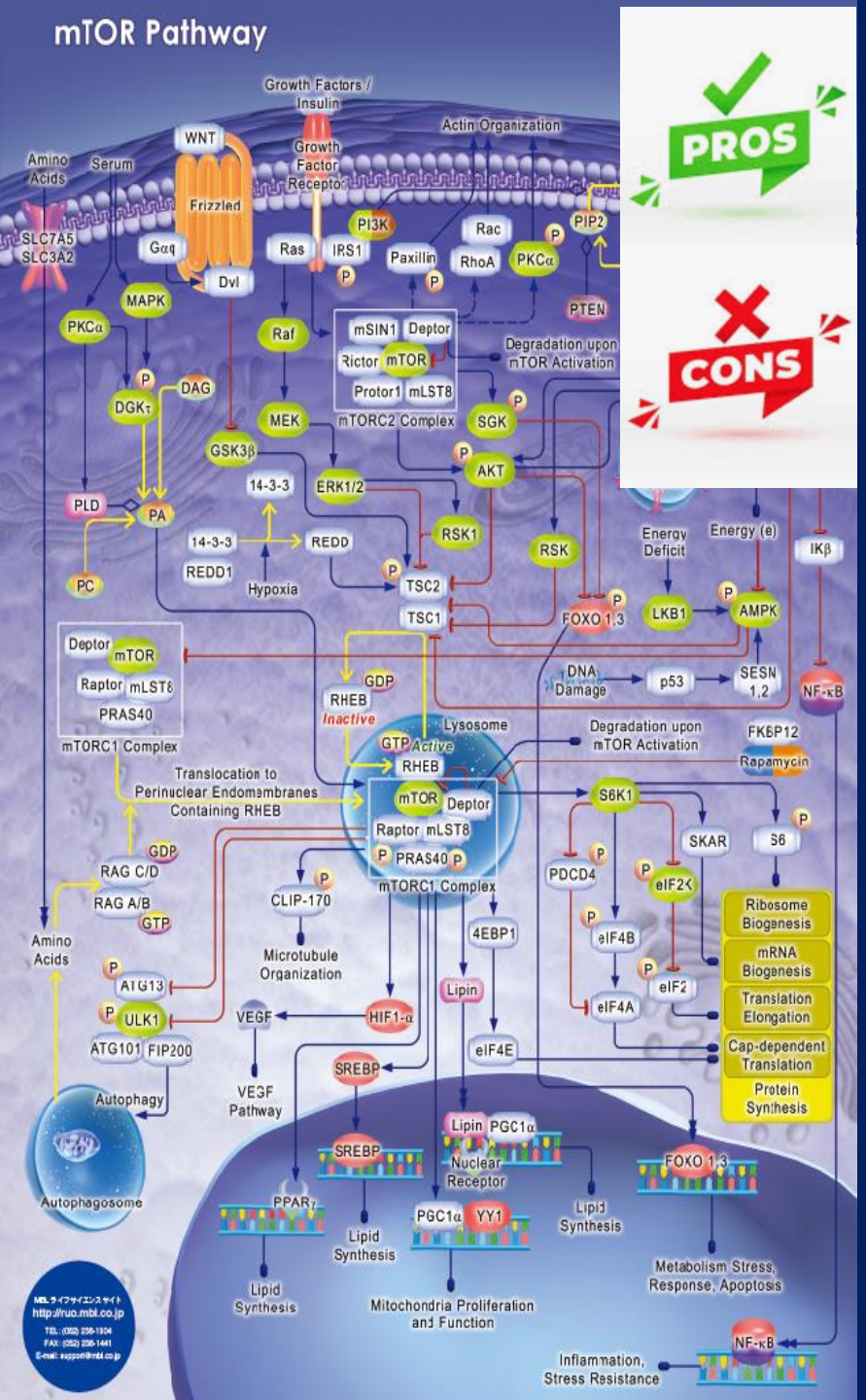


IN THE NAME OF GOD

Late Conversion To mTORi Pros and Cons

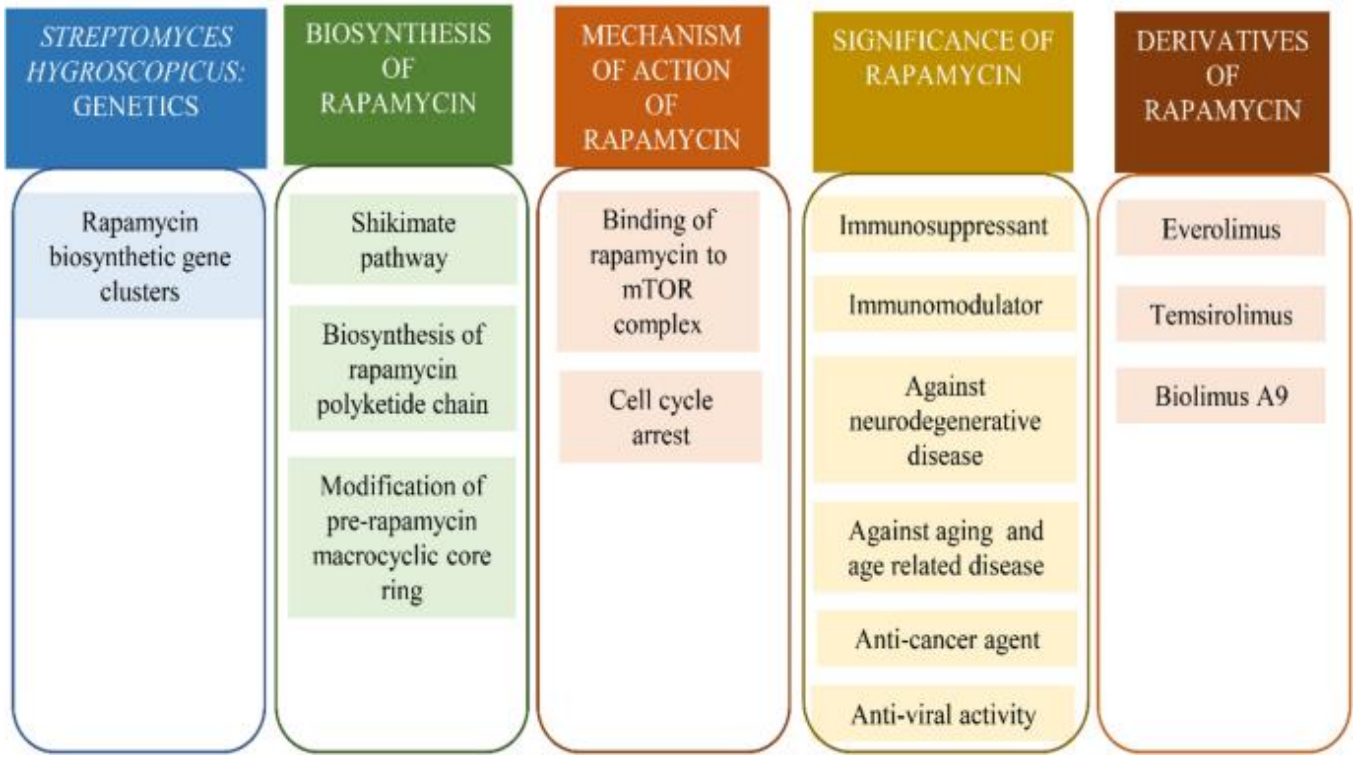
F.Samadian
Shaheed beheshti university of medical science

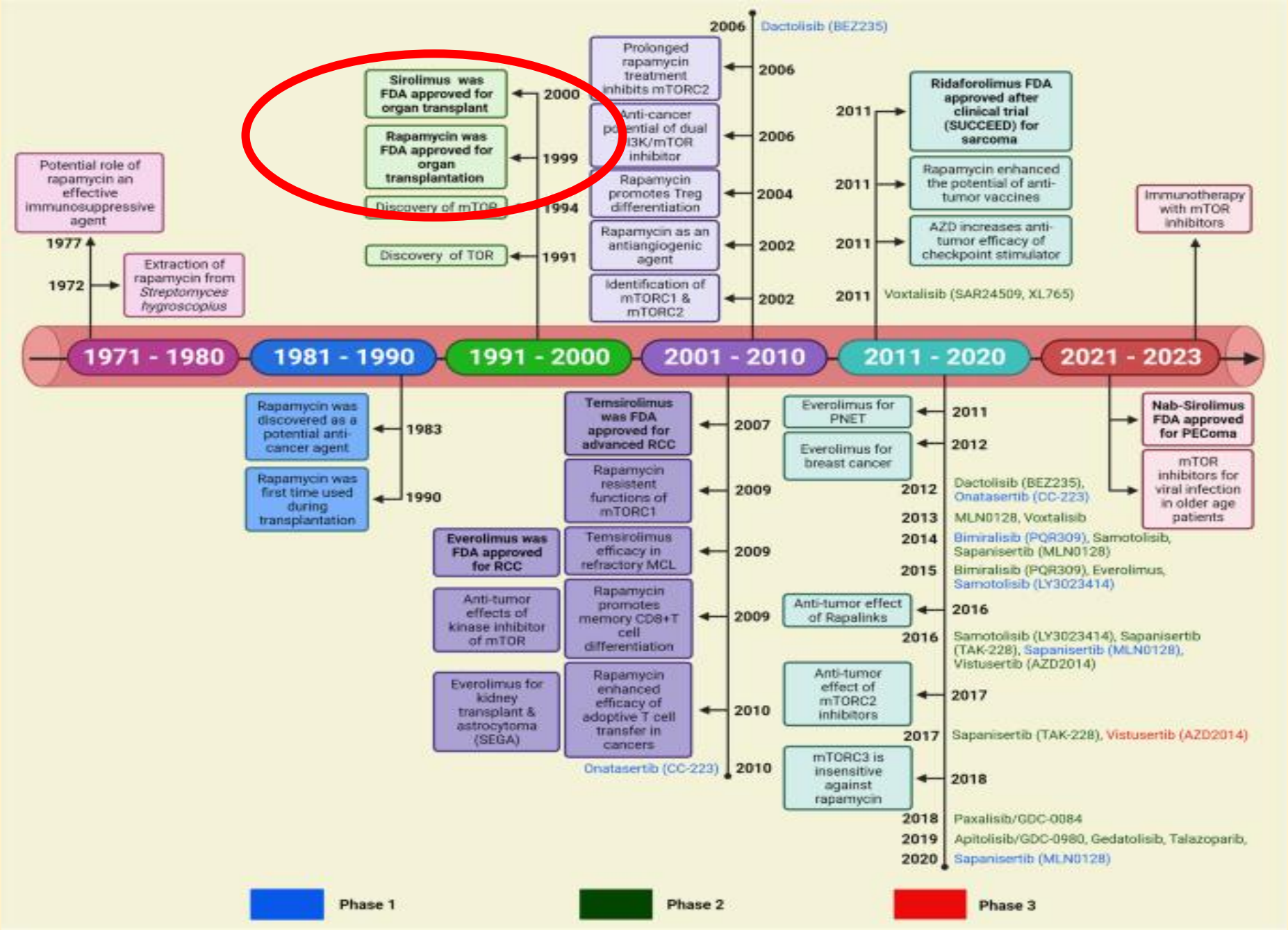
IN BRIEF

The story of the natural product rapamycin begins more than 50 years ago in one of the most isolated places on Earth. Through the curiosity, commitment, and hard work of scientists, the compound has led to several approved

Rapamycin: A versatile bioactive compound from *Streptomyces hygroscopicus*

Streptomyces hygroscopicus
had immunosuppressive, antitumor and antifungal activity





History of research on the discovery and development of mTOR signaling

The landscape of kidney transplantation has changed notably, moving from an incidence of acute kidney graft rejection of >80% in the early ages to <10% nowadays, as a result of the advances in transplant immunosuppression.

The advances in transplant immunosuppression have reduced substantially the incidence of kidney graft rejection.

In recent years, the focus has moved from preventing rejection to preventing the long-term consequences of long-standing immunosuppression, including nephrotoxicity induced by calcineurin inhibitors (CNI), as well as infectious and neoplastic complications.

Since the appearance in the late 1990s of mTOR inhibitors (mTORi), these unmet needs in immunosuppression management could be addressed thanks to their benefits (reduced rate of viral infections and cancer).

However, management of side effects can be troublesome and hands-on experience is needed.

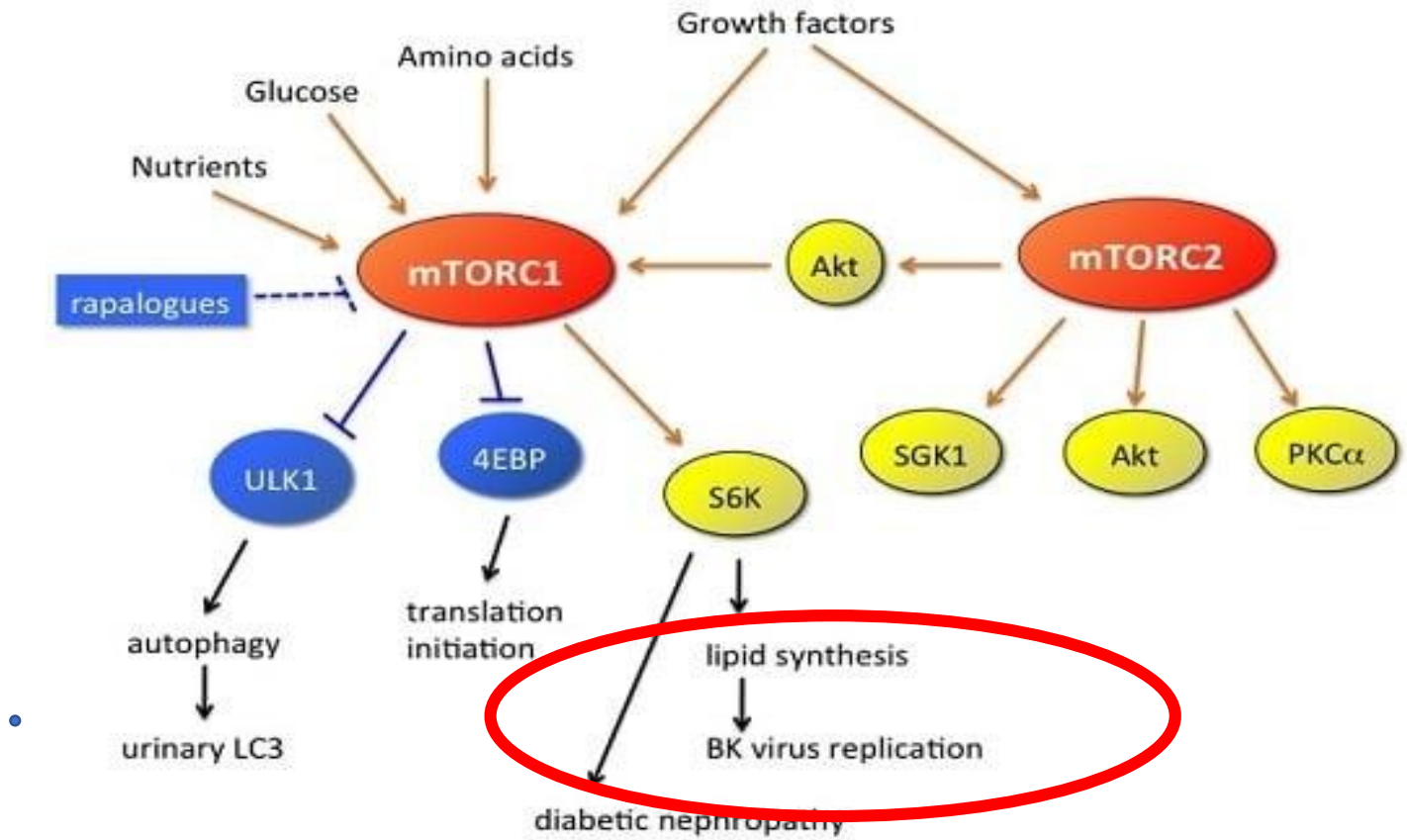
International Journal of
Molecular Sciences

MDPI

Review

Role of mTOR Inhibitors in Kidney Disease

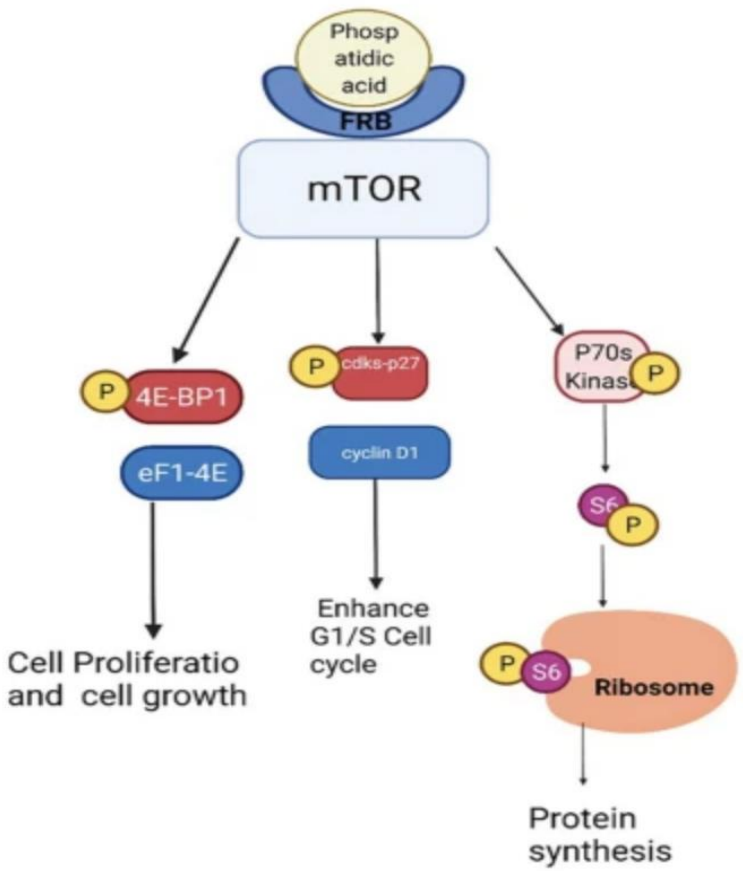
Moto Kajiwara and Satohiro Masuda *

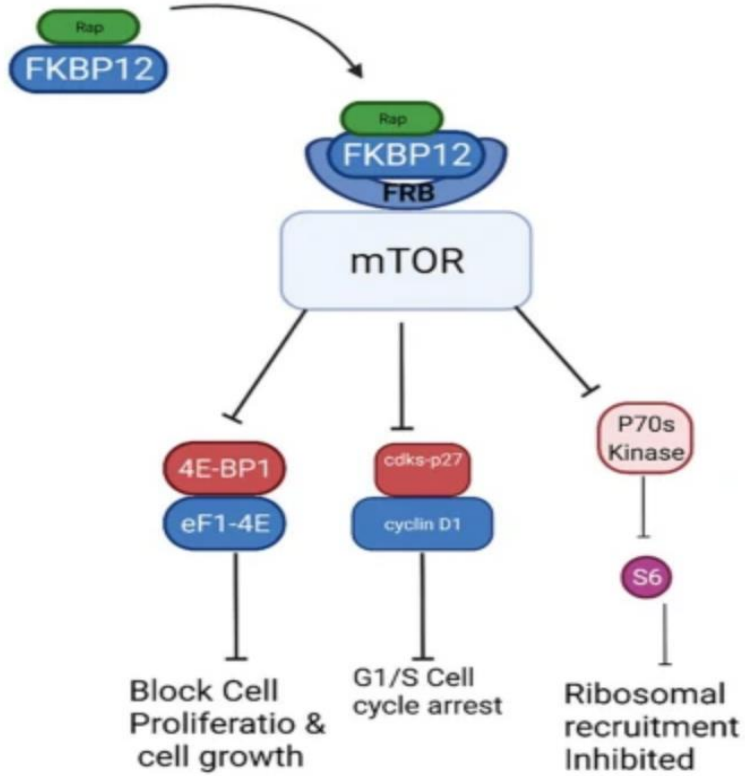


(mTOR) is a central controller of cell growth, proliferation, metabolism and angiogenesis.

Mechanism of action

- Rapamycin and its analogs (all termed rapalogs) first form a complex with the intracellular receptor FK506 binding protein 12 (FKBP12) and then bind a domain separated from the catalytic site of mTOR, blocking mTOR function





1. Reduced CNI Toxicity

CNIs are nephrotoxic over time, potentially causing chronic kidney damage

Switching to mTOR inhibitors can preserve renal function by reducing CNI exposure.

2. Anti-Cancer Properties

mTOR inhibitors have anti-proliferative and anti-angiogenic effects, lowering the risk of certain cancers, especially post-transplant malignancies like Kaposi sarcoma and skin cancer.

3. Improved Protein Synthesis

By inhibiting mTOR, these drugs can help modulate cell growth and proliferation, potentially reducing chronic allograft damage.

4. Potential Cardiovascular Benefits

mTOR inhibitors may improve lipid metabolism and have anti-atherosclerotic effects, which can benefit cardiovascular health in transplant patients.

5. Reduced Risk of Viral Infections

- mTOR inhibitors are associated with a lower risk of CMV (cytomegalovirus) and BK virus reactivation compared to CNIs

6. Bone Health Preservation

- They may have a lesser impact on bone mineral density compared to CNIs, which can cause osteoporosis.

1. Delayed Wound Healing

mTOR inhibitors impair wound healing due to their anti-proliferative effects, making them unsuitable for …

2. Adverse Effects on Proteinuria

Patients with pre-existing proteinuria may experience worsening of this condition

3. Side Effects Common adverse effects include mouth ulcers, hyperlipidemia, edema, and pneumonitis, which can affect patient compliance.

4. Risk of Acute Rejection

Transitioning to mTOR inhibitors may increase the risk of acute rejection if not carefully managed, particularly in patients with *borderline or unstable graft function*.

5. Impact on Quality of Life

- mTOR inhibitors can cause side effects like fatigue, rash, or stomatitis, which may negatively impact the patient's quality of life.

6. Need for Close Monitoring

- The transition requires careful monitoring of drug levels, renal function, and side effects, necessitating *more frequent medical visits and adjustments*.

7. Not Suitable for All Patients

- Contraindications include severe proteinuria, recent infections, or high immunologic risk, limiting the applicability of mTOR inhibitors

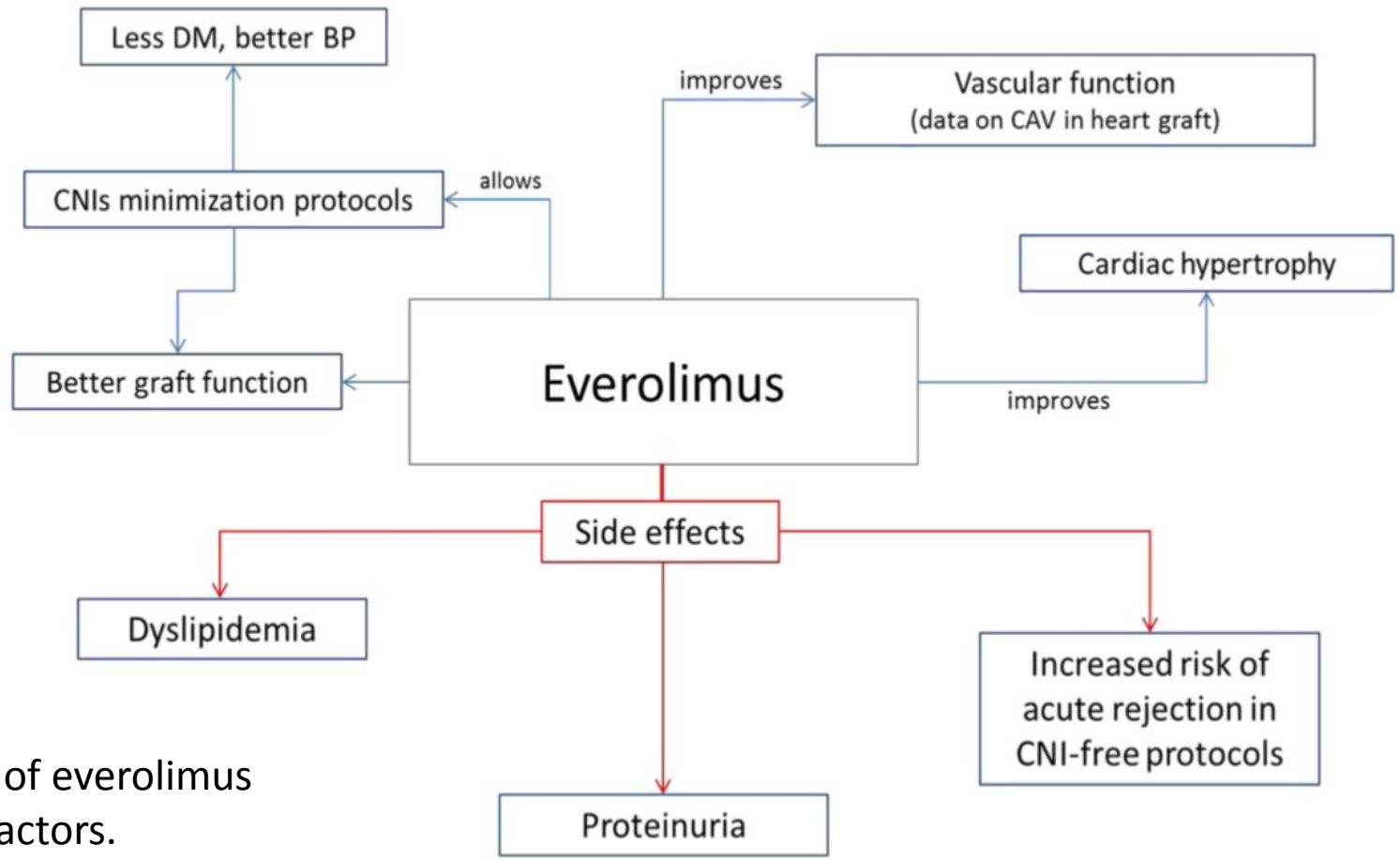
Journal of Nephrology (2020) 33:69–82
https://doi.org/10.1007/s40620-019-00609-y

REVIEW

Everolimus in kidney transplant recipients at high cardiovascular risk: a narrative review

Ernesto Paoletti[1] · Franco Citterio[2] · Alberto Corsi
Elisabetta Bussalino[1] · Giovanni Stallone[8] · ENTROP

Received: 2 January 2019 / Accepted: 5 April 2019 / Published onlin



The potential association of everolimus
With cardiovascular risk factors.

Sirolimus and mTOR Inhibitors: A Review of Side Effects and Specific Management in Solid Organ Transplantation

Lee S. Nguyen[1,2] · Mathieu Vautier[3] · Yves Allenbach[3] · Noel Zahr[1] · Olivier Benveniste[3] · Christian Funck-Brentano[1] · Joe-Elie Salem[1]

late healing

thrombotic microangiopathy

pneumonitis

hypertriglyceridaemia, hypercgolesterolaemia

proteinuria

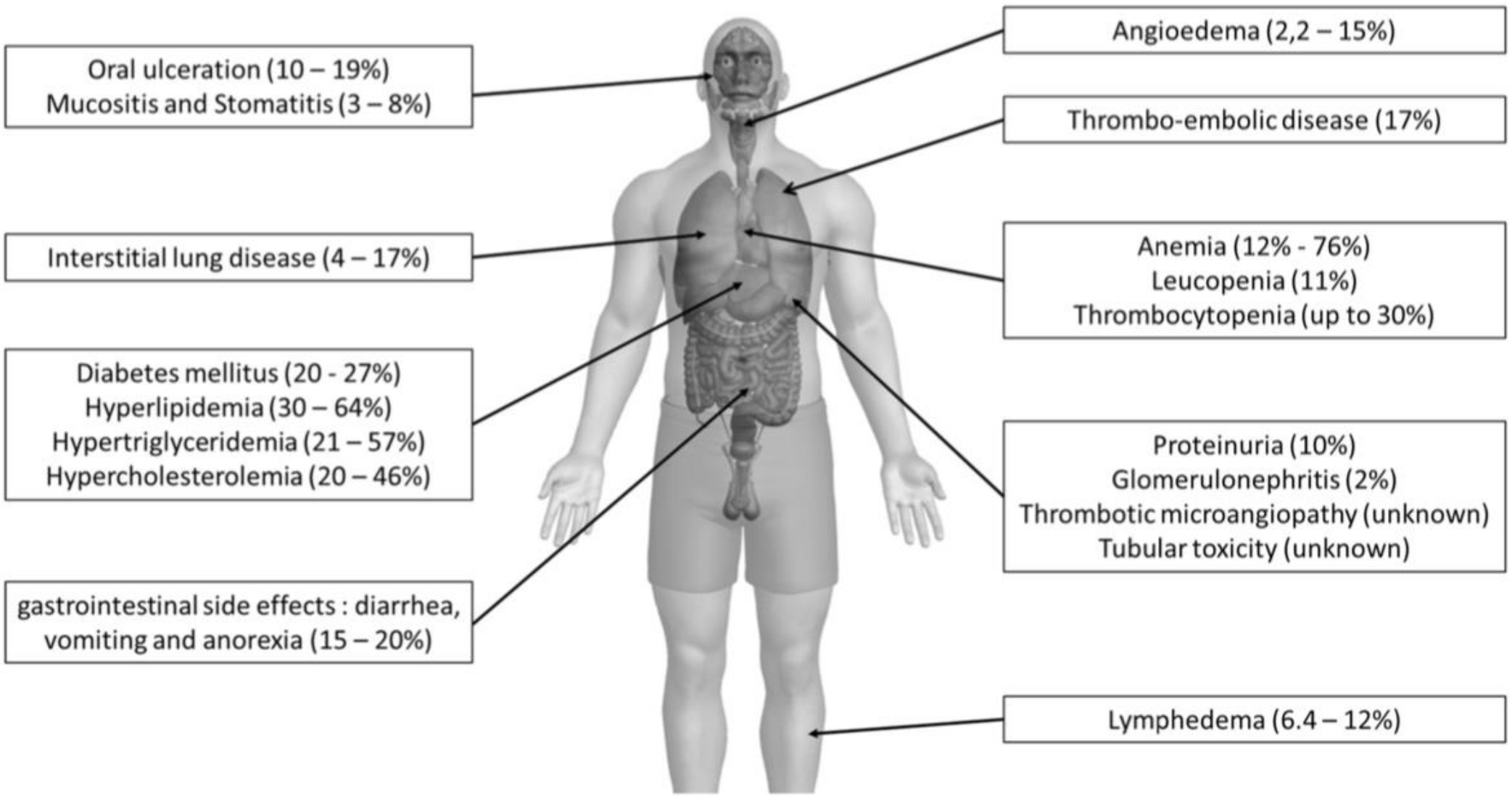
surgical scar infection

lymphocele

The use of mechanistic target of rapamycin (mTOR) inhibitors is associated with various adverse events, all related to mTOR-induced pathways that are blocked. They include (but are not limited to) insulin resistance and diabetes, glomerular dysfunction and renal failure, dyslipidemia, mucositis, pneumonitis, lymphedema, angioedema and osteonecrosis.

Discontinuation of mTOR inhibitors usually leads to resolution of adverse events, but long-term sequelae can occur. Therefore, close monitoring is required when using such treatments.

PTDM



KnoWn side effects associated With (mTOR) inhibitors

- In 1996, the first study about the use of mTORi in kidney transplant recipients was published

Kidney International, Vol. 49 (1996), pp. 209–216

The side effect profile of sirolimus: A phase I study in quiescent cyclosporine-prednisone-treated renal transplant patients

MARIA G. MURGIA, SAMANTHA JORD

Division of Immunology and Organ Transplantation, Department of Surgery,

study was conducted in 43 quiescent renal transplant patients who for at least **six months had borne well-functioning allografts,** as defined by glomerular filtration rates (GFR) > 40 ml/min. All patients had been maintained for at least three months on CsA oral doses that achieved stable therapeutic blood levels

The side effect profile of sirolimus: A phase I study in quiescent cyclosporine-prednisone-treated renal transplant patients. A 14-day ascending dose course of sirolimus (rapamycin, RAPA) was administered to quiescent renal transplant patients receiving a double-drug cyclosporine (CsA)/corticosteroid regimen in a double-blinded randomized study. Oral sirolimus or placebo was delivered twice daily in divided doses for 13 days

respo
chem
trans

proteins that regulate induction of cytokine transcription, thereby preventing the progression of T cells from the G_0 to the G_1 phase

NO difference in terms of renal function, liver function tests, cyclosporine levels and blood pressure.

Side effects were thrombocytopenia (dose-related) and mild leucopenia (dose-unrelated), as well as an increase in total cholesterol level, while triglycerides were not affected

PubMed®

Advanced

Clinical Trial > Transplantation 1999 Apr 15;67(7):1036-42

doi: 10.1097/00007890-199904150-00017.

Sirolimus (rapamycin)–based thera transplantation: similar efficacy ar toxicity compared with cyclosporin European Renal Transplant Study G

Methods: In 11 European centers, first cadaveric renal allograft recipients were randomized to CsA (n=42) or sirolimus (n=41). Dosing of these agents was concentration-controlled and open-labeled. All patients received corticosteroids and azathioprine.

n a phase-II trial, 83 patients were randomized to receive either cyclosporine (200–400 ng/mL for the first two months and 100–200 thereafter, *n* = 42) or SRL, (target trough levels 30 ng/mL for the first two months and 15 ng/mL thereafter, *n* = 41) without induction

The two drugs were associated with AZA and steroids.

Results were comparable in terms of acute rejection (41% for SRL and 38% for CsA), while a consistent improvement in renal function was noted in the mTORi group, along with less incidence of tremor and hypertension.

However, the ***very high trough levels*** reached with SRL were associated with leuco thrombocytopenia, dyslipidemia and mTORi-associated pneumonia

Conclusions: Results at 12 months suggest that *sirolimus can be used as base therapy in the prophylaxis of acute renal transplant rejection,* and has a safety profile that differs from CsA.

A phase-III double-blind multicenter trial published in the Lancet in 2000 validated the benefit of the CsA and SRL combination in comparison with CsA and AZA [58].

Clinical Trial > Lancet. 2000 Jul 15;356(9225):194-202.
doi: 10.1016/s0140-6736(00)02480-6.

Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. The Rapamune US Study Group

B D Kahan [1]

prospective, multicentre, randomised, double-blind trial to investigate the impact of the addition of sirolimus, compared with azathioprine, to a cyclosporin and prednisone regimen.

Interpretation: Use of sirolimus reduced occurrence and severity of biopsy-confirmed acute rejection episodes with no increase in complications. Further studies are needed to establish the optimum doses for the combined regimen.

big question was the possibility to avoid the use of CNI

JOHNS HOPKINS UNIVERSITY

Home Profiles Research units **Research output**

Inhibitors of mTOR and risks of allograft failure and mortality in kidney transplantation

T. Isakova, H. Xie, S. Messinger, F. Cortazar, J. J. Scialla, G. Guerra, G. Contreras, D. Roth, G. W. Burke, M. Z. Molnar, I. Mucsi, M. Wolf

between 1999 through 2010

139,370 recipients

comparing clinical outcomes among users of mTORIs versus calcineurin inhibitors (CNI) in their primary immunosuppresive regimen.

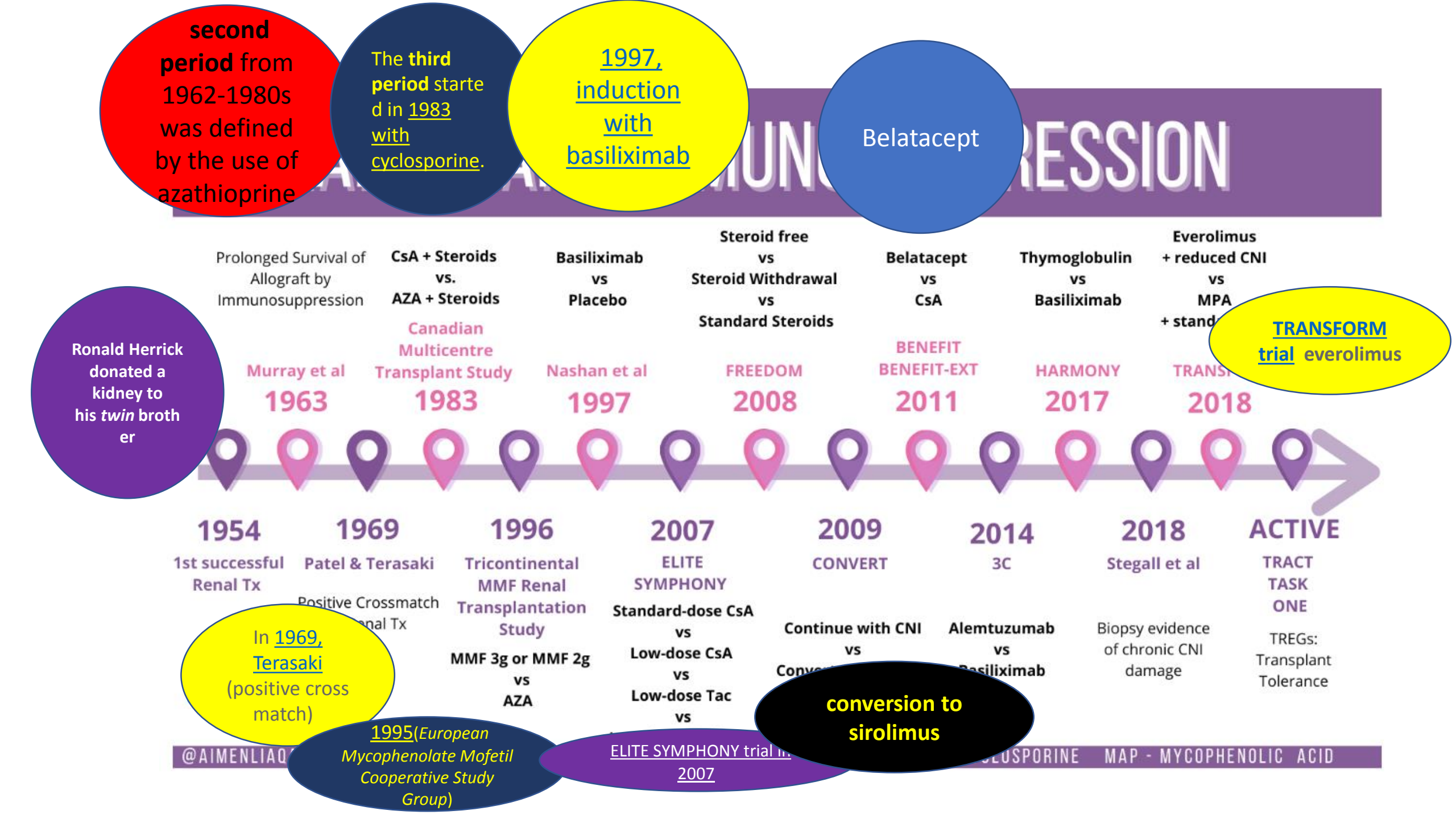
During the first 2 years posttransplantation, primary use of mTORIs without CNIs (N = 3237) was associated with greater risks of allograft failure and death compared with a CNI-based regimen (N = 125

During years 2–8, primary use of mTORIs without CNIs was independently as- sociated with greater risks of death (HR 1.25; 95% CI, 1.11–1.41) and the composite (HR 1.17; 95%CI, 1.08– 1.27) in fully adjusted analyses.

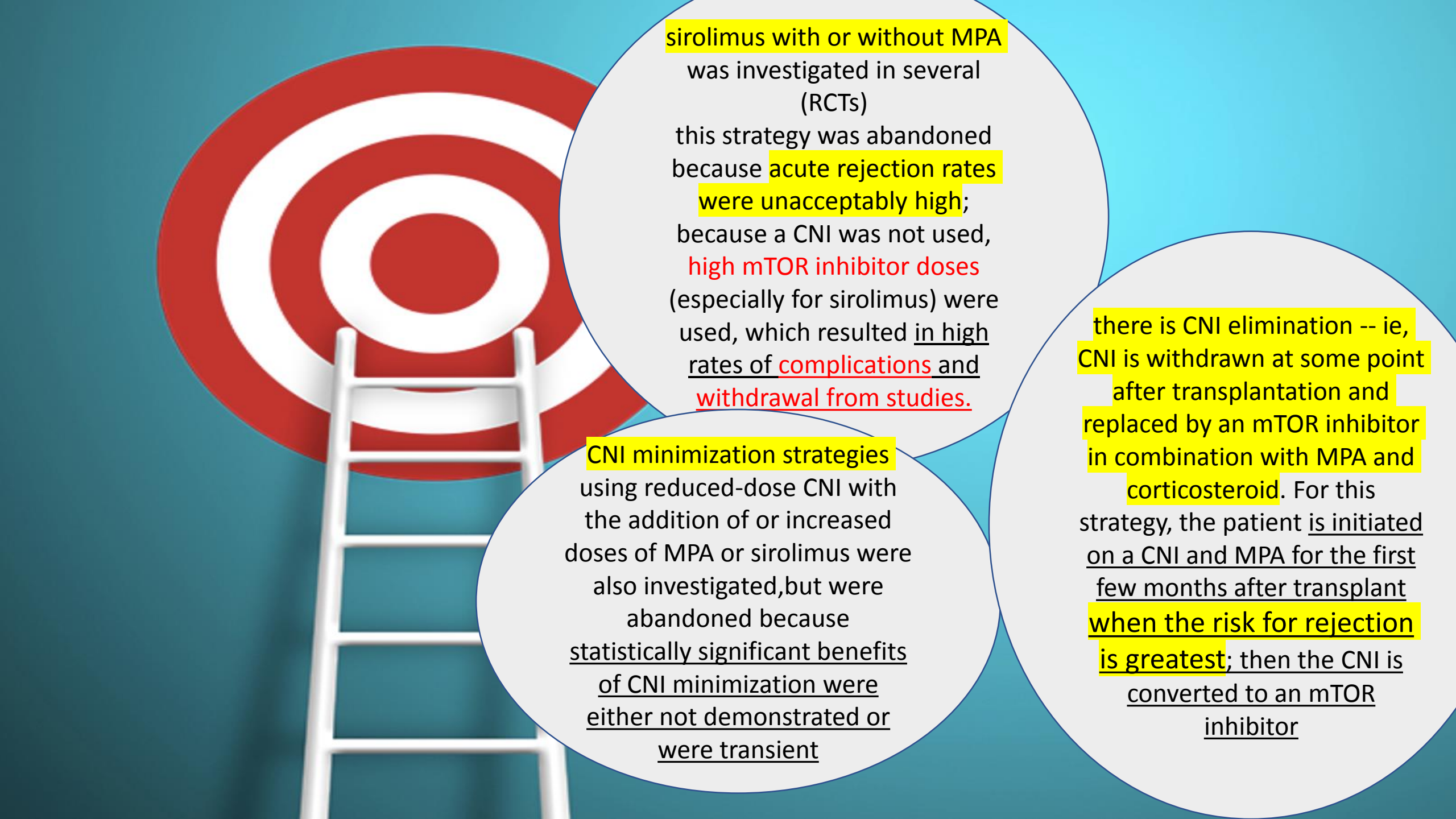
Compared with CNI-based regimens, use of an mTORI-based regimen for primary immunosup- pression in kidney transplantation was associated with inferior recipient survival

Calcineurin Inhibitor Conversion

In order to avoid early acute rejection while preserving kidney function in the long term, a number of calcineurin inhibitor conversion regimens have been explored using either **belatacept** or **mTOR inhibitors** as the primary immu- nosuppressive agent


second period from 1962-1980s was defined by the use of azathioprine
The third period started in 1983 with cyclosporine.
1997, induction with basiliximab
Belatacept
RESSION
Prolonged Survival of Allograft by Immunosuppression
CsA + Steroids vs. AZA + Steroids
Basiliximab vs Placebo
Steroid free vs Steroid Withdrawal vs Standard Steroids
Belatacept vs CsA
Thymoglobulin vs Basiliximab
Everolimus + reduced CNI vs MPA + stand
Ronald Herrick donated a kidney to his twin brother
TRANSFORM trial everolimus
Murray et al
1963
Canadian Multicentre Transplant Study
1983
Nashan et al
1997
FREEDOM
2008
BENEFIT
BENEFIT-EXT
2011
HARMONY
2017
TRANSF
2018
1954
1st successful Renal Tx
1969
Patel & Terasaki
Positive Crossmatch
nal Tx
1996
Tricontinental MMF Renal Transplantation Study
MMF 3g or MMF 2g vs AZA
2007
ELITE SYMPHONY
Standard-dose CsA vs Low-dose CsA vs Low-dose Tac vs
2009
CONVERT
Continue with CNI vs
Conv
2014
3C
Alemtuzumab vs
asiliximab
2018
Stegall et al
Biopsy evidence of chronic CNI damage
ACTIVE
TRACT
TASK
ONE
TREGs: Transplant Tolerance
In 1969, Terasaki (positive cross match)
1995(European Mycophenolate Mofetil Cooperative Study Group)
ELITE SYMPHONY trial in 2007
conversion to sirolimus
@AIMENLIAQ
LOSPORINE
MAP - MYCOPHENOLIC ACID

Three renal-sparing strategies aimed at decreasing exposure of kidney transplant allografts to the nephrotoxic effects of CNIs have been studied

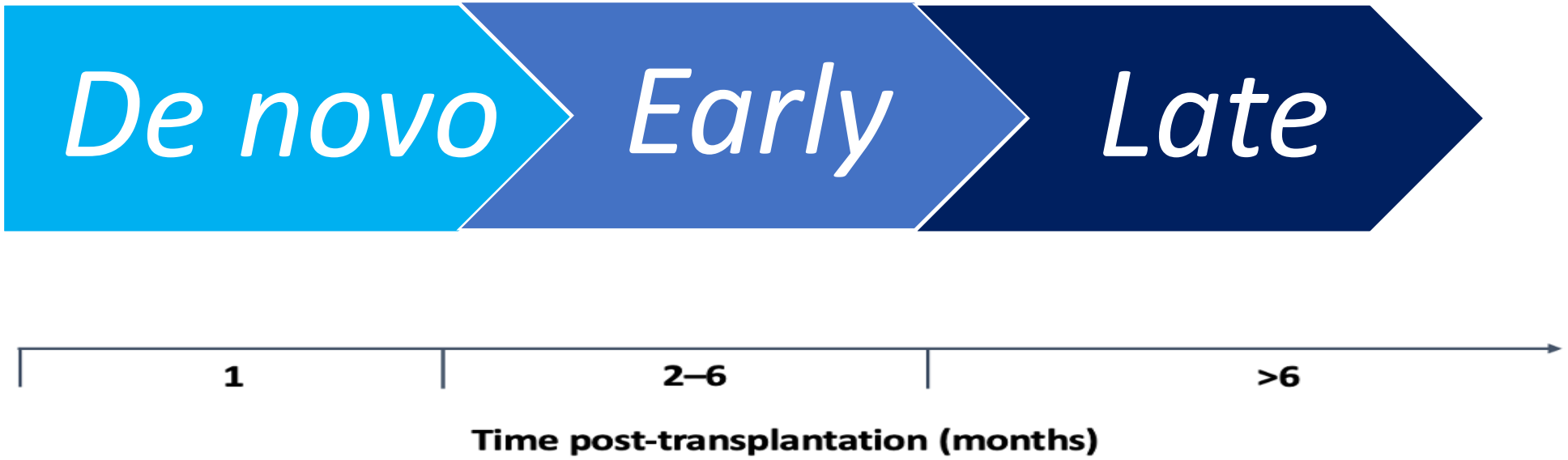


sirolimus with or without MPA was investigated in several (RCTs)
this strategy was abandoned because acute rejection rates were unacceptably high;
because a CNI was not used, high mTOR inhibitor doses (especially for sirolimus) were used, which resulted in high rates of complications and withdrawal from studies.

CNI minimization strategies using reduced-dose CNI with the addition of or increased doses of MPA or sirolimus were also investigated,but were abandoned because statistically significant benefits of CNI minimization were either not demonstrated or were transient

there is CNI elimination -- ie, CNI is withdrawn at some point after transplantation and replaced by an mTOR inhibitor in combination with MPA and corticosteroid. For this strategy, the patient is initiated on a CNI and MPA for the first few months after transplant when the risk for rejection is greatest; then the CNI is converted to an mTOR inhibitor

CNI Conversion



Comparisons between early and late conversion to mTOR inhibitors (mTORi) in kidney transplantation reveal key differences in outcomes:

1. Early Conversion:

Switching from calcineurin inhibitors (CNIs) to mTORi within the first months post-transplantation generally improves renal function.
Trials like SMART and ZEUS observed ***significant increases in glomerular filtration rate (GFR).***

However, early conversion may increase the risk of ***proteinuria*** and adverse events like ***stomatitis*** or ***hyperlipidemia.***

2. Late Conversion:

Later transitions often carry fewer risks of acute rejection but may result in **less pronounced renal benefits compared to early conversion.**

Both strategies can maintain similar patient and graft survival rates, but side effects and long-term outcomes vary

The SYMPHONY study

Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

The NEW ENGLAND JOURNAL of MEDICINE

Regimen tested	n	eGFR (C-G)	BPAR (%)	Allograft Survival (%)
Standard-dose CSA (100-200 ng/mL thereafter)	390	57 ± 25	30.1	91.9
Low-dose CSA (50-100 ng/mL)	399	59 ± 25	27.2	94.3
Low-dose TAC (3-7 ng/mL)	401	65 ± 27	15.4	96.4
Low-dose SRL	399	57 ± 27	40.2	91.7

Ekberg, et al. *New Eng J Med* 2007;357:2562–2575.

The worst results in terms of graft survival, biopsy-proven acute rejection, and eGFR were observed in the sirolimus groups (3)

How to Use mTOR Inhibitors? The Search Goes On

ORION trial

443 patients with kidney transplants were randomized to:

sirolimus plus tacrolimus with tacrolimus elimination at week 13 (group 1)

sirolimus and mycophenolate (group 2)

tacrolimus and mycophenolate (group 3)

At 2 years, mean Nankivell **GFR** were not different among the 3 groups.
At 1 and 2 years, there were no statistically signifi- cant differences in patient or graft survival between groups 1 and 3 or groups 2 and 3

Group 2 experienced a 1-year acute rejection rate of 31.3% and was sponsor terminated.

The 1-year acute rejection rates for groups 1 and 3 were 15.2% and 8.2%, respectively.

American Journal of Transplantation 2011; 11: 1551–1552
Wiley Periodicals Inc.

American Journal of Transplantation 2012; 12: 1528–1540
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2012.03994.x

Conversion From Cyclosporine to Everolimus at 4.5 Months Posttransplant: 3-Year Results From the Randomized ZEUS Study

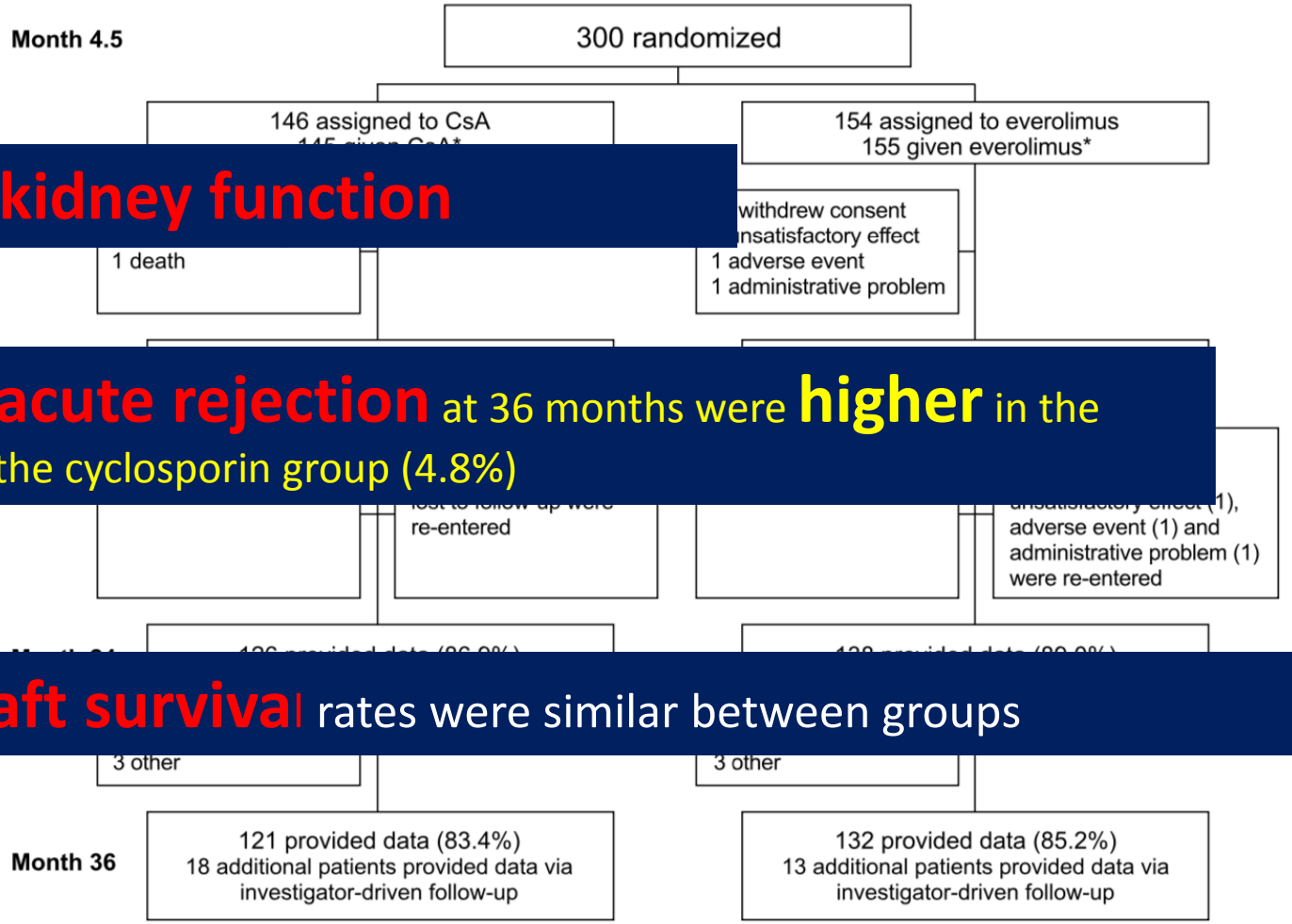
significant **improvement in kidney function**

Rates of **biopsy-proven acute rejection** at 36 months were **higher** in the **everolimus** group (13%) than in the cyclosporin group (4.8%)

Patient and graft survival rates were similar between groups

12-month, open-label, multicenter

300 kidney trans
randomized to continue cyclosporine (CsA) or convert to everolimus at 4.5 months posttransplant, outcomes were assessed at month 36 (n = 284; 94.7%).

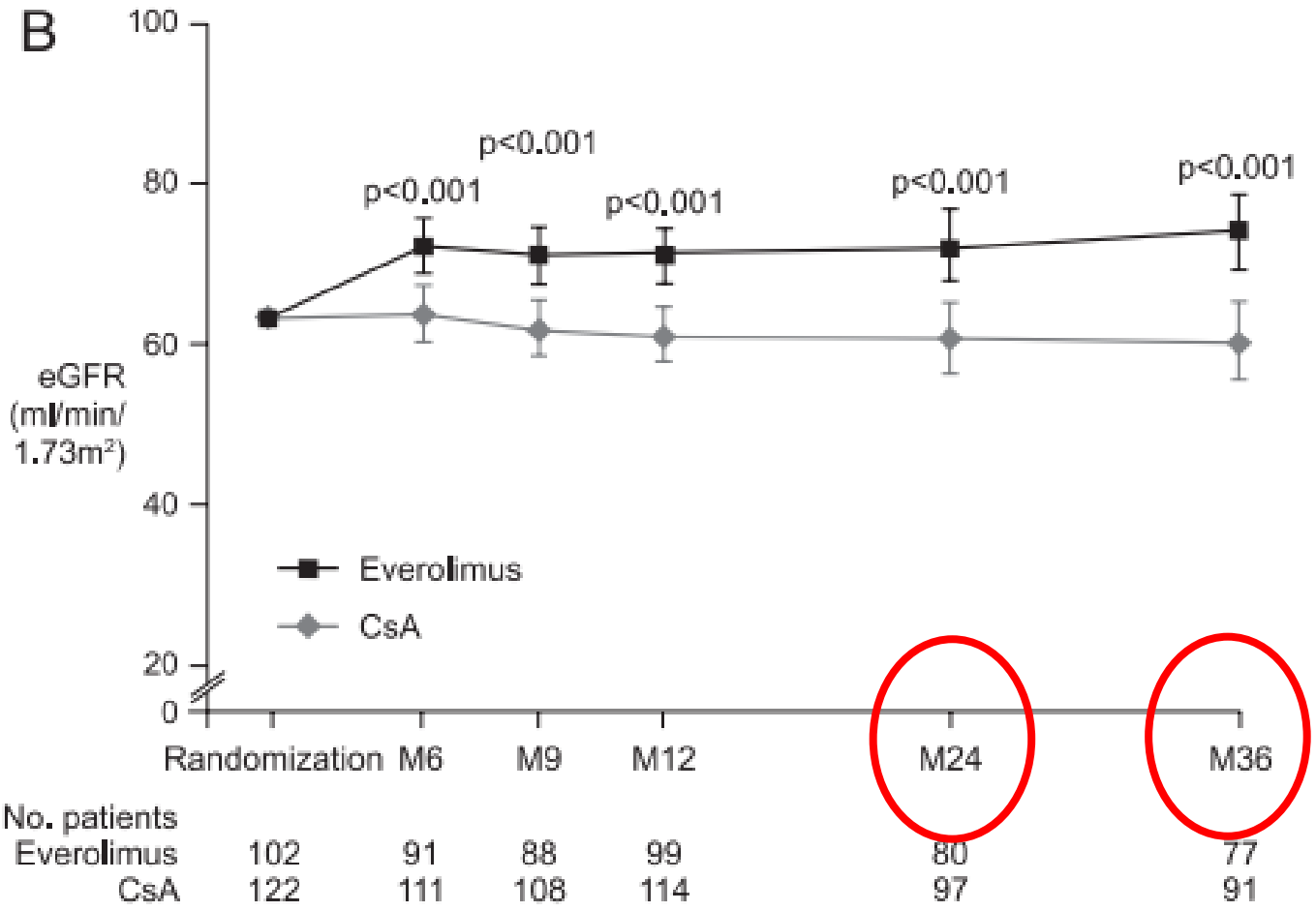


American Journal of Transplantation 2012; 12: 1528–1540
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2012.03994.x

Conversion From Cyclosporine to Everolimus at 4.5 Months Posttransplant: 3-Year Results From the Randomized ZEUS Study

patients who remain on an everolimus-based regimen beefit from a significant and clinically relevant improvement in renal function that is maintained to 3 years posttrans-plant, as demonstrated by the improved renal function in the on-therapy population.

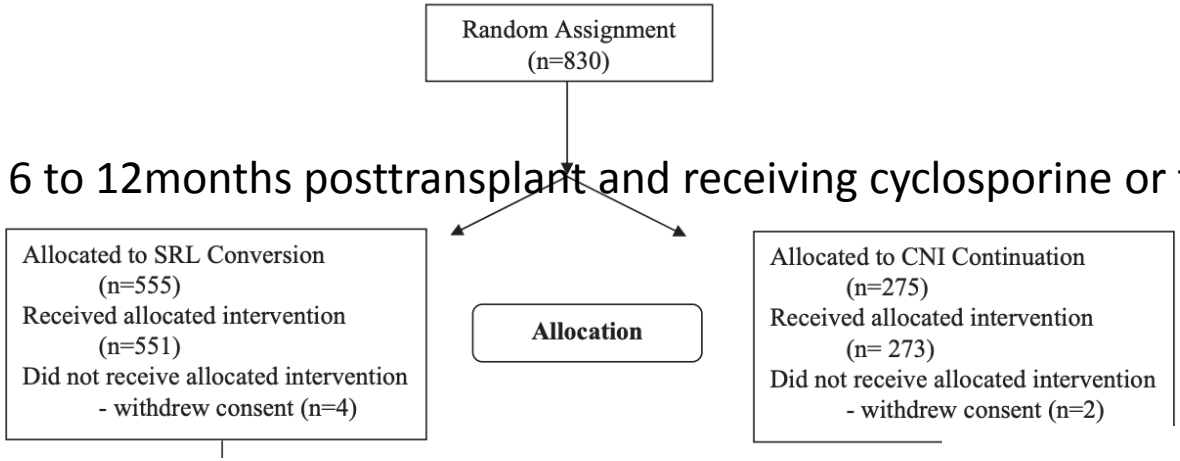


Conversion From Calcineurin Inhibitors to Sirolimus Maintenance Therapy in Renal Allograft Recipients: 24-Month Efficacy and Safety Results From the CONVERT Trial

Francesco P. Schena,[1,11] Michael D. Pascoe,[2] Josefina Alberu,[3] Maria del Carmen Rial,[4] Rainer Oberbauer,[5] Daniel C. Brennan,[6] Josep M. Cantisto[7] Lorraine Racusen,[8] Martin S. Polinsky,[9]

The efficacy and safety of converting maintenance renal transplant recipients CNIs to sirolimus was evaluated.

(Transplantation 2009;87: 233–242)



6 to 12months posttransplant and receiving cyclosporine or tacrolimus,

BCAR, graft survival, and patient survival were similar between groups

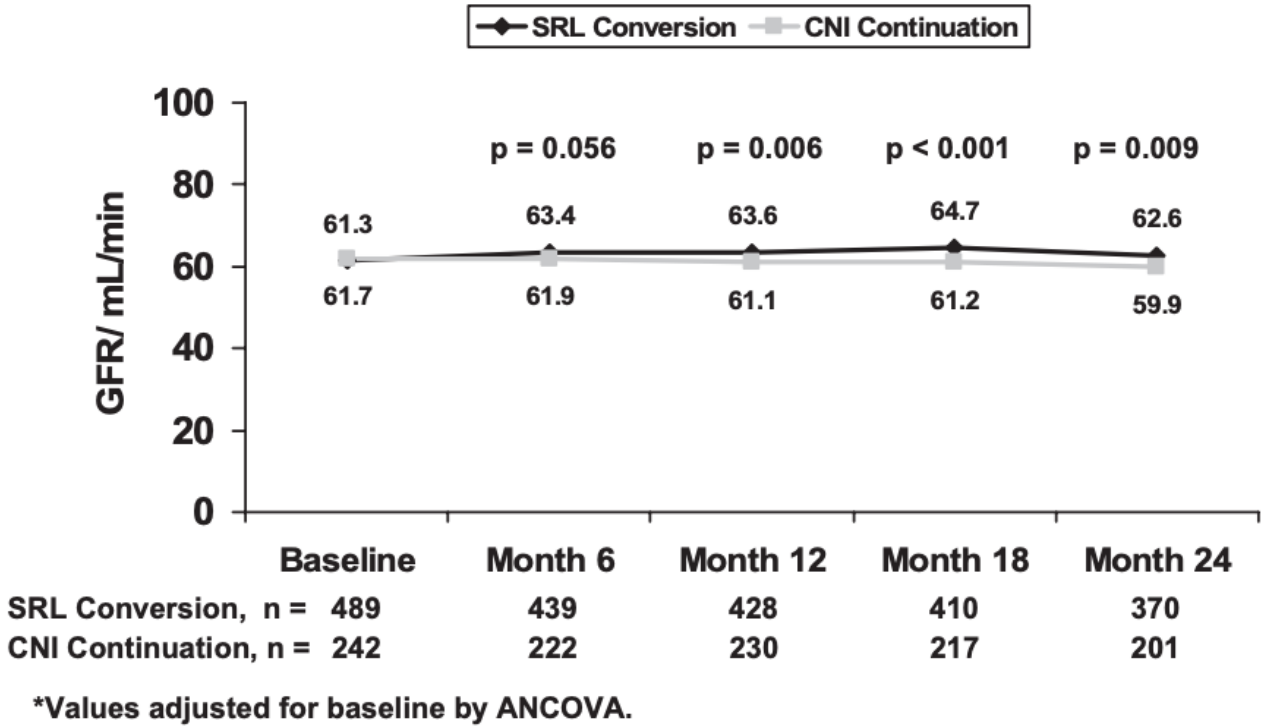
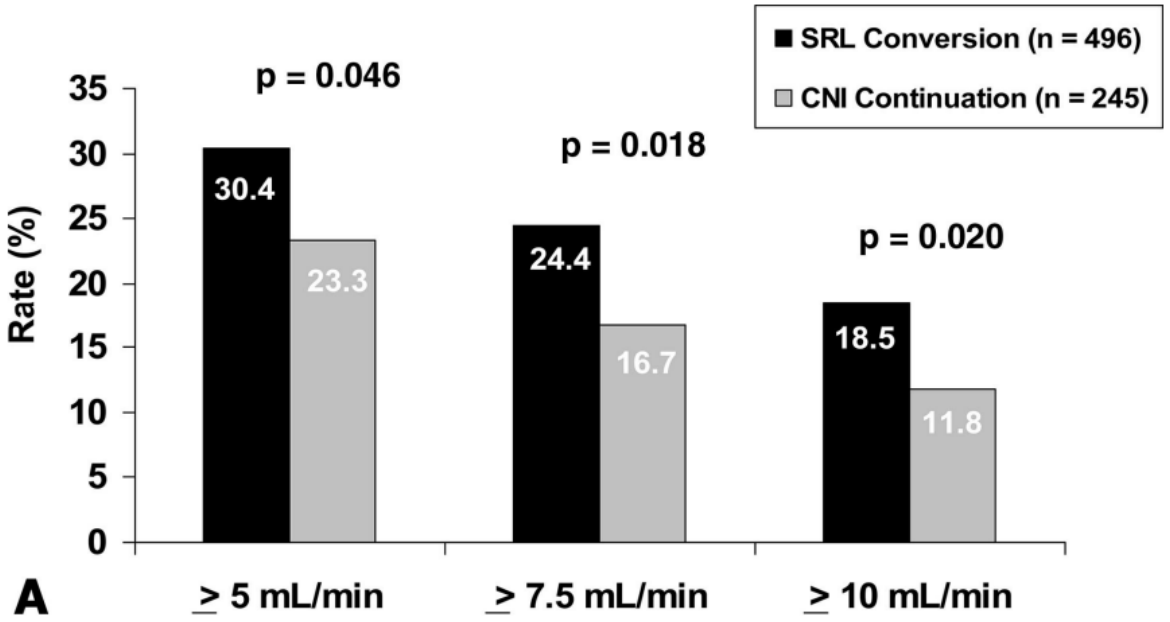
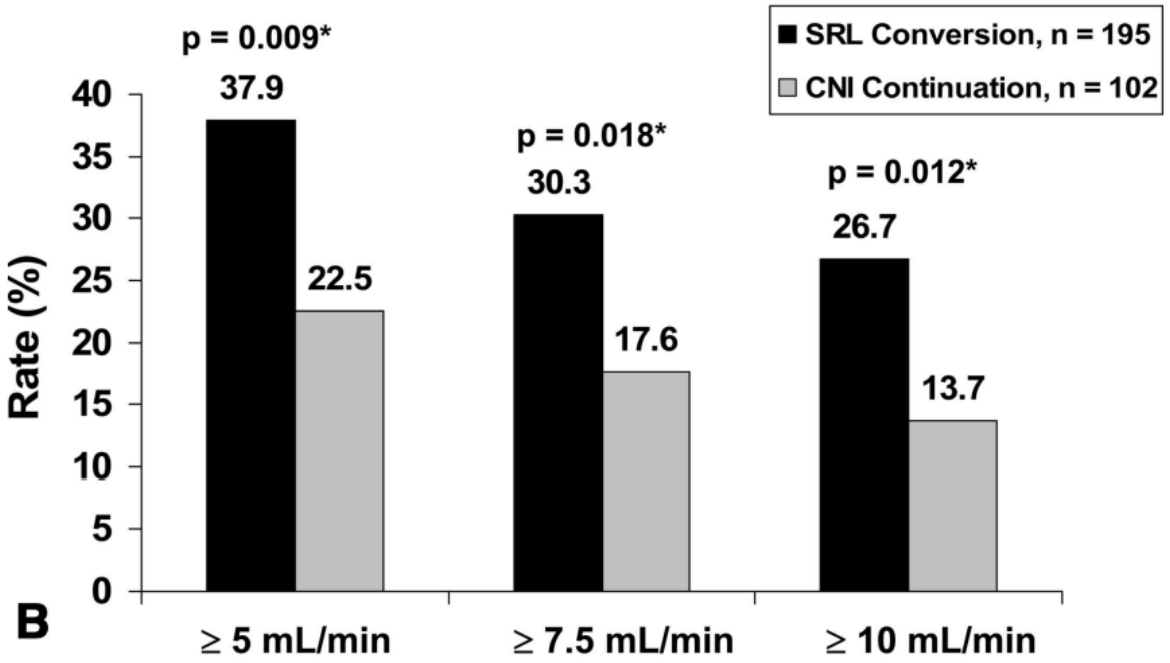


FIGURE 2. Mean Nankivell GFR (mL/min) in on-therapy patients with baseline GFR more than 40 mL/min.*





Median urinary protein-to-creatinine ratios (UPr/Cr) were similar at baseline but increased significantly after SRL conversion.

Post hoc analyses identified a subgroup with baseline GFR more than 40 mL/min and UPr/Cr less than or equal to 0.11, whose risk-benefit profile was more favorable after conversion than that for the overall SRL conversion cohort.

Percentage of patients showing clinically meaningful improvements in GFR at 24 months. (A) ITT analysis of patients with Nankivell GFR more than 40 mL/ min. (B) ITT analysis of subgroup of patients with baseline GFR more than 40 mL/min and UPr/Cr less than or equal to 0.11.

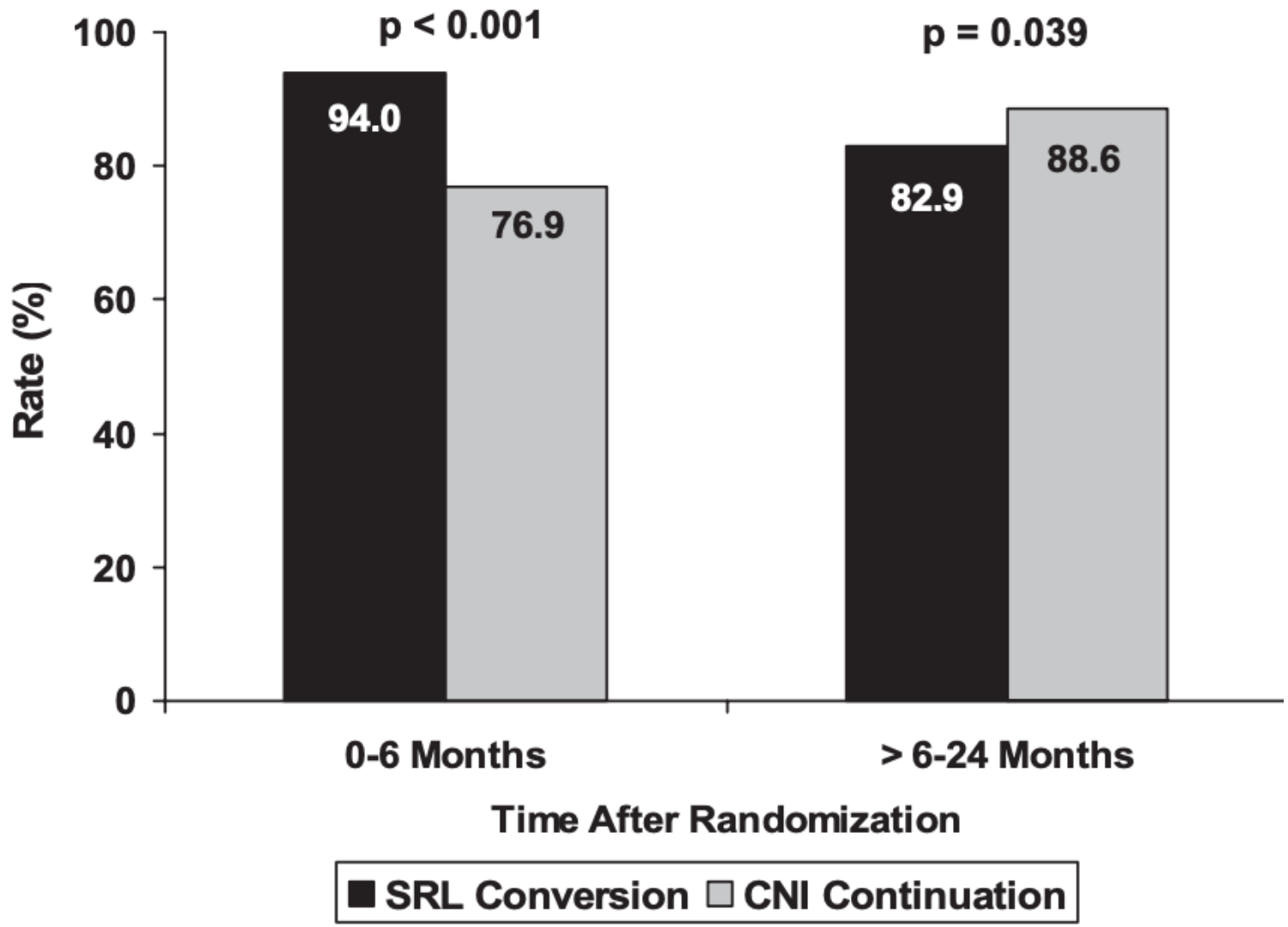


FIGURE 4. Rates of investigator-reported TEAEs.

FACTORS TO CONSIDER

Before Late Conversion

- **Graft Function**: Patients with stable graft function and low proteinuria are better candidates for conversion.
- **Cancer Risk**: High-risk cancer patients may benefit more from mTOR inhibitors.
- Patient Preference and Tolerance: Individual tolerance to side effects and willingness to undergo frequent monitoring are crucial.

Borderline or unstable graft function: Patients with impaired graft function are more susceptible to immune attacks during the transition phase.

High immunologic risk: Patients with a history of rejection, high panel-reactive antibodies (PRA), or poor HLA matching may face elevated ris

Suboptimal transition protocols: **Inadequate overlap** or improper dosing adjustments can lead to insufficient immunosuppression.

Mitigation Strategies

Gradual Transition: Carefully phase out CNIs while introducing mTOR inhibitors to maintain a balanced immunosuppressive effect.

Therapeutic Drug Monitoring (TDM): Ensure target drug levels are achieved to prevent under- or over-suppression.

Patient Selection: Avoid transitioning high-risk patients or those with unstable grafts unless absolutely necessary and under strict supervision.

Adjunctive Therapies: Combine mTOR inhibitors with antiproliferative agents (like mycophenolate mofetil) or low-dose steroids to bolster immunosuppression during transition.

Close Monitoring: Perform ***frequent monitoring of graft function***, serum ***creatinine***, and ***biomarkers like donor-derived cell-free DNA*** to detect early signs of rejection.

Monitoring and Management Post-Conversion

Lipid profiles and metabolic parameters.

Regular monitoring of kidney function (eGFR, proteinuria).

Adjusting dosages based on therapeutic drug monitoring (TDM).

Late conversion to mTOR inhibitors is a nuanced decision that balances potential long-term benefits (e.g., reducing cancer risk, preserving kidney function) against possible short-term complications and side effects.

Timing and Criteria for Late Conversion

Late conversion typically occurs **at least 6-12 months** post-transplant, once the graft function and immune stability are established.

Factors influencing timing:

- Stable graft function.
- Absence of acute rejection episodes.
- Absence of severe proteinuria (often a contraindication for mTORi use).

Is Early Conversion to mTOR Inhibitors Represent a Suitable Choice in Renal Transplant Recipients? A Systemic Review of Medium-term Outcomes

J. Kumar*, I. Reccia, T. Kusano

Department of Surgery and Cancer, Imperial College London, London, UK

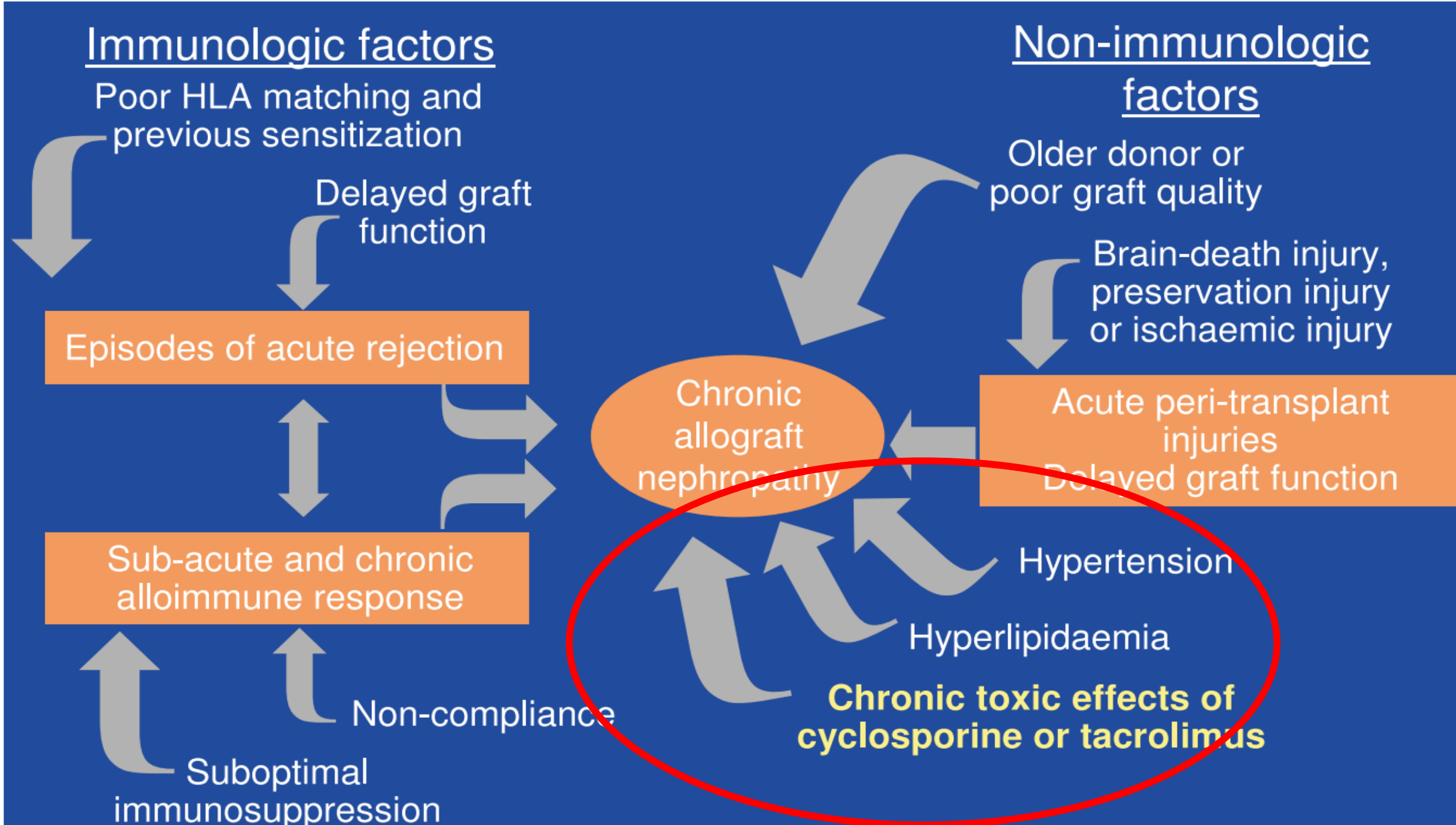
Table 1: Criteria for the inclusion of early mTOR inhibitor conversion studies

Study design	Prospective cohort design with a well-defined study population
Study group	Post-renal transplantation
Conversion time	Period of 2 weeks to 6 months post-transplantation
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 function and long-term survival

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	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* (SMART T [26]				
Weir, *et al*, (Spare the ron Trial)				
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)

Conclusion: On the basis of present literature, the early introduction of mTOR inhibitors causes substantial CNI minimization. The mTOR inhibitors are more favorable due to their complementary mechanism of action and favorable nephrotoxicity profile, better glomerular filtration, and lower serum creatinine with equivalent survival. However, the higher rejection rate may influence the use of these regimens in patients with moderate to high immunological risk.

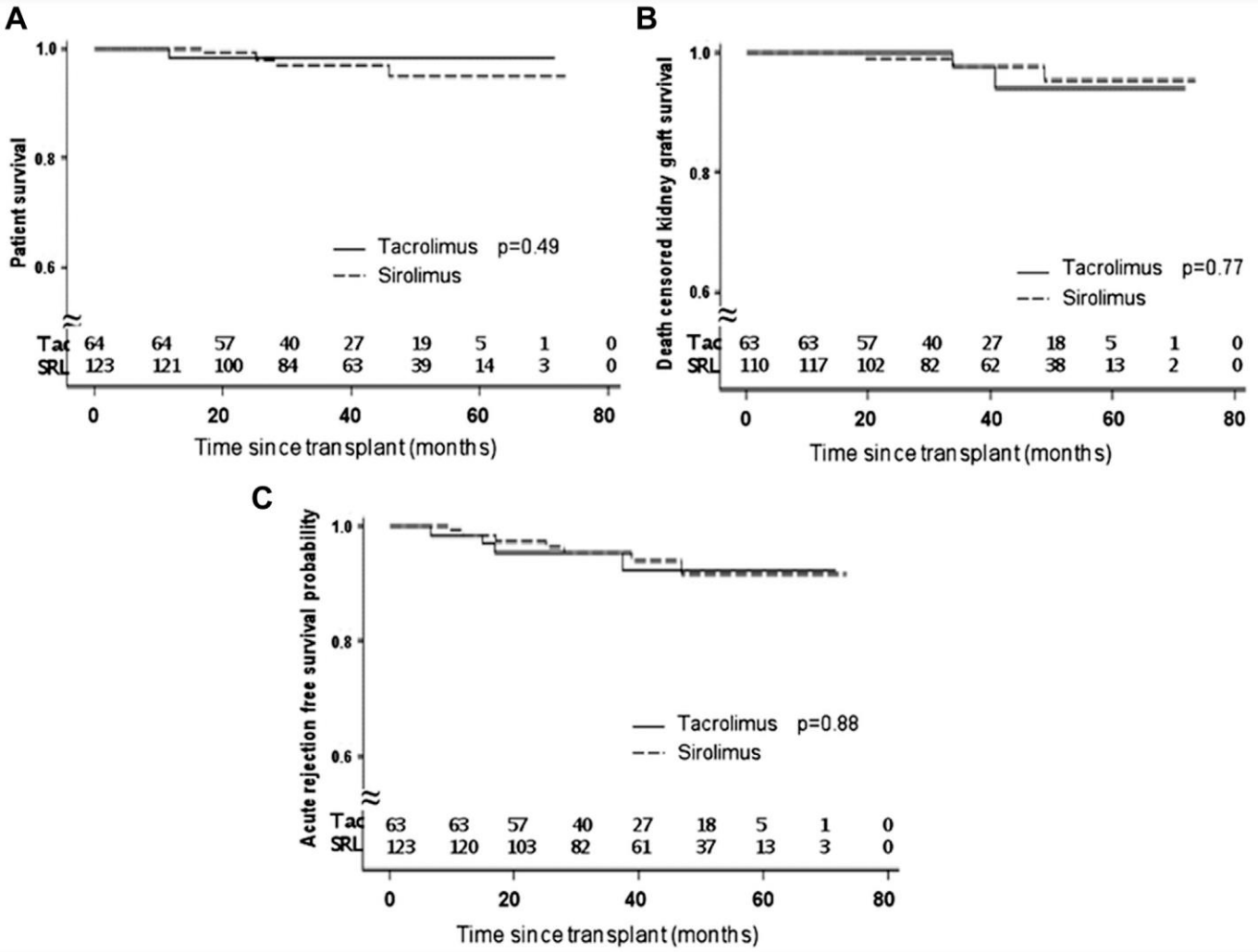

Immunologic factors
Poor HLA matching and previous sensitization
Delayed graft function
Episodes of acute rejection
Sub-acute and chronic alloimmune response
Non-compliance
Suboptimal immunosuppression
Non-immunologic factors
Older donor or poor graft quality
Brain-death injury, preservation injury or ischaemic injury
Acute peri-transplant injuries
Delayed graft function
Chronic allograft nephropathy
Hypertension
Hyperlipidaemia
Chronic toxic effects of cyclosporine or tacrolimus

American Journal of Transplantation 2013; 13: 2902–2911
Wiley Periodicals Inc.

doi: 10.1111/ajt.12437

Impact of Calcineurin-Inhibitor Conversion to mTOR Inhibitor on Renal Allograft Function in a Prednisone-Free Regimen

randomized trial in 200 patients

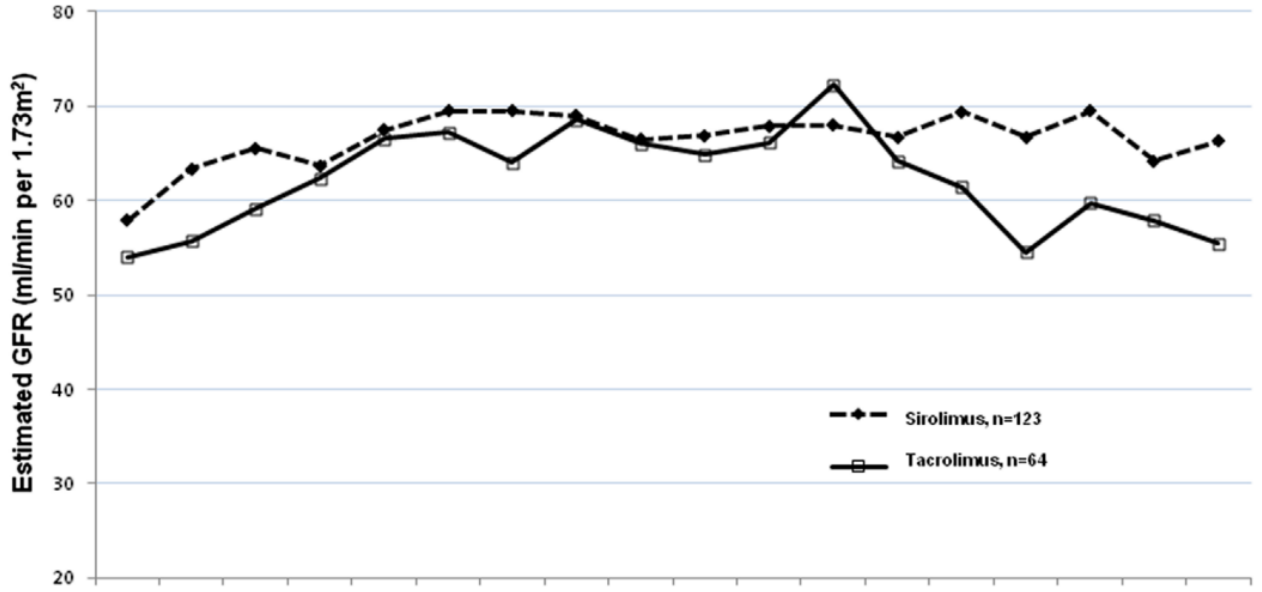


Kaplan–Meier curve in the tacrolimus (Tac) maintained group and sirolimus (SRL) converted group, for cumulative patient survival.

Biopsy-proven acute rejection at 24 months postrandomization was similar between the groups.

Patient survival, graft survival and estimated GFR were also not statistically different.

Based on this study a prednisone-free immunosuppressive regimen, conversion from Tac to SRL at 12 months posttransplantation is not associated with increased rates of acute rejection and graft loss.



Group	1	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
SRL, Mean	57.9	63.3	65.5	63.7	67.5	69.5	69.5	69.0	66.5	66.9	67.9	68.0	66.7	69.5	66.8	69.5	64.2	66.3
S.D	19.0	18.8	17.3	17.2	19.0	20.9	24.2	21.6	23.7	20.5	23.7	25.0	21.5	27.7	22.5	19.1	28.1	23.1
N	123	122	118	110	119	115	100	90	83	73	66	53	48	40	36	28	28	21
Tac, Mean	54.0	55.7	59.1	62.4	66.6	67.2	64.0	68.6	66.0	64.9	66.1	72.3	64.2	61.4	54.6	59.8	57.9	55.5
S.D.	18.1	14.7	14.2	15.2	17.1	18.4	21.2	23.5	18.2	20.8	23.9	24.7	22.0	23.3	31.0	26.9	21.2	23.5
N	64	64	60	57	63	50	45	51	42	38	33	29	33	19	15	14	13	10
p value	0.19	0.003	0.01	0.63	0.75	0.5	0.2	0.92	0.92	0.63	0.72	0.46	0.61	0.28	0.12	0.18	0.48	0.23

Estimated GFR according to treatment groups; tacrolimus (Tac) maintained versus sirolimus (SRL) converted group.

frontiers in Immunology

SYSTEMATIC REVIEW
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performed to investigate the efficacy and safety of conversion from calcineurin inhibitors (CNIs) to mammalian target of rapamycin inhibitors (mTORi) in kidney transplant recipients (KTRs).

Twenty-nine RCTs (5,747 KTRs)

Conclusions:

Posttransplant patients have a better graft function and lower incidence of malignancy after conversion from CNI to mTORi therapy.

OPEN ACCESS

Edited by:

Conversion From Calcineurin Inhibitors to Mammalian Target of Rapamycin Inhibitors in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

However, this conversion strategy may be prevented by the higher drug discontinuation rate due to mTORi associated adverse events, such as more acute rejection, infection, proteinuria, leukopenia, acne, and mouth ulcer, indicating that conversion therapy may only be a treatment option in selected patients.

Journal of
Clinical Medicine

MDPI

Article

Long-Term Redistribution of Peripheral Lymphocyte Subpopulations after Switching from Calcineurin to mTOR Inhibitors in Kidney Transplant Recipients

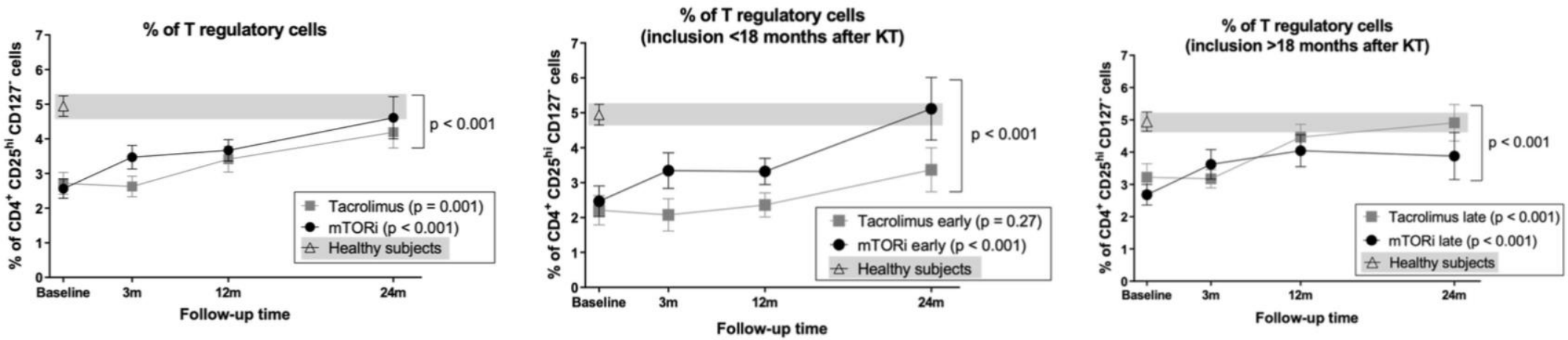

Figure 2. Evolution of Tregs after switching from tacrolimus to mTORi in all cases and according to time of inclusion in the study. Immunophenotyping of (**A**) total Tregs, (**B**) Tregs in patients included in the study during the first 18 months after transplantation, and (**C**) Tregs in patients included in the study after 18 months posttransplant. Patients before and after switching to mTORi are depicted with black dots, and patients maintaining tacrolimus are depicted with grey squares. HS data is depicted with white triangles, and the grey background corresponds to range. Plots show mean and SEM for each time point.

Transplantation Proceedings
Volume 55, Issue 4, May 2023, Pages 803-808

Long-Term Results in Recipients of Late Conversion to a Calcineurin Inhibitor-Free Regimen with Everolimus Afte Kidney Transplantation

Conclusions

Late conversion to an EVR-based regimen without CNI may be a promising therapeutic strategy against CNIT, particularly for recipients without proteinuria before the EVR add-on.

Highlights

- Nine recipients underwent a conversion from a calcineurin inhibitor (CNI) to an everolimus.
- nctions were stable after conversion in recipients proteinuria.
- ient developed de novo donor-specific antibodies nversion.
- ion to a CNI-free regimen is a promising strategy CNI toxicity.

A randomized controlled trial to evaluate efficacy and safety of early conversion to a low-dose calcineurin inhibitor combined with sirolimus in renal transplant patients

Chinese Medical Journal 2022

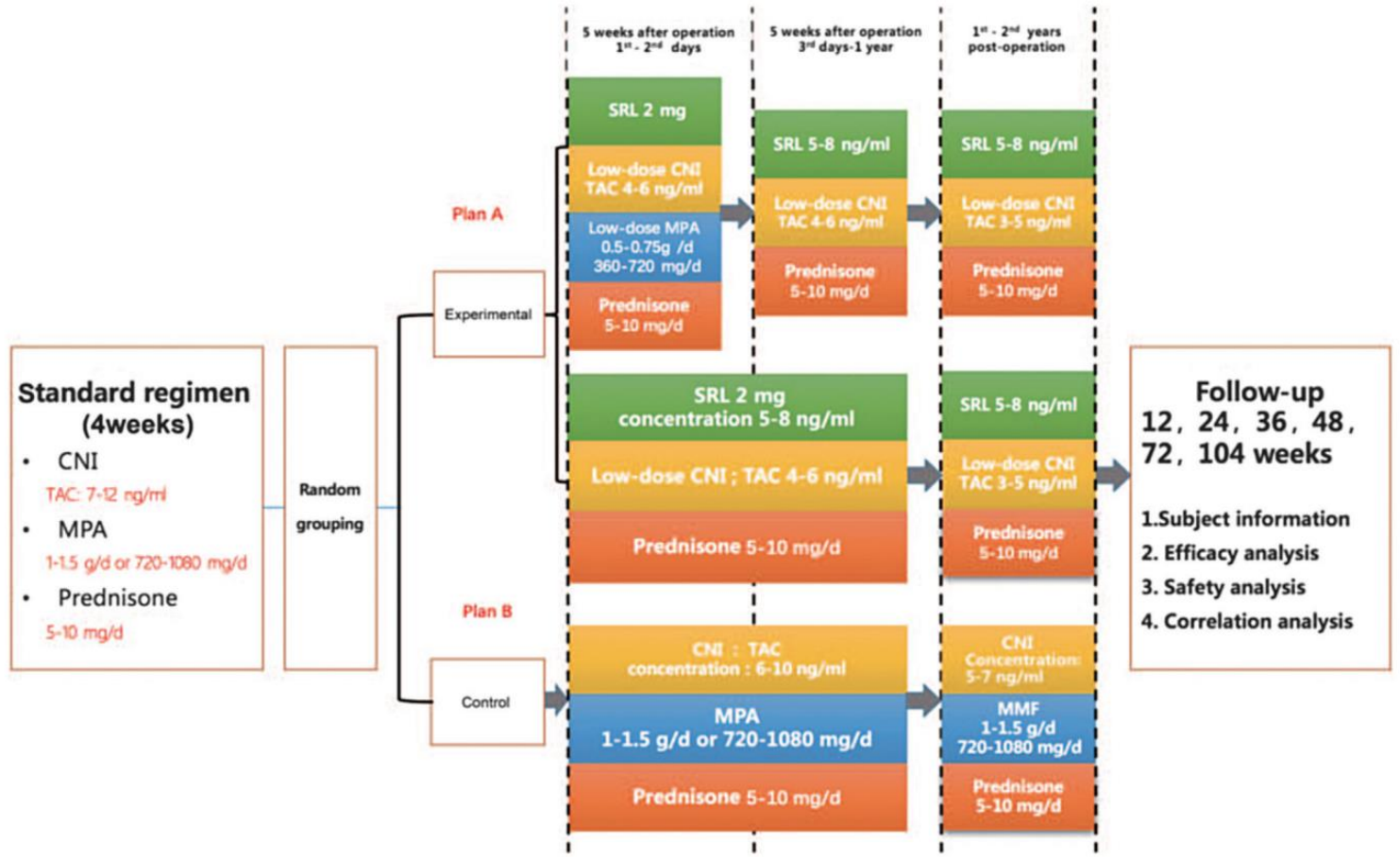

Figure 1: Study flow diagram. CNI: Calcineurin inhibitor; MPA: Mycophenolic acid; SRL: Sirolimus; TAC: Tacrolimus; MMF: Mycophenolate mofetil.

Challenges and Risks of mTOR Inhibitors

- **Proteinuria:** Increased proteinuria is a common side effect of mTOR inhibitors.
- Wound healing complications: mTOR inhibitors impair wound healing, which may be problematic if the patient has a surgical history.
- Metabolic side effects: Includes dyslipidemia and mouth ulcers.
- Risk of rejection: Switching to mTOR inhibitors can slightly increase the risk of acute rejection if not carefully managed.

http://www.revistanefrologia.com

short review

Clinical evidence on the use of anti-mTOR drugs in renal transplantation

D. Hernández, D. Martínez, E. Gutiérrez, V. López, C. Gutiérrez, P. García, C. Cobelo, M. Cabello, D. Burgos , E. Sola, M. González-Molina

Nephrology Department. Carlos Haya Regional Hospital. Malaga. Spain

KEY CONCEPTS

1. The use anti-mTOR in *de novo* transplantation without a CNI leads to a greater risk of rejection and surgical wound complications after TX.
2. The initial combination of low doses of an anti-mTOR and a CNI provides acceptable short-term immune protection.
3. The early conversion from a CNI to SRL/EVE may, at least, offer stable renal function. Whether this therapeutic manoeuvre prevents chronic graft dysfunction is still unknown.
4. With a low level of evidence, the anti-mTOR drugs reduce the left ventricular mass and may potentially slow atheromatosis after TX.
5. Anti-mTOR drugs can increase the risk of post-TX diabetes, especially in predisposed individuals.
6. SRL and EVE reduce the incidence of post-TX *de novo* neoplasms.

Benefits vs. Risks

- In summary, transitioning to mTOR inhibitors requires a **meticulously tailored approach** with **vigilant monitoring to balance the benefits** of reduced CNI toxicity against the heightened risk of rejection.

- Current data suggest that patients with an **already reduced eGFR** and/or **proteinuria** will receive **no benefit** from calcineurin inhibitor elimination with mTOR inhibitor conversion, and **early use** of mTOR inhibitors without a calcineurin inhibitor may be mired by **high rejection rates** and a high side effect profile, thus potentially limiting their use.

Overall, the role of mTOR inhibitors to replace calcineurin inhibitors as part of a conversion strategy has been met with ***mixed results.***

Comparisons between early and late conversion to mTOR inhibitors (mTORi) in kidney transplantation reveal key differences in outcomes:

1. Early Conversion:
Switching within the first months post-transplantation generally improves renal function.
Trials like SMART and ZEUS observed significant increases in glomerular filtration rate (GFR). However, early conversion may increase the risk of proteinuria and adverse events like stomatitis or hyperlipidemia.

2. Late Conversion:
Later transitions often carry fewer risks of acute rejection but may result in less pronounced renal benefits **(Late is too late)** compared to early conversion.

Both strategies can maintain similar patient and graft survival rates, but side effects and long-term outcomes vary