Combination Therapy with mTOR inhibitors

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ORIGINAL ARTICLE

ADHERE: randomized controlled trial comparing renal function in *de novo* kidney transplant recipients receiving prolonged-release tacrolimus plus mycophenolate mofetil or sirolimus

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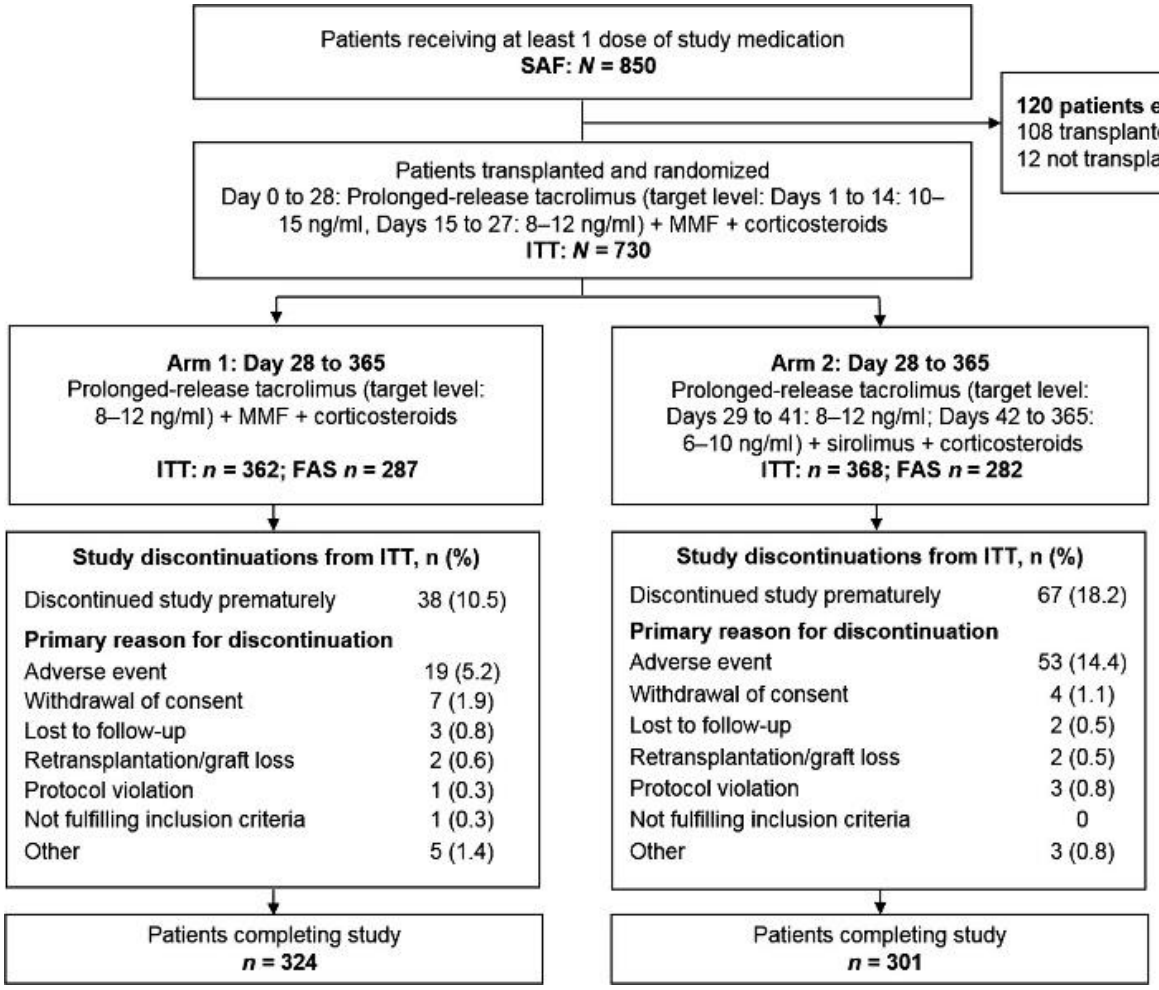
SUMMARY

ADHERE was a randomized, open-label, Phase IV study comparing renal function at Week 52 postkidney transplant, in patients who received prolonged-release tacrolimus-based immunosuppressive regimens. On Days 0–27, patients received prolonged-release tacrolimus (initially 0.2 mg/kg/day), corticosteroids, and mycophenolate mofetil (MMF). Patients were randomized on Day 28 to receive either prolonged-release tacrolimus plus MMF (Arm 1) or prolonged-release tacrolimus (≥25% dose reduction on Day 42) plus sirolimus (Arm 2). The primary endpoint was glomerular filtration rate by iohexol clearance (mGFR) at Week 52. Secondary endpoints included eGFR, creatinine clearance (CrCl), efficacy failure (patient withdrawal or graft loss), and patient/graft survival. Tolerability was analyzed. The full-analysis set comprised 569 patients (Arm 1: 287; Arm 2: 282). Week 52 mean mGFR was similar in Arm 1 versus Arm 2 (40.73 vs. 41.75 ml/min/1.73 m^2; $P = 0.405$), as were the secondary endpoints, except composite efficacy failure, which was higher in Arm 2 versus 1 (18.2% vs. 11.5%; $P = 0.002$) owing to a higher postrandomization withdrawal rate due to adverse events (AEs) (14.4% vs. 5.2%). Results from this study show comparable renal function between arms at Week 52, with fewer AEs leading to study discontinuation with prolonged-release tacrolimus plus MMF (Arm 1) versus lower dose prolonged-release tacrolimus plus sirolimus (Arm 2).

Flow of patients through the ADHERE study



- Tacrolimus from Day 0 to Day 365 with an initial postoperative dose of 0.2 mg/kg/day
- All patients received oral MMF each day (1 g twice daily until Day 14, reduced to 0.5 g twice daily until Day 27)
- Sirolimus once daily from Day 28 to the EOS, with an initial daily dose of 1 mg and a target trough level range of 2–4 ng/ml (maximum dose 2 mg daily)

Table 2. Renal function at Week 52 as assessed by primary and secondary endpoints.

	Arm 1: prolonged-release tacrolimus + MMF (n = 287)	Arm 2: prolonged-release tacrolimus + sirolimus (n = 282)	P value*
Primary endpoint			
GFR by iohexol clearance (ml/min/1.73 m^2)			
Mean	40.73	41.75	0.405
Difference†	1.02		
95% CI for mean difference	–1.39, 3.44		
Secondary endpoints			
eGFR by MDRD4 (ml/min/1.73 m^2)			
Mean	50.54	51.03	0.720
Difference†	0.49		
95% CI for mean difference	–2.21, 3.20		
eGFR by CKD-EPI (ml/min/1.73 m^2)			
Mean	51.46	51.77	0.823
Difference†	0.31		
95% CI for mean difference	–2.44, 3.07		
Calculated CrCl by Cockcroft–Gault (ml/min)			
Mean	56.61	57.14	0.736
Difference†	0.53		
95% CI for mean difference	–2.54, 3.59		

All patients received oral MMF until Day 27. For patients randomized to Arm 2 only, MMF was discontinued and sirolimus was initiated on Day 28 and continued throughout the study.

CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FAS, full-analysis set; GFR, glomerular filtration rate; LS, least square; MDRD4, modification of diet in renal disease-4; MMF, mycophenolate mofetil.

Table 3. Kaplan–Meier estimates of secondary efficacy variables at Week 52 (ITT).

	Patients with postrandomization event*		Kaplan–Meier estimate difference†	
	Arm 1: prolonged-release tacrolimus + MMF (n = 362)	Arm 2: prolonged-release tacrolimus + sirolimus (n = 368)	% Difference (95% CI)	P value‡
Composite efficacy failure, n (%)	40 (11.5)	67 (18.2)	6.7 (1.5, 11.9)	0.002
Acute rejection, n (%)	26 (7.3)	30 (8.3)	1.0 (−2.9, 4.9)	0.624
BCAR, n (%)	14 (4.3)	13 (3.6)	−0.7 (−3.6, 2.3)	0.892
Graft loss, n (%)	10 (2.9)	8 (2.2)	−0.7 (−3.0, 1.6)	0.676
Patient death, n (%)	4 (1.1)	1 (0.3)	−0.9 (−2.1, 0.4)	0.177
NODM, n (%)	24 (8.5)	36 (12.8)	4.3 (−0.9, 9.5)	0.183

All patients received oral MMF until Day 27. For patients randomized to Arm 2 only, MMF was discontinued and sirolimus was initiated on Day 28 and continued throughout the study.

BCAR, biopsy-confirmed acute rejection; CI, confidence interval; ITT, intent to treat; MMF, mycophenolate mofetil; NODM, new-onset diabetes mellitus.

*Events that happened at or after Week 52 were grouped into Week 52+.

†Kaplan–Meier survival estimates for the incidence of patients with the event (Arm 2–Arm 1).

‡Wilcoxon–Gehan test.

Table 4. Most commonly reported postrandomization adverse events (≥5% in either treatment arm) from Day 28 to Week 52 (ITT).

Adverse event	Arm 1: prolonged-release tacrolimus + MMF (*n* = 362)	Arm 2: prolonged-release tacrolimus + sirolimus (*n* = 368)
Overall, *n* (%)	307 (84.8)	309 (84.0)
Diarrhea	47 (13.0)	36 (9.8)
Leukopenia	47 (13.0)	9 (2.4)
Cytomegalovirus infection	43 (11.9)	14 (3.8)
Edema peripheral	42 (11.6)	66 (17.9)
Escherichia UTI	39 (10.8)	24 (6.5)
Blood creatinine increased	33 (9.1)	32 (8.7)
UTI bacterial	33 (9.1)	18 (4.9)
Nasopharyngitis	30 (8.3)	29 (7.9)
Tremor	28 (7.7)	26 (7.1)
Cough	24 (6.6)	14 (3.8)
Hypertension	21 (5.8)	22 (6.0)
Renal impairment	21 (5.8)	17 (4.6)
Dyslipidemia	20 (5.5)	22 (6.0)
UTI	20 (5.5)	21 (5.7)
UTI enterococcal	19 (5.2)	26 (7.1)
Anemia	18 (5.0)	22 (6.0)
Kidney transplant rejection	18 (5.0)	17 (4.6)
Diabetes mellitus	14 (3.9)	25 (6.8)
Hypercholesterolemia	13 (3.6)	22 (6.0)
Hyperlipidemia	12 (3.3)	24 (6.5)
Proteinuria	6 (1.7)	22 (6.0)

Conclusions

- findings suggest that:

❖ **low-dose SRL** in combination with TAC can be effective in preventing acute rejection, while being safe and preserving graft renal function.

❖ **Low dose SRL allows minimization of TAC dosage**, thereby maintaining good renal function and a low incidence of acute rejection, comparable to the outcomes observed with MMF plus TAC

Transplant International

ORIGINAL ARTICLE

Long-term, prolonged-release tacrolimus-based immunosuppression in *de novo* kidney transplant recipients: 5-year prospective follow-up of the ADHERE study patients

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Transplant International 2020; 33: 161–173

From 838 patients in the randomized study, 587 were included in the long-term follow-up, of whom 510 completed the study at year 5.

Results

- Patients randomized to receive prolonged-release tacrolimus in combination with mycophenolate mofetil (MMF) (Arm 1) or sirolimus (Arm 2).
- At 5 year post-transplant, graft and patient survival rates were 84.0% and 90.8%, respectively.
- Renal function remained stable over the follow-up period

Conclusion

The findings support the role of long-term once-daily prolonged-release tacrolimus-based immunosuppression, in combination with sirolimus or MMF, for renal transplant recipients in routine clinical practice.

Journal of Nephrology
https://doi.org/10.1007/s40620-019-00675-2

ORIGINAL ARTICLE

Combination of calcineurin and mTOR inhibitors in kidney transplantation: a propensity score analysis based on current clinical practice

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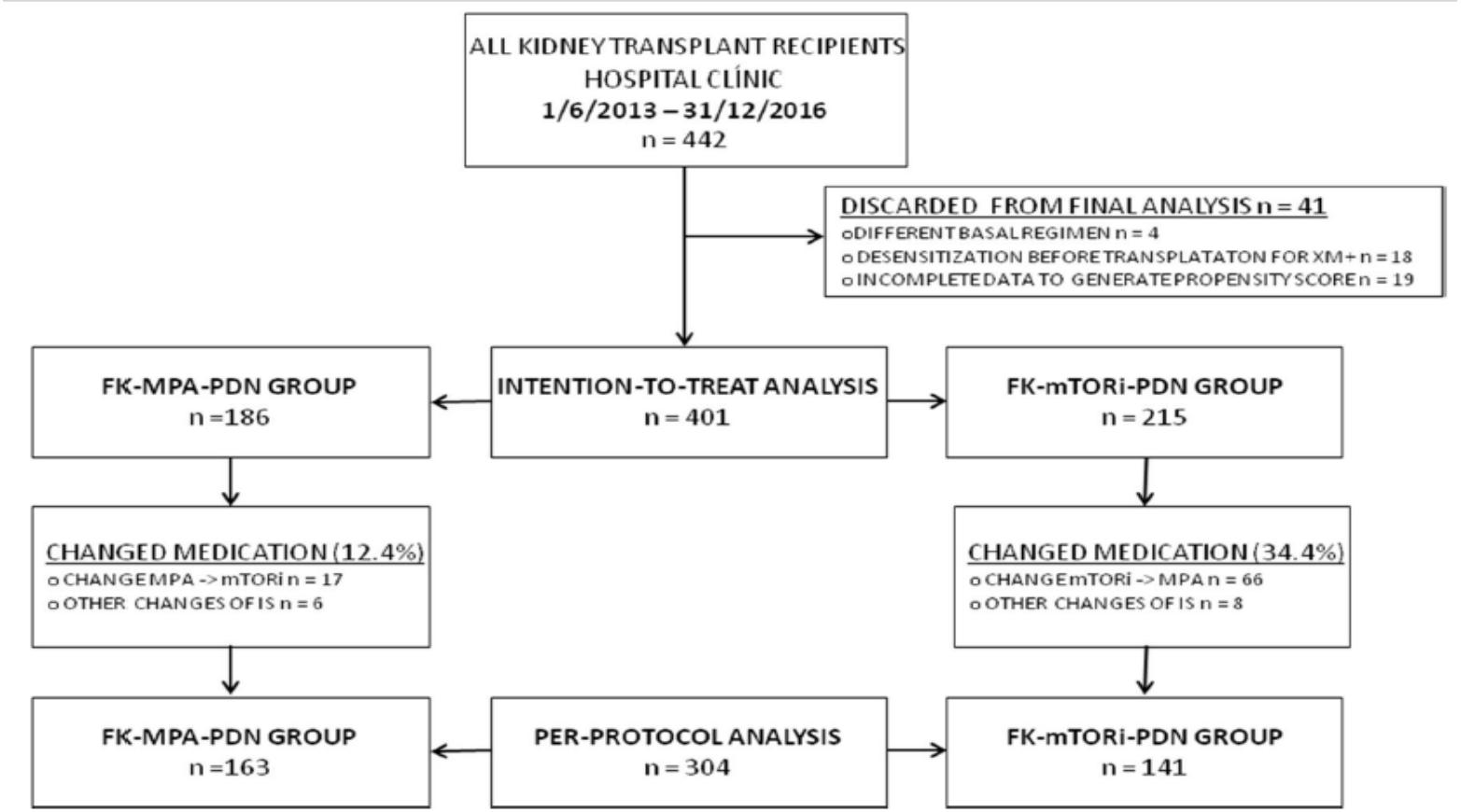
Received: 14 September 2019 / Accepted: 18 November 2019

Flow chart of the study

- From June 2013 to December 2016, 442 patients have received a kidney transplant at the Hospital clinic of Barcelona.



- Patients in mycophenolate (MPA) group treated with 720 mg or 1000 mg bid and later reduced progressively to 360 mg or 500 mg bid during the first year
- In other group, patients received mTORi (either everolimus or sirolimus) target **trough level 3–8 ng/ml**
- Tacrolimus target trough levels were 6–10 ng/ml, adjusted according to the immunological risk profile of the patient and progressively reduced in the mTORi group to 3–8 ng/ml during the first year.
- Patients received induction with anti-thymocytes polyclonal immunoglobulins or basiliximab

- Primary endpoints:

✓ Incidence of 1-year biopsy-proven acute rejection

✓ Renal function expressed as creatinine

✓ Graft loss and patient survival

- Secondary endpoints:

✓ 1-year incidence of infections

✓ Common side effects

✓ Neoplasia

Results

- Patients receiving mTOR have the same results in terms biopsy-proven acute rejection, with an observed tendency towards better results ($P = 0.063$)
- Graft survival at one year favored the mTORi group ($P = 0.025$)
- One-year and last follow-up patient survival favored the mTOR group ($P < 0.001$ and $P < 0.001$, respectively)
- There were no differences between MPA and mTORi for rejection or graft failure, although the better result about patients' survival for mTORi group persisted.
- One-year creatinine was not different between groups ($P > 0.90$) but in living donors was better in mTORi group ($P = 0.02$)
- Banff chronicity index at 1-year renal biopsy were not different

The analysis of common immunosuppression-related side effects

	Intention-to-treat population (n = 401)		Per-protocol population (n = 304)	
	OR (95% CI)	P-value	OR (95% CI)	P-value
NODAT	1 (0.65–1.55)	0.997	1.27 (0.78–2.07)	0.334
Hospitalization for infection	0.70 (0.52–0.93)	0.014	0.47 (0.33–0.66)	<0.001
CMV reactivation	0.45 (0.33–0.61)	< 0.001	0.36 (0.25–0.52)	< 0.001
Hospitalization for CMV disease	0.19 (0.10–0.39)	< 0.001	0.20 (0.09–0.43)	< 0.001
Neoplasia	1.07 (0.57–2.02)	0.837	1.07 (0.54–2.09)	0.854

✓ Patients taking mTORi had favorable outcomes in terms of CMV reactivation and hospitalization for CMV disease

✓ The probability to be hospitalized for any infection during the first year was lower in the mTORi group (P = 0.014)

✓ There were no difference regarding the development of neoplasia at last follow-up (P = 0.837) or 1-year New-Onset Diabetes (P = 0.997)

✓ One-year triglycerides were comparable between groups (P = 0.869) while total cholesterol was higher in the mTORi group (P = 0.005).

✓There was a tendency towards higher Proteinuria in the mTORi group (P = 0.084)

Conclusion

- In the present study, the use of a de-novo immunosuppressive regimen based on mTORi and CNI is an effective approach in a real-life setting, with good results in terms of rejection, graft loss, and survival when compared with a classical regimen based on MPA and CNI

Comparison of Sirolimus Combined With Tacrolimus and Mycophenolate Mofetil Combined With Tacrolimus in Kidney Transplantation Recipients: A Meta-Analysis

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- A total of 10 officially published studies were included in this meta-analysis
- A total of 2357 patients undergoing SRL combined with TAC (n=1256, 53.3%) and MMF combined with TAC(n=1101, 46.7%) were analyzed.

Table 2. Main Outcomes of the Enrolled Studies

Author	Year	No. of patients		Delayed graft function		Acute rejection		Graft survival rate		Infectious complications	
		SRL	MMF	SRL	MMF	SRL	MMF	SRL	MMF	SRL	MMF
Joshua J	2006	79	19	18	61	17	3	NM	NM	NM	NM
Gaetano	2006	50	50	NM	NM	13	5	41	44	32	22
John F	2003	74	84	19	55	6	10	NM	NM	10	0
Flechner et al	2011	152	139	36	116	26	17	135	133	NM	NM
Gallon et al	2006	37	45	3	34	NM	NM	NM	NM	3	7
Thomas	2003	185	176	42	143	24	20	172	168	NM	NM
Jane	2009	307	211	21	286	44	27	NM	NM	NM	NM
Oleg	2016	282	287	NM	NM	10	12	NM	NM	21	20
Edison L	2007	50	50	21	29	7	6	49	46	20	24
Aneesh	2009	40	40	NM	NM	6	8	NM	NM	5	11

Abbreviations: MMF, mycophenolate mofetil; NM, not mentioned; SRL, sirolimus.

- The outcomes showed no significant differences, including:

  Graft function, anemia, graft survival, AR, infectious complications

- The MMF group showed slightly lower rates of diabetes, and hyperlipidemia compared to the SRL group.

Conclusion

- In general, there were no significant differences between the SRL group and MMF group.
- They were equally safe and effective for kidney transplantation recipients.

Transplantation Proceedings, XX, 1–9 (2020)

Determinants of Successful Use of Sirolimus in Renal Transplant Patients

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Introduction

- The German Sirolimus Study Group has established a database among 10 transplant centers in Germany to study indications, contraindications, adverse events, and outcomes in more than 700 renal transplant patients who were switched to a SRL-based therapy.

- Aim of the present analysis is to identify predictors, which can help to assign those patients for SRL who benefit from this therapy most likely.

Methods

- Multicenter, retrospective study
- includes patients with a kidney or combined kidney transplantation with another solid organ
- Patients were put on an SRL-based maintenance immunosuppressive therapy at 3 months post-transplantation or later
- Data were collected in the first year of sirolimus therapy at 3, 6, and 12 months, and semiannually thereafter
- **eGFR** was calculated by the MDRD formula
- **Urinary protein** determinations were recorded

- Clinical Condition at the Time of Sirolimus Initiation:

✓ **The eGFR at the time of sirolimus initiation was 39 mL/min**

✓ **Median Protein excretion was 108 mg/L**

- Graft-related reasons were implicated in half of patients, mostly CNI toxicity and chronic GFR decline.
- A second common cause was the presence of malignancies (24.9%).

Results

- From 726 Patients, Successful sirolimus therapy was observed in 304 patients.
- Therapy failures included graft loss (n =106) and sirolimus-discontinuation for various reasons (n= 276).

- **Most favorable results for sirolimus-use were observed in patients:**

✓ **eGFR: above 32 mL/min.**

✓ **Proteinuria: below 300 mg**

Conclusions

- ✓ **eGFR and proteinuria are the major determinants for successful sirolimus therapy.**

- ✓ **The findings help stratifying patients who will benefit most from this therapy and avoid toxicities in patients without potential benefits for this therapy.**