Rapamune and Graft Survival

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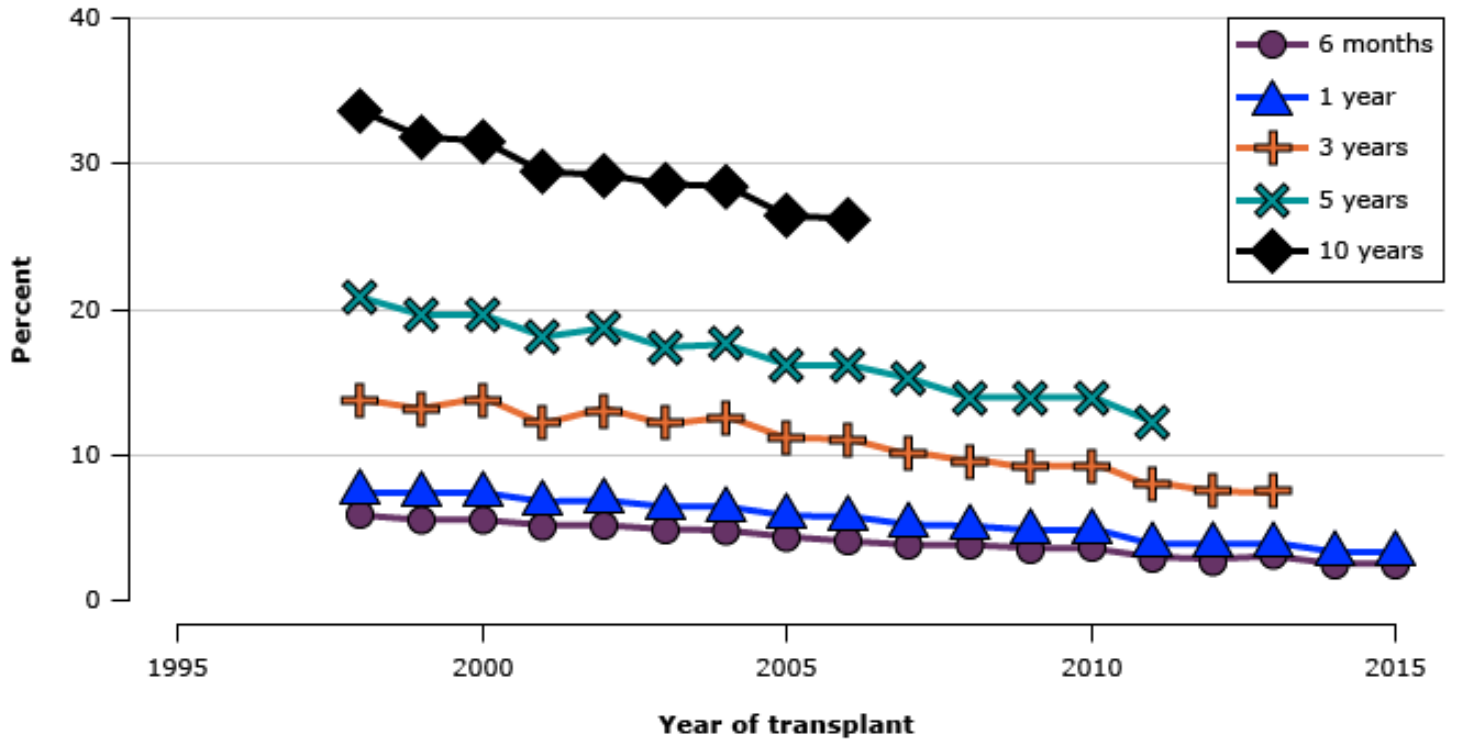
Kidney transplant allograft failure and survival

- Despite significant improvements in one-year kidney allograft survival, the rate of chronic graft loss after the first year remains substantial, although it seems to be improving over time.

Death-censored graft failure among adult deceased-donor kidney transplant recipients



Estimates are unadjusted, computed using Kaplan-Meier competing risk methods. Recipients are followed to the earliest of kidney graft failure; kidney retransplantation; return to dialysis; death; for 6 months, 1, 3, 5, or 10 years posttransplant. Death-censored graft failure is defined as a return to dialysis, reported graft failure, or kidney retransplantation.

Reproduced from: OPTN/SRTR 2016 Annual Data Report: Kidney. US Department of Health & Human Services. Available at:
https://srtr.transplant.hrsa.gov/annual_reports/2016/Kidney.aspx#KI_65_tx_adult_dd_outcomes_DCGF_1_b64
(Accessed on July 20, 2020).

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Risk factors for graft failure
The determinants of short-term and long-term graft survival

- **Short-term graft survival:** Delayed allograft function, Human leukocyte antigen (HLA) antibodies, Type of donor kidney, Donor illness, Donor age, Medical center factors, and Dialysis and preemptive transplantation.

- **Long-Term Survival:**
  - Alloantigen-dependent factors :history of acute rejection, a greater degree of human leukocyte antigen (HLA) mismatching, infection, and/or inadequate immunosuppressive therapy.
  - Alloantigen-independent factors: inadequate renal mass, prior and ongoing tissue injury, noncompliance, posttransplant hypertension, hyperlipidemia, a more marginal kidney, calcineurin toxicity, CMV seropositivity, and recurrent or de novo glomerular disease.

Graft survival and imTOR

- The clinical use of mTOR pathway inhibitors following kidney transplantation remains challenging even after more than 20 years of clinical trials.
- During these years, several analyses using database registration data indicate that patients receiving imTOR, mainly sirolimus (SRL), are at increased risk of mortality and graft loss compared to patients receiving cyclosporine or tacrolimus in combination with mycophenolate.

Description of the main studies that showed a higher risk of graft loss or death in renal transplant recipients who used imTOR

Ref	Study type	Year Inclusion Time Follow up	iCN	imTOR with iCN n (%)	imTOR without iCN n(%)	imTOR use	imTOR Group characteristics	Graft survival	Patient survival
(1)	SRTR Registry	1998 to 2013 4 years	21,017	1999	-	*De novo*	CsA/SRL: lower use of indication in the group	79.3% CsA/MMF 74.6 CsA/SRL (HR = 1.22)	ns.
(2)	SRTR Registry	2000 to 2004 3 years	44,915	5393	-	*de novo*		85.9% TAC/MMF 85.3% CsA/MMF (HR = 1.15) 82.2% CsA/SRL (HR = 1.38) 80.3% TAC/SRL (HR = 1.47)	92.2% TAC/MMF 91.0% CsA/MMF (HR = 1.22) 90.0% CsA/SRL (HR = 1.49) 89.9% TAC/SRL (HR = 1.41)
(3)	SRTR Registry	2000 to 2005 5 years	49,412	6394 (73%)	2325 (27%)	*de novo*	SRL/MMF: higher donor age, higher rate of deceased donor	73.8% TAC/MMF 71.8% CSA/MMF (HR = 1.16) 68.9% TAC/SRL (HR = 1.38) 67.6% CSA/SRL (HR = 1.37) 57.7% SRL/MMF (HR = 2.01)	TAC/MMF CSA/MMF (HR = 1.17) TAC/SRL (HR = 1.33) CSA/SRL (HR = 1.49) SRL/MMF (HR = 1.75)

Andrade LG.J Bras Nefrol. 2017 Mar;39(1):70-78.

Description of the main studies that showed a higher risk of graft loss or death in renal transplant recipients who used imTOR

(4)	Hungary cohort	2007 3 years	1241	37 (37%)	64 (63%)	conversio	Higher number with neoplasia and diabetes	ns.	ns. Patients with a history of neoplasia (HR = 2.6-5.6)
(5)	UNOS Registry	1999 to 2010 2-8 years	125,623	10,510 (76.4%)	3,237 (23.5%)	*de novo*	imTOR without iCN: higher number with a history of malignancy, diabetes and kidney from expanded-criterion donor; higher PRA and TIF	iCN/imTOR (HR = 1.07) imTOR/ MMF (HR = 1.17)	iCN/imTOR (HR = 1.13) imTOR/ MMF (HR = 1.25)
(6)	Systematic review	1999 to 2013 1 year to 4 years	2,600			*de novo* 4,717 (80.3%) conversion 1,159 (19.7%)	unreported	Not analyzed	imTOR (HR = 1.43)

Graft survival and imTOR

- In an study, published in 2005, also analyzed data from the United States transplant registry of 44,915 adult kidney transplants performed between 2000 and 2004. In this analysis, 3,524 (7.8%) patients received TAC/SRL; 27,007 (60.1%) TAC/MMF; 1,869 (4.2%) CSA/SRL and 12,515 (27.9%) CSA/MMF.
- No differences were found in the incidence of acute rejection between the groups (11.5- 12.6%) during the first six months of transplantation. Graft survival over 3 years was 85.9% (TAC/MMF); 85.3% (CsA/MMF); 82.2% (CsA/SRL) and 80.3% (TAC/SRL).

Mortality and graft loss outcomes in studies involving new proposals for imTOR use

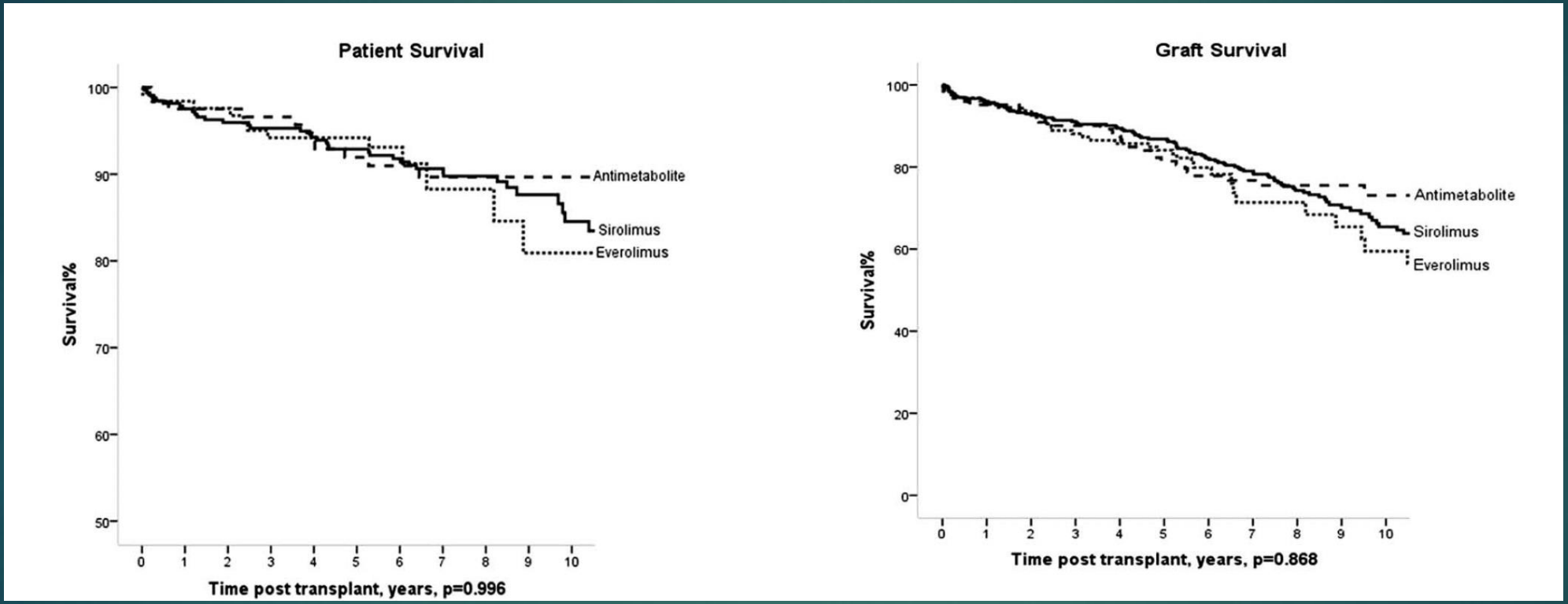
- The most recent proposals for the use of imTORs are based on the use of reduced doses of imTORs and iCNs adjusted to maintain blood concentrations within predetermined therapeutic ranges, either in combination from the start of transplantation or in early conversion strategies of iCN for imTOR.
- In these studies, the incidence of adverse reactions typically associated with imTORs was lower than that observed in previous studies, resulting in a lower incidence of treatment discontinuation, especially when imTORs were combined with iCNs

Randomized clinical trials with medium term assessments using more recent immunosuppression with imTOR

Ref.	N	Regimens	Follow up time	Acute rejection (%)	Graft loss (%)	Death (%)
(40)	162	CSA → SRL/MMF (n =77) CSA/MMF (n = 85)	4 years	2.6 2.6	5.2 2.4	2.6 0
(43)	60	BAS/TAC/MMF (n = 30) BAS/CSAr/EVE (n = 30)	3 years	17 23	6.6 6.6	3 0
(34)	833	BAS/EVE (3-8 ng/ml)/CSAr (n = 277) BAS/EVE (6-12 ng/ml)/CSAr (n = 279) BAS/CSA/MPS (n = 277)	2 years	19.9 15.1 19.1	5.8 6.1 4.0	3.2 3.6 2.9
(46)	300	CSA → EVR/MMF (n = 155) CSA/MMF (n = 145)	5 years	13.6 7.5	2.6 2.1	2.6 2.6
(42)	182	CSA → CSA/MMF (n = 90) EVR/MMF (n = 92)	3 years	13 11.1	1.1 3.3	1.1 3.3
(44)	99	rATG (7,5mg/kg)/SRL/MMF rATG(7,5mg/kg)/CSA/MMF	8 years	nr nr	14 14.8	11 8
(45)	128	iCN → SRL/MMF (n = ?) iCN/MMF (n = ?)	8 years	22.7 14.5	15.2 19.4	7.6 9.7
(47)	581	iCN/SRL (n = 347) iCN/EVE (n = 128) iCN/AZA-MPA (n = 124)	10 years	22.2 22.7 22.6	19 18 23	12 10 13

Meta-Analysis > Ther Drug Monit. 2016 Feb;38(1):22-31. doi: 10.1097/FTD.0000000000000227.

Long-Term Follow-Up of De Novo Use of mTOR and Calcineurin Inhibitors After Kidney Transplantation



Kidney transplant
recipients (n = 581) receiving calcineurin inhibitors (CNIs) combined with sirolimus (n = 329), everolimus (n = 128), or antimetabolites (n = 124).