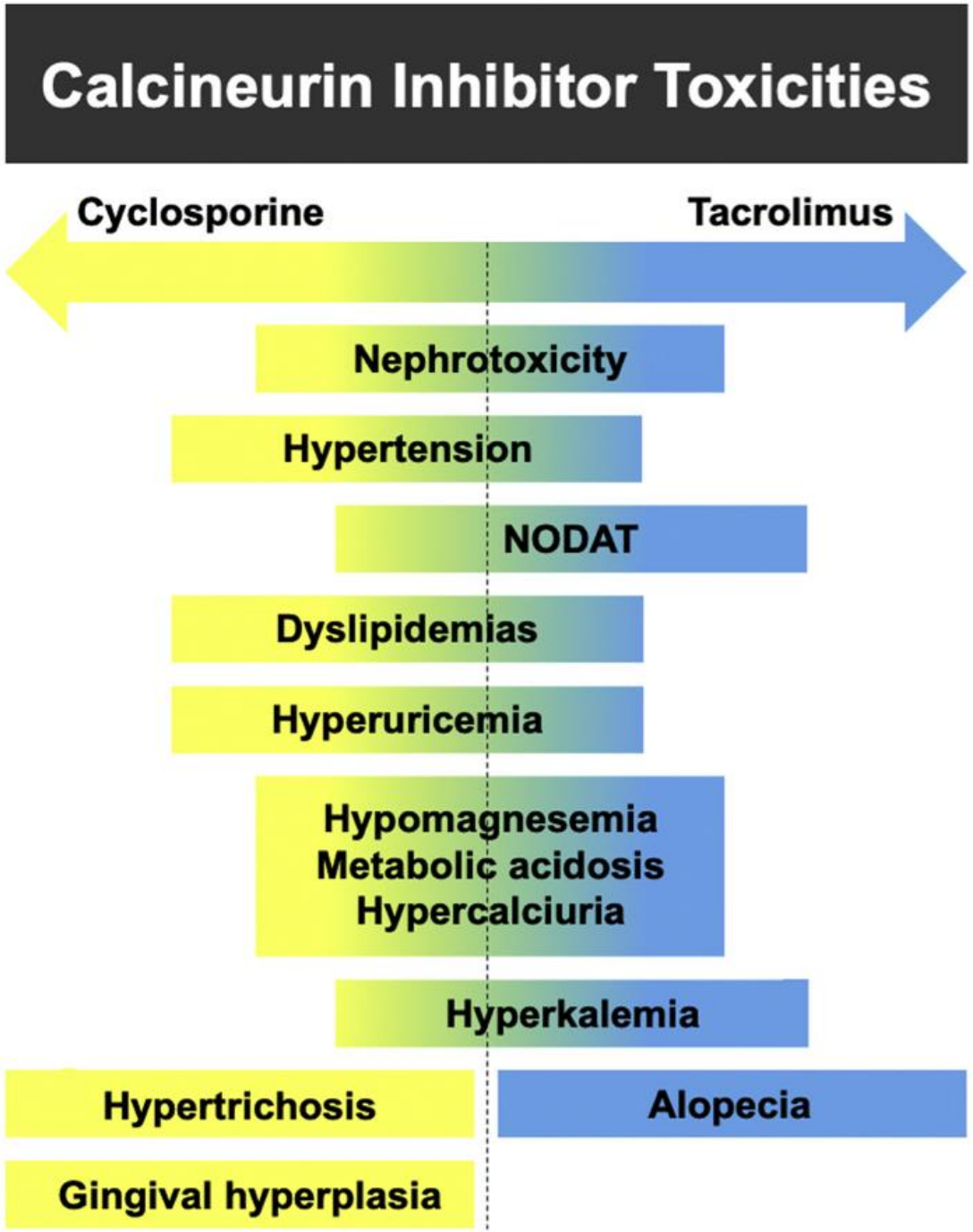
Low dose CNI plus mTOR inhibitors

revisiting an old strategy

Marieh Farrokhy Moghaddam


Calcineurin Inhibitor Toxicities
Cyclosporine
Tacrolimus
Nephrotoxicity
Hypertension
NODAT
Dyslipidemias
Hyperuricemia
Hypomagnesemia
Metabolic acidosis
Hypercalciuria
Hyperkalemia
Hypertrichosis
Alopecia
Gingival hyperplasia

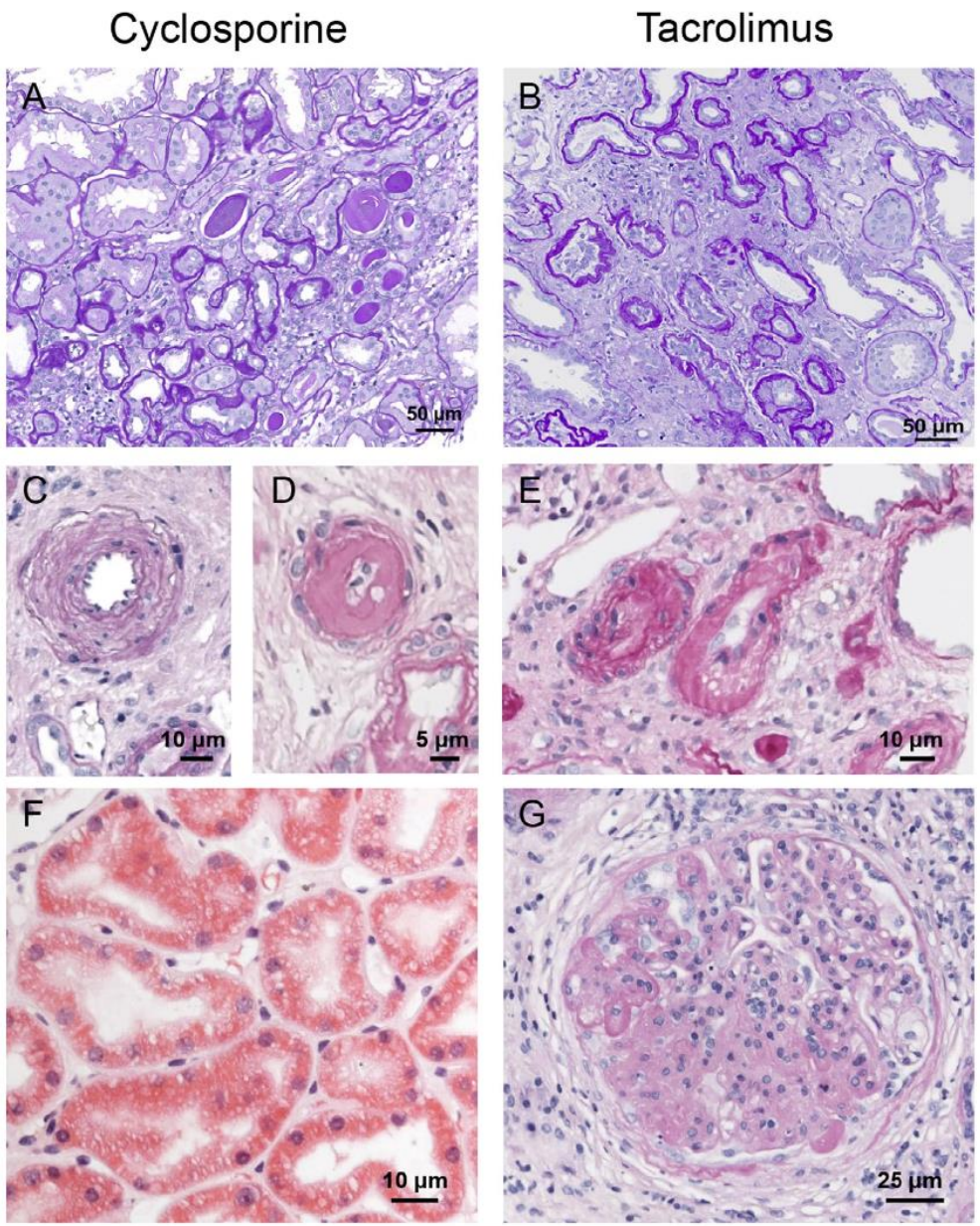


FIGURE 1 | Histopathology of CNT in human kidney biopsies from cyclosporine and tacrolimus-based treatment regimens. (A, B) Interstitial fibrosis/tubular atrophy; note hyaline tubular casts in (A). (C–E) Arteriolar wall changes. Media hypertrophy and hyalinosis in Cyclosporine (C, D), luminal narrowing and perivascular inflammation in tacrolimus-based treatment regimen (E). (F) Tubular vacuolization in proximal tubule. (G) Focal segmental glomerulosclerosis with focal adhesions to capsule. PAS staining (A–E, G), hematoxylin eosin (F); bars indicate magnification. Courtesy of Kerstin Amann, Marie-Christine Heinrich.

Renal Allograft Histology at 10 Years After Transplantation in the Tacrolimus Era: Evidence of Pervasive Chronic Injury

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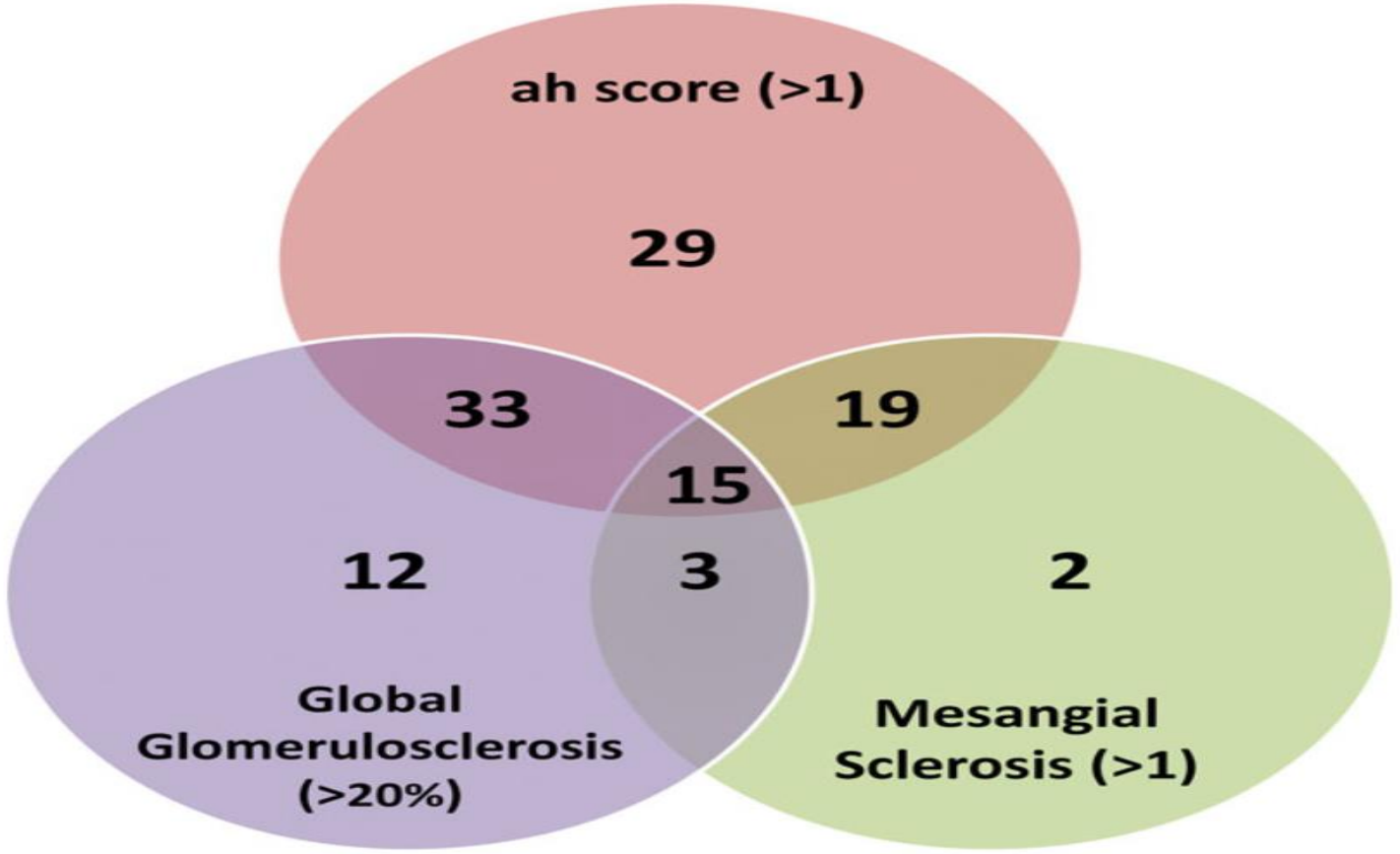


Figure 3: Overlap among major histologic findings at 10 years. ah score, arteriolar hyalinosis score.

How to reduce CNI toxicity?

- **minimization**
- **conversion**
- **withdrawal**
- **avoidance**

Does reduced CNI exposure lead to better outcomes in kidney transplantation? The ELITE-SYMPHONY Trial

1645 patients awaiting kidney transplant
Aged 18-75 yrs

83 centres

Follow up 12 months

Methodology

Open label parallel 4 arm RCT

Steroids + MMF +

Daclizumab +

	Primary outcome	Secondary outcomes	
	eGFR- at 1yr (ml/min)	Acute rejection (At 1 yr)	Graft survival (At 1 yr)
STANDARD dose CyA (target C_0 level – 0-3 months- 100-300ng/ml, >3 months 100-200ng/ml)	57.1 *P<0.001*	25.8% *P<0.001*	89.3% *P=0.01*
↓ dose CyA (target C_0 level – 50-100 ng/ml)	59.1 *P=0.001*	24.0% *P<0.001*	93.1% *P=0.56*
SRL (target C_0 level – 4-8 ng/ml)	56.7 *P<0.001*	37.2% *P<0.001*	89.3% *P=0.01*
TAC (target C_0 level – 3-7 ng/ml)	**65.4** *(Ref.)*	**12.3%** *(Ref.)*	**94.2%** *(Ref.)*

Conclusion : A regimen of daclizumab, MMF, and steroids in combination with low-dose TAC may be advantageous for renal function, allograft survival, and acute rejection rates, as compared with regimens containing daclizumab induction plus either low-dose CyA or low-dose SRL or with standard-dose CyA without induction.

Ekberg, H. *et al. NEJM*, 2007
DOI: 10.1056/NEJMo[illegible]7411

VA by @Dilushiwijay

Calcineurin Inhibitor Associated Nephrotoxicity in Kidney Transplantation—A Transplant Nephrologist's Perspective

Carla M. Hansen | Sebastian Bachmann | Mingzhen Su | Klemens Budde | Mira Choi

5.3 | Conversion to Belatacept

Conversion from a CNI-based immunosuppression to belatacept is also an alternative treatment strategy in patients with concerns to continue with a CNI-based regimen or to ensure better therapy adherence [116, 117].

In conclusion, belatacept offers a viable alternative to CNIs in kidney transplantation, demonstrating benefits such as improved allograft function, lower rates of NODAT, dyslipidemia, and dnDSA formation. However, its use is limited by an increased risk of acute rejection and PTLD, particularly in EBV-seronegative patients. Further research is needed to refine patient selection and optimize immunosuppressive strategies to balance rejection risk with long-term graft preservation.

5.2 | Conversion From CNI to MTOR Inhibitor

MTORis have been used in de novo kidney transplantation to reduce or omit CNI or as an option to convert from, for example, CNI or MMF. Several trials and meta-analyses comparing mTORi-based and CNI-based immunosuppression post-kidney transplantation found a higher GFR, increased acute rejection rates, fewer Cytomegalovirus (CMV) infections, reduced malignancy, and more lymphoceles in the mTORi group [88, 91–94]. De Fijter et al. investigated early conversion to mTORi 10–14 days post-transplant versus continued CNI. At 12 months, the groups showed similar GFR; however, in the mTORi group a higher incidence of biopsy-proven acute rejection and a potential increase in de novo donor-specific antibodies (dnDSA) was observed [95]. In a related single-center study, 23% (14/61) of patients converted from cyclosporine to mTORi between 3- and 4.5-months post-transplant developed dnDSAs, compared with 11% (7/65) patients who remained on cyclosporine [96].

Late conversion, defined as conversion from CNI to mTORi after more than 6 months post-transplant, showed reduced malignancy rates and improved GFR with no significant differences in graft loss, chronic allograft nephropathy, and mortality [97, 98]. Common side effects included increased infection rates, myelosuppression, gastrointestinal symptoms, impaired wound healing, dyslipidemia, post-transplant diabetes mellitus, pneumonitis, and dermatologic disorders.

Notably, discontinuation of medication secondary to adverse events was more common in patients on mTORi than in patients on CNI [95, 98].

In summary, conversion to an mTORi-based regimen may be appropriate for selected patients, such as those experiencing severe CNI-associated adverse effects (e.g., neurotoxicity or CNT).

TABLE 1 | Overview on findings from meta-analyses that examined various CNI-sparing immunosuppressive regimens in kidney transplantation.

First author	Publication year	Intervention[a]	Observation periods	Number of trials included[b]	Result mortality	Result graft loss	Result rejection rates	Result GFR
Karpe KM	2017	CNI withdrawal (avoidance or late withdrawal)	6–24 months; endpoint mortality: 9–20 years	$n=17$	RR 1.09, 95% CI 0.96–1.24	RR 0.85, 95% CI 0.74–0.98	RR 2.54, 95% CI 1.56–4.12	MD 3.56, 95% CI −1.25 to 8.25
		Low dose CNI versus standard dose CNI		$n=18$	RR 0.79, 95% CI 0.50–1.27	RR 0.75, 95% CI 0.55–1.02	RR 0.87, 95% CI 0.76–1.01	MD 4.10, 95% CI 2.07–6.12
		CNI withdrawal or avoidance with mTOR-I		$n=29$	RR 0.96, 95% CI 0.68–1.36	RR 0.94, 95% CI 0.75–1.19	RR 1.43, 95% CI 1.15–1.78	MD 5.29, 95% CI 2.08–8.51
		Low dose CNI and mTORi		$n=14$	RR 1.16, 95% CI 0.71–1.90	RR 0.67, 95% CI 0.45–1.01	RR 1.13, 95% CI 0.91–1.40	MD 6.24, 95% CI 3.28–9.19
Liu J	2017	CNI conversion to Everolimus	12 months	$n=15$	RR 0.70, 95% CI 0.22–2,18	RR 1.43, 95% CI 0.44–4.68	RR 1.82, 95% CI 1.11–2.99	MD 5.36, 95% CI 2.32–8.39
			5 years		RR 0.70, 95% CI 0.29–2,46	RR 1.10, 95% CI 0.51–5.70	RR 1.85, 95% CI 0.94–3.65	MD 6.50, 95% CI 2.38–10.63
Sawinski D	2016	CNI minimization	12 months with variability	$n=36$	RR 0.91, 95% CI: 0.72–1.14	RR 0.76, 95% CI: 0.61–0.94	RR 0.84, 95% CI: 0.75–0.95	MD 0.32, 95% CI: 0.22–0.41
		CNI conversion to mTORi or Belatacept		$n=23$	No difference	No difference longterm	More acute rejections	GFR higher
		CNI withdrawal		$n=13$	No difference	No difference	More acute rejections	GFR higher
		CNI avoidance		$n=9$	No difference	No difference	More acute rejections	GFR higher
Talawila N	2015	CNI minimization/ withdrawal + Belatacept	12 months	$n=6$	OR 1.46, 95% CI 0.61–3.5	OR 1.20, 95% CI 0.75–1.92	OR 1.65, 95% CI 0.83–3.30	MD 11.7, 95% CI 0.09–23.35
			24 months	$n=2$	OR 1.67, 95% CI 0.99–2.81	OR 1.03, 95% CI 0.65–1.64	OR 1.77, 95% CI 0.83–3.79	MD 13.7, 95% CI 6.34–21.10
Bai H	2015	CNI withdrawal	6–24 months	$n=7$	RR 0.99, 95%, CI 0.98–1.01	RR 1.00, 95% CI 0.98–1.02	RR 1.64, 95% CI 1.19–2.27	MD 9.50, 95% CI 2.96–16.03
Su L	2014	CNI sparing + Everolimus	12–24 months	$n=7$	RR 1.07, 95% CI 0.73–1.58[c]		RR 2.51, 95% CI 1.63–3.87	SC MD −9.94 µmol/L, 95% CI −16.66–(−3.22 µmol/L)

TABLE 1 | (Continued)

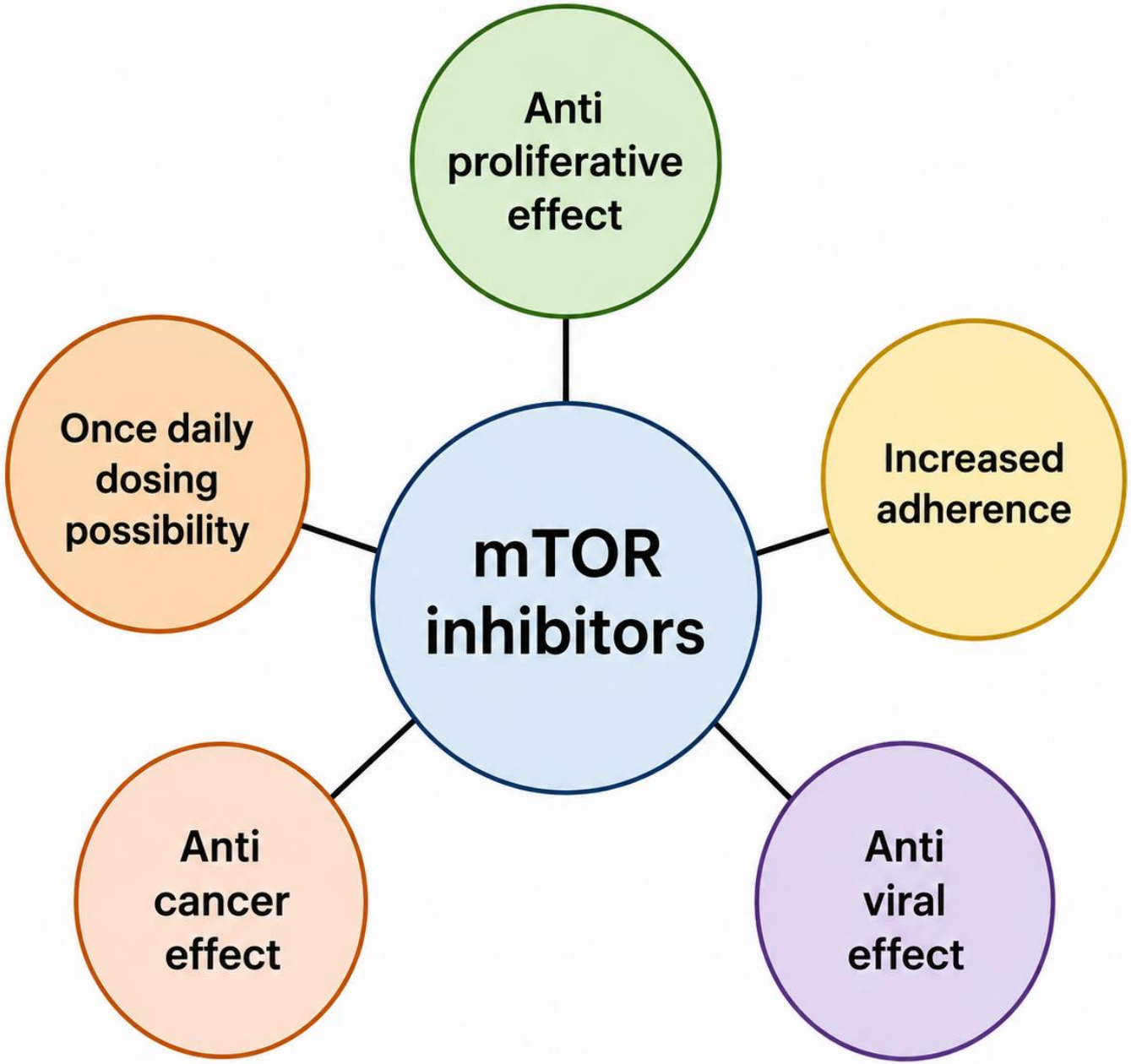
First author	Publication year	Intervention[a]	Observation periods	Number of trials included[b]	Result mortality	Result graft loss	Result rejection rates	Result GFR
Yan HL	2014	CNI avoidance	12 months	$n=16$	OR 0.90, 95% CI 0.47–1.69	OR 0.73, 95% CI 0.47–1.12	OR 1.74, 95% CI 1.08–2.81	MD 5.31, 95% CI 0.30–10.31
			24 months		OR 0.91, 95% CI 0.44–1.87	OR 0.87, 95% CI 0.48–1.57, $p=0.64$	OR 0.92, 95% CI 0.33–2.51	MD 13.96, 95% CI 7.32–20.60
		CNI withdrawal	12 months	$n=11$	OR 0.74, 95% CI 0.41–1.32	OR 0.69, 95% CI 0.46–1.03	OR 1.78, 95% CI 1.35–2.34	MD 7.03, 95% CI 4.84–9.23
			24 months		OR 0.73, 95% CI 0.42–1.29	OR 0.81, 95% CI 0.56–1.16	OR 2.42, 95% CI 1.01–5.82	
Sharif A	2011	CNI avoidance	6–36 months	$n=32$	OR 0.92, 95% CI 0.76–1.11	OR 1.05, % CI 0.85–1.29	OR 1.24, 95% CI 1.01–1.53	MD 5.31, 95% CI 2.82–7.81
		CNI minimization		$n=17$		OR 0.73, 95% CI 0.58–0.92	OR 0.99, 95% CI 0.76–1.28	MD 3.44, 95% CI 1.21–5.68
		Delayed introduction of CNI		$n=10$		OR 1.04 95% CI 0.75–1.44	OR 1.00, 95% CI 0.67–1.50	MD 2.83, 95% CI 0.09–5.76
Moore J	2009	CNI minimization and elimination	6–24 months	$n=19$	OR 1.08, 95% CI 0.68–1.72	OR 0.72, 95% CI 0.52–1.01	Strong hetero-genity	MD 4.4, 95% CI 2.9–5.9
Kasiske BL	2000	Cyclosporine withdrawal	12–93 months	$n=13$		RR 1.06, 95% CI 0.82–1.29	Pooled difference 0.11, 95% CI 0.07–0.15	
Kasiske BL	1993	Elective cyclosporine withdrawal	12–36 months	$n=17$[d]	Weighted difference in deaths per patient per year, −0.005, 95% CI −0.016 to 0.006	Weighted difference in grafts lost per patient per year, −0.009, 95% CI −0.022 to 0.004	Weighted difference in episodes per patient, 0.126, 95% CI 0.085 to 0.167	Mean SC level standard group 163 ± 26 μmol/L vs. cyclosporine withdrawal group 144 ± 25 μmol/L

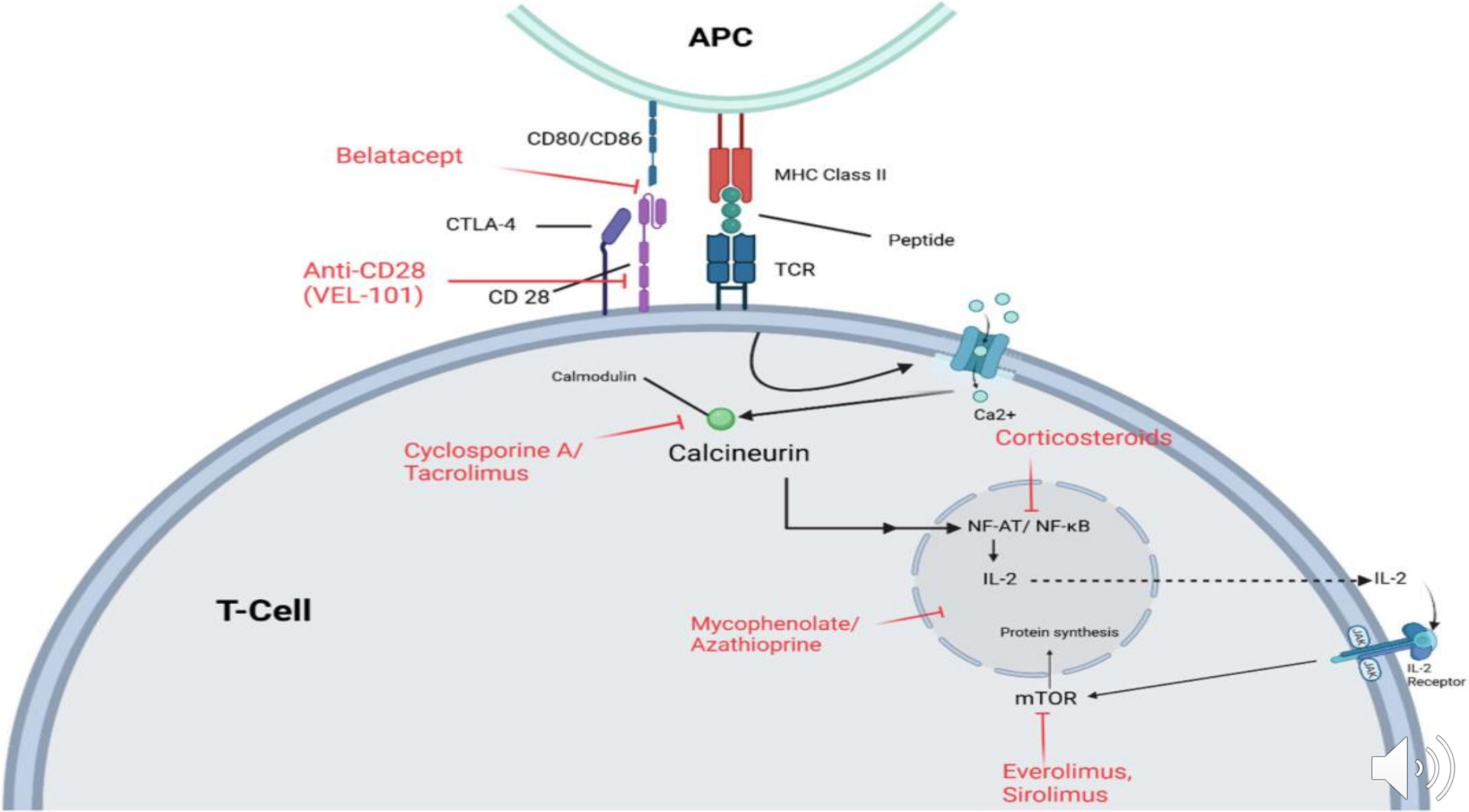
Note: green = intervention had a favorable impact, red = intervention had an unfavorable impact, gray = intervention did not show to have a statistically significant effect compared to control group.
Abbreviations: CI, confidence interval; CNI, calcineurin inhibitor; GFR, glomerular filtration rate in mL/min/1.73 m^2; MD, mean difference; mTORi, mammalian target of rapamycin inhibitor; OR, odds ratio; RR, relative risk; SC, serum creatinine; vs., versus.
[a]Versus standard dose CNI.
[b]Number of trials analyzed for each outcome varied.
[c]Death and graft loss = categorized as event.
[d]$n=10$ NRCT.

Calcineurin Inhibitor Minimization, Conversion, Withdrawal, and Avoidance Strategies in Renal Transplantation: A Systematic Review and Meta-Analysis

Analysis of the 19 studies that paired CNI minimization with mycophenolic acid formulations (14 CsA, five tacrolimus) revealed high-strength evidence of improved renal function and reduced BPAR (RR 0.80; 95% CI 0.68–0.95) and graft loss (RR 0.71; 95% CI 0.56–0.9) with these regimens (Figure 2). Low-strength evidence suggested no difference in mortality (RR 0.87; 95% CI 0.66–1.15). Data regarding BKV infection were insufficient. When analyzed by CNI subgroup, we found moderate- to high-strength evidence that low-dose CsA was associated with improved renal function and reduced risk of BPAR and graft loss. The evidence for other outcomes was insufficient. High-strength evidence suggested low-dose tacrolimus improved renal function compared with standard-dose tacrolimus or CsA; evidence for other outcomes was insufficient.

Fourteen RCTs examined sirolimus or everolimus in combination with reduced-dose CNI (nine CsA, four tacrolimus) (Figure 3). Analysis of these studies found moderate-strength evidence of improvement in renal function, driven by studies using CsA. Meta-analysis of the trials using low-dose CsA with an mTOR inhibitor resulted in moderate-strength evidence of improved renal function without an increased risk of BPAR. Four studies used low-dose tacrolimus with an mTOR inhibitor, but the evidence was insufficient to draw conclusions. In 10 trials that used basiliximab induction therapy with minimized CNI dosing and an mTOR inhibitor, there was moderate-strength evidence for improved renal function and lower risk of graft loss. It should be noted that standard-dose CNI plus mTOR inhibitors potentiates CNI nephrotoxicity; therefore, conclusions regarding renal function from studies that use this regimen as the control group should be viewed with caution.


Anti proliferative effect
Once daily dosing possibility
mTOR inhibitors
Increased adherence
Anti cancer effect
Anti viral effect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Belatacept
MHC Class II
CTLA-4
Peptide
Anti-CD28
(VEL-101)
CD 28
TCR
Calmodulin
Ca2+
Cyclosporine A/
Tacrolimus
Calcineurin
Corticosteroids
NF-AT/ NF-κB
IL-2
IL-2
T-Cell
Mycophenolate/
Azathioprine
Protein synthesis
JAK
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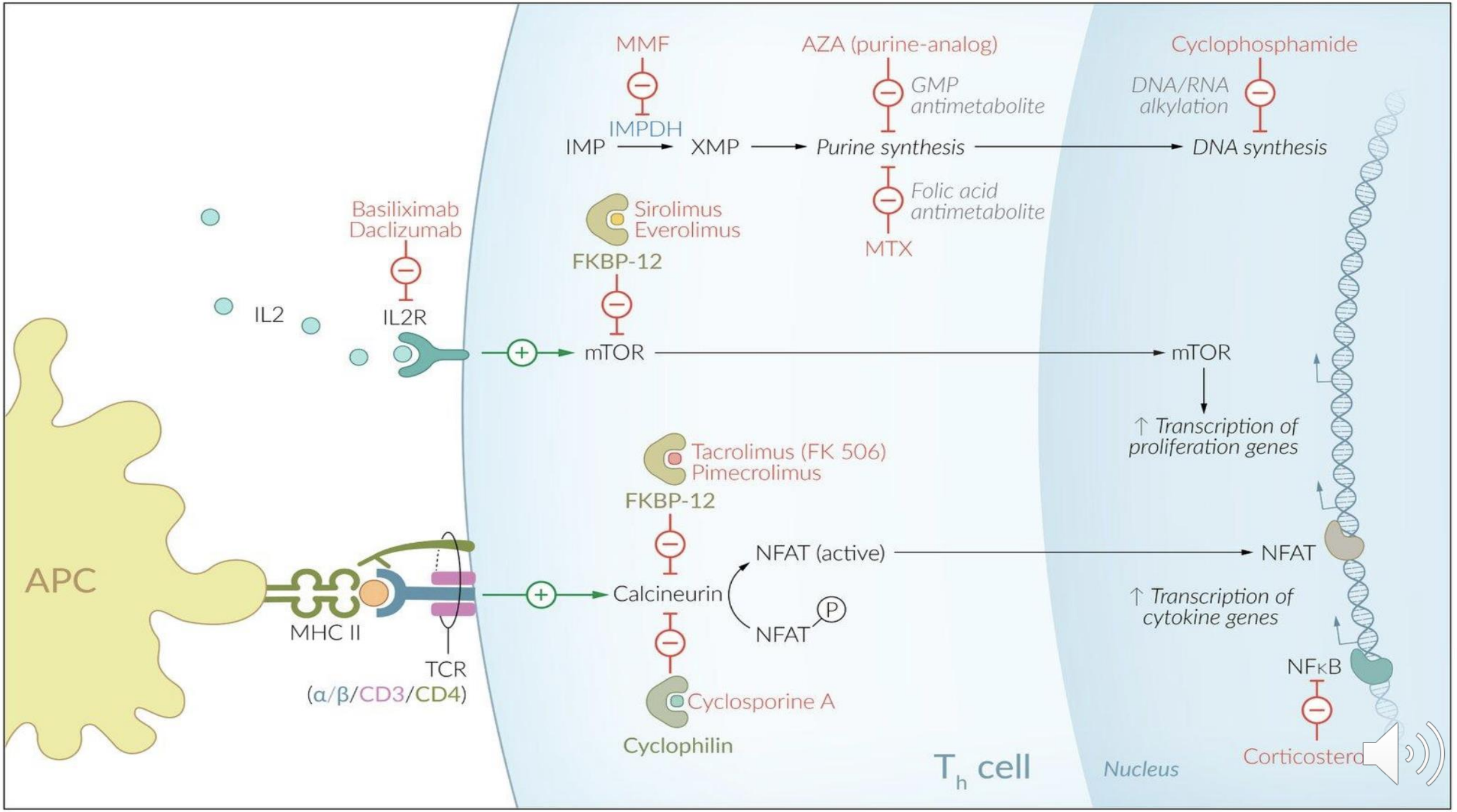
IL-2
Receptor
mTOR
Everolimus,
Sirolimus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IMPDH
IMP
XMP
AZA (purine-analog)
GMP antimetabolite
Purine synthesis
Folic acid antimetabolite
MTX
Cyclophosphamide
DNA/RNA alkylation
DNA synthesis
Basiliximab
Daclizumab
IL2
IL2R
Sirolimus
Everolimus
FKBP-12
mTOR
mTOR
↑ Transcription of proliferation genes
Tacrolimus (FK 506)
Pimecrolimus
FKBP-12
APC
MHC II
TCR
(α/β/CD3/CD4)
Calcineurin
NFAT (active)
NFAT
P
↑ Transcription of cytokine genes
Cyclosporine A
Cyclophilin
NFκB
Corticosterd
T h cell
Nucleus

Multicenter, Randomized Study of the Use of Everolimus With Tacrolimus After Renal Transplantation Demonstrates its Effectiveness

Laurence Chan,[1,10] Stuart Greenstein,[2] Mark A. Hardy,[3] Erica Hartmann,[4] Suphamai Bunnapradist,[5] Diane Cibrik,[6] Leslie M. Shaw,[7] Laura Munir,[8] Bettina Ulbricht,[8] and Matthew Cooper[9] for the CRADUS09 Study Group

Background. Clinical data are lacking concerning concomitant administration of everolimus and tacrolimus in renal transplant recipients.

Methods. In a prospective, multicenter, open-label, exploratory, randomized, 6-month study, 92 de novo renal transplant patients received everolimus, steroids, and basiliximab with low or standard tacrolimus exposure. The primary objective was to compare renal function at 6 months after transplant.

Results. Mean 6-month serum creatinine (primary safety variable) was 112±31 μmol/L (1.26±0.35 mg/dL) and 127±50 μmol/L (1.44±0.57 mg/dL) in the low and standard tacrolimus groups, respectively, (n.s.); mean estimated GFR (Nankivell) was 75.3±16.6 mL/min and 72.5±15.2 mL/min (n.s.). Biopsy-proven acute rejection occurred in 13 patients: seven (14%) in the low tacrolimus group and six (14%) in the standard tacrolimus group, n.s. One graft was lost in the standard tacrolimus group. No patients died.

Conclusions. Tacrolimus exposure reduction in the presence of everolimus, steroids and basiliximab induction results in good efficacy in de novo renal transplant recipients with very well-preserved renal function. Additional studies are warranted because between-group comparisons were limited by the relatively small differences in tacrolimus exposure in the 2 arms; trough levels were toward the upper end of the low-exposure ranges and toward the bottom of the standard-exposure ranges.

Keywords: Everolimus, Tacrolimus, Certican, Efficacy.

Immunosuppression

The mean everolimus dose increased from 1.70±0.60 mg/day at week 1 posttransplant to 2.0±0.9 mg/day at week 2, 1.8±1.3 mg/day at month 3 and 2.9±1.3 mg/day at the last study visit; values were similar in both groups throughout the trial. The mean everolimus trough level was 3.8±3.04 ng/mL by week 2 in both groups and remained in target range thereafter; at month 6 it was 5.2±2.2 ng/mL in the low tacrolimus group and 5.2±2.3 ng/mL in the standard tacrolimus group (Fig. 1a). Tacrolimus trough levels were slightly greater than target range for the first and last 2 months of the trial in the low tacrolimus cohort and were toward the lower end of the target range in the standard tacrolimus cohort at the end of the study (Fig. 1b). Mean tacrolimus level was 8.7±6.1 ng/mL and 11.3±12.6 ng/mL at day 3 in the low and standard tacrolimus groups, respectively; 7.5±2.9 ng/mL and 9.9±2.8 ng/mL at week 4; 6.7±2.4 ng/mL and 9.2±3.4 ng/mL at month 3 and 7.1±5.3 ng/mL and 7.2±2.5 ng/mL, at month 6. Mean steroid dose was similar in both treatment groups throughout the trial, including or excluding steroids administered to treat rejection. All patients in the low tacrolimus group received two doses of basiliximab; one patient in the standard tacrolimus group received only one dose and another received no basiliximab, against protocol. Five patients with DGF received antithymocyte immunoglobulin (2 in the lower tacrolimus group and 3 in the standard tacrolimus group), against protocol.

TABLE 2. Renal function and efficacy events at month 6

	Low tacrolimus (n=49)	Standard tacrolimus (n=43)	*P* value
Serum creatinine (μmol/L)			
Mean±SD	112±31	127±50	0.114[a]
Median [range]	106 [88–132]	115 [97–132]	
Estimated GFR (mL/min)[b]			
Mean±SD	75.3±16.6	72.5±15.2	0.466[a]
Median [range]	74.3 [66.4–86.0]	72.4 [62.7–81.7]	
Creatinine clearance (mL/min)[c]			
Mean±SD	82.8±26.8	77.2±21.8	0.335[a]
Median [range]	80.8 [60.4–107.8]	77.1 [65.0–91.0]	
Biopsy-proven acute rejection, graft loss or death	7 (14%)	7 (16%)	0.916[d]
Biopsy-proven acute rejection	7 (14%)	6 (14%)	0.872[a]
Chronic allograft nephropathy	0	2 (5%)[e]	—
Graft loss	0	1 (2%)	0.371[d]
Death	0	0	—

ORIGINAL ARTICLE

Everolimus plus early tacrolimus minimization: a phase III, randomized, open-label, multicentre trial in renal transplantation

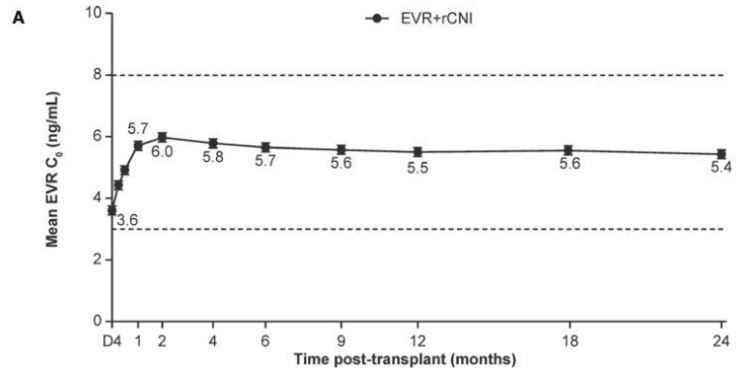
Robert M. Langer,[1] Ronald Hené,[2] Stefan Vitko,[3] Maarten Christiaans,[4] Helio Tedesco-Silva Jr,[5] Kazimierz Ciechanowski,[6] Elisabeth Cassuto,[7] Lionel Rostaing,[8] Mario Vilatoba,[9] Uwe Machein,[10] Bettina Ulbricht,[10] Guido Junge,[10] Gaohong Dong[11] and Julio Pascual[12]

Summary

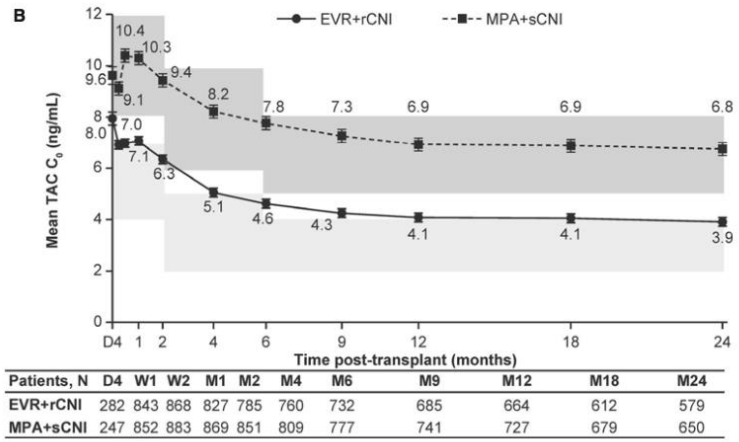
There is increasing interest in tacrolimus-minimization regimens. ASSET was an open-label, randomized, 12-month study of everolimus plus tacrolimus in *de-novo* renal-transplant recipients. Everolimus trough targets were 3–8 ng/ml throughout the study. Tacrolimus trough targets were 4–7 ng/ml during the first 3 months and 1.5–3 ng/ml ($n = 107$) or 4–7 ng/ml ($n = 117$) from Month 4. All patients received basiliximab induction and corticosteroids. The primary objective was to demonstrate superior estimated glomerular filtration rate (eGFR; MDRD-4) at Month 12 in the tacrolimus 1.5–3 ng/ml versus the 4–7 ng/ml group. Secondary endpoints included incidence of biopsy-proven acute rejection (BPAR; Months 4–12) and serious adverse events (SAEs; Months 0–12). Statistical significance was not achieved for the primary endpoint (mean eGFR: 57.1 vs. 51.7 ml/min/1.73 m^2), potentially due to overlapping of achieved tacrolimus exposure levels (Month 12 mean ± SD, tacrolimus 1.5–3 ng/ml: 3.4 ± 1.4; tacrolimus 4–7 ng/ml: 5.5 ± 2.0 ng/ml). BPAR (months 4–12) and SAE rates were comparable between groups (2.7% vs. 1.1% and 58.7% vs. 51.3%; respectively). Everolimus-facilitated tacrolimus minimization, to levels lower than previously investigated, achieved good renal function, low BPAR and graft-loss rates, and an acceptable safety profile in renal transplantation over 12 months although statistically superior renal function of the 1.5–3 ng/ml tacrolimus group was not achieved. (ClinicalTrials.gov: NCT00369161) is registered at http://www.clinicaltrials.gov.

Two-year outcomes in de novo renal transplant recipients receiving everolimus-facilitated calcineurin inhibitor reduction regimen from the TRANSFORM study

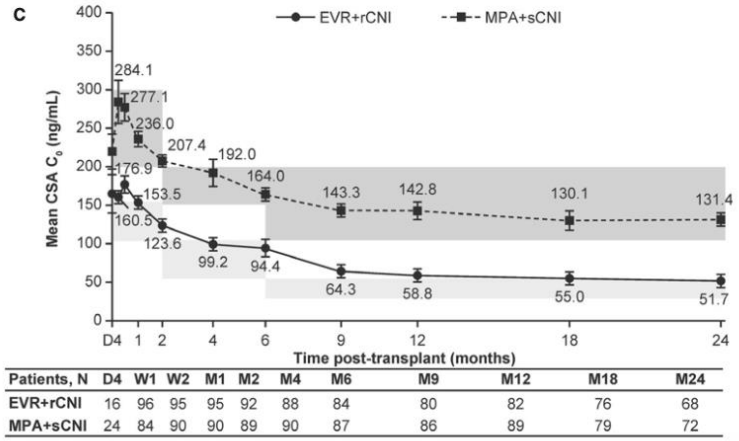
TRANSFORM (TRANSplant eFficacy and safety Outcomes with an eveRolimus-based regiMen) was a 24-month, prospective, open-label trial in 2037 de novo renal transplant recipients randomized (1:1) within 24 hours of transplantation to receive everolimus (EVR) with reduced-exposure calcineurin inhibitor (EVR + rCNI) or mycophenolate with standard-exposure CNI. Consistent with previously reported 12-month findings, noninferiority of the EVR + rCNI regimen for the primary endpoint of treated biopsy-proven acute rejection (tBPAR) or estimated glomerular filtration rate (eGFR) <50 mL/min per 1.73 m^2 was achieved at month 24 (47.9% vs 43.7%; difference = 4.2%; 95% confidence interval = −0.3, 8.7; *P* = .006). Mean eGFR was stable up to month 24 (52.6 vs 54.9 mL/min per 1.73 m^2) in both arms. The incidence of de novo donor-specific antibodies (dnDSA) was lower in the EVR + rCNI arm (12.3% vs 17.6%) among on-treatment patients. Although discontinuation rates due to adverse events were higher with EVR + rCNI (27.2% vs 15.0%), rates of cytomegalovirus (2.8% vs 13.5%) and BK virus (5.8% vs 10.3%) infections were lower. Cytomegalovirus infection rates were significantly lower with EVR + rCNI even in the D+/R− high-risk group (*P* < .0001). In conclusion, the EVR + rCNI regimen offers comparable efficacy and graft function with low tBPAR and dnDSA rates and significantly lower incidence of viral infections relative to standard-of-care up to 24 months. Clinicaltrials.gov number: NCT01950819.



Patients, N	D4	W1	W2	M1	M2	M4	M6	M9	M12	M18	M24
EVR+rCNI	223	903	946	910	869	840	804	758	737	683	639



Patients, N	D4	W1	W2	M1	M2	M4	M6	M9	M12	M18	M24
EVR+rCNI	282	843	868	827	785	760	732	685	664	612	579
MPA+sCNI	247	852	883	869	851	809	777	741	727	679	650



Patients, N	D4	W1	W2	M1	M2	M4	M6	M9	M12	M18	M24
EVR+rCNI	16	96	95	95	92	88	84	80	82	76	68
MPA+sCNI	24	84	90	90	89	90	87	86	89	79	72

TABLE 3 Efficacy endpoints at month 24 by CNI subgroups (full analysis set)

	TAC-receiving patients				CsA-receiving patients			
n (%)	EVR + rCNI N = 915	MPA + sCNI N = 917	Difference (95% CI)	*P* value	EVR + rCNI N = 100	MPA + sCNI N = 95	Difference (95% CI)	*P* value
Primary endpoint[a]	429 (46.9)	391 (42.6)	4.3 (−0.4, 9.1)	.071	54 (54.0)	50 (52.6)	1.5 (−12.8, 15.7)	.842
tBPAR, graft loss, or death	148 (17.8)	126 (16.8)	1.0 (−4.8, 6.8)	.733	19 (19.2)	18 (19.1)	0.0 (−11.1, 11.2)	.994
tBPAR	102 (12.4)	83 (11.7)	0.7 (−4.7, 6.2)	.790	15 (15.5)	15 (16.0)	−0.5 (−10.9, 9.9)	.929
Graft loss	31 (3.5)	25 (2.8)	0.7 (−1.0, 2.3)	.429	5 (5.0)	5 (5.3)	−0.3 (−6.5, 5.9)	.922
Death	29 (3.8)	33 (4.3)	−0.5 (−2.8, 1.7)	.642	3 (3.2)	2 (2.2)	1.0 (−3.7, 5.7)	.684
eGFR < 50 mL/min per 1.73 m^2[a]	415 (45.4)	374 (40.8)	4.6 (−0.1, 9.4)	.055	53 (53.0)	47 (49.5)	4.2 (−10.1, 18.5)	.566

An open-label, randomized trial indicates that everolimus with tacrolimus or cyclosporine is comparable to standard immunosuppression in *de novo* kidney transplant patients.

ATHENA STUDY

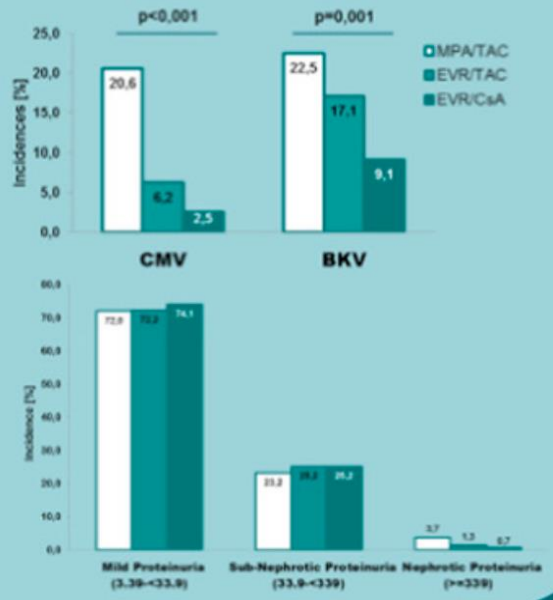
ATHENA – 12-month, prospective, randomised and controlled multicentre trial

First randomised study in *de novo* kidney Tx comparing:
(i) Everolimus with tacrolimus (EVR/TAC),
(ii) EVR with cyclosporine (EVR/CsA),
(iii) Mycophenolic acid with TAC (MPA/TAC),
requiring similar TAC exposure in both TAC groups; and including prospective analyses on the elderly (>65 years).

- **EVR/TAC** 208 pts
- **EVR/CsA** 199 pts
- **MPA/TAC** 205 pts

12-month data confirm:

- EVR with either TAC or CsA shows comparable efficacy to MPA/TAC
- EVR-treated patients show significantly less frequent CMV and BKV infections
- No difference in proteinuria between groups



European trial.
Population including organs from deceased donors >65 years of age.

CONCLUSION:
Everolimus with TAC or CsA in *de novo* kidney Tx demonstrates comparable efficacy and no difference in proteinuria compared with MPA/TAC. Patients receiving everolimus had signifi[illegible]tly less frequent CMV and BKV infections.

ISN kidney INTERNATIONAL
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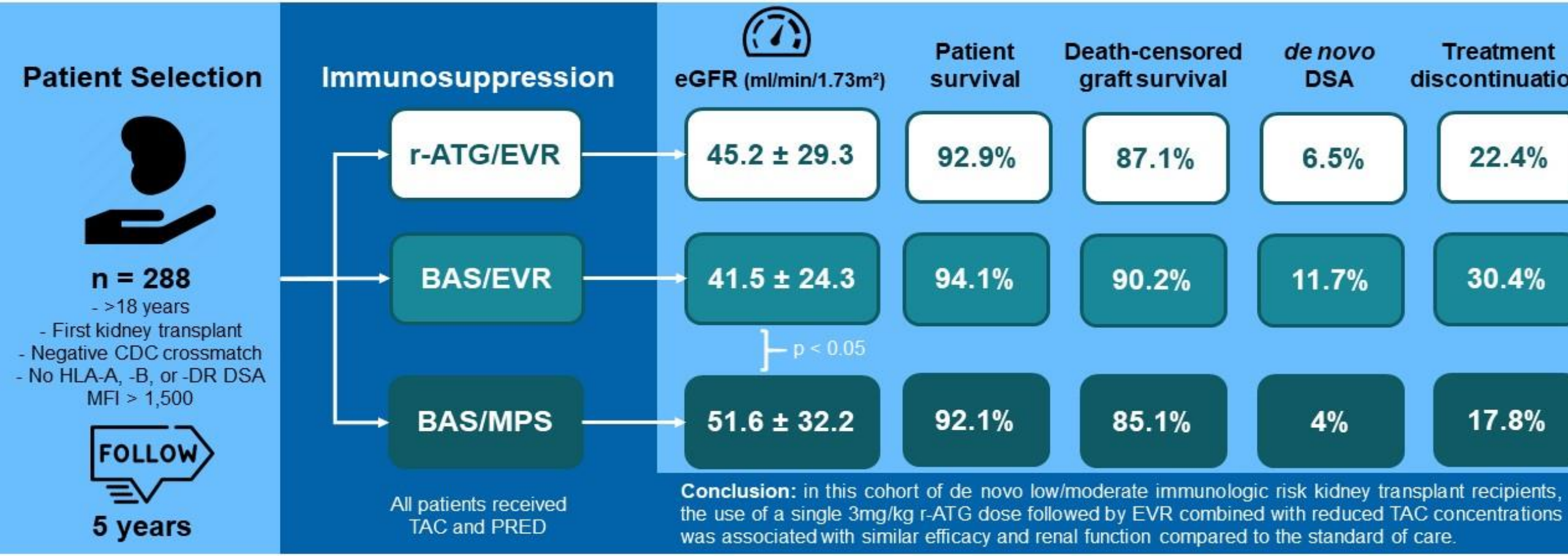
Sommerer et al., 2019

Long-term efficacy and safety of everolimus versus mycophenolate in kidney transplant recipients receiving tacrolimus.



r-ATG: rabbit antithymocyte globulin; EVR: everolimus; BAS: basiliximab; MPS: mycophenolate sodium; TAC: tacrolimus; PRED: prednisone

Ficher KN et al. *Transplantation*. 2021

Transplantation

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Sirolimus in combination with low-dose extended-release tacrolimus in kidney transplant recipients

Zhi-yu Zou[1], Lin-rui Da

Introduction: Many challenges remain for long-term survival of renal allografts. Once-daily sirolimus (SRL) combined with low-dose extended-release tacrolimus (LER-TAC) may improve medication adherence and reduce the potential nephrotoxicity of calcineurin inhibitors (CNI) compared with standard immunosuppression regimens, thus potentially improving long-term graft survival.

Methods: This retrospective, observational, single-center, propensity score matching (PSM) study compared conversion to SRL combined with low-dose ER-TAC and mycophenolic acid (MPA) combined with standard-dose TAC in kidney transplant recipients. After PSM, there were 56 patients in each group. Efficacy, safety, and medication adherence were evaluated over 12 months.

Results: There was no significant difference between the two groups in terms of graft and recipient survival and incidence of biopsy-proven acute rejection ($p = 1.000$), and none of the recipients developed dnDSA after conversion. The mean eGFR improved in SRL + LER-TAC group after conversion compared to before conversion ($51.12 \pm 20.1\,ml/min/1.73\,m^2$ vs. $56.97 \pm 19.23\,ml/min/1.73\,m^2$, $p < 0.05$). The medication adherence at 12 months after conversion was superior to before conversion ($p = 0.002$).

Discussion: Our findings suggest that an immunosuppressive regimen of SRL combined with low-dose ER-TAC is no less effective and safe than standard immunosuppressive regimens for renal transplant recipients and may improve graft renal function and medication adherence.

Comparison of the efficacy and safety of low-dose calcineurin inhibitors plus sirolimus plus mycophenolic acid with the standard-dose calcineurin inhibitors plus mycophenolic acid regimen in patients who received kidney transplants

Li Li[1], Jiao Wan[1], Yizhi Li[2], Jiali Fang[1], Guanghui Li[1], Junjie Ma[1] and Zheng Chen[1]*

Background: Sirolimus (SRL) has shown its anti-rejection and renoprotective efficacy in patients with kidney transplantation. However, more evidence is still needed. The current study aimed to evaluate the efficacy and safety of an SRL-containing regimen in patients who received kidney transplants.

Methods: Fifty patients with end-stage renal disease who received kidney transplants were enrolled and divided into the calcineurin inhibitors (CNI) + mycophenolic acid (MPA)+ glucocorticoid (N = 22) and CNI + MPA + SRL + glucocorticoid groups (N = 28) according to the actual regimen that they received. The minimal plasma concentration of tacrolimus and cyclosporin was maintained at 6–10 ng/mL and 150–250 ng/mL in the CNI + MPA + glucocorticoid group and 4–6 ng/mL and 75–125 ng/mL in the CNI + MPA + SRL + glucocorticoid group. The minimal plasma concentration of SRL was maintained at 5–8 ng/mL.

Results: The Cr at month (M)6, M12, and uric acid at M3 were lower, while the eGFR at M12 was higher in the CNI + MPA + SRL + glucocorticoid group compared with the CNI + MPA + glucocorticoid group (all $P < 0.05$). The acute rejection rate showed a lower trend in the CNI + MPA + SRL + glucocorticoid group compared with the CNI + MPA + glucocorticoid group without statistical significance. The urine BK virus at M3, M6, M9, and M12 was lower in the CNI + MPA + SRL + glucocorticoid group compared with the CNI + MPA + glucocorticoid group (all $P < 0.05$). Incidence of most adverse events was similar between groups, except that BK virus was lower in the CNI + MPA + SRL + glucocorticoid group compared with the CNI + MPA + glucocorticoid group (0.0% vs. 36.4%, $P < 0.01$).

Article

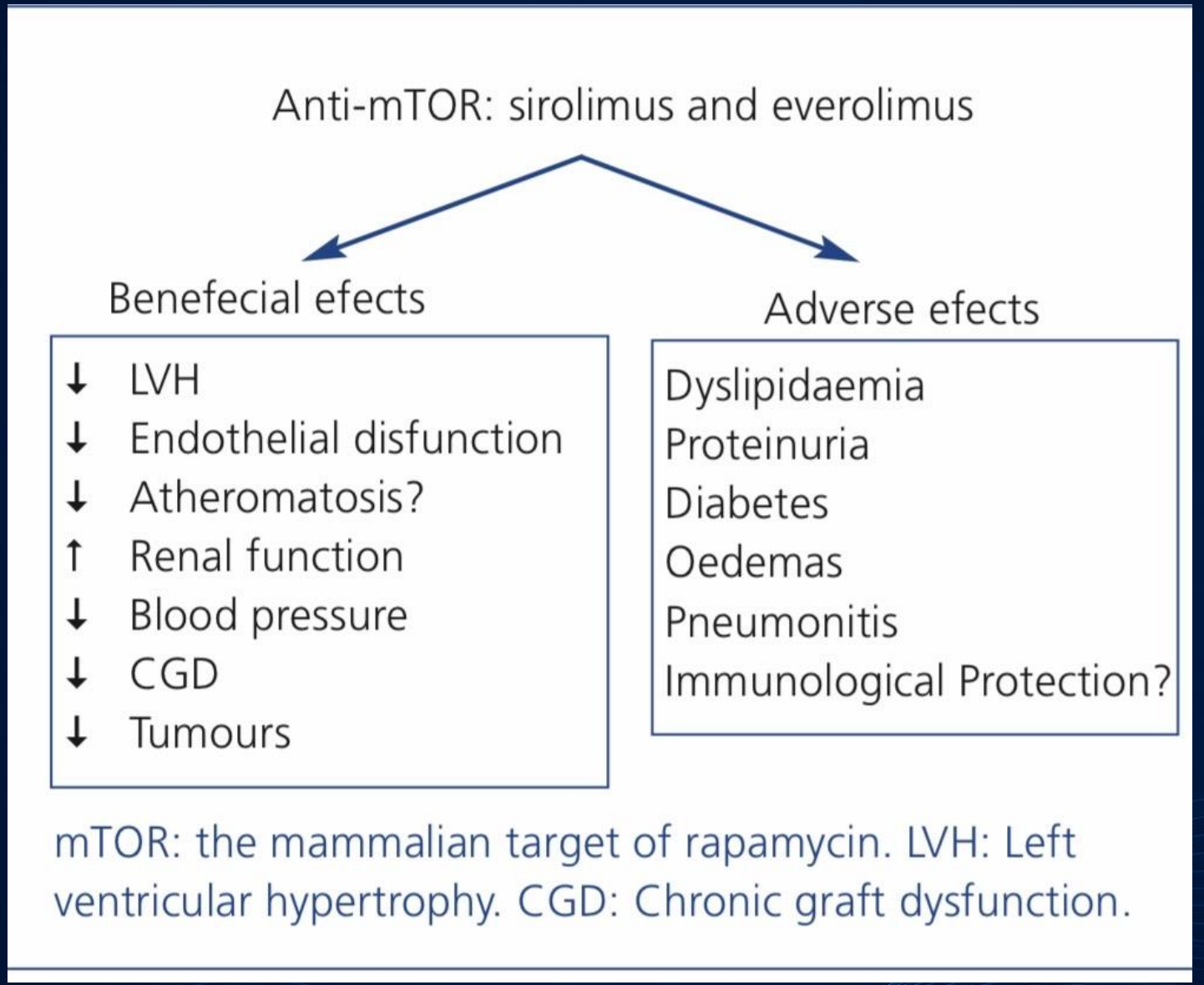
Tacrolimus–Sirolimus Combined Exposure and Acute Rejection in Kidney Transplant Recipients Undergoing Early Conversion to Sirolimus: A Multicenter Retrospective Cohort Threshold Analysis

Byunghyun Choi [1,†], Youngmin Ko [2,†], Jin-Myung Kim [2], Hye Eun Kwon [2], Young Hoon Kim [2], Sung Shin [2], Joo Hee Jung [2] and Hyunwook Kwon [2,*]

- Maintaining a combined trough level ≥11.6 ng/mL may provide the safest immunosuppressive coverage, while 8.5–11.6 ng/mL could be considered in lower-risk or dose-reduction settings

- concentrations below 8.5 ng/mL within the first post-transplant year appear to carry a markedly increased rejection risk.

- possible nephrotoxic synergy between sirolimus and higher tacrolimus exposure (≥7.0 ng/mL), underscoring the need for careful trough level optimization


Anti-mTOR: sirolimus and everolimus
Benefecial efects
↓ LVH
↓ Endothelial disfunction
↓ Atheromatosis?
↑ Renal function
↓ Blood pressure
↓ CGD
↓ Tumours
Adverse efects
Dyslipidaemia
Proteinuria
Diabetes
Oedemas
Pneumonitis
Immunological Protection?
mTOR: the mammalian target of rapamycin. LVH: Left ventricular hypertrophy. CGD: Chronic graft dysfunction.

- Calcineurin inhibitors remain the cornerstone of kidney transplant immunosuppression, but long-term toxicity?

- Combining mTOR inhibitors + reduced dose CNI allows effective immunosuppression while minimizing toxicity

- • Clinical consistently support the feasibility of CNI minimization in appropriately selected recipients

- “The goal is not CNI elimination; the goal is achieving the lowest effective CNI exposure while preserving long-term graft function

THANK YOU!