Mammalian target of rapamycin inhibitors combined with calcineurin inhibitors as initial immunosuppression in renal transplantation: a meta-analysis

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ABBREVIATIONS

AR: acute rejection;

AZA: azathioprine;

BPAR: biopsy proven acute rejection;

CI: confidence interval;

CMV: cytomegalovirus;

CNI: calcineurin inhibitors;

CsA: cyclosporine;

DGF: delayed graft function;

EVR: everolimus;

HLA: human leukocyte antigen;

MD: mean difference;

MMF: mycophenolate mofetil;

MPA: mycophenolic acid or enteric-coated mycophenolate sodium;

mTORi: mammalian target of rapamycin inhibitors;

rATG: rabbit anti-thymocyte globulin;

RR: risk ratio;

SRL: rapamycin or sirolimus;

TAC: tacrolimus

ABSTRACT

Background: The current standard of care immunosuppressive regimen in kidney transplantation (KT) includes a combination of mycophenolates (MMF/MPA) with a calcineurin inhibitor (CNI).

Methods: We designed a systematic review including all randomized clinical trials (RCTs) assessing the outcomes in KT recipients receiving mTORi+CNI compared with regimens containing MMF/MPA or azathioprine with CNI.

Results: A total of 24 studies with 7356 participants were included. The comparison of mTORi-CNI versus MMF/MPA-CNI did not show differences in acute rejection, mortality or graft loss rates. Better graft function was observed using MMF/MPA-CNI than using mTORi+CNI, but this difference was not evident when the mTORi was associated with reduced dose CNI in more recent studies with everolimus. Dyslipidemia, lymphoceles and impaired wound healing were more frequent with mTORi-CNI and diarrhea and leukopenia more frequent with MMF/MPA-CNI. Viral infections at any time and malignant neoplasia beyond 2 years were less frequent with mTORi-CNI. Rates of discontinuation due to adverse effects in the mTORi groups varied between 17% and 46% compared to 0-26.6% in MMF/MPA groups. The current use of lower mTORi dosage has decreased discontinuation rates.

Conclusions: Efficacy is similar with mTORi+CNI and MMF/MPA-CNI. The safety profile is the predominant difference between the two regimens.

INTRODUCTION

Calcineurin inhibitors (CNI), initially cyclosporine, changed the standard of care with a substantial increase of graft survival at one year after kidney transplantation (KT)[1]. Since the mid 1990s, a variety of immunosuppressive drugs were introduced, such as tacrolimus, mycophenolate mofetil (MMF) and mycophenolic acid (MPA) and the mammalian target of rapamycin inhibitors (mTORi), sirolimus and everolimus.

The current standard of care for initial immunosuppression after KT includes a combination of MPA and CNI with corticosteroids and variable induction antibody treatment. This regimen further improved short term graft survival, but the rate of graft loss of 4-5% annually after the first year, has remained almost unchanged[2–4]. The mTORi containing immunosuppressive regimens were developed as part of CNI minimization/withdrawal strategies for KT recipients, with the goal of avoiding CNI associated nephrotoxicity. The two available mTORi are prodrugs that bind to cytoplasmic FKBP12 immunophilin to block cell cycle progression from G1 to S phase[5].

There are both detrimental and beneficial effects of the mTORi including wound healing impairment, myelosuppression, hyperlipidemia, edema, pneumonitis and proteinuria. The latter related to the effect of mTORi on podocytes, thus altering the integrity of the glomerular capillary wall[6]. The pharmacodynamic effect of combining mTORi and CNI, may increase exposure to the CNI, exacerbating CNI-related nephrotoxicity unless doses are adjusted[7]. There are reductions in CMV infection rates among other infections[8,9] and a reduced rate of malignancy after transplantation[10].

The objective of this systematic review is to investigate the benefits and harms of immunosuppressive regimens containing mTORi with CNI as initial therapy for KT recipients, compared to standard of care MMF/MPA plus CNI.

MATERIALS AND METHODS

Study design

Using the search strategy described in Supplementary material, Appendix S1, the titles and abstracts of studies potentially relevant were extracted and screened independently by two reviewers. They retained those satisfying inclusion criteria, if necessary examining the full text. The search included CENTRAL, MEDLINE and EMBASE, handsearching of major conferences proceedings and the International Clinical Trials Registers Search Portal & Clinical Trials.gov (to 05/31/2018). Letters or emails were sent to investigators seeking information about unpublished or incomplete trials. The protocol is published in PROSPERO (#CRD42016032588).

Selection Criteria for studies

All randomised controlled trials (RCTs), assessing the outcomes in patients receiving immunosuppressive regimens in de novo KT containing mTORi and CNI compared with regimens containing CNI without mTORi were included. We excluded multiorgan transplantations.

Data extraction, outcomes and quality assessment

Two reviewers independently used standard data extraction forms on: donor and recipient demographics and clinical characteristics; cause specific mortality and graft loss; acute rejection (AR); graft function (serum creatinine (SCr) or measured or calculated glomerular filtration rate (GFR)); and delayed graft function (DGF). In addition, we extracted available data on harms including: infections; cardiovascular events; malignant neoplasia; donor specific antibodies; and direct drug related adverse reactions (thrombocytopenia, leukopenia, anemia, hypokalemia, dyslipidemia, diabetes mellitus, hypertension, lymphocele, wound infection, fistulae, and edema).

Risk of bias assessment

Risk of bias was assessed independently by three authors using the Cochrane risk of bias assessment tool[11].

Data synthesis and analysis

Outcome analyses were performed in three ways: including all RCTs; including only recent era RCTs (by excluding studies published before 2008) that compared TAC and MMF/MPA with a reported discontinuation rate of <25% and including the Transform trial[12–24]; and finally splitting the RCTs into those with mTORi combined with full dose/exposure CNI and those with mTORi combined with CNI minimization.

For dichotomous outcomes, results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment, the mean difference (MD) was used. We approached time to event outcomes as continuous variables. For counts and rates the results of a study were expressed as a RR and the (natural) logarithms of the rate ratios were combined across studies using the generic inverse variance method. Data were pooled using the random-effects model.

Multiple intervention groups studies were analyzed with different methods: 1) using only the groups with the intervention of interest to create a single pair-wise comparison (if there were 3 groups including different induction therapies, only one induction therapy was included) and 2) including each pair-wise comparison separately, but with shared intervention groups divided out approximately evenly among the comparisons. In this last case, for dichotomous outcomes, both the number of events and the total number of patients were divided up and for continuous outcomes, only the total number of participants have been divided up and the means and standard deviations left unchanged.

Evaluation of important numerical data such as screened, randomized patients, intention-to-treat (ITT), as-treated and per-protocol (PP) population was carefully performed. Dropouts, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods were critically appraised. Heterogeneity was analyzed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test[25]. I^2 values of 30-60%, 50-90% and 75-100% correspond to moderate, substantial and considerable levels of heterogeneity. Subgroup analysis were used to explore possible sources of heterogeneity: induction agent used, use of steroids, the mTORi used (sirolimus or everolimus) and the combination of immunosuppressive co-interventions. Funnel plots were used to assess for the potential existence of small study bias.

We have followed the PRISMA Guidelines to report this systematic review (Appendix S3)[26].

RESULTS

Search strategy, selection criteria and included studies

A total of 1488 reports were found. Of these, 241 were duplicates, 304 non-randomized studies, 417 investigated a wrong intervention, 459 included wrong population and 1 was an ongoing study without results. Twenty-four studies (66 reports) involving 7356 participants were included in the meta-analyses[14–76]. The combined search results are presented in Figure 1.

Risk of bias

We found unclear risk of bias in the majority of studies because no details were given by the authors. The majority of studies were open-label so there was a high risk of performance bias. We found a low risk of reporting and attrition bias (Figure 2). All the detailed biases are presented in Supplementary Table 1.

Systematic review

Tables 1-5 show the description of the characteristics of included studies as well as the main results. Numerical meta-analysis results are shown in Table S2 and S3. In one trial, results of the group with everolimus with rabbit anti-thymocyte globulin (rATG) were excluded, so only the two groups with basiliximab induction were included to create a single pair-wise comparison [14,20–24]. In the group of sirolimus with tacrolimus, in those studies with more than one arm of treatment, only the group with sirolimus 2 mg was included in the analysis [41,42]. In the combination of everolimus with cyclosporine, there were 3 studies that presented 3 treatment groups depending on everolimus dose [43,45,49,55,62,77–79], we performed different subgroup analysis based on everolimus dose by making multiple pair-wise comparisons between all possible pairs of intervention groups (everolimus 1.5 mg versus MPA and everolimus 3 mg versus MPA).

Discontinuation and drop-out rates

The major concern about the use of mTORi is tolerability. Ninteen out the 24 included studies reported the rate of discontinuation in the each of the treatment groups. The majority of studies reported a statistically significant higher rate of discontinuation due to side effects in mTORi arm (13 studies) compared to MPA group (only 3 studies), with 3 studies that did not find differences.

Rates of mTORi discontinuation varied between 17% (Machado2004) and 46% (Guerra2011) compared to MPA (0% (Favi 2013) to 26.6% (Ciancio2016)). Four studies compared different mTORi doses in 3 treatment arms (Vitko2005-Vitko2006-Lorber2005-A2309), and all demonstrated that higher doses of mTORi where related to higher discontinuation rates due to side effects. Many of those details are depicted in tables 1-5.

Incidence of acute rejection

The comparison of mTORi with CNI versus MPA with CNI did not show any difference in the incidence of AR: at 1 year (10 studies, 2918 participants, RR 0.87, CI95% [0.68, 1.11]), ≥2 years (4 studies, 420 participants, RR 1.09, CI95% [0.76, 1.54]) or in biopsy proven AR (BPAR) at 6 months (9 studies, 2543 participants, RR 0.9, CI95% [0.75, 1.09]), 1 year (21 studies, 5958 participants RR 0.96, CI95% [0.83, 1.12]), ≥2 years (10 studies, 2426 participants, RR 0.93, CI95% [0.79, 1.10]) (Figure 3, Appendix S2, section 1). Subgroup analyses did not find differences.

Mortality

No differences in mortality were found (any mTORi-CNI versus any MMF/MPA/azathioprine- CNI) at 6 months (4 studies, 1721 participants, RR 1.38 [0.70,2.71]), 1 year (18 studies, 6387 participants, RR 1.01 [0.74,1.38]) or ≥2 years (11 studies, 2110 participants, RR 1.26 [0.91,1.77]) (Figure 4, Appendix S2, section 2). When specific causes of death where divided into malignancy, infections or cardiovascular diseases, we did not find differences between groups. When the different possible immunosuppressive combinations and subgroup analysis depending on reduced versus standard dose of CNI were analyzed, we did not find differences.

Kidney graft loss

Graft loss was similar when mTORi-CNI strategy was compared to MMF/MPA-CNI at 6 months, 1 year and 2 years (Figure 5, Appendix S2, section 3). The analysis of specific causes of graft loss was also performed, without differences between groups. The dose of CNI did not bring heterogeneity in the results.

Graft function

Based on SCr data we found better graft function when any standard dose CNI with MMF/MPA was compared to any mTORi-CNI at 6 months (4 studies, 555 participants, MD 15.90µmol/L, CI95% [2.10,29.71]), at 1 year (13 studies, 2782, MD 11.13µmol/L [5.73,16.53], and 2 years (6 studies, 1158 participants, MD 19.72µmol/L [15.95,23.48]) (Appendix S2, section 4.1). When we performed a subgroup analysis, we found heterogeneity at 6 months depending on the CNI dose: SCr was worse when mTORi was combined with standard dose of CNI (2 studies, MD 27.93µmol/L [14.26,41.60]) compared to reduced dose of CNI (2 studies, MD 8.53µmol/L [3.75,13.31]) (p=0.009). Results were similar when the analysis included only RCTs published after 2008 and with a known discontinuation rate of <25% (at 1 year: 3 studies, MD 13.73µmol/L [5.84,21.62]). Similar graft function was observed when estimated GFR-MDRD was evaluated at 6 months, 1 year and more than 2 years (Appendix S2, section 4.2.a). Splitting studies into the different mTORi, estimated GFR was lower using sirolimus plus CNI than CNI-MPA (at 6 months, MD 19.15 [8.08,22.03] and at 1 year, MD 15.06mL/Kg/1.73m^2 [8.08,22.03]), but similar using everolimus plus CNI than CNI-MMF/MPA (at 6 months, MD 3.25 [0.21,6.30] and at 1 year, MD 0.78 [-2.16,3.73]) (Figure 6). This effect could result from a learning effect gained from the early sirolimus studies impacting the study design of the subsequent everolimus trials. When the subgroup of recent RCTs with low discontinuation rates were evaluated[12–24], a better renal function was found when the combination of mTORi-MPA was used at 6 months (MD 6 mL/Kg/1.73m^2 [2.76,9.24]). This beneficial effect was lost at 1 year (MD -0.53 [-4.84,3.78]).

Proteinuria showed a tendency to increase with the use of the combination of mTORi-CNI (4 studies), but with high heterogeneity between them (I^2>90%) (Appendix S2, section 4.3).

Delayed graft function

Regarding DGF, we did not find differences between the use of CNI-mTORi compared to CNI-MPA/MMF/azathioprine (17 studies, 5167 participants, RR 1.11 [0.93,1.32]) (Appendix S2, section 5). The duration of the DGF was evaluated in 4 studies with high heterogeneity (I^2 91%) and it was shorter in MPA/MMF group (MD -5.34 days [2.74-7.94]). In the subgroup analysis based on the type of mTORi, we did not find differences in DGF, but a slightly longer DGF duration was confirmed in the combination of CNI-sirolimus (3 studies, MD 5.5 days, [2.37,8.64]) compared to CNI-MPA/MMF (4 studies, MD 5.34 days [2.74,7.94]). When the results were splitted depending on standard versus reduced dose of CNI we did not find heterogeneity.

Infections

Overall, less infections were found in mTORi-CNI group compared to MPA/MMF/AZA-CNI group at 1 year or less (12 studies, RR 0.90 [0.85,0.95], p=0.0003) without differences at 3 years (3 studies, RR 0.97 [0.88,1.07]) (Appendix S2, section 6.1.a). In the subgroup analyses, this reduction in infections was particularly significant with reduced dose CNI (Appendix S2, section 6.1.h). This effect of was maintained in the subgroup analysis including more recent studies (4 studies) with a RR at 1 year of 0.88 [0.82,0.94]. Lower risk of viral infections was reported in mTORi-CNI group compared to MMF/MPA-CNI at all-time points (Appendix S2, section 6.2). Similar results were found in all subgroups without differences depending on the CNI dose. CMV infections, including all definitions, were less frequent in mTORi-CNI combination compared to MMF/MPA-CNI in all time points: at 6 months (1013 participants, RR 0.63 [0.40,0.97], p=0.04), one year (3833 participants RR 0.50 [0.40,0.62], p<0.001), 2 years (825 participants, RR 0.14 [0.07,0.28], p<0.001) and 3 years (588 participants, RR 0.56 [0.41,0.77], p<0.001). (Figure 7). The same pattern was seen when CMV disease was evaluated. In subgroup comparisons, this difference was repeated except for SRL-CNI or SRL-CsA or SRL-TAC vs MMF/MPA/AZA-CNI groups. The effect of heterogeneity depending on CNI dose, did not change these results. No relevant data about BK virus

was reported in the studies, so meta-analysis was not possible. No differences between groups in terms of bacterial or fungal infections were found (Appendix S2, section 6.4 and S2, section 6.5).

Cardiovascular events

We did not find meaningful differences in cardiovascular events between mTORi-CNI vs CNI-MPA (data at ≤1 year, 3248 participants, RR 0.85 [0.55, 1.30]) (Appendix S2, section 7). Significantly less events at 1 year were noted in the mTORi patients when reduced CNI was used in combination with mTORi (2787 participants, RR 0.76 [0.59,0.97], p=0.03) (Figure 8).

Malignant neoplasia

Considering all studies, we found a decreased risk of malignant neoplasia in mTORi-CNI compared to MPA/MMF/AZA-CNI at long-term follow-up (more than 2 years) (1466 participants, RR 0.51 [0.31,0.83], p=0.007) (Figure 9, Appendix S2, section 8.1). This effect is mainly based on Kumar et al's studies[17,36] and study A2309[49,50,59–62,51–58], where the reduction of the risk of neoplasia in mTORi-CNI group was higher. No difference in PTLD was found (Appendix S2, section 8.2).

Postransplant diabetes mellitus

The meta-analysis of all studies did not show differences in the risk of post-transplant diabetes mellitus either at 6 months (3 studies, 951 participants, RR 0.81, CI95% [0.52, 1.28], p=0.38), at 1 year (13 studies, 4561 participants, RR 1.16, CI95% [0.97, 1.38], p=0.10) or at 3 years (3 studies, 670 participants, RR 1.75, CI95% [0.93, 3.28], p=0.08) (Appendix S2, section 9). The slightly higher incidence with mTORi at 3 years disappeared when excluding studies with high dose EVR with CsA (initial 3mg per day) [48–61,77–79], (RR 1.44, CI95% [0.57, 3.63], p=0.44). No differences were found when subgroup analysis based of CNI dose was performed (p=0.84).

Hypertension

Risk of hypertension was similar between groups (Appendix S2, section 10). The subgroup analysis based on CNI dose showed a trend to a beneficial effect of the use of mTORi with reduced CNI compared to MMF/MPA/AZA-CNI (4 studies, RR 0.89, CI95% [0.76-1.05], p=0.18), while in the combination of mTORi with standard dose of CNI that effect was not seen (3 studies, RR 1.02, CI95% [0.87-1.20], p=0.79) (test for subgroup differences: p=0.25).

Adverse effects

a) Cutaneous adverse effects (acne, folliculitis, hypertrichosis, mouth ulcers)

A total of 6 studies reported events related to cutaneous adverse effects at different time points without differences between treatment groups. Subgroup analysis based on CNI dose did not report heterogeneity (Appendix S2, section 11.1).

b) Anemia, leukopenia, thrombocytopenia.

No differences were found in the reported number of patients with anemia or haemoglobin levels (Appendix S2, section 11.2). A decreased risk of leukopenia was seen in mTORi-CNI combination compared to MMF/MPA-CNI at 1 year (3856 participants, RR 0.46 [0.38,0.56], p<0.001) and 2 years (1691 participants, RR 0.37 [0.14,0.97], p=0.04, heterogeneity I^2=88%) (Appendix S2, section 11.3). An increased risk of thrombocytopenia was noted with mTORi-CNI especially at 1 year (3246 participants, RR 1.95 [1.36,2.78], p<0.001). The risk was not significant with longer follow-up (Appendix S2, section 11.4).

c) Dyslipidemia

mTORi-CNI combination increased hypercholesterolemia compared to MMF/MPA/AZA-CNI at 1 year (4923 participants, RR 1.96 [1.35,1.99] (p<0.001) and at 2 years (1514 participants, RR 1.29 [1.07,1.55], p=0.006). MD increase of total cholesterol was of 0.62mmol/L at 1 year (2656 participants [0.33,0.92], p<0.001) and

0.49mmol/L at more than 2 years (5 studies, 790 participants [0.24,0.73], p<0.001). The subgroup analysis based on the dose of CNI showed that reduced CNI combined with higher doses of mTORi presented worse results in dyslipidemia (Appendix S2, section 11.5). Although the effects of the combination using mTORi-TAC in more recent publications (after 2008) with low discontinuation rates (<25%) showed an increase risk of dyslipidemia, actual blood level increase was minimal (at 1 year, MD 0.72mmol/L [0.46, 0.99]). mTORi-CNI combination increased hypertriglycerideemia levels at 6 months (872 participants, RR 2.09 [1.21,3.62], p=0.008) and at 1 year (RR 1.30 [1.14,1.49], p<0.001). The MD increase of triglyceride levels was of 0.59mmol/L at 6 months (431 participants [0.27,0.91], p<0.001) and 0.51mmol/L at 1 year (2465 participants [0.32,0.71], p<0.001). As opposed to hypercholesterolemia, the higher risk of hypertriglyceridemia was maintained in the subgroup analyses without differences depending on mTORi dose (Appendix S2, section 11.6).

d) Lymphoceles

There was a higher risk of lymphocele formation in mTORi-CNI compared to MMF/MPA/AZA-CNI at 1 year (4032 participants, RR 1.39 [1.09,1.78], p=0.009) and 3 years (RR 1.64, [1.13, 2.39], p=0.009) (Appendix S2, section 11.7).The difference in incidence of lymphocele at 1 year was very limited comparing mTORi-CNI vs MMF/MPA-CNI when reduced CNI dose was used with mTORi (4 studies, 867 participants, RR 1.43 [0.98, 2.08], p=0.06) (Appendix S2, section 11.7.h).

e) Diarrhea

We found a decreased risk of diarrhea with the use of mTORi-CNI compared to MMF/MPA-CNI at 6 months (652 participants, RR 0.63 [0.43,0.92], p=0.02) and at 1 year (3090 participants, RR 0.68 [0.58,0.80], p<0.001), these differences were lost after 2 years. The subgroup analysis based on CNI dose showed no effect on the results (Appendix S2, section 11.8).

f) Wound infection, healing complications, urinary fistulae

A higher risk of wound healing complication was found at ≤1 year with the combination of mTORi-CNI (652 participants, RR 1.30 [1.11,1.51], p<0.001). No changes were seen in subgroup analyses (Appendix S2, section 11.9). No differences between both immunosuppression strategies were found in urinary fistulae incidence (Appendix S2, section 11.10).

g) Edema

More edema was noted in mTORi-CNI compared to MMF/MPA-CNI at 1 year (3815 participants, RR 1.30 [1.18,1.44], p<0.001) without differences later (Appendix S2, section 11.11).

h) Serum potassium

Hyperkalemia was less frequent with mTORi (2 studies), and hypokalemia, which was only evaluated in Transform study[16] was more frequent (Appendix S2, section 11.12).

i) De novo HLA donor-specific antibodies

Four studies reported the outcome *de novo* HLA donor-specific antibodies at the end of the follow-up at different time points [16,22,48,63]. The meta-analysis did not find any difference between the use of mTORi or MMF/MPA combined with CNI (RR 0.74, CI95% [0.46, 1.19], p=0.21) (Figure 10, Appendix S2, section 12).

DISCUSSION

One of the main concerns regarding the use of mTORi has been the reduced immunosuppressive potency compared to CNI when used as initial immunosuppression in KT [80,81]. However, several large studies recently published have reported that the combination of CNI with mTORi entails immunosuppressive synergy

and achieves acute rejection rates of less than 15%[42]. As an example, the large TRANSFORM trial including 2037 participants, showed similar rejection outcomes when EVR was combined with reduced dose of CNI versus MMF/MPA with standard dose of CNI[16]. In this systematic review we found comparable efficacy results using data from 24 studies, without differences neither in clinical AR nor in BPAR. One previous systematic review has evaluated the same intervention [82] with similar results but with half of the studies included. In our review, we did not find differences in the development of de novo anti-HLA antibodies in the 4 studies reporting this outcome. In addition to equivalent anti-rejection potency, our meta-analysis showed no differences in patient survival between the immunosuppressive strategies, contrary to less-powered studies showing a higher mortality when using an mTORi [83].

Graft loss was not different between the two strategies, unlike the study of Xie et al in 2015 [82] that reported a higher risk of overall graft loss with mTORi associated with more de-novo DSA. They found renal allograft function was slightly worse with CNI+mTORi combination in studies using serum creatinine. In our analysis when we split the analyses between the two mTORi, estimated GFR was lower using sirolimus-CNI than MMF/MPA-CNI, but similar using everolimus-CNI than CNI-MMF/MPA. One hypothesis to explain this effect is the learning of knowledge from early SRL studies impacting study design of the subsequent EVR trials[16]. When the subgroup of recent RCTs with low discontinuation rates were evaluated, better renal function was found with the combination of CNI-mTORi at 6 months, but disappearing at 1 year. Consequently, the potential of mTORi plus CNI minimization to improve graft function, cannot be confirmed. Combining low exposure mTORi and reduced exposure CNI may avoid potential podocyte damage [5,84,85] and impact on glomeruli and interstitium[86,87]. Pharmacokinetic experiments have suggested that the interaction of CsA and SRL leads to an increase of renal tissue CsA concentration that is disproportionate to blood drug levels; thus the combination of mTORi and CNI may amplify the nephrotoxic effects of the CNI[88].

The antiproliferative action of mTORi has been reported to impair recovery from DGF after KT[84], but these results are not uniform[85]. Our systematic review showed equal risk of DGF in the two strategies, but with a mean increased duration of 5.3 days when mTORi plus CNI was used compared to MMF/MPA plus CNI.

There is a difference in viral infection between mTORi and MMF/MPA as demonstrated in other systematic reviews[82,86]. We found a decreased risk of CMV infection with the use of mTORi-CNI compared to MMF/MPA-CNI. The biological mechanism for this effect could be the inhibition of translation of CMV viral proteins, the stimulation of TH1-specific interferon-γ–producing T cells and virus-specific CD8 T cells[89].

We found a reduced risk of cardiovascular events at one year despite the increased incidence of hypercholesterolemia[87]. The negative effect on lipid profile was worse when mTORi dose was higher. This paradoxical effect may be associated with a more general impact of mTORi on growth factor-driven cell proliferation in general, and vascular smooth muscle cells in particular[90]. Post-transplant diabetes mellitus was not different between groups

We found a reduced risk of neoplasia in mTORi-CNI compared to MMF/MPA-CNI as expected[5,10,88,91]. This results are also consistent with Knoll's meta-analysis of individual patient data[92].

Bone marrow suppression was associated with both combinations, with leukopenia worse in the combination of MPA/MMF-CNI and thrombocytopenia with mTORi-CNI. No differences in anaemia were found. This may be the result of two alternate effects - the mTOR downstream pathway is critical for erythroid cell replication at the level of the erythropoietin receptor[93] and MMF induces bone marrow suppression.

In this review, as previous reports have shown, the gastrointestinal adverse events were more frequent in MMF combinations with more diarrhea noted. Similarly the known inhibitory effect of mTORi on angiogenesis and fibrosis were observed with

more wound healing complications in mTORi-CNI, particularly when high level exposure of mTORi occurred in combination with high levels of exposure to CNI.

One of the main concerns about mTORi and a limitation of this systematic review is that the analyses are based on the intention-to-treat population and in some studies more than 20% of patients discontinued initial assigned therapy. The underlying problem of poor overall tolerability was demonstrated in a number of studies. Thirteen studies reported higher discontinuation rates in the mTORi-CNI groups, and only three studies showed higher dropout rates with MMF/MPA-CNI. These results were maintained when the analyses were limited to studies published after 2008. Of interest, the mTORi-CNI tolerability was better when using lower mTORi dosages: higher exposures to mTORi were significantly associated with higher dropout rates.

Another limitation of this meta-analysis is that we combined different immunosuppression doses that may change the effect of the intervention. It is also important to consider the high risk of bias of some aspects of the included studies and that some outcomes have not been analyzed because of heterogeneity.

The main strength of this systematic review is that it is the largest meta-analysis evaluating the combination of mTORi-CNI in de novo KT. The current work provides novel insight by giving consistency in outcomes such as acute rejection, patient survival, and secondary effects. We have included analysis of the humoral immunity and the appearance of DSAs and examined in more detail than previously the effect on the incidence and duration of DGF.

We conclude that the efficacy of initial mTORi-CNI is similar to MMF/MPA-CNI after KT. The safety profile is substantially different between the regimens with different benefits and harms attributable to the two combinations. Available evidence suggests that treatment with low dose mTORi combined with CNI minimization may improve renal outcomes without compromising efficacy or safety.

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TABLES

FIGURES

Figure 8. Cardiovascular events at one year comparing mTORi plus CNI vs MPA plus CNI, stratified by CNI exposure: standard (not significant difference) or reduced (favours mTORi-CNI).

Figure 9. Comparison in incidence of malignant neoplasia between both groups, stratified in one year or longer follow-up.

Figure 10. Donor specific antibodies comparing mTORi plus CNi vs MPA plus CNI.

SUPPLEMENTARY DIGITAL CONTENT

Appendix S1: Search strategy

Appendix S2: Forest plot of different comparisons

Appendix S3: PRISMA checklist

Supplementary Table 1. Risk of bias assessment of included studies.

Supplementary Table 2. Results obtained from the meta-analysis: dichotomous outcomes

Supplementary Table 3. Results obtained from the meta-analysis: continuous outcomes

TABLES

Table 1. Characteristics of included studies evaluating the combination: sirolimus with cyclosporin.

Author, year and location	Methods	Participants	Interventions			Notes
			name	**n**	**regimen (and cointerventions)**	
Machado 2004 [27,28]	• Unicenter parallel RCT • Country: Brazil • n=70 • Length of follow-up: 1 year	• Inclusion criteria: recipients of primary renal allograft from one-haplotype living-related donor, negative T cell crossmatch • Exclusion criteria: antibody induction therapy, as well as MMF or TAC • Mean age:SRL 35.8±10.5, AZA 32.7±10.4 • Sex (M/F): SRL 23/12; AZA 23/12	SRL + CsA	35	• SRL loading dose of 6 mg, followed by 2 mg/d	Prophylaxis for CMV infection 3 months in CMV-negative patients who received CMV-positive kidney. Discontinuation rates were 17% in SRL vs 9% AZA
			AZA + CsA	35	• AZA1.5-2 mg/kg/d	
			All received induction: 8-10 mg/kg/d of cyclosporine and 0.5 mg/kg of prednisone Maintenance treatment: • CsA at 1 month: 200-400 ng/mL, 2 month: 200-300 ng/mL, thereafter: 150–250 ng/mL • ST: 1 month: 0.5 mg/kg/d(maximum 30 mg/d); 2 month: 20 mg/d, reaching 10 mg/between months 3 and 6.			
Stallone 2004 [29]	• Unicenter parallel RCT • Country: Italy • n=90 • Length of follow-up: 2 years	• Inclusion criteria: recipients of expanded criteria donor with pretransplantation biopsy score ≥4, • Mean age: SRL 50.4±7.8, MMF 51.8±6.3 • Sex (M/F): N/S • Other relevant information: mean HLA mismatches: SRL 3.25±0.7, MMF 3.14±0.6	SIR + CsA	42	• SRL 15 mg loading dose, then 5 mg/d adjusted to C2 levels 6-10, at month 3 10-15 ng/ml • CsA (4-7 mg/kg/d, C2 600 and 800 ng/ml), if DGF 400 and 600, withdrawal at month 3	Similar rate of DGF, but longer duration in SRL group (20 vs 10 days). One-year graft function, however, was not significantly different in the two groups of patients. No drop-outs reported in any of the groups.
			MMF + CsA	48	• MMF 2 g/d • CsA 10 mg/kg/d, C2 levels 1200-1400, if DGF 800-1000, by the end of month 6 C2 levels 700-900 ng/ml	
			Additional treatment**:** • ST: 500 mg intraoperatively, then 250 mg of prednisone daily, tapered to 25 mg by day 8 and to 5 mg by month 2 • basiliximab 20 mg 2 doses (day 0 and day 4)			
Peeters 2014 [32]	• Multicenter parallel RCT • Country: Belgium • n=122 • Follow-up: 3 years	• Inclusion criteria: N/S • Exclusion criteria: N/S • Mean age: N/S • Sex (M/F): N/S Other relevant information: N/S	CsA+ MMF	61	• ST discontinued after month 3	Proportion of patients with ≥1 adverse effect similar (68.9% vs 69%). No dropouts reported in any of the groups.
			CsA+ SRL	59	• CsA reduced dose converted to MPA after 3 months	
			Induction: Basiliximab			

** AEs: Adverse Effects; BAS: basiliximab; BMI: body mass index; C_0: measured plama concentration at time; CDC: complement-dependent cytotoxicity-based assay; CMV: cytomegalovirus; CNI: calcineurin inhibitor; Cr: creatinine; CrCl: creatinine clearance; CsA: cyclosporin; d: day; DGF: delayed graft function;*

EVE: everolimus; h: hour/s; HLA: human leukocyte antigen; IQR: interquartilic range; IL-2: interleukin-2; IV: intravenous; KT: kideny transplantation; m: months; MMF: mycophenolate mofetil; MPS: enteric-coated mycophenolate sodium; n: number of participants; N/S: not shown; PRA: panel reactive antibodies; RCT: randomised controlled trial; rATG: rabbit anti-thymocyte globulin; SRL: sirolimus; ST: steroids; TAC: tacrolimus; y: year

Table 2. Characteristics of included studies evaluating the combination: sirolimus with tacrolimus.

Author, year and location	Methods	Participants	Interventions			Notes
			name	**n**	**• regimen (and cointerventions)**	
Méndez 2003 [33–35]	• Multicenter parallel RCT (27 centres) • Country: United States of America • n=361 • Length of follow-up: 1 year	• Inclusion criteria: ≥18 years old, deceased or non-HLA identical living donor • Exclusion criteria: recipients of organs from nonheart-beating donors • Mean age: SRL 45.3±12.4, MMF 47.8±12.3 • Sex (M/F): SRL 123/62, MMF 123/53 • Other relevant information: mean HLA mismatches: SRL3.4±1.8, MMF 3.6±1.6	**SRL + TAC**	**185**	• SRL initial oral loading dose of 6 mg up to 48 hr following KT, then 2 mg/d adjusted to achieve levels of 4–12 ng/ml	CMV prophylaxis was administered for at least 3 months to all CMV seronegative patients receiving a kidney from a CMV-positive donor. Greater number of patients had permanent discontinuation of sirolimus (26.5% vs 14.8% MMF; P=0.006). Reasons for SRL discontinuation: dislipidemia (31%), rejection (10%) and infection (15%). Reasons for MMF discontinuation: diarrhea (19%), leucopenia (15%).
			MMF + TAC	**176**	• MMF 2 g/day orally in two doses	
			Induction: • Methylprednisolone 500 mg or 7–10 mg/kg/IV. Oral prednisone dosing started at 200 mg/day (or 3 mg/kg/day)with a target of 10 mg/day by 6 months • 13.5% SRL-treated patients received induction: thymoglobulin in 15 patients and an IL-2 receptor-blocking agent in 8. • 20.4% MMF-treated patient: thymoglobulin in 24 patients and an IL-2 receptor-blocking agent in 11. Maintenance treatment: • TAC (Prograf) starting dose of 0.15– 0.20 mg/kg/day in two divided doses, the adjusted to maintain levels 8–16 ng/ml for 3 months, then 5–15 ng/ml			
Anil Kumar 2008 [17]	• Unicenter parallel RCT • Country: United States • n=200 • Length of follow-up: 5 years	• Inclusion criteria: recipients ≥ 20 years old, HIV and HBV negative, deceased or living donors, primary and secondary transplants and current panel reactive antibody < 11%. • Mean age: CsA+MMF 51±14, SRL+CsA 56±13, TAC+MMF 48±14, SRL+TAC 59±12 • Sex (M/F): 35/15, 37/13, 34/16, 34/16 respectively • Other relevant information: ○ mean HLA mismatches: 4.0±1.9, 4.1±2.0, 4.0±2.1,	CsA+ MMF	50	• TAC initiated on day 1 at 0.02 mg/kg/d, adjusted to levels 15**–**18 ng/ml* by day 4 to 1 month, 10 ng/ml by the end of 1 year • CSA initiated on day 1 at 3 mg/kg/d, adjusted to C2 1000**–**1200 ng/ml at 1 month*, 700 ng/ml at 1 year • MMF initiated day 1 at 2 g/d, levels 1-3 µg/ml • SRL initiated on day 4 at 2 mg/day; adjusted to 5-10 ng/ml	9 switches to TAC/MMF (5) or CsA/SRL (4) Discontinuations: 18%
			SRL+ CsA	50		8 switches to TAC/MMF (6) or CsA/MMF (2) Discontinuations: 16%
			TAC+ MMF	50		9 switches to CsA/MMF (3) or TAC/SRL (6) Discontinuations: 18%
			SRL+ TAC	50		5 switches to CsA/SRL (3) or TAC/MMF (2) Discontinuations: 10%
			All received induction:			100 days of CMV

		4.1±1.8 respectively ○ Diabetes: 24%, 52%, 26%, 46% respectively	• basiliximab 20 mg 2 doses (day 0 and day 4) • methylprednisolone 250mg on day 0 and 125 mg on day 1, withdrawn on post-transplant day 2 **In the first 10 patients, clinical observations and surveillance biopsy of recipients in CNI strategies showed a lower renal function and acute CNI toxicity confirmed by biopsy. The protocol was then modified to maintain CSA C2 levels 500-800ng/ml and TAC levels 5-9ng/ml.*			prophylaxis in all CMV seronegative patients receiving a kidney from a CMV-positive donor
Anil Kumar 2005 [36]	• Unicenter parallel RCT • Country: United States • n=150 • Length of follow-up (mean): 7 months	• Inclusion criteria: recipients aged ≥18 years, HIV negative, and PRA<10%. • Mean age: TAC/MMF: 49.0±13.7, TAC/SRL55±12 • Sex (M/F): TAC/MMF: 48/27, TAC/SRL 46/29 • Other relevant information: ECD kidneys: TAC/MMF: 16%, TAC/SRL 28%	TAC+MMF	75	• TAC initiated on day 1 at 0.02 mg/kg/d, adjusted to levels 12–18 ng/ml* by day 7 • MMF initiated on day 1 at 2 g/d (dose was adjusted according to patients' tolerance) • SRL initiated on day 4 at 2 mg/day; adjusted to 6-10ng/ml	All recipients were given CMV and Pneumocystis carinii prophylaxis with valganciclovir and trimethoprim-sulfaxazone respectively for 100 days after transplantation. No dropouts reported in any of the groups.
			TAC+SRL	75		
			All received induction: • basiliximab 20 mg 2 doses (day 0 and day 4) • methylprednisolone 250mg on day 0 and 125 mg on day 1, withdrawn on post-transplant day 2			
Gallon 2006 [37]	• Single-center parallel RCT • Country: United States (Chicago) • n=94 randomised, 82 included in the final analysis • Duration: October 2000 and September 2001 • Length of follow-up: 3 years	• Inclusion criteria: recipients' age 30–70 years old. • Exclusion criteria: ABO-incompatible, multi-organ, non heart-beating donor or ECD; serum cholesterol >350 mg/dL, patients with HIV or BMI>35 kg/m^2 • Mean age: TAC/SRL 46,3±12,6, TAC/MMF 42,3±11,9 • Mean donor age in TAC/MMF group was lower than TAC/SRL group (33.2±11.4 vs. 39.9±12.9 years, p=0.04). • Sex (M/F): TAC/SRL 21/15, TAC/MMF28/17 • Other relevant information: mean HLA mismatches: TAC/SRL 3,1±1,9, TAC/MMF 3,6±1,8, p=0.02; Deceased donor TAC/SRL 27%, TAC/MMF33%	TAC + MMF	45	• MMF (Cellcept) was started on post-operative day 1 with a dose of 1g twice/day. MMF doses were adjusted as indicated for leukopenia.	All recipients of a kidney from a CMV-positive donor were treated with CMV prophylaxis with valganciclovir 450 mg/day for 6 months. Discontinuation: 1 MMF (first month, secondary to severe diarrhea) and 7 SRL (first month, 1 patient secondary to severe hyperlipidemia and 6 due to wound healing complications They were not included in the analysis.
			TAC + SRL	37	• SRL was started on post-operative day 1 at 3 mg once/day.The target 24-h levels were 7–10 ng/mL.	
			All received induction: • basiliximab 20 mg 2 doses (day 0 and day 2) • methylprednisolone 500mg on day 0, 250mg on day 2, 125 mg on day 2. No further steroids were given* Maintenance: • TAC(Prograf) started on post-operative day 1, adjusted to levels 8-10 ng/ml during the first 3 months,7–9 ng/mL from 4 to 6 months post-transplant and 6–8 ng/mL thereafter. **At 3 years post-transplant, 86% in the TAC/SRL group were off steroids as compared to 98% in the TAC/MMF group (p = 0.056). This difference was secondary to the higher rates of acute rejection in the TAC/SRL group than in TAC/MMF requiring initiation of prednisone during the post-transplant period.*			

Guerra 2011 Miami Trial [38–40]	• Single center parallel RCT • Country: United States (Miami) • n=150 • Duration: May 2000 and December 2001 • Length of follow-up: 96 months (range: 88 to 107)	• Inclusion criteria: recipients between 14 to 78 years of age, of either deceased donor or non-HLA identical living donor first kidney transplants, • Mean age: TAC/SRL 49.6±1.8; TAC/MMF 47.4±2.3; CsA/SRL43.9±2.3 • Sex (M/F): 35/15; 32/18; 32/18 • Other relevant information: mean HLA mismatches: 3.82± 0.19; 3.94±0.17; 3.80 ±0.15	TAC+SRL	50	• TAC initiated at 0.1 mg/kg twice daily, during first 2 m: 10 ng/ml, then lowered to 6–10 ng/ml between 3-6 m, and 4–8 ng/ml • CSA was initiated at 5 mg/kg twice daily with an initial target trough level 200–250 ng/ml, then 100–200 ng/ml • SRL: loading dose of 4mg on the evening after surgery, and then daily, with a target trough level 6–10 ng/ml • MMF: 1 g/12h, maintained as tolerated	For CMV prophylaxis, all received ganciclovir IV 3 days, followed by daily valganciclovir for 3 months. The protocol violation rate TAC/SRL and CSA/SRL combined in comparison with TAC/MMF: 68% vs 18%. The percentage of graft failure due to non-compliance was of 13/29, with 11/13 occurring beyond 36m post-transplant. Discontinuations of SRL in TAC/SRL or CSA/SRL 46%; of CNI in CSA/SRL 56%, TAC/SRL 24% and TAC/MMF 8%.
			TAC + MMF	50		
			CsA+ SRL	50		
			All received induction: • daclizumab1 mg/kg, was given in five doses, one every 2 weeks, beginning at surgery • Methylprednisolone Maintenance: • ST **In each arm, the CNI was not started until renal function had improved (serum creatinine <4 mg/dl and absent dialysis).*			
Van Hooff 2003 [41]	• Multicenter parallel RCT (5 centres) • Countries: The Netherlands, Belgium, Poland • n= 104 • Length of follow-up: 6 months	• Inclusion criteria: recipients aged ≥18 years, non–heart-beating donors were permitted. • Exclusion criteria: PRA>50% or a previous graft survival <1year because of immunologic reasons • Mean age: TAC 48,4; TAC/SRL0,5 43,6; TAC/SRL1 48,9; TAC/SRL2 47 • Sex (M/F): 16/12; 13/12; 18/7; 16/10 respectively • Other relevant information: mean HLA mismatches: 2,3; 0,5 2; 1 2,5; 2,5 respectively	• TAC	• 28	• TAC: started within 12 hours before graft reperfusion at 0.2 mg/kg (in two doses), for days 0-14: 10-20 ng/mL, for days 15-42: 10-15 ng/mL, and 5 to 15 ng/mLthereafter. • SRL*: administered together with the second dose of Tac within 12 hours after reperfusion. SRL loading doses were three times the maintenance doses (i.e., 1.5 mg, 3 mg, or 6 mg). Subsequent daily maintenance doses were 0.5 mg, 1 mg, or 2 mg and were not to bealtered.	Prophylactic Cotrimoxazole (960 mg/d) for the entire study. Ganciclovir (5 mg/kg /12h intravenously) in case of CMV mismatch for 7–14 days. Another randomisation was done at 3 month time 1:1 in SRL/TAC groups to eliminate SRL. Unreported results.
			• TAC + SRL 0,5	• 25		
			• TAC+SR L 1	• 25		
			• TAC+SR L 2	• 26		
			ST doses were 500 mg on day 0, 125 mg day 1, oral prednisone 20 mg/day (up to day 14), 15mg (up to day 28), and 10 mg (up to day 42) to 5 mg until study end.			
Sampaio 2008 [12]	• Single center parallel RCT	• Inclusion criteria: first kidney allograft from either a deceased or non-HLA identical living donor	TAC+MM F	50	• MMF 2 g/d in two divided doses	CMV prophylaxis was not used and seronegative patients receiving a
			TAC+SRL	50	• SRL: initial oral loading dose of 15mg	

	• Country: Brazil • n=100 • Length of follow-up: 1 year	• Exclusion criteria: non heart beating, ABO incompatible donors • Mean age: MMF 42.6±14.2, SRL 37.4±10.3 • Sex (M/F): 38/12, 31/19 • Other relevant information: mean HLA mismatches: MMF 3.3±1.2, SRL3.4±1.3; Donor source (%): MMF vs SRL: Living-related 50 vs 60, Living-unrelated 26 vs 16, Deceased 24 vs 24; Ethnicity, black recipients: MMF: 32%, SRL 46%			within 48 h after KT, followed by 5mg/d till day 7 and 2 mg/d till the end of first year	kidney from a seropositive donor were followed with sequential antigenemia. Dropouts: TAC/SRL 26% vs. TAC/MMF 8%. Five patients discontinued SRL, 4 discontinued TAC and 3 discontinued both drugs.
			No induction therapy allowed. Maintenance: • ST: methylprednisolone 1g perioperative. Oral prednisone 30 mg/d with a target of 10 mg/d by 3 months and 5 at 6 months. • TAC at a starting dose of 0.10–0.15 mg/kg twice daily. From 0 to day 15, 15–20 ng/mL; from 15 to day 30: 10–15 ng/mL, from 1 to 3 months: 8–12 ng/mL, thereafter: 5–10 ng/mL.			
Vitko 2006 [42]	• Multicenter parallel RCT (72 centers) • Countries: 15 European and 3 centers in Australia • n=977 • Length of follow-up: 6 months	• Inclusion criteria: primary renal transplantation or retransplantation (unless the previous graft was lost due to rejection within <12 m) • Exclusion criteria: PRA>85% in the previous 6m); grafts from non-heart-beating donors; cold ischemia time >40 h; hepatitis C, hepatitis B or HIV positive donor • Mean age: TAC/SRL-2 44.6±12.9; TAC/SRL-0.5 47.3±12.4; TAC/MMF 46.0±11.7 • Sex (M/F): TAC/SRL-2 210/115; TAC/SRL-0.5 196/129; TAC/MMF 218/108 • Other relevant information: mean HLA mismatches: 2.9; 2.9; 2.8 respectively	TAC + SRL-2	325	SRL: loading dose 6 mg, thereafter 2mg/d	Dropouts due to adverse events 34 patients (10.5%)
			TAC + SRL-0.5	325	SRL: loading dose 1.5 mg, thereafter 0.5mg/d	Dropouts due to adverse events 19 patients (5.8%)
			TAC + MMF	327	MMF: 500 mg/12h orally	Dropouts due to adverse events: 16 patients (4.9%)
			Induction: • No one received antibody induction therapy • ST: 500 mg or less of methylprednisolone or an equivalent on day 0 and 125 mg on day 1. Up to day 14: doses were tapered from 20 mg, up to day 28: 15 mg , up to day 42: 10 mg and 5 mg thereafter Maintenance: • TAC 0.2 mg/kg twice daily (0.1 mg/kg pre-operatively within 12 h prior to graft reperfusion, and within 3 h of anesthesia), between days 0-14 adjusted to 8–16 ng/mL, and between days 15-183 to 5–15 ng/mL.			In cases of CMV positive donor to a CMV negative recipient, oral ganciclovir for up to 3 months.
Huh K 2017 [76]	• Multicenter parallel RCT (7 Korean centers) • n=151 • Length of follow-up: 12 months	• Inclusion criteria: ≥20 years, • Exclusion criteria: multi-organ or a kidney donated after cardiac death; rATG induction; identical HLA; cold ischaemic time >30 h; hepatitis B or C virus • Mean age: lTAC/lSRL 46.1±13; lTAC/MMF 46±10.8	lTAC* + lSRL	76	SRL: 2mg within 24 h after reperfusion, and thereafter goal of 3-5 ng/mL	Discontinuation rates: 10.5% in SRL/TAC, 2.7% in MMF/TAC (p=0.10).
			lTAC* + MMF	75	MMF: 500mg within 24 h after reperfusion, then 1 or 2g/day (at the discretion of the investigator)	
			• BAS 20 mg IV on day 0 and day 4 • ST according to standard practice at centres • Extended-release TAC: if living donor 0.2mg/kg/day 2 days			

		• Sex (M/F): 57/19; 53/22 • Donor source (%): Living 82.9 vs 78.7, Deceased 17.1 vs 21.3; • BMI 23±3;22.5±3.2	before KT and 0.1 the day before KT; if deceased donor one dose 0.1mg/kg/day before KT. Goal: 3-12 ng/mL first month, then: 3-8 ng/mL.	

** AEs: Adverse Effects; BAS: basiliximab; BMI: body mass index; C_0: measured plama concentration at time; CDC: complement-dependent cytotoxicity-based assay; CMV: cytomegalovirus; CNI: calcineurin inhibitor; Cr: creatinine; CrCl: creatinine clearance; CsA: cyclosporin; d: day; DGF: delayed graft function; EVE: everolimus; h: hour/s; HLA: human leukocyte antigen; IQR: interquartilic range; IL-2: interleukin-2; IV: intravenous; KT: kideny transplantation; m: months; MMF: mycophenolate mofetil; MPS: enteric-coated mycophenolate sodium; n: number of participants; N/S: not shown; PRA: panel reactive antibodies; RCT: randomised controlled trial; rATG: rabbit anti-thymocyte globulin; SRL: sirolimus; ST: steroids; TAC: tacrolimus; y: year*

Table 3. Characteristics of included studies evaluating the combination: everolimus with tacrolimus

Author, year and location	Methods	Participants	Interventions			Notes
			name	**n**	**• regimen (and cointerventions)**	
Qazi 2017 [13,18,19]	• Multicenter parallel RCT (50 American and 2 Canadian centers) • n=613 • Length of follow-up: 12 months	• Inclusion criteria: 18**–**70 years, deceased donor (including ECD and donor after cardiac death) or non-HLA identical living • Exclusion criteria: cold ischemic time **>**30 h; ABO-incompatible or, hepatitis B or C infections • Mean age: ITAC/EVE 48.4±12.9; sTAC/MMF 50.0±13.3 • Sex (M/F): 205/101; 202/102 • Other relevant information: Donor source (%): Living-related 22.2 vs 27, Living-unrelated 22.2 vs 21.7, Deceased 24 vs 24; black recipients: 22.9% vs 24.3%	sTAC+ MMF	304	• MMF 1 g/12h. Only if patients experienced any adverse event dose was reduced • TAC: day 3: 8–12 ng/mL; month 2: 7–10 ng/mL; and month 6: 5–8 ng/mL.	Recipients at high risk of CMV infection received valganciclovir for **≥**6 months 177 Dropouts, the reasons were: TAC/MMF: 72 (23.7%) • 39 due to adverse events (12.8%) • 8 protocol deviation (2.6%) • 9 withdrew consent (3.0%) • 1 no longer required drug (0.3%) • 5 Administrative problems (1.6%) • 2 abnormal test result(s) (0.7%) • 1 Lost to follow-up (0.3%) • 5 Graft loss (1.6%) • 2 Deaths (0.7%) TAC/EVR: 105 (34%) • 66 due to adverse events (21.4%) • 9 protocol deviation (2.9%) • 8 withdrew consent (2.6%) • 7 unsatisfactory therapeutic effect (2.3%) • 7 Administrative problems (2.3%) • 4 abnormal test result(s) (1.3%) • 2 Graft loss (0.6%) • 2 Deaths (0.6%)
			ITAC + EVR	306	• EVR 0.75 mg/12h (trough level [C0]: 3–8 ng/mL). Dose adjustments were made from Day 5 to range (C0: 3–8 ng/mL) • TAC: day 3: 4–7ng/mL; Month 2: 3–6 ng/mL; and month 6: 2–5 ng/mL.	
			If PRA**<**20% basiliximab 20 mg day 0 and day 4 If PRA **≥**20% or recipients of ECD or DCD received the rATG per center practice. All patients received an oral ST per local practice.			
Favi 2013 [46,47]	• Single center parallel RCT • Country: Italy • n=42 • Length of follow-up: 1 year	• Inclusion criteria: kidney transplantation from deceased donors • Exclusion criteria: recipients >65 years, PRA> 50%, cold ischemia time >24 h • Mean age: N/S • Sex (M/F): N/S	TAC+ MMF	21	• standard extended-release TAC* and MMF	Steroid withdrawal: 43% in TAC/MMF and 45% in TAC/EVE. Drop-out: TAC/MMF 0, TAC/EVR: 5 patients (p=ns). No reasons given.
			TAC+EVR	21	• low-dose extended-release TAC and EVE*	
			• BAS 20 mg IV on day 0 and day 4, • rATG (50 mg/day IV from day 0 to day 3) • ST: methylprednisolone 500 mg IV on day 0 and 125 mg IV on day 1). At 6 months ST were			

		• Quote:" Demographics were similar between groups"	selectively withdrawn if no acute rejection, serum creatinine <2 mg/dL and proteinuria <300 mg/L/24 h. **Assigned study medications were orally administered once daily starting on day* 4.			
Tedesco-Silva 2015 [14,20–24]	• Single center parallel RCT • Country: Brazil • n=288 • Length of follow-up: 12 months	• Inclusion criteria: Low/moderate immunological risk living or deceased donors • Exclusion criteria: recipients of kidneys from HLA identical or ECD donors, positive cytotoxic crossmatch or PRA≥50% • Mean age: rATG/EVR 43.7±13.6, BAS/EVR 45.1±14.0, BAS/MPS 44.8±12.2 • Sex (M/F): 54/31, 68/34, 68/33 • Other relevant information: mean HLA mismatches: 2.6±1.2, 2.7±1.2, 2.7±1.2; recipient Caucasian race:48%, 50%, 54%; time on dialysis (months): 37.1±30.9, 42.2±42.2, 43.8±38.7	rATG+ EVR	85	• r-ATG: a single 3 mg/kg dose IV beginning within first 24 h after revascularization • TAC: initiated on day 1: 0.05 mg/kg twice daily, adjusted to 3-5 ng/ml • EVR 1.5mg twice daily adjusted to 4-8 ng/ml	No prophylaxis for CMV infection. Pre-emptive strategy instead: weekly monitoring of CMV viral replication (pp65 CMV antigenemia test) for 6 months. Discontinuation rates were similar between groups: 5 (rATG/EVR) and 13 in both TAC/EVR, TAC/MPS. No differences were observed in the incidence of adverse events leading to drug discontinuation (4.7 vs. 6.9 vs. 12.9%, p=0.107).
			lTAC+ EVR	101	• TAC: On day 1, 0.1 mg/kg twice daily, adjusted to 3-8 ng/ml for 3 months then, 3–5 ng/ml • EVR 1.5mg twice daily, adjusted to 4-8 ng/ml.	
			sTAC+ MPS	102	• TAC: On day 1, 0.1 mg/kg twice daily, adjusted to 6-8 ng/ml • MPS 720mg twice daily.	
			Induction and maitenance: • BAS induction on days 0 and 4. • ST: 1 g methylprednisolone before graft revascularization followed by oral prednisone 0.5 mg/kg/day (maximum 30 mg) beginning on day 1 tapered to 5 mg/day by day 45.			
Shetty 2015 [48]	• Single center parallel RCT • Country: United States (Chicago) • n=39 • Length of follow-up (months): lTAC/EVR 13 ± 4; sTAC/ MMF 14±4	• Inclusion criteria: adult living donor kidney transplant recipients • Mean age (years): lTAC/EVR 47±16; sTAC/ MMF 50±14 • Sex (M/F): N/S	lTAC + EVR	19	• EVR levels 3-8 ng/mL • TAC levels 4-7 ng/ml up to 2 months, 3-5 ng/ml from 3-6 months and 2-5 ng/ml after 6 months post-transplant	No withdrawals reported
			sTAC + MMF	20	• TAC levels 8-10 ng/mL up to 2 months, 6-8 ng/ml from 2- 6 months and 4-8 ng/ml after 6 months post-transplant	
			Induction**:** Alemtuzumab			
Ciancio 2016 [15]	• Single-center parallel RCT	• Inclusion criteria: 30**-**70 years of age, of deceased or non**-**HLA-	TAC + EVR	15	• EVR initiated within 24 hours posttransplantation at 0.75mg	For CMV prophylaxis, ganciclovir IV for 3 days, followed by daily valganciclovir

	• Country: United States • n=30 • Duration: November 2011 and January 2014 • Length of follow-up: 12 months	identical living donor first kidney transplants • Exclusion criteria: ECD, or donation after cardiac death • Mean age: TAC/EVR 49.9±2.7; TAC/MMF 48.5±2.9 • Sex (M/F): 12/3; 11/4 • Other relevant information: mean HLA mismatches: 3.87±0.29; 3.07±0.43; living donor: 73%; 73%; Recipient race: african American 33%; 13%			twice daily, adjusted to 3-8 ng/mL.	orally for 3 months. No patient withdrew TAC or EVL. 3 patients withheld MPS because of leukopenia and 1 because colon cancer.
			TAC + MPS	15	• MPS initiated within 24 hours posttransplantation at 720 mg twice daily	
			Induction: • rATG 1 mg/kg intraoperatively, with an equivalent additional dose given on day 4 posttransplantation • BAS 20 mg IV on day 0 and day 4, • Methylprednisolone IV 500 mg/d for 3 consecutive days starting on the day of surgery, with subsequent tapering until withdrawal after 7-10 days Maintenance: TAC 0.1 mg/kg twice daily initiated after Cr<353.7µmol/L, with a target level of 5-8 ng/mL.			

** AEs: Adverse Effects; BAS: basiliximab; BMI: body mass index; C_0: measured plama concentration at time; CDC: complement-dependent cytotoxicity-based assay; CMV: cytomegalovirus; CNI: calcineurin inhibitor; Cr: creatinine; CrCl: creatinine clearance; CsA: cyclosporin; d: day; DGF: delayed graft function; EVE: everolimus; h: hour/s; HLA: human leukocyte antigen; IQR: interquartilic range; IL-2: interleukin-2; IV: intravenous; KT: kideny transplantation; m: months; MMF: mycophenolate mofetil; MPS: enteric-coated mycophenolate sodium; n: number of participants; N/S: not shown; PRA: panel reactive antibodies; RCT: randomised controlled trial; rATG: rabbit anti-thymocyte globulin; SRL: sirolimus; ST: steroids; TAC: tacrolimus; y: year*

Table 4. Characteristics of included studies evaluating the combination: everolimus with cyclosporin.

Author, year and location	Methods	Participants	Interventions			Notes
			name	**n**	**regimen (and cointerventions)**	
Vitko 2005 RAD B201 [77–79]	• Multicenter parallel RCT (54 centres) Countries: 4 centres in Australia, 48 in Europe, and 2 in South Africa • n=588 • Length of follow-up: 36-month	• Inclusion criteria: recipients of 18–68 years old, cadaveric or living related donor kidney with an ischemic time **<**40 h. • Mean age: EVR 1.5 45.2, EVR 3 44.1, MMF 46.1 • Other relevant information: type of donor: living donor (%): EVR 1.5 , EVR 3 , MMF; Recipient race: african American (%): EVR 1.5 , EVR 3 , MMF	EVR 1.5	194	Started 48h post-KT: • EVR 1.5mg/d • EVR 3mg/d • MMF 2g/d	CMV prophylaxis with ganciclovir, CMV hyperimmune globulin or acyclovir was mandatory for CMV-negative recipients of CMV-positive donor. Discontinuation of medication because of adverse events was similar in the EVR 1.5 mg/d and MMF groups (31 vs 28%) but higher in EVR 3mg group (39%)
			EVR 3	198		
			MMF	196		
			Maintenance: • CsA after the first year was adjusted to 100–300 ng/mL. In January 2001, an amendment to the protocol allowed a reduction to 50–75 ng/mL (while maintaining EVR levels of ≥3 ng/mL) in patients who had suboptimal renal function • ST: tapered from a minimum of 20 mg/d initially to ≥5 mg/day for at least 6 months			
Lorber 2005 B251 [43–45]	• Multicenter parallel RCT (44 centers) • Countries: 33 in the United States, 7 in Canada, 2 in Argentina, 2 in Brazil. • n=583, at 3y: 236 • Duration: July 1998-August 2002 • Length of follow-up: 36 months	• Inclusion criteria: recipients of 16 - 65 years, single primary cadaveric or living (donor age 10–65 years) • Exclusion criteria: cold ischemia >40 hours and patients with DGF or hepatitis B or C or HIV • Mean age (range): EVR1.5 43.3 (16-71), EVR3 43.7 (19–70), MMF 43.4 (16–68) • Other relevant information (%): living donor 48.7,48.4, 54,1; Recipient black race 15,18.6,16.8	EVR 1.5	193	Protocol amendment was done 1.5 years after commencement, for reduction of CsA levels trough level of 50-75 ng/mL with EVR target level of 3 ng/mL or greater.	Before day 450, a higher incidence of discontinuation of study medication was recorded in patients receiving everolimus 3 mg (42.3%) compared with everolimus 1.5 mg (29.0%) and MMF (25.5%).
			EVR 3	194		
			MMF	196	• MMF 2g/d	
			Maintenance: • CsA starting at 6-12 mg/kg/d with adjustment to 200-350 ng/ml during weeks 1 to 4 and 100-300 thereafter. • ST: 1 g methylprednisone immediately before KT, 500mg 12 hours later, then 20 mg/d or 0.25 mg/kg/d by day 30, and 5 mg/d for the first 6 months.			
Study A2309 2010 [49,50,59–62,51–58]	• Multicenter parallel RCT • Countries: Brazil, Australia, United States, Korea • n=833	• Inclusion criteria: Recipients 18–70 years old, primary KT • Exclusion criteria: kidneys donated after cardiac death or cold ischemia time **>**40 hours; donor age **>**65 years; multiorgan, ABO-incompatible, or HLA	EVR 1.5	277	• EVR 0.75mg/12h* (from day 5 targeted to 3–8ng/mL) • CsA reduced dose levels: starting day 5: 100-200ng/mL, from month 2: 75-150, from month 4: 50-100, from month 6: 25-50	CMV prophylaxis (≥30 days; ganciclovir, CMV hyperimmune globulin, acyclovir or valacyclovir) for all CMV-negative recipients who received a kidney from a CMV-
			EVR 3	279	• EVR 1.5mg/12h* (from day 5 targeted to 6–12 ng/mL)	

	• Length of follow-up: 24 months and 7.3 years in a subgroup of Australia	identical living-related-donor; or most recent anti-HLA Class I >20% by a CDC or >50% by flow cytometry or ELISA. • Mean age: EVR 1.5 45.7, EVR 3 45.3, MPA 47.2 • Other relevant information: mean HLA mismatches: 3.5±1.54, 3.3±1.59, 3.4±1.57; living donor (%):53, 54.1, 53.5			• CsA reduced dose (same as EVR1.5)	positive donor. During the first year, discontinuation because of adverse events was higher in the EVR groups (23.4% and 28.4%) compared to MPA (15.8%%)
			MPA	277	• MPA* 720 mg/12h • CsA standard dose levels: starting day 5: 200-300ng/mL, from month 2: 100-250	
			Induction: • BAS 20 mg IV on day 0 and day 4, • ST according to local practice: ST were used in more than 99% of patients in each group during the study with more than 70% receiving corticosteroids without discontinuation ** first dose of study drug within 24 hours post-KT*			
Study A1202 2013 [63–72]	• Multicenter parallel RCT (centres) • Country: Japan • n=122 • Length of follow-up: 24 months (a unicentric cohort from the study was followed until 7 years)	• Inclusion criteria: Patients aged 18 to 65 years primary KT • Exclusion criteria: no graft function within 24 hours, cold ischemia >24 h; donor age >65 years; multiorgan, ABO-incompatible, HLA identical living-related-donor; or most recent anti-HLA class I PRA>20%. • Mean age: EVR 42.5 ± 14.13, MMF 38.6 ± 11.36 • Other relevant information: donor: living (%): EVR 98.3, MMF 97.9	EVR 1.5	61	• EVR 1.5 mg/d (target: 3 to 8 ng/ml) • CsA reduced-dose: started with 100-200 ng/ml, at month 2: 75-150 ng/ml, at month 4: 50-100 ng/ml, from month 6: 25-50 ng/ml	CMV prophylaxis (including pre-emptive therapy) was mandatory for all donor positive and recipient negative for CMV. A higher proportion of the MMF patients (85.2%) versus the everolimus patients (24.6%) had AEs requiring study drug dose adjustment/interruption
			MMF	61	• MMF 2 g/d • CsA standard: target 200 to 300 ng/ml, from month 2: 100 to 250 ng/ml	
			Induction: • BAS 20 mg IV on day 0 and day 4, • ST according to local practice at a minimum dose of 5 mg/d for 12 months **The initial dose of study medication was given within 24 hours (if difficult due to the patient's condition, then within 36 hours)*			
Bertoni 2011 [73]	• Unicentric parallel RCT • Country: Italy • n= 106 • Duration: 12 months • Length of follow-up: N/S	• Exclusion criteria: donor and recipient age >65 years, PRA >50%, retransplants, , focal glomerular sclerosis as primary disease, BMI> 25. • Mean age: EVR+CsA 45.7±12.77 MPA+CsA 49.75±12.06 • Donor age: 47.4±15.9 vs 50.2±16.2, mean HLA mismatches: 3.4±1.1 vs 3.5± 1.3	EVR+ CsA	56	• EVR: target levels C0 8-12 ng/mL • CsA: starting dose 4mg/kg, C2 250-300 ng/mL	CMV preemptive therapy, not prophylaxis. Dropout rate equal in both groups: MPS 3/50, EVR 5/56.
			MPA+ CsA	50	• MPA: 1,440 mg/day • CsA: starting dose 6mg/kg, C2 500-700 ng/mL	
			Induction: Basiliximab Maintenance: ST in all groups			
Paoletti 2012 [74]	• Unicentric parallel RCT • Country: Italy • n= 30 • Length of follow-up: 1y	• Inclusion criteria: Patients aged 18 to 70 years single KT • Exclusion criteria: diabetes, dual KT, living-related donor, kidney donor cardiac death and cardiac abnormalities at enrollment.	EVR + lCsA	10	• EVR: 3-8 ng/mL • Low CsA: 75-125ng/mL first 2 months, 50 -100 ng/mL thereafter	MMF was discontinued due to intolerance in 1/20. No discontinuations in EVR group were reported.
			MMF + sTAC	20	• Standard CsA: 150- 300 ng/mL in the first 2 months, 125 -250 ng/mL thereafter • MMF	

		• Mean age (mean, range): EVR: 51 (28-65), MMF 47 (32-67)	Induction: IL-2 receptor antibody; ST the entire follow-up period ** Titration of immunosuppression was done twice monthly*	

** AEs: Adverse Effects; BAS: basiliximab; BMI: body mass index; C_0: measured plama concentration at time; CDC: complement-dependent cytotoxicity-based assay; CMV: cytomegalovirus; CNI: calcineurin inhibitor; Cr: creatinine; CrCl: creatinine clearance; CsA: cyclosporin; d: day; DGF: delayed graft function; EVE: everolimus; h: hour/s; HLA: human leukocyte antigen; IQR: interquartilic range; IL-2: interleukin-2; IV: intravenous; KT: kideny transplantation; m: months; MMF: mycophenolate mofetil; MPS: enteric-coated mycophenolate sodium; n: number of participants; N/S: not shown; PRA: panel reactive antibodies; RCT: randomised controlled trial; rATG: rabbit anti-thymocyte globulin; SRL: sirolimus; ST: steroids; TAC: tacrolimus; y: year*

Table 5. Characteristics of included studies evaluating the combination: everolimus with tacrolimus/cyclosporin.

Author, year and location	Methods	Participants	Interventions			Notes
			name	n	regimen (and cointerventions)	
TRANSFORM [16]	• Multicenter parallel RCT (189 centres) • Countries: 42 • n= 2037 • Follow-up: 1 year	• Inclusion criteria: ≥18 years, recipients of a graft from a living or deceased heart-beating donor, second KT only if first graft had not been lost due to immunological reasons • Exclusion criteria: multiorgan, HLA-identical living-related, cold ischemia time >30 h, high risk of rejection, recipient or donor positive for hepatitis C virus and BMI >35 kg/m2 • Mean age: MMF 49.3±14.52, EVR 49.3±14.11 • Sex (M/F): MMF 710/312, EVR 707/308 • Other relevant information: BMI (mean±SD): MMF 25.6±4.24; EVR 25.6±4.25	EVR + reduced CNI	1022	2 possibilities: • EVR 1.5 mg /12h (target C0 3–8 ng/mL) + TAC (target C0 concentrations of 4–7 ng/mL during months 0–2, 2–5 ng/mL months 3–6 and 2–4 ng/mL thereafter) • EVR 0.75 mg /12h (target C0 3–8 ng/mL) + CsA (target C0 concentrations of 100–150 ng/mL during months 0–2, 50–100 ng/mL months 3–6 and 25–50 ng/mL thereafter)	• Cytomegalovirus (CMV) prophylaxis (for ≥3 months post-transplant) was recommended for all donor positive/recipient - negative cases. • Discontinuation of study drug: EVR: 23.0% and MMF: 11.9% because of adverse events.
			MMF + standard CNI	1015	2 possibilities: • TAC (target C0 concentrations of 8–12 ng/mL during months 0–2, 6–10 ng/mL during months 3–6, and 5–8 ng/mL thereafter) + MPS 1.44 g/day (reduced after week 2 to EC-MPS 1.08 g/day) or MMF 2 g/day (reduced after week 2 to 1.5 g/day) • CsA (target C0 concentrations of 200–300 ng/mL during months 0–2, 150–200 ng/mL during months 3–6, and 100–200 ng/mL thereafter) + MPS 1.44 g/day or MMF 2 g/day.	
			Induction: • Basiliximab 20 mg IV on day 0 and day 4 (83.1% of included patients) or rabbit antithymocyte globulin (1.5 mg/kg/day, total dose ≤6 mg/kg). • ST according to local practice Maintenance: ST in all patients, at least prednisolone 5 mg/day			

** AEs: Adverse Effects; BAS: basiliximab; BMI: body mass index; C_0: measured plama concentration at time; CDC: complement-dependent cytotoxicity-based assay; CMV: cytomegalovirus; CNI: calcineurin inhibitor; Cr: creatinine; CrCl: creatinine clearance; CsA: cyclosporin; d: day; DGF: delayed graft function; EVE: everolimus; h: hour/s; HLA: human leukocyte antigen; IQR: interquartilic range; IL-2: interleukin-2; IV: intravenous; KT: kideny transplantation; m: months; MMF: mycophenolate mofetil; MPS: enteric-coated mycophenolate sodium; n: number of participants; N/S: not shown; PRA: panel reactive antibodies; RCT: randomised controlled trial; rATG: rabbit anti-thymocyte globulin; SRL: sirolimus; ST: steroids; TAC: tacrolimus; y: year*