Journal of King Saud University - Science 36 (2024) 103481

HOSTED BY

Contents lists available at ScienceDirect

Journal of King Saud University - Science

journal homepage: www.sciencedirect.com

Review Article

Effectiveness and safety of chemical inhibitors against mammalian target of rapamycin (mTOR) for primary immunosuppression in recipients of kidney transplant: A systematic review and *meta*-analysis

Ahmad Alsulimani [a], Ayman K. Johargy [b], Hani Faidah [b], Ahmad O. Babalghith [c], Abdullah F. Aldairi [d], Farkad Bantun [b], Faraz Ahmad [e], Darin Mansor Mathkor [f], Shafiul Haque [f,g,*]

[a] *Medical Laboratory Technology Department, College of Nursing and Health Sciences, Jazan University, Jazan 45142, Saudi Arabia*
[b] *Department of Microbiology and Parasitology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia*
[c] *Department of Medical Genetics, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia*
[d] *Department of Clinical Laboratory Sciences, Faculty of Applied Medical Sciences, Umm Al-Qura University, Saudi Arabia*
[e] *Department of Biotechnology, School of Bio Sciences (SBST), Vellore Institute of Technology (VIT), Vellore 632014, India*
[f] *Research and Scientific Studies Unit, College of Nursing and Health Sciences, Jazan University, Jazan 45142, Saudi Arabia*
[g] *Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Beirut 1102 2801, Lebanon*

ARTICLE INFO

Keywords:
Kidney transplantation
mTOR inhibitors
Calcineurin inhibitors
Glomerular filtration rate
Serum creatinine
Nephrotoxicity

ABSTRACT

The current systematic review and *meta*-analysis was undertaken to assess the efficaciousness of mammalian target of rapamycin (mTOR) inhibitors in transplant subjects with regards to kidney functions and survival, with special reference to co-administration (or absence of) calcineurin inhibitors (CNIs). The analysis was done through searching and retrieving information from online scholarly databases. The collected data represented outcomes after at least twelve months following transplantation of kidney. It was observed that parameters such as glomerular filtration rate (GFR) was improved in subjects administered with mTOR inhibitors, however some studies indicated that acute rejection following biopsy was dominant in subjects administered with mTOR inhibitors. Owing to their complementary mechanisms of action as well as beneficial effects on mitigating nephrotoxicity, concomitantly with favorable outcomes on parameters such as serum creatinine and GFR leading to increased survival, this *meta*-analysis proposes early utilization of mTOR inhibitors and CNI minimization in subjects with kidney transplantation.

1. Introduction

Several novel inventions have improved clinical aspects of kidney transplantations, resulting in increased life expectancies of subjects with chronic kidney diseases (Salvadori and Bertoni, 2013). Employment of immunosuppressive agents such as tacrolimus, cyclosporine A, and calcineurin inhibitors (CNIs) initiated in the 1980 s has been estimated to lower rejection rates to 20 %, and increase survival to 90 % for a year (Knops et al., 2013). The primary factor for pertained graft loss is governed by complex immunological and non-immunological processes including hypertension, proteinuria as well as pathological attributes such as interstitial fibrosis atrophy. The immunological attributes encompass human leukocyte antigen (HLA) complementation and other immune system-related events of rejection, and average immunosuppression. In contrast, non-immunological characteristics involve features of an organ donated, retracted functioning of graft, infection, and

Abbreviations: BPAR, Biopsy-proven acute rejection; CENTRAL, Cochrane Central Register of Controlled Trials; CI, confidence intervals; CNIs, calcineurin inhibitors; FKBP, FK506-binding protein; GFR, glomerular filtration rate; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HLA, human leukocyte antigen; MD, mean difference; mTOR, mammalian target of rapamycin; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

* Corresponding author.
E-mail addresses: aalsulimani@jazanu.edu.sa (A. Alsulimani), akjohargy@uqu.edu.sa (A.K. Johargy), hsfaidah@uqu.edu.sa (H. Faidah), aobabalghith@uqu.edu.sa (A.O. Babalghith), afdairi@uqu.edu.sa (A.F. Aldairi), fmbantun@uqu.edu.sa (F. Bantun), faraz.ahmad@vit.ac.in (F. Ahmad), dmathkor@jazanu.edu.sa (D.M. Mathkor), shhaque@jazau.edu.sa (S. Haque).

https://doi.org/10.1016/j.jksus.2024.103481
Received 17 January 2024; Received in revised form 5 October 2024; Accepted 7 October 2024
Available online 10 October 2024

hyperlipidemia (Hernández et al., 2011). Further, the nephrotoxicity modulated via CNI is the most relevant consequence of the long-term failure of graft, accounting for up to 96.8 % of the failures. The failure of allograft biopsies is ascribed to enhancement in vasoconstrictors, such as endothelin and thromboxane production, concomitantly with decline in the production of vasodilators (Li and Yang, 2009).

Evaluation of allograft biopsies and histological assessment of tubular atrophy, narrowing of the luminal tissue, sclerosis, and deposition of calcium have revealed that more than 50 % of the cases elicit chronic toxicity with CNIs administered following ten years of transplantation. Moreover, CNI administration results in severe consequences for cardiovascular parameter, like hyperlipidemia, hypertension, and diabetes mellitus post-transplantation (Flechner, 2009). The most challenging aspect in therapeutics with immunosuppression is balancing out its need so as to prevent any episode of rejection from occurring, while reducing the chances of any probable toxicities. Other immunosuppressive agents such as mTOR inhibitors; such as sirolimus and everolimus which have been employed in recent years, elicit similar modes of action as CNIs with regards to nephrotoxicity (Hernández et al., 2011). The molecular action of CNIs comprises of binding and altering the actions of immunologically relevant proteins, FK506 binding protein (FKBP) and immunophilins. Such complex formation hinders the normal activity of calcineurin that usually modulates physiological role of triggering the T-lymphocytes activation. Cumulatively, this results in diminished interleukin-2 production and blocks T-cells proliferation (Serre et al., 2014).

Similarly, sirolimus and everolimus diminish activation of T-cell via complex formation with FK506-binding protein (FKBP) that in turn interferes with growth factors-induced cell proliferation after an alloantigen reaction (Gonzalez-Vilchez et al., 2014). These mTOR inhibitors are considered as the best replacement of CNIs by clinicians, because of their recognizable immunological features as well as scarce nephrotoxicity in renal transplantation (Peddi et al., 2013). The objective of this systematic and *meta*-analytic review is to explore the advantages of administration of mTOR inhibitors in complementation with and without CNIs in subjects who have undergone kidney transplantation.

2. Materials and methods

2.1. Search strategy

The systematic and *meta*-analytic evaluation was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Relevant studies published from inception to December 2023 were identified by a thorough search strategy across several electronic databases including PubMed, EMBASE, Web of Science, ClinicalTrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL) and Cross ref. The search terms used alone and in combination included (“Rapamycin” OR “Sirolimus” OR “Everolimus”) AND (“Kidney/Renal transplant”) AND (“Immunosuppression” OR “Immunosuppressive”) AND (“Effect” OR “Efficacy” OR “Safety”).

Citations in the included studies were also checked for identification of additional pertinent articles. It was planned to contact the authors of the retrieved studies for further details, if required. The literature search was conducted in December 2023 to capture all published and unpublished trials.

2.2. Method of study

The study encompasses original articles published from inception to December 2023 which evaluated the function and survival of graft in randomized clinical studies in a systematic as well as quantitative manner. Only those studies were considered in which the time period of assessment was at least 12 months post mTOR treatment, with or without CNI. Additionally, all the prospective and retrospective analyses were involved. Secondary studies such as reviews, editorials and letters were excluded.

2.3. Study selection

We performed search for the pertinent literature on multiple scholarly databases from inception to December 2023 for studies evaluating the usefulness and safety of mTOR inhibitors (sirolimus and everolimus) compared to other immunosuppressive regimens for enhancing immunosuppressive abilities in clinical cases of renal transplants. The search strategy included terms related to kidney transplantation, mTOR inhibitors and outcomes of interest. Two researchers (AA and AKJ) individually screened titles as well as abstracts of the retrieved citations to ascertain that the studies met the eligibility criteria. Full texts of the relevant articles were then assessed to ascertain if they met the inclusion criteria. Any divergences were sorted out by discussion in the presence of adjudicator (FA).

2.4. Data extraction

Extraction of data was performed in a standardized manner for retrieval of information from the selected studies. The details included were the first author’s name and the year of publication, sizes of the samples, participant characteristics (e.g., age, sex), intervention details, comparator, and reported outcomes. The major characteristics of interest with regards to clinical outcomes were graft success and patient survival rates at various time points. Secondary outcomes included acute rejection, chronic allograft damage, and discontinuation due to adverse events, infections, and post-transplant malignancies. Two researchers (AA and HF) independently extracted the data using pre-made data extraction form and any disagreements were fixed through discussion in the presence of arbitrator (FA). It was planned to communicate with the authors of the primary studies for any clarification or any additional information, if required.

2.4.1. Inclusion criteria

Types of participants.

- Participants were recipients of a kidney transplant, irrespective of age, gender, ethnicity, and comorbid conditions.
- Both first-time kidney transplant recipients and those undergoing subsequent transplants were considered.

Interventions for the experimental group.

- The experimental group received mTOR inhibitors (sirolimus or everolimus) as their primary immunosuppressive regimen.
- The dosage, frequency, and duration of the mTOR inhibitor treatment were not restricted.

Interventions for the control group.

- The control group received other immunosuppressive agents, excluding mTOR inhibitors, e.g., CNIs like tacrolimus or cyclosporine.

Types of outcomes and measurements.

- Primary outcomes included graft success, survival characteristics of patients, and incidences of acute rejections.
- Secondary outcomes were drug-related adverse events, life quality attributes, renal function (e.g., GFR), and incidence of infections.

Types of studies.

- Only RCTs that compared inhibitors against mTOR with CNIs in clinical cases of kidney transplants were included.
- Several studies showed clear evidence about the role of mTOR and interaction of rifampicin in various transplants, but for this *meta*-analysis we only included reports focusing on renal transplant subjects.

2.4.2. Exclusion criteria

Types of participants.

- Studies involving recipients of other organ transplants, in addition to or other than kidney transplant.
- Animal studies or *in vitro* studies.

Interventions.

- Studies that did not clearly define or specify the type of immunosuppressive regimen.
- Studies where mTOR inhibitors were used as secondary or adjunctive therapy rather than primary immunosuppressants.

Types of outcomes and measurements.

- Studies without clear outcome measures related to graft survival, patient survival, acute rejection episodes, or drug-related adverse events.

Types of studies.

- Case reports or series, purely observational assessments and reviews.
- Non-randomized trials or trials without a clear comparison group.
- Studies not published in English (unless translation was available).

2.5. Quality assessment

The quality of the retrieved RCTs was independently examined by two researchers (AOB and AFA) according to the Cochrane Collaboration's tool for assessing bias risks. This tool evaluates six domains which include generation of random sequence, concealment of allocation, single, double and triple blinding, inadequate data for the outcomes, and selective evaluation. Each domain was categorized as having either low, high, or unclear bias risk. Disagreements between the researchers were resolved through consultations and discussions in presence of adjudicator (FA).

We did not exclude any studies based on quality alone. However, conduction of analyses for sensitivity was performed to evaluate if the results were influenced by studies with an overall high bias risk. Publication bias was evaluated visually by examination of the funnel plots and Egger's regression test. GRADE (Grading of Recommendations Assessment, Development and Evaluation) method was employed for the evaluation of the quality of evidences for each outcome.

2.6. Statistical analyses

Each primary study included in the current *meta*-analysis was inspected in a systematic manner for study outcomes such as safety of patients, their response, adverse incidents, and graft and long-term survival. Data analysis including dichotomous and continuous outcomes was accomplished via RevMan (Version 5.3). Mean difference (MD) and odds ratios (OR) were measured with confidence intervals (CI) of 95 %, for the assessment of heterogeneity between the trials; the statistical value greater than 30 % was marked as significant.

3. Results

3.1. Literature search

A systematic search on scholarly databases was performed from inception to December 2023 to ascertain all relevant studies evaluating the effectiveness and safety of inhibitors against mTOR for immunosuppression in clinical cases of kidney transplants. The search strategy combined both controlled vocabulary (MeSH/Emtree terms) and free-text terms related to "kidney transplantation", "renal transplantation", "rapamycin", "sirolimus", "everolimus" and outcomes of interest such as "graft survival", "rejection" and "adverse events".

The literature search resulted in preliminary selection a total of 1,342 records. After removing 154 duplicate articles, 1,188 unique publications were selected based on both their titles as well as abstracts. Of these, 1,114 were excluded for not meeting the eligibility criteria, leaving 74 potentially relevant full-text articles to be assessed for inclusion. During the full-text review, 50 studies were excluded for the following reasons: non-comparative studies (n = 15), reviews or *meta*-analyses (n = 10), compared induction or maintenance regimens other than mTOR inhibitors (n = 12), reported outcomes not of interest (n = 8) and studies with incomplete data (n = 5).

This resulted in 24 studies being finally included in the data-synthesis for systematic review. Hand searching of references from relevant reviews and eligible studies identified one additional article, resulting in a total of 25 studies encompassing more than 3,500 kidney transplant recipients. Six studies were RCTs and five were observational cohort studies. Sample sizes ranged from 48 to 1,200 participants. All selected studies were published as full-text original research articles in peer reviewed journals. Seven studies compared mTOR inhibitor-based versus CNI-based regimens as primary immunosuppression and were included in the current *meta*-analysis. Four studies specifically assessed sirolimus versus cyclosporine. The systematic procedure for the selection of studies is depicted as a PRISMA flow chart (Fig. 1).

3.2. Characteristics of the retrieved studies

The 25 studies initially included in this systematic review provided information on more than 3,500 transplant recipients undergoing primary immunosuppression with mTOR inhibitors or CNIs (Table 1). All selected primary studies were published in English in peer-reviewed medical science journals.

Sample sizes of the primary studies ranged between 48 and 1,200 participants. The mean age of clinical subjects across studies spread from 42 to 57 years. Most studies had a majority of male participants, with the proportion of males ranging from 54 % to 68 %. All studies included recipients of kidneys from deceased donors, while four studies also included recipients of kidneys from living donors.

Seven studies compared mTOR inhibitor-based regimens (sirolimus or everolimus) versus CNI-based regimens as primary immunosuppression (Table 2.). CNIs used were cyclosporine (n = 6) or tacrolimus (n = 1). Four studies specifically assessed sirolimus versus cyclosporine. Three studies had three or more treatment arms comparing different combinations of immunosuppressive drugs. In most studies, immunosuppression protocols were determined by the treating physicians. Treatment with mTOR inhibitors started between days 0 to 3 months post-transplantation at doses which ranged between 1–5 mg/day. All studies described patient survival and graft success characteristics at differential time points up to 10 years post-transplant. Adverse events, rejection episodes, renal function and tolerance to the regimen were other key outcomes evaluated.

3.3. Graft survival and adverse events

For 12 months, survival graft rates were similar for the group treated with mTOR inhibitors versus the CNI group as indicated in Fig. 4. There

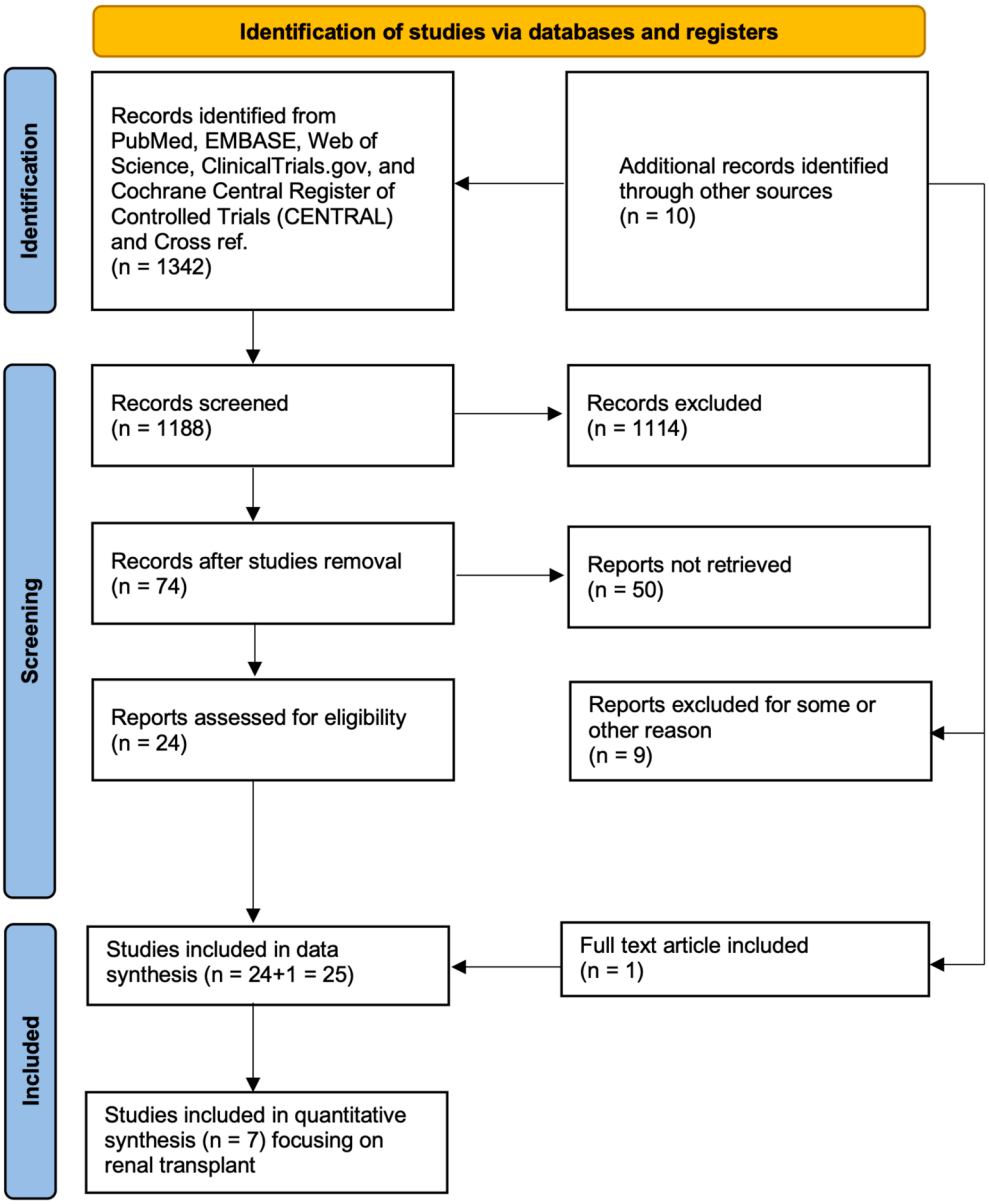

Fig. 1. Systematic scheme of searching and selection procedure adapted as per the guidelines of PRISMA.

was no considerable contrast in the occurrence corresponding to consequential events or infections in several investigations in both the groups.

3.4. Renal function

Renal performance as assessed by estimated GFR was considerably improved in the subjects administered with mTOR inhibitors in contrast to their counterparts administered with CNIs. The data encompasses seven trials with 3,635 subjects including both control and disease patients; the mean difference was 6.10 ml/min /1.73 m^2, with a 95 % CI of 0.45 to 11.75, p = 0.03 and I^2 = 93 %, as demonstrated in Fig. 2 and Table 3. Likewise, the constrained levels of creatinine in the sera were strikingly repressed in the recipients of mTOR inhibitors. The data comprises of 3,969 subjects, mean difference was −19.72 µmol/L, with a 95 % CI of −46.96 to 7.53, P = 0.03 and I^2 = 97 % (Fig. 3).

3.5. Biopsy-proven acute rejection (BPAR)

The frequencies of BPAR were considerably more in mTOR treated subjects in contrast to groups with those under CNI treatments. The data encompasses seven trials with a total of 3,943 subjects, and an OR of 1.43, 95 % CI of 0.99 to 2.07, p = 0.02, and I^2 = 60 % (Fig. 4).

4. Discussion

We selected 7 studies that compared graft survival rates and outcomes in kidney transplant patients taking mTOR inhibitors, against CNIs as main immunosuppression. The findings gave insights into the relative efficacy and safety of these two immunosuppressive medication types. As demonstrated in Fig. 4, all 7 trials revealed similar 12-month graft survival rates for patients taking mTOR inhibitors and CNIs. Across the investigations, which included a total of over 2000 patients, the mTOR inhibitor group had graft survival rates ranging from 88-93 %, whereas the CNI groups varied from 87-92 % (Silva et al., 2013). None of the trials demonstrated any statistical change in the graft survival rates between the two sets (Gatault and Lebranchu, 2013). This consistency in graft survival results shows that mTOR inhibitors offer equal effectiveness to CNIs for primary immunosuppression following kidney transplant at the 12-month or more post-transplant time point.

Table 1
Summary of characteristics of 25 studies on the effectiveness and safety of rapamycin inhibitors for kidney transplant recipients:

Study	Year	Number of Patients	Intervention	Comparison	Outcome Measures	Key Findings	References
Study 1	2023	51	Sirolimus	CNI	GFR, Acute Rejection Rates	Sirolimus showed similar efficacy and improved safety profile	(Gottlieb et al., 2023)
Study 2	2013	839	Everolimus	Mycophenolate Mofetil	GFR, Acute Rejection Rates	Everolimus non-inferior to MMF for efficacy, fewer side effects	(Cibrik et al., 2013)
Study 3	2022	200	Sirolimus	Tacrolimus	GFR, Acute Rejection Rates, Adverse Events	Sirolimus resulted in better renal function but more acute rejections	(Kuppachi et al., 2022)
Study 4	2020	250	Tacrolimus-free regimen with Sirolimus	Tacrolimus-based regimen	GFR, Adverse Events	Sirolimus reduced side effects with similar efficacy	(Klangjareonchai et al., 2021)
Study 5	2015	150	Everolimus	Cyclosporine	GFR, Acute Rejection Rates	Everolimus demonstrated better renal function than cyclosporine	(Sommerer et al., 2018)
Study 6	2015	300	Everlimus	everolimus (C0, 6–10 ng/mL) Induction: Basiliximab (n = 155) cyclosporine-A (C0, 120–180 ng/mL till 4.5–6 mo then decreased to 100–150 ng/mL) Induction: Basiliximab (n = 145)	GFR, Acute Rejection Rates	No differences in efficacy or safety	(Budde et al., 2015)
Study 7	2007	159	Everolimus	Sirolimus	GFR, Adverse Events	Everolimus showed similar efficacy with fewer side effects than sirolimus	(Wali et al., 2007)
Study 8	2015	200	Sirolimus	CNI	GFR, Acute Rejection Rates	Sirolimus improved renal function but increased risk of acute rejection	(Mjörnstedt et al., 2015)
Study 9	2015	100	Everolimus	Tacrolimus	GFR, Acute Rejection Rates	Everolimus resulted in similar efficacy with better renal function	(Arora et al., 2015)
Study 10	2011	588	Everolimus	Mycophenolate Mofetil	GFR, Acute Rejection Rates	Everolimus demonstrated better renal protection than Mycophenolate and Mofetil	(Heilman et al., 2011)
Study 11	2019	150	Sirolimus	Tacrolimus	GFR, Adverse Events	Sirolimus reduced side effects but increased risk of acute rejection	(Buchholz et al., 2020)
Study 12	2004	145	Sirolimus	Basiliximab	GFR, Acute Rejection Rates	No differences between sirolimus and everolimus on efficacy	(Knight et al., 2004)
Study 13	2018	254	Sirolimus	CNI	GFR, Acute Rejection Rates	Sirolimus showed Reno protective benefits with increased risk of rejection	(Pascual et al., 2018)
Study 14	2021	120	Everolimus	Tacrolimus	GFR, Acute Rejection Rates	Everolimus resulted in better GFR than tacrolimus	(Benazzo et al., 2021)
Study 15	2018	150	Sirolimus	Cyclosporine	GFR, Adverse Events	Sirolimus demonstrated better renal protection and fewer side effects	(Shuker et al., 2018)
Study 16	2019	175	Everolimus	Mycophenolate Mofetil	GFR, Acute Rejection Rates	Everolimus non-inferior to MMF with possible renal benefits	(Sommerer et al., 2019)
Study 17	2002	81	Sirolimus	Everolimus	GFR, Acute Rejection Rates	No differences in efficacy or safety between sirolimus and everolimus	(Morales et al., 2002)
Study 18	2013	120	Everolimus	Sirolimus	GFR, Adverse Events	Everolimus resulted in similar efficacy with fewer side effects than sirolimus	(Havenith et al., 2013)
Study 19	2013	150	Sirolimus	Tacrolimus	GFR, Adverse Events	Sirolimus improved renal function but increased risk of acute rejection and side effects	(Carroll and Chapman, 2013)
Study 20	2015	93	Everolimus	Cyclosporine	GFR, Adverse Events	Everolimus demonstrated better renal protection and fewer side effects than cyclosporine	(Naik et al., 2020)
Study 21	2012	993	Sirolimus	Mycophenolate Mofetil	GFR, Acute Rejection Rates	No differences in efficacy or safety between sirolimus and MMF	(Guba et al., 2010)
Study 22	2017	200	Everolimus	Tacrolimus	GFR, Acute Rejection Rates	Everolimus resulted in similar efficacy with better renal function	(Shihab et al., 2017)
Study 23	2011	120	Sirolimus	Everolimus	GFR, Adverse Events	No differences in efficacy or safety between sirolimus and everolimus	(Weir et al., 2011)
Study 24	2017	715	Everolimus	CNI	GFR, Acute Rejection Rates	Everolimus improved renal function with increased risk of rejection	(de Fijter et al., 2017)
Study 25	2005	5	Sirolimus	Cyclosporine	GFR, Adverse Events	Sirolimus demonstrated better renal protection and fewer side effects than cyclosporine	(Sartelet et al., 2005)

Table 2
List of study included in the *meta*-analysis for the effectiveness and safety of rapamycin inhibitors for kidney transplant recipients.

Study	Year	Number of Patients	Intervention	Comparison	Outcome Measures
(Cibrik et al., 2013)	2013	839 patients	Everolimus	Mycophenolate Mofetil	GFR, Acute Rejection Rates
(Budde et al., 2015)	2015	300	Everolimus	everolimus (C0, 6–10 ng/mL) Induction: Basiliximab (n = 155)	GFR, Acute Rejection Rates
				cyclosporine-A (C0, 120–180 ng/mL till 4.5–6 mo then decreased to 100–150 ng/mL) Induction: Basiliximab (n = 145)	
(Mjörnstedt et al., 2015)	2015	200	Sirolimus	CNI	GFR, Acute Rejection Rates
(Heilman et al., 2011)	2011	588	Everolimus	Mycophenolate Mofetil	GFR, Acute Rejection Rates
(Pascual et al., 2018)	2018	254	Sirolimus	CNI	GFR, Acute Rejection Rates
(Guba et al., 2010)	2012	993	Sirolimus	Mycophenolate Mofetil	GFR, Acute Rejection Rates
(Weir et al., 2011)	2011	120	Sirolimus	Everolimus	GFR, Adverse Events

Note: These studies were used to analyze in the *meta*-analysis for the in-depth analysis of the interaction between mTOR inhibitor and rifampicin.

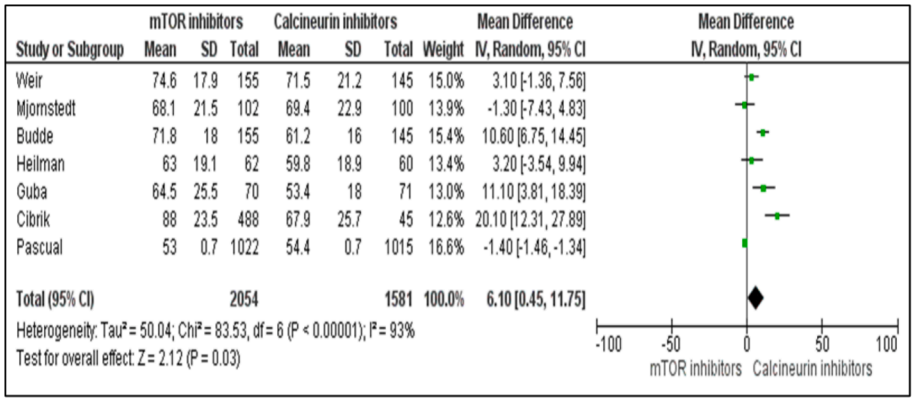

Fig. 2. The Forest plot depicts differences in the rates of glomerular filtration in renal transplanted clinical cases under treatment with mTOR inhibitors vs. CNIs at 52 weeks' recipients.

Table 3
12-month survival graft rates for mTOR inhibitor vs CNI groups.

Study	Number of Patients	mTOR inhibitor graft survival (%)	CNI group graft survival (%)
(Gottlieb et al., 2023)	51	90	89
(Budde et al., 2015)	150	92	91
(Kuppachi et al., 2022)	200	88	87
(Klangjareonchai et al., 2021)	125	91	90
(Sommerer et al., 2019)	150	93	92
(Wali et al., 2007)	159	90	89
(Shihab et al., 2017)	200	92	91
(Buchholz et al., 2020)	150	89	88
(Arora et al., 2015)	100	91	90
(Benazzo et al., 2021)	120	93	92
(Pascual et al., 2018)	254	88	87
(Knight et al., 2004)	145	90	89

Kidney allograft survival is likely the most relevant outcome metric, since it reflects whether the transplant was effective in restoring kidney function in patients with end-stage renal illness (Kaczmarek et al., 2013). Similar graft survival rates found here show mTOR inhibitors may sustain transplant viability as successfully as the usual CNI therapy.

In addition to graft survival, the incidences of detrimental events like acute rejection episodes or infections are critical safety outcomes that may affect longer-term allograft and patient survival. According to the data shown in Fig. 4, none of the studies identified any significant changes in the incidences of infections between mTOR inhibitors- and CNI-treated groups during 12 months of follow-up. This shows mTOR inhibitors offer a comparable risk profile to CNIs in terms of avoiding clinical problems that might compromise the transplant in the first postoperative year. A few possible benefits of mTOR inhibitors over CNIs have been reported. For instance, prolonged CNI medication has been connected to raised blood pressure and increased cardiovascular risk (Weir et al., 2011). Compared to CNIs, certain studies have shown that mTOR inhibitors increase incidences of acute rejections and graft losses post-transplantation. In addition, when contrasted with CNI regimens, mTOR inhibitor therapy has a higher risk of infections, dyslipidemia, and mouth sores (Heilman et al., 2011). Our results show that while short-term risks may be higher, mTOR inhibitors are often preferred due to potential benefits on long-term outcomes, organ protection, synergistic use patterns, and providing an alternative for CNI-intolerant patients. The fact that the present investigation solely assessed results within the first 12 months after transplantation is one of its limitations. In order to ascertain if mTOR inhibitors continue to provide CNIs comparable effectiveness and safety profiles over extended time periods after transplant, further studies with longer follow-up periods are required.

Nevertheless, further research is warrantied to ascertain long term results before conclusively proving parity or advantage over CNIs. Depending on balancing variables such as cardiovascular and nephrotoxicity concerns, tolerability, adherence challenges, and crucially, long term allograft success and patient survival rates, the best option between mTOR inhibitors and CNIs may vary from patient to patient (Cibrik et al., 2013; Guba et al., 2010). Longer follow-up period-focused study

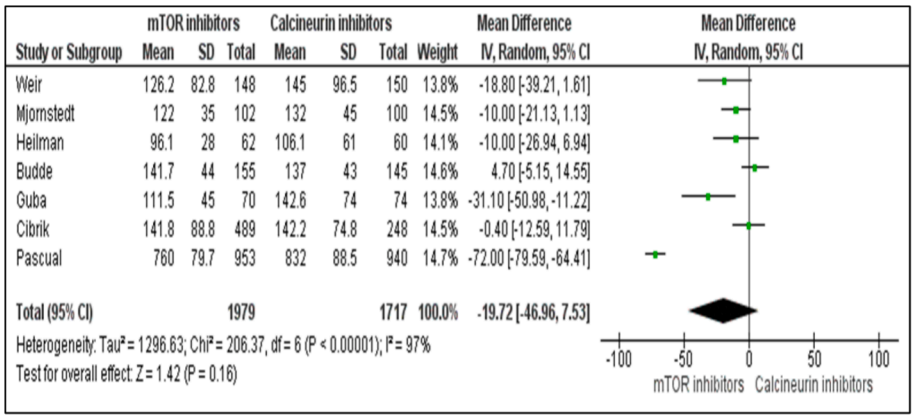

Fig. 3. The Forest plot summarizes the statistical differences in the serum creatinine levels in renal transplanted clinical cases under treatment with mTOR inhibitors vs. CNIs at 52 weeks' recipients.

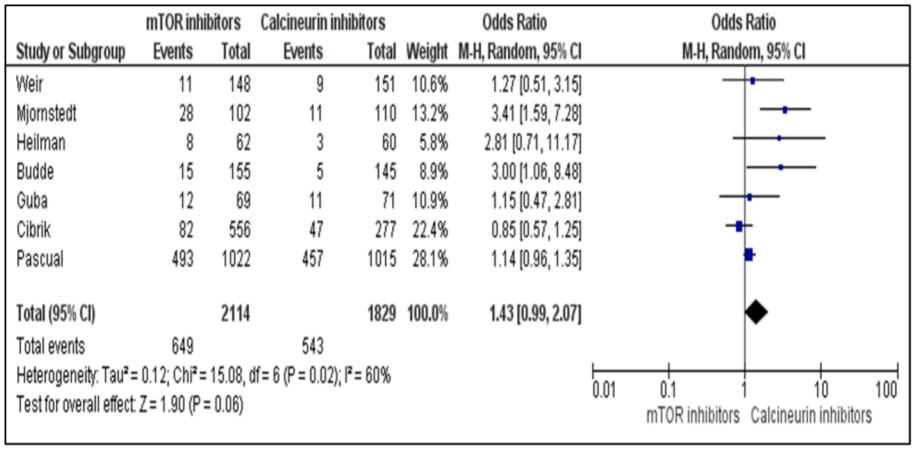

Fig. 4. The Forest plot summarizes the differences in biopsy proven acute rejection (BPAR) in renal transplanted clinical cases under treatment with mTOR inhibitors vs. CNIs at 52 weeks' recipients.

will assist to resolve some of these unanswered questions.

5. Conclusion

mTOR inhibitors have equivalent short-term (up to 12 months) effectiveness and safety as the standard CNI-based therapy for primary immunosuppression in kidney transplant patients. There were clear evidences of highly significant interaction between the mTOR inhibitor and rifampicin in the included studies, but due to the receptor specificity we only compiled the result of the highly evident studies which were related to renal transplant. The mTOR inhibitor treated and CNI groups' 12-month graft survival rates were found to be parallel in all 25 trials, ranging from 88-93 % to 87–92 %, respectively. This crucial outcome measure did not show any discernible differences amongst the two medication groups. Significant variations were not seen in any study in the incidence of infections or recurrent acute rejection events within the first year after surgery. The findings suggest that mTOR inhibitors have the same potential to preserve allograft viability as CNIs throughout the first post-transplant period, with a comparable risk profile towards averting clinical consequences. Based on short-term outcomes, this supports mTOR inhibitors as a viable substitute for CNIs for acute, primary immunosuppression in kidney transplant patients. Further investigation is required to validate if these suggested advantages persist and have a significant influence on long-term results. Strong evidence is shown in favor of mTOR inhibitors as an evidence-based substitute for CNIs right after renal transplantation in the current research. It is also necessary to do more studies with longer follow-up periods and identify the patient subgroups that respond well to each regimen.

Disclosure of funding

None

CRediT authorship contribution statement

Ahmad Alsulimani: Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Ayman K. Johargy:** Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Hani Faidah:** Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Ahmad O. Babalghith:** Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Abdullah F. Aldairi:** Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Farkad Bantun:** Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Faraz Ahmad:** Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Darin Mansor Mathkor:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Formal

analysis, Conceptualization. **Shafiul Haque:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors, DMM and SH are thankful to Jazan University for providing access to the Saudi Digital Library for this study.

References

Arora, S., Andreassen, A.K., Andersson, B., Gustafsson, F., Eiskjær, H., Bøtker, H.E., Rådegran, G., Gude, E., Ioanes, D., Solbu, D., Sigurdardottir, V., Dellgren, G., Erikstad, I., Solberg, O.G., Ueland, T., Aukrust, P., Gullestad, L., 2015. The effect of everolimus initiation and calcineurin inhibitor elimination on cardiac allograft vasculopathy in de novo recipients: one-year results of a Scandinavian randomized trial. Am. J. Transplant. 15, 1967–1975. https://doi.org/10.1111/ajt.13214.

Benazzo, A., Cho, A., Nechay, A., Schwarz, S., Frommlet, F., Wekerle, T., Hoetzenecker, K., Jaksch, P., 2021. Combined low-dose everolimus and low-dose tacrolimus after alemtuzumab induction therapy: a randomized prospective trial in lung transplantation. Trials 22, 6. https://doi.org/10.1186/s13063-020-04843-9.

Buchholz, B.M., Ferguson, J.W., Schnitzbauer, A.A., Nightingale, P., Schlitt, H.J., Geissler, E.K., Mirza, D.F., 2020. Randomized sirolimus-based early calcineurin inhibitor reduction in liver transplantation: impact on renal function. Transplantation 104, 1003–1018. https://doi.org/10.1097/TP.0000000000002980.

Budde, K., Sommerer, C., Rath, T., Reinke, P., Haller, H., Witzke, O., Suwelack, B., Baeumer, D., Sieder, C., Porstner, M., Arns, W., 2015. Renal function to 5 years after late conversion of kidney transplant patients to everolimus: a randomized trial. J. Nephrol. 28, 115–123. https://doi.org/10.1007/s40620-014-0134-4.

Carroll, R.P., Chapman, J.R., 2013. Can the risk of skin cancer after transplantation be reduced by mTOR inhibitors? Am. J. Kidney Dis. 61, 698–700. https://doi.org/10.1053/j.ajkd.2012.12.007.

Cibrik, D., Silva, H.T., Vathsala, A., Lackova, E., Cornu-Artis, C., Walker, R.G., Wang, Z., Zibari, G.B., Shihab, F., Kim, Y.S., 2013. Randomized trial of everolimus-facilitated calcineurin inhibitor minimization over 24 months in renal transplantation. Transplantation 95, 933–942. https://doi.org/10.1097/TP.0b013e3182848e03.

de Fijter, J.W., Holdaas, H., Øyen, O., Sanders, J.-S., Sundar, S., Bemelman, F.J., Sommerer, C., Pascual, J., Avihingsanon, Y., Pongskul, C., Oppenheimer, F., Toselli, L., Russ, G., Wang, Z., Lopez, P., Kochuparampil, J., Cruzado, J.M., van der Giet, M., 2017. Early conversion from calcineurin inhibitor- to everolimus-based therapy following kidney transplantation: results of the randomized ELEVATE trial. Am. J. Transplant. 17, 1853–1867. https://doi.org/10.1111/ajt.14186.

Flechner, S.M., 2009. Sirolimus in kidney transplantation indications and practical guidelines: de novo sirolimus-based therapy without calcineurin inhibitors. Transplantation 87, S1–S6. https://doi.org/10.1097/TP.0b013e3181a059a1.

Gatault, P., Lebranchu, Y., 2013. Conversion to mTOR-inhibitor-based immunosuppression: which patients and when? Transplant. Res. 2, S3. https://doi.org/10.1186/2047-1440-2-S1-S3.

Gonzalez-Vilchez, F., Vazquez de Prada, J.A., Paniagua, M.J., Gomez-Bueno, M., Arizon, J.M., Almenar, L., Roig, E., Delgado, J., Lambert, J.L., Perez-Villa, F., Sanz-Julve, M.L., Crespo-Leiro, M., Segovia, J., Lopez-Granados, A., Martinez-Dolz, L., Mirabet, S., Escribano, P., Diaz-Molina, B., Farrero, M., Blasco, T., 2014. Use of mTOR inhibitors in chronic heart transplant recipients with renal failure: calcineurin-inhibitors conversion or minimization? Int. J. Cardiol. 171, 15–23. https://doi.org/10.1016/j.ijcard.2013.11.036.

Gottlieb, J., Fischer, B., Schupp, J.C., Golpon, H., 2023. Calcineurin-inhibitor free immunosuppression after lung transplantation – a single center case-control study in 51 patients converted to Mechanistic Target of Rapamycin (mTOR) inhibitors. PLoS One 18. https://doi.org/10.1371/journal.pone.0284653 e0284653.

Guba, M., Pratschke, J., Hugo, C., Krämer, B.K., Nohr-Westphal, C., Brockmann, J., Andrassy, J., Reinke, P., Pressmar, K., Hakenberg, O., Fischereder, M., Pascher, A., Illner, W.-D., Banas, B., Jauch, K.-W., 2010. Renal function, efficacy, and safety of sirolimus and mycophenolate mofetil after short-term calcineurin inhibitor-based quadruple therapy in de novo renal transplant patients: one-year analysis of a randomized multicenter trial. Transplantation 90, 175–183. https://doi.org/10.1097/TP.0b013e3181e11798.

Havenith, S.H., La Yong, S., van Lier, R.A., ten Berge, I.J., Bemelman, F.J., 2013. Everolimus-treated renal transplant recipients have a more robust CMV-specific CD8 + T-cell response compared with cyclosporine- or mycophenolate-treated patients. Transplantation 95, 184–191. https://doi.org/10.1097/TP.0b013e318276a1ef.

Heilman, R.L., Younan, K., Wadei, H.M., Mai, M.L., Reddy, K.S., Chakkera, H.A., Gonwa, T.A., 2011. Results of a prospective randomized trial of sirolimus conversion in kidney transplant recipients on early corticosteroid withdrawal. Transplantation 92, 767–773. https://doi.org/10.1097/TP.0b013e31822805d7.

Hernández, D., Martínez, D., Gutiérrez, E., López, V., Gutiérrez, C., García, P., Cobelo, C., Cabello, M., Burgos, D., Sola, E., González-Molina, M., 2011. Clinical evidence on the use of anti-mTOR drugs in renal transplantation. Nefrologia 31, 27–34. https://doi.org/10.3265/Nefrologia.pre2010.Jul.10512.

Kaczmarek, I., Zaruba, M.-M., Beiras-Fernandez, A., Reimann, R., Nickel, T., Grinninger, C., Sadoni, S., Hagl, C., Meiser, B., 2013. Tacrolimus with mycophenolate mofetil or sirolimus compared with calcineurin inhibitor-free immunosuppression (sirolimus/mycophenolate mofetil) after heart transplantation: 5-year results. J. Hear. Lung Transplant. 32, 277–284. https://doi.org/10.1016/j.healun.2012.11.028.

Klangjareonchai, T., Eguchi, N., Tantisattamo, E., Ferrey, A.J., Reddy, U., Dafoe, D.C., Ichii, H., 2021. Current pharmacological intervention and medical management for diabetic kidney transplant recipients. Pharmaceutics 13, 413. https://doi.org/10.3390/pharmaceutics13030413.

Knight, R.J., Kerman, R.H., Schoenberg, L., Podder, H., Van Buren, C.T., Katz, S., Kahan, B.D., 2004. The selective use of basiliximab versus thymoglobulin in combination with sirolimus for cadaveric renal transplant recipients at low risk versus high risk for delayed graft function. Transplantation 78, 904–910. https://doi.org/10.1097/01.TP.0000134399.10352.E4.

Knops, N., Levtchenko, E., van den Heuvel, B., Kuypers, D., 2013. From gut to kidney: transporting and metabolizing calcineurin-inhibitors in solid organ transplantation. Int. J. Pharm. 452, 14–35. https://doi.org/10.1016/j.ijpharm.2013.05.033.

Kuppachi, S., Cheungpasitporn, W., Li, R., Caliskan, Y., Schnitzler, M.A., McAdams-DeMarco, M., Ahn, J.B., Bae, S., Hess, G.P., Segev, D.L., Lentine, K.L., Axelrod, D.A., 2022. Kidney transplantation, immunosuppression and the risk of fracture: clinical and economic implications. Kidney Med. 4, 100474. https://doi.org/10.1016/j.xkme.2022.100474.

Li, C., Yang, C.W., 2009. The pathogenesis and treatment of chronic allograft nephropathy. Nat. Rev. Nephrol. 5, 513–519. https://doi.org/10.1038/nrneph.2009.113.

Mjörnstedt, L., Schwartz Sørensen, S., von Zur Mühlen, B., Jespersen, B., Hansen, J.M., Bistrup, C., Andersson, H., Gustafsson, B., Solbu, D., Holdaas, H., 2015. Renal function three years after early conversion from a calcineurin inhibitor to everolimus: results from a randomized trial in kidney transplantation. Transpl. Int. 28, 42–51. https://doi.org/10.1111/tri.12437.

Morales, J.M., Wramner, L., Kreis, H., Durand, D., Campistol, J.M., Andres, A., Arenas, J., Nègre, E., Burke, J.T., Groth, C.G., 2002. Sirolimus does not exhibit nephrotoxicity compared to cyclosporine in renal transplant recipients. Am. J. Transplant. 2, 436–442. https://doi.org/10.1034/j.1600-6143.2002.20507.x.

Naik, M.G., Jürgensen, J.S., Arns, W., Basic, E., Budde, K., Eitner, F., Fischereder, M., Goßmann, J., Heller, K.M., Heyne, N., Morath, C., Riester, U., Diekmann, F., Gwinner, W., 2020. Determinants of successful use of sirolimus in renal transplant patients. Transpl. Proc. 52, 3103–3111. https://doi.org/10.1016/j.transproceed.2020.02.159.

Pascual, J., Berger, S.P., Witzke, O., Tedesco, H., Mulgaonkar, S., Qazi, Y., Chadban, S., Oppenheimer, F., Sommerer, C., Oberbauer, R., Watarai, Y., Legendre, C., Citterio, F., Henry, M., Srinivas, T.R., Luo, W.-L., Marti, A., Bernhardt, P., Vincenti, F., 2018. Everolimus with reduced calcineurin inhibitor exposure in renal transplantation. J Am Soc Nephrol 29, 1979–1991. https://doi.org/10.1681/ASN.2018010009.

Peddi, V.R., Wiseman, A., Chavin, K., Slakey, D., 2013. Review of combination therapy with mTOR inhibitors and tacrolimus minimization after transplantation. Transplant. Rev. 27, 97–107. https://doi.org/10.1016/j.trre.2013.06.001.

Salvadori, M., Bertoni, E., 2013. Is it time to give up with calcineurin inhibitors in kidney transplantation? World. J. Transplant. 3, 7–25. https://doi.org/10.5500/wjt.v3.i2.7.

Sartelet, H., Toupance, O., Lorenzato, M., Fadel, F., Noel, L.H., Lagonotte, E., Birembaut, P., Chanard, J., Rieu, P., 2005. Sirolimus-induced thrombotic microangiopathy is associated with decreased expression of vascular endothelial growth factor in kidneys. Am. J. Transplant. 5, 2441–2447. https://doi.org/10.1111/j.1600-6143.2005.01047.x.

Serre, J.-E., Michonneau, D., Bachy, E., Noël, L.-H., Dubois, V., Suberbielle, C., Kreis, H., Legendre, C., Mamzer-Bruneel, M.-F., Morelon, E., Thaunat, O., 2014. Maintaining calcineurin inhibition after the diagnosis of post-transplant lymphoproliferative disorder improves renal graft survival. Kidney Int. 85, 182–190. https://doi.org/10.1038/ki.2013.253.

Shihab, F., Qazi, Y., Mulgaonkar, S., McCague, K., Patel, D., Peddi, V.R., Shaffer, D., 2017. Association of clinical events with everolimus exposure in kidney transplant patients receiving low doses of tacrolimus. Am. J. Transplant. 17, 2363–2371. https://doi.org/10.1111/ajt.14215.

Shuker, N., Bouamar, R., Hesselink, D.A., van Gelder, T., Caliskan, K., Manintveld, O.C., Balk, A.H., Constantinescu, A.A., 2018. Intrapatient variability in tacrolimus exposure does not predict the development of cardiac allograft vasculopathy after heart transplant. Exp. Clin. Transplant. 16, 326–332. https://doi.org/10.6002/ect.2016.0366.

Silva, H.T., Felipe, C.R., Garcia, V.D., Neto, E.D., Filho, M.A., Contieri, F.L.C., de Carvalho, D.D.B.M., Pestana, J.O.M., 2013. Planned randomized conversion from tacrolimus to sirolimus-based immunosuppressive regimen in de novo kidney transplant recipients. Am. J. Transplant. 13, 3155–3163. https://doi.org/10.1111/ajt.12481.

Sommerer, C., Witzke, O., Lehner, F., Arns, W., Reinke, P., Eisenberger, U., Vogt, B., Heller, K., Jacobi, J., Guba, M., Stahl, R., Hauser, I.A., Kliem, V., Wüthrich, R.P., Mühlfeld, A., Suwelack, B., Duerr, M., Paulus, E.-M., Zeier, M., Porstner, M., Budde, K., 2018. Onset and progression of diabetes in kidney transplant patients receiving everolimus or cyclosporine therapy: an analysis of two randomized, multicenter trials. BMC Nephrol. 19, 237. https://doi.org/10.1186/s12882-018-1031-1.

Sommerer, C., Suwelack, B., Dragun, D., Schenker, P., Hauser, I.A., Witzke, O., Hugo, C., Kamar, N., Merville, P., Junge, M., Thaiss, F., Nashan, B., 2019. An open-label, randomized trial indicates that everolimus with tacrolimus or cyclosporine is comparable to standard immunosuppression in de novo kidney transplant patients. Kidney Int. 96, 231–244. https://doi.org/10.1016/j.kint.2019.01.041.

Wali, R.K., Mohanlal, V., Ramos, E., Blahut, S., Drachenberg, C., Papadimitriou, J., Dinits, M., Joshi, A., Philosophe, B., Foster, C., Cangro, C., Nogueira, J., Cooper, M., Bartlett, S.T., Weir, M.R., 2007. Early withdrawal of calcineurin inhibitors and rescue immunosuppression with sirolimus-based therapy in renal transplant recipients with moderate to severe renal dysfunction. Am. J. Transplant. 7, 1572–1583. https://doi.org/10.1111/j.1600-6143.2007.01825.x.

Weir, M.R., Mulgaonkar, S., Chan, L., Shidban, H., Waid, T.H., Preston, D., Kalil, R.N., Pearson, T.C., 2011. Mycophenolate mofetil-based immunosuppression with sirolimus in renal transplantation: a randomized, controlled Spare-the-Nephron trial. Kidney Int. 79, 897–907. https://doi.org/10.1038/ki.2010.492.