Research Article

Calcineurin inhibitor old but gold: Mammalian target of rapamycin inhibitor versus calcineurin inhibitor as an immunosuppression regime combined with mycophenolate mofetil in kidney transplantation – A meta-analysis study

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ABSTRACT

Aim: The clinical experience of the mammalian target of rapamycin inhibitors in post kidney transplantation remains challenging even after more than 30 years of clinical studies. After these years, several studies using database registration data indicate that patients receiving mammalian target of rapamycin inhibitors (mTOR-I), as sirolimus (SRL), are at increased risk of acute rejection. Graft loss is increased compared to patients receiving cyclosporine (CSA) or tacrolimus (TAC) in combination with mycophenolate mofetil (MMF). **Materials and Methods:** A meta-analysis study research has performed in Nasr City Insurance Hospital and Nile Badrawi Hospital from September 2011 to September 2018 on the patients with renal transplantation who follow up with the team of transplantation. All patients were transplanted from an unrelated living donor and have zero PRA (no donor-specific antibody [DSA]) before transplantations. **Results:** We have excluded any comorbidities, risk of rejection as non-compliance with cytotoxic drugs, recurrent glomerular disease, patients have positive DSA before transplantation or already known with graft rejection before shifting from calcineurin inhibitor (CNI) to mTOR-I. We have followed those patients after transplantation, and all cases were transplanted at Nasr City Hospital and Nile Badrawi Hospital. We have classified the patient on two groups: Group I: On mTOR-I (SRL or everolimus) there were 658 patients. Group II: On CNI (cyclosporin or tacrolimus) there were 800 patients. The selection of group number one has depended on patients who have shifted from CNI to mTOR-I due to different causes. Our protocol of conversion from CNI to mTOR-I was: Six months after transplant and patients should be a low immunologic risk, have (eGFR) > 40 mL/min and no significant proteinuria (i.e., below 800 mg/day). The causes of shifting from CNI to mTOR-I were different, but CNI toxicity was the leading cause and diagnosed by biopsy. The group of mTOR-I showed a significant increase in the rate of biopsy proved acute rejection (41.8%) in comparison with the group of CNI which showed less incidence of biopsy-proven acute rejection (11.1%). **Conclusion:** CNI-based immunosuppression remains the cornerstone of our current immunosuppression protocols. The current mainstay immunosuppression protocol is the one used, i.e., antibody induction, low-dose CNI, MMF, and steroids avoid the use of mTOR-I *de novo.*

KEY WORDS: Calcineurin inhibitor, Mammalian target of rapamycin inhibitor, Mycophenolate mofetil

INTRODUCTION

In the field of renal transplantation, any new drug is helpful for the nephrologist. Introduction of new immunosuppression drugs such as MMF in 1995, sirolimus (SRL) in 1999, everolimus in 2010, and belatacept in 2011 has led to efforts directed toward CNI sparing. The group of mTOR-I presented to the nephrologist as a dream. It will help in the prevention of CNI toxicity, and they presented this group as a savior, but, unfortunately, this dream turned to nightmares. Some studies and systematic reviews have shown a higher risk for proteinuria and graft loss in patients in the use of mTOR inhibitors (mTOR-I) compared to (CNI) immunosuppressive regimens.[1-5]

Furthermore, mTOR-I has many side effects as proteinuria, dyslipidemia, diabetes, and the most serious one are acute rejection.

However, still, mTOR inhibitors certainly have a role to play in reducing nephrotoxicity, especially when used within the 1st year after transplant but, a significant number of patients do not tolerate them.[5-7]

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The most of the studies of mTOR inhibitors and CNI pooled information from trials comparing different regimens such as a combination of the high dose mTOR inhibitors with a standard dose of CNI or high dose mTOR-I combined with mycophenolate, these studies have depended on deceased donor but, in our study, we depend here on living unrelated donor at hospital of insurance (2). The results of the previous studies have shown considerable heterogeneity (10). Nevertheless, more research is mandatory to diagnose the adverse events and to explore further the potential beneficial effects of mTOR inhibitors.

Our study is unique in comparison of two groups between CNI and mTOR inhibitors in living unrelated donor in different years from 2011 up to 2018.[8-10]

MATERIALS AND METHODS

A meta-analysis study search performed in Nasr City Insurance Hospital and Nile Badrawi Hospital from September 2011 to September 2018 on the patients with renal transplantation who still follow up post-transplantation at the hospitals.

All patients were transplanted from an unrelated living donor and have zero PRA (no DSA) before transplantations.

Our protocol in insurance hospitals depends mainly on CNI based regimen with MMF and steroid.

The shifting to mTOR-I occurs 6 months after renal transplantation in special conditions as CNI toxicity, malignancy, and other rare causes.

Exclusion Criteria

The following criteria were excluded from the study:

1. Previous history of rejection before shifting from CNI to m-TOR-I.
2. History of diabetics before intuition of cytotoxic drugs.
3. History of recurrent glomerular disease at the graft.
4. Patients have positive DSA before transplantation.
5. Patients have a history of non-compliance on cytotoxic drugs or have any risk of rejection rather than the regimen of the immunosuppressive drugs.
6. Patients with a history of chronic hypertension.

We have followed those patients after transplantation. All cases transplanted at Nasr City Hospital and Nile Badrawi Hospital. They were classified the patient into two groups:

*Group I: On mTOR-I (SRL or everolimus) there were 658 patients.

*Group II: On CNI (cyclosporin or tacrolimus) there were 800 patients.

The selection of group one depended on patients who shifted from CNI to mTOR-I due to different causes.

The causes of shifting from CNI to mTOR-I were different, but CNI toxicity was the most common and diagnosed by biopsy.

This study depended on follow-up and comparison of mTOR-I (everolimus or SRL) with CNI (tacrolimus or cyclosporin) in the post-transplant period.

The first outcome measures investigated were biopsy-proven acute rejection (BPAR) in the 1st year of following either the CNI group or mTOR-I group. The other outcomes were graft function including serum creatinine, creatinine clearance, or calculated glomerular filtration rate [GFR] also we reported the frequent and severe side effect of each group in the 1st year of conversion from CNI to m-TOR-I as proteinuria, thrombocytopenia, diabetes, and hypertension.

Statistical Methodology

Analysis of data was done by IBM computer using SPSS v16.

- Description of quantitative variables as mean, SD.
- Description of qualitative variables as number and percentage.
  - Independent sample *t*-test was used to compare quantitative variables in parametric data (SD<50% mean)'.
  - Chi-square test was used to compare two groups as regard qualitative variables.
  - Analysis of variance test (ANOVA) was used to compare the multinominal parameter as regard quantitative data.
  - Multivariate linear regression analysis was done
- $P > 0.05$ insignificant
- $P < 0.05$ significant
- $P < 0.01$ highly significant (Miller and Knapp, 1992)

Bias

We tried to avoid bias with qualitative data analysis and using multiple people to code the data, and we reviewed findings with peers.

RESULTS

In our study, 1458 patients on renal transplantation were classified into two groups:

*Group I: Includes 658 patients on mTOR-I (SRL or everolimus). They were shifted from CNI to mTOR-I due to different causes. They were classified into subgroups according to the year of shifting.

*Group II: Includes 800 patients on CNI (cyclosporin or tacrolimus). They were 237 (36%) males and 421 (64%) females in Group I, 400 (50%) males and

400 (50%) females in Group II, with no statistically significant difference between all groups.

Their mean age was 45.64 years for the Group I, and 48.75 years for Group II, with no statistically significant difference between all groups.

There was a highly statistically significant difference as regard BPAR between patients of Group I and Group II ($P < 0.001$) as the incidence of BPAR in Group I was 41.8 % and 11.1% for Group II [Table 1].

There is highly statistically significant difference between incidence of proteinuria in both groups ($P < 0.001$), the incidence of proteinuria in mTOR-I group was 33% but in CNI group was 1.9% [Table 2] and a highly statistically significant difference between both groups as regard thrombocytopenia ($P < 0.001$) the incidence of thrombocytopenia in Group I was 20.7% but in Group II was 1.9% [Table 2].

The table shows a significant difference in proteinuria in both groups, the group of CNI has a less rate of proteinuria than mTOR, in mTOR there were 33% of patients had proteinuria, but in CNI group there were only 1.9% of patient had proteinuria.

Furthermore, there is a significant difference between both groups in thrombocytopenia, the rate in mTOR group is 20.7%, $P<0.001$.

There were different causes in shifting from CNI to mTOR, but the most important one is CNI toxicity.

The percent of CNI toxicity was 50.9% of the overall causes of shifting.

DISCUSSION

In this study, we have combined data from 1458 patients and examined the efficacy and safety of mTOR-I versus CNI when combined with MPA (3).

In our study, 1458 patients on renal transplantation were classified into two groups:

*Group I: Includes 658 patients on mTOR-I (SRL or everolimus). They were shifted from CNI to mTOR-I due to different causes. They were classified into subgroups according to the year of shifting.

*Group II: Includes 800 patients on CNI (cyclosporin or tacrolimus).

They were 237 (36%) males and 421 (64%) females in Group I, 400 (50%) males and 400 (50%) females in Group II, with no statistically significant difference between all groups. Our study demonstrates that the use of mTOR-I as an immunosuppression regimen combined with MPA has a significant effect on the risk of BPAR.

Patients treated with an mTOR-I have an increased risk of BPAR (by 41.8%). Creatinine clearance was also reduced by approximately 3.5 ml/min in mTOR-I-treated patients (4).[11]

For secondary outcomes, patients were treated with mTOR-I showed an increased risk of proteinuria (33%).

Our study also showed that mTOR-I treated patients significantly reduced the risk of CMV infections and malignancy compared with CNI.

When mTOR-I was compared with CNI, the risk of diabetes was increased by 46%.

A previous study has reported similar results, in that diabetes and thrombocytopenia were observed more frequently after mTOR-I became available, particularly in direct comparison with CNI (12). CNI-based immunosuppression remains the cornerstone of our current immunosuppression protocols. The current mainstay immunosuppression protocol is the one used, i.e., antibody induction, low-dose CNI, MMF, and steroids avoid the use of mTOR-I *de novo*.

The choice of the appropriate immunosuppressive regimen requires clinical experience and careful consideration of recipient and transplant characteristics to achieve an optimal long-term graft survival.[12-14]

Table 1: Comparison between mTOR and CNI in the incidence of BPAR

Year	Group I (mTOR-I)		Group II (CNI)		*P*-value
	Total number	(BPAR) rejection *n* (%)	Total number	(BPAR) rejection *n* (%)	
2011	50	1 (2)	98	8 (8.2)	0.138
2012	64	4 (6.3)	122	12 (9.8)	0.407
2013	65	10 (15.4)	120	14 (11.7)	0.473
2014	50	18 (36)	100	10 (10)	<0.001*
2015	100	45 (45)	103	15 (14.6)	<0.001*
2016	98	45 (45.9)	67	13 (19.4)	0.001*
2017	124	76 (61.3)	79	12 (15.2)	<0.001*
2018	107	76 (71)	111	5 (4.5)	<0.001*
Overall time	658	275 (41.8)	800	89 (11.1)	<0.001*

Chi-square test for qualitative data between the two groups, *Significant level at $P<0.05$. There was a significant difference between CNI and mTOR-I in the rate of BPAR**.** The percentage of BPAR in mTOR-I is 41.8%, in CNI group 11.1% the $P<0.001$. BPAR: Biopsy-proven acute rejection, mTOR: Mammalian target of rapamycin, CNI: Calcineurin inhibitor

Table 2: Comparison between mTOR-I and CNI in the complications rather than rejection

Overall time	Group I mTOR	Group II CNI	*P*-value
	n=658 (%)	*n*=800	
Proteinuria	217 (33)	15 (1.9)	<0.001*
Thrombocytopenia	136 (20.7)	15 (1.9)	<0.001*
Diabetes	46 (7)	32 (4)	0.012*
Hypertension	31 (3.9)	51 (7.8)	0.001*

Chi-square test for qualitative data between the two groups. *Significant level at *P*<0.05. mTOR: Mammalian target of rapamycin, CNI: Calcineurin inhibitor

Table 3: The different causes of shifting from CNI to mTOR at our hospital

Cause of shift (overall time)	mTOR
	n=658 (%)
CNI toxicity	335 (50.9)
Malignancy	76 (11.6)
Polyomavirus	60 (9.1)
Others	55 (8.4)

mTOR: Mammalian target of rapamycin, CNI: Calcineurin inhibitor

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