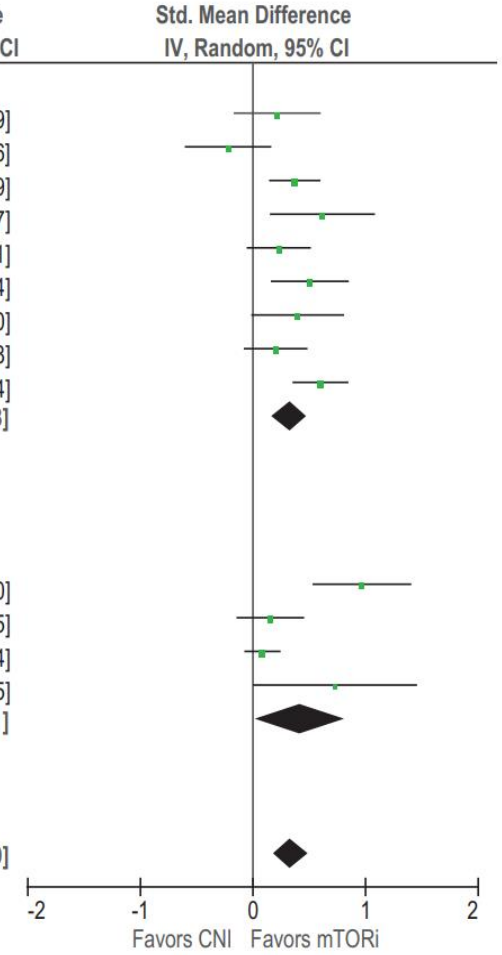
When stratified according to time posttransplant

Patients converted to mTORi had a more favorable GFR in both early and late-conversion trials

Lim et al

Table 1B: Mammalian target of rapamycin inhibitor (mTORi) versus calcineurin inhibitor (CNI); mean GFR up to 1 year posttransplant stratified by time posttransplant (intention-to-treat analysis)

	mTORi			CNI				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.2.1 Early conversion								
ERIC	57.3	18	54	53.4	18	54	7.0%	0.22 [-0.16, 0.59]
Heilman	57.4	20.7	54	62.7	26.5	55	7.0%	-0.22 [-0.60, 0.16]
HERAKLES	69	16.2	163	63	16	159	9.9%	0.37 [0.15, 0.59]
MECANO	55	20	38	44	15	39	5.8%	0.62 [0.16, 1.07]
Mjornstedt	51.2	14.1	102	47.8	15.4	100	8.8%	0.23 [-0.05, 0.51]
SMART	64.5	25.2	69	53.4	18	70	7.7%	0.50 [0.17, 0.84]
SOCRATES	72.3	2.5	49	71.3	2.5	47	6.6%	0.40 [-0.01, 0.80]
Tedesco/Pestana	74.8	25.7	110	70.2	19.1	95	8.8%	0.20 [-0.07, 0.48]
ZEUS	71.8	18.5	143	61.2	16.7	137	9.5%	0.60 [0.36, 0.84]
Subtotal (95% CI)			**782**			**756**	**71.0%**	**0.33 [0.17, 0.48]**
Heterogeneity: Tau² = 0.03; Chi² = 17.52, df = 8 (P = 0.03); I² = 54%								
Test for overall effect: Z = 4.15 (P < 0.0001)								
1.2.2 Late conversion								
APOLLO	62.9	3.69	46	59.3	3.69	47	6.2%	0.97 [0.54, 1.40]
Baboolal	37.3	13.6	116	35	16.7	74	8.5%	0.15 [-0.14, 0.45]
CONVERT	59	15.4	497	57.7	15.4	246	11.1%	0.08 [-0.07, 0.24]
Watson	46.3	14.8	17	31.8	23.6	15	3.2%	0.73 [0.01, 1.45]
Subtotal (95% CI)			**676**			**382**	**29.0%**	**0.42 [0.02, 0.81]**
Heterogeneity: Tau² = 0.12; Chi² = 16.56, df = 3 (P = 0.0009); I² = 82%								
Test for overall effect: Z = 2.08 (P = 0.04)								
Total (95% CI)			**1458**			**1138**	**100.0%**	**0.34 [0.19, 0.49]**
Heterogeneity: Tau² = 0.05; Chi² = 37.23, df = 12 (P = 0.0002); I² = 68%								
Test for overall effect: Z = 4.39 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%								



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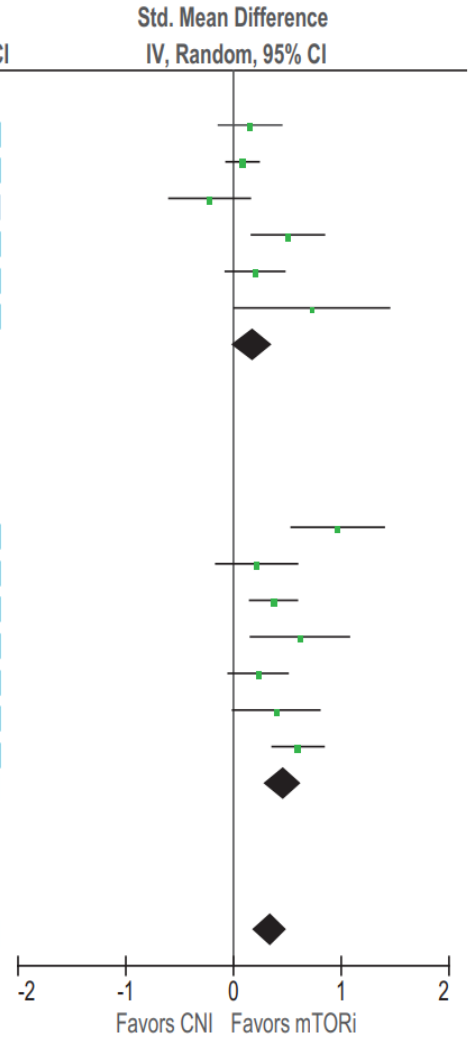
When stratified by type of mTORi

There was a more favorable GFR in the <u>everolimus-conversion</u> trials compared with the sirolimus-conversion trials

Table 1C: Mammalian target of rapamycin inhibitor (mTORi) versus calcineurin inhibitor (CNI); mean GFR up to 1 year posttransplant stratified by type of mammalian target of rapamycin inhibitor sirolimus and everolimus (intention-to-treat analysis)

	mTORi			CNI				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
3.7.2 SRL								
Baboolal	37.3	13.6	116	35	16.7	74	8.5%	0.15 [-0.14, 0.45]
CONVERT	59	15.4	497	57.7	15.4	246	11.1%	0.08 [-0.07, 0.24]
Heilman	57.4	20.7	54	62.7	26.5	55	7.0%	-0.22 [-0.60, 0.16]
SMART	64.5	25.2	69	53.4	18	70	7.7%	0.50 [0.17, 0.84]
Tedesco/Pestana	74.8	25.7	110	70.2	19.1	95	8.8%	0.20 [-0.07, 0.48]
Watson	46.3	14.8	17	31.8	23.6	15	3.2%	0.73 [0.01, 1.45]
Subtotal (95% CI)			**863**			**555**	**46.3%**	**0.18 [-0.01, 0.37]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 11.27$, df = 5 (P = 0.05); $I^2 = 56\%$								
Test for overall effect: Z = 1.88 (P = 0.06)								
3.7.3 EVL								
APOLLO	62.9	3.69	46	59.3	3.69	47	6.2%	0.97 [0.54, 1.40]
ERIC	57.3	18	54	53.4	18	54	7.0%	0.22 [-0.16, 0.59]
HERAKLES	69	16.2	163	63	16	159	9.9%	0.37 [0.15, 0.59]
MECANO	55	20	38	44	15	39	5.8%	0.62 [0.16, 1.07]
Mjornstedt	51.2	14.1	102	47.8	15.4	100	8.8%	0.23 [-0.05, 0.51]
SOCRATES	72.3	2.5	49	71.3	2.5	47	6.6%	0.40 [-0.01, 0.80]
ZEUS	71.8	18.5	143	61.2	16.7	137	9.5%	0.60 [0.36, 0.84]
Subtotal (95% CI)			**595**			**583**	**53.7%**	**0.46 [0.29, 0.63]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 12.02$, df = 6 (P = 0.06); $I^2 = 50\%$								
Test for overall effect: Z = 5.22 (P < 0.00001)								
Total (95% CI)			**1458**			**1138**	**100.0%**	**0.34 [0.19, 0.49]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 37.23$, df = 12 (P = 0.0002); $I^2 = 68\%$								
Test for overall effect: Z = 4.39 (P < 0.0001)								
Test for subgroup differences: $Chi^2 = 4.70$, df = 1 (P = 0.03), $I^2 = 78.7\%$								



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Reported on BPAR risk

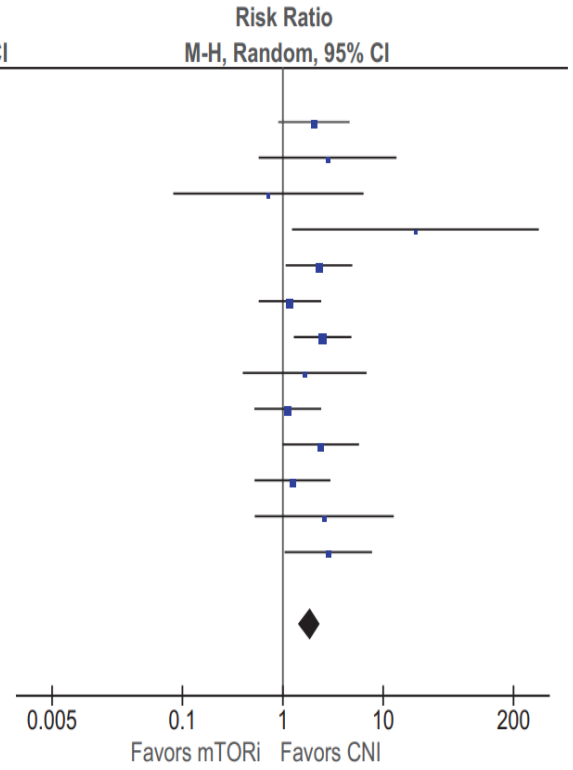
Showed that patients converted to mTORi were at a higher risk of rejection up to 1 year posttransplant

Table 5B: Mammalian target of rapamycin inhibitor (mTORi) versus calcineurin inhibitor (CNI); biopsy-proven acute rejection up to 1 year posttransplant

	mTORi		CNI			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
APOLLO	0	46	0	47		Not estimable
CONCEPT	16	95	8	97	10.4%	2.04 [0.92, 4.55]
Duerr	4	15	2	21	2.7%	2.80 [0.59, 13.36]
ECSEL	1	13	3	28	1.4%	0.72 [0.08, 6.26]
ERIC	10	54	0	54	0.8%	21.00 [1.26, 349.61]
Heilman	19	62	8	60	11.9%	2.30 [1.09, 4.85]
HERAKLES	16	161	13	154	13.6%	1.18 [0.59, 2.37]
Mjornstedt	28	102	11	100	16.2%	2.50 [1.32, 4.74]
Pankewycz	4	25	3	31	3.4%	1.65 [0.41, 6.71]
SMART	12	69	11	71	11.9%	1.12 [0.53, 2.37]
SOCRATES	15	49	6	47	9.0%	2.40 [1.02, 5.66]
Spare the Nephron	13	148	9	151	9.2%	1.25 [0.53, 2.92]
Tedesco/Pestana	6	110	2	95	2.7%	2.59 [0.54, 12.54]
ZEUS	15	154	5	146	6.8%	2.84 [1.06, 7.63]
Total (95% CI)		**1103**		**1102**	**100.0%**	**1.86 [1.44, 2.40]**
Total events	157		81			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.69$, df = 12 (P = 0.56); $I^2 = 0\%$

Test for overall effect: Z = 4.71 (P < 0.00001)



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- Mean GFR 1–2 years and 2–5 years post randomization for patients converted to mTORi showed a **significantly higher GFR** compared with those remaining on CNI
- There was **no significant difference in graft loss** up one year and 2–5 years posttransplant between patients converted to mTORi and those remaining on CNI
- There was **no difference in mortality** up to 1 year and 5 years posttransplant between the two groups was similar.
- Patients converted to mTORi generally had **lower risk of any cancers** compared with those remaining on CNI up to 1 year ,1–2 years and 2–5 years posttransplant

- ✓Discontinuation from adverse events up to 1 year posttransplant was greater in patients converted to mTORi compared with those on CNI

- ✓Up to 1 year posttransplant, patients converted to mTORi had higher risk of hyperlipidemia, infections, edema ,proteinuria, pneumonitis

- ✓Lower risk of CMV infection

Review > Cochrane Database Syst Rev. 2017 Jul 21;7(7):CD006750.
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Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients

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Free PMC article

Abstract

Background: Calcineurin inhibitors (CNI) can reduce acute transplant rejection and immediate graft loss but are associated with significant adverse effects such as hypertension and nephrotoxicity which may contribute to chronic rejection. CNI toxicity has led to numerous studies investigating CNI withdrawal and tapering strategies. Despite this, uncertainty remains about minimisation or withdrawal of CNI.

Objectives: This review aimed to look at the benefits and harms of CNI tapering or withdrawal in terms of graft function and loss, incidence of acute rejection episodes, treatment-related side effects (hypertension, hyperlipidaemia) and death.

There were 29 studies (252 reports, 5012 participants) that compared standard dose CNI with CNI withdrawal or avoidance combined with mTOR-I substitution

1. There was little or no difference in death and graft loss between the CNI withdrawal with mTOR-I and standard dose CNI regimens.
2. There was an increase in acute rejection episodes in the mTOR-I group.
3. Patients in the CNI withdrawal with mTOR-I group had a higher GFR compared to standard dose CNI regimen
4. SCr was lower at one year in the CNI withdrawal with mTOR-I group
5. CNI withdrawal with mTOR-I group had a higher incidence of hyperlipidaemia
6. There was little or no difference in hypertension, diabetes mellitus ,and infections between the two groups.
7. There was a reduction in malignancy and CMV infection in the mTORI group compared to those treated with standard dose CNI regimen.
8. There was an increase in lymphoceles in the CNI withdrawal in mTORI group

CONCLUSION

Protocols of early CNI withdrawal with conversion to mTOR inhibitors have been performed with three main aims:

The first is to achieve optimal renal function at 1 year because :

- long-term graft and patient survival have been associated with 1-year renal function .
- A 10 ml/minute decrease in GFR at 1 year is associated with a 2.1 odds ratio of kidney allograft loss 3 years after transplantation .

…conclusion

The second aim is to reduce the incidence of viral infection, because :

- Previous studies have shown a low incidence of cytomegalovirus (CMV) infection in SRL treated patients in comparison with CNI-treated patients .
- Furthermore, a significant increase in CMV-specific CD8+ T-cell count has been observed in EVL-treated renal recipients compared with CsA-treated patients
- Functional mTOR has recently been reported to be essential to CMV replication, suggesting a direct antiviral effect of mTOR inhibitors .
- A study has suggested that mTOR inhibitors also reduce the incidence of BK virus infection after trans plantation

…conclusion

The third aim is to decrease the incidence of malignancies.

- Several studies showing that mTOR-inhibitor-based regimens could reduce the incidence of neoplasia .
- Conversion from a CNI to SRL in kidney transplant patients following a first skin cancer episode prevented the recurrence of skin cancer .
- mTOR inhibitors have anti-neoplastic properties , in contrast to CNIs, which may induce cancer progression through mechanisms independent of host immunity .

…conclusion

- The above studies suggest that renal graft function is better if conversion from a CNI to an mTOR inhibitor is performed between 1 and 6 months post transplant

- Screening biopsy prior to conversion is important in selecting appropriate patients

…conclusion

From these studies we can consider that the more suitable patients for early conversion are:

1) Non immunized patients with good renal function (GFR>40 ml/minute)
2) Without previous severe acute rejection
3) Without subclinical rejection or CAN
4) In the absence of proteinuria >1 g/day
5) In the absence of donor specific antibodies

با تشکر از توجه همه شما بزرگواران