

## ORIGINAL ARTICLE

WILEY

# Infections after kidney transplantation: A comparison of mTOR-Is and CNIs as basic immunosuppressants. A systematic review and meta-analysis

Sebastian Wolf<sup>1</sup>  | Michael Lauseker<sup>2</sup> | Tobias Schiergens<sup>3</sup> | Ulrich Wirth<sup>3</sup> | Moritz Drefs<sup>3</sup> | Bernhard Renz<sup>3</sup> | Martin Ryll<sup>3</sup> | Julian Bucher<sup>3</sup> | Jens Werner<sup>3</sup> | Markus Guba<sup>3</sup> | Joachim Andrassy<sup>3</sup>

<sup>1</sup>Department of General-, Visceral- and Transplantation-Surgery, University Hospital Augsburg, Augsburg, Germany

<sup>2</sup>IBE, Ludwig-Maximilian's University Munich, Munich, Germany

<sup>3</sup>Department of General-, Visceral- and Transplantation-Surgery, Ludwig-Maximilian's University, Munich, Germany

## Correspondence

Joachim Andrassy, Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Ludwig-Maximilians-Universität, Campus Großhadern, Marchioninistrasse 15, 81377 München, Deutschland.  
Email: joachim.andrassy@med.uni-muenchen.de

## Funding information

Funding was received by Pfizer GmbH.

## Abstract

**Background:** Side effects of the immunosuppressive therapy after solid organ transplantation are well known. Recently, significant benefits were shown for mTOR-Is with respect to certain viral infections in comparison with CNIs. However, reported total incidences of infections under mTOR-Is vs CNIs are usually not different. This raises the question to additional differences between these immunosuppressants regarding development and incidence of infections.

**Methods:** The current literature was searched for prospective randomized controlled trials in renal transplantation. There were 954 trials screened of which 19 could be included (9861 pts.). The 1-year incidence of infections, patient and graft survival were assessed in meta-analyses.

**Results:** Meta-analysis on 1-year incidence of infections showed a significant benefit of an mTOR-I based therapy when combined with a CNI vs CNI-based therapy alone (OR 0.76). There was no difference between mTOR-I w/o CNI and CNI therapy (OR 0.97). For pneumonia, a significant disadvantage was seen only for mTOR-I monotherapy compared to CNI's (OR 2.09). The incidence of CMV infections was significantly reduced under mTOR-I therapy (combination with CNI: OR 0.30; mTOR w/o CNI: OR: 0.46). There was no significant difference between mTOR-I and CNI therapy with respect to patient survival (mTOR-I w/o CNI vs CNI: OR 1.22; mTOR-I with CNI vs CNI: OR 0.86). Graft survival was negatively affected by mTOR-I monotherapy (OR 1.52) but not when combined with a CNI (OR 0.97).

**Conclusion:** Following renal transplantation the incidence of infections is lower when mTOR-Is are combined with a CNI compared to a standard CNI therapy. Pneumonia occurs more often under mTOR-I w/o CNI.

**Abbreviations:** BKV, BK virus; BKVAN, BK virus-associated nephropathy; BPAR, biopsy-proven acute rejection; CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CsA, cyclosporine A; ERL, everolimus; IL, interleucine; ITT, intention to treat; MHC, major histocompatibility complex; mTOR-I, mTOR inhibitor; OPTN, Organ Procurement and Transplantation Network; OR, odds ratio; RCT, randomized controlled trial; SRL, sirolimus; SRTR, Scientific Registry of Transplant Recipients; TAC, tacrolimus.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. *Transplant Infectious Disease* published by Wiley Periodicals, Inc.

## KEYWORDS

calcineurin inhibitor, infection, mTOR inhibitor, renal transplantation

## 1 | INTRODUCTION

Side effect profile of a continuous immunosuppression following renal transplantation is well known.<sup>1</sup>

Cardiovascular problems, malignancy, and infections are the main reasons for death with functioning graft and significant reasons for post-transplant morbidity. mTOR inhibitors raised hopes to alleviate some of these problems. Infection post transplantation is a large field and thus not easy to assess. Classifications exist which divide infections in operative and perioperative nosocomial, activation of latent infections, and community-acquired infections.<sup>2</sup> Furthermore, the vast number of different pathogens which can result in infections has to be taken into account. Viruses remain the most common cause of infection in transplanted patients.<sup>3,4</sup> Recently, mTOR-Is either in combination with or instead of CNIs have been shown to reduce the incidence of CMV infections significantly.<sup>5</sup> The use of mTOR-Is may also be beneficial against BK virus infections.<sup>6,7</sup> On the contrary, affections of the lung, that is, pneumonitis have been known to be increased under mTOR-Is.<sup>8</sup>

Do these effects translate into a net difference of the overall incidence of infections under mTOR-Is vs CNIs? Most trials do not show a benefit for one regimen over the other.<sup>9,10</sup> Naturally, the large prospective randomized trials are not powered to detect differences in the incidence of infections. This may contribute to the fact that description of infections and overall infection incidence remains imprecise all too often.

Here, we collected the existing evidence comparing mTOR-Is with CNIs as basic immunosuppressants trying to draw a clearer picture on their effects on post-transplant infections.

## 2 | MATERIALS AND METHODS

### 2.1 | Identification of the eligible trials

Full reports of controlled prospective trials were searched via PubMed (<http://www.ncbi.nlm.nih.gov>), ScienceDirect (<http://www.sciencedirect.com>), and the Cochrane Central Register of Controlled Trials ([http://www.mrw.interscience.wiley.com/cochrane/cochrane\\_clcentral\\_articles\\_fs.html](http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html)) up to January 2019 using the optimally sensitive strategies for the identification of eligible trials, combined with the following MeSH terms: (mTOR inhibitor OR sirolimus OR everolimus) AND transplant AND infection.

### 2.2 | Inclusion criteria

Only prospective randomized multicenter and three single center renal transplantation trials were included starting 2002. These trials

were required to have at least two treatment arms, one with an mTOR-I based immunosuppression either with or without a CNI and one arm containing an mTOR-I free CNI-based immunosuppression. The mTOR-I had to be introduced within 3 months after the transplantation. The retrieved trials were screened for information on post-transplant infections, graft and patient survival. When several publications showed the same cohort of patients, the information was summarized. Screening and inclusion of the articles was performed by two reviewers (S.W., J.A.).

### 2.3 | Data analysis

To summarize the available evidence, we calculated odds ratios (ORs) for the incidence of post-transplant infections, patient and graft survival under CNI- and mTOR-I-based immunosuppression. Post-transplant infections were further subdivided in "Overall infections," "pneumonia" and "urinary tract infections (UTI)" and CMV. If no infection was observed in a study arm, 0.5 cases were added to both study arms to facilitate the calculation of the OR. If the incidence in both study arms was zero, the incidence was set to 1% to receive a OR of 1. Publication bias was assessed by plotting study results against precision of the study (funnel plots) and the according regression tests.<sup>11</sup> Between-study heterogeneity was examined using Q test for heterogeneity and the  $I^2$  statistic.<sup>12</sup> Accounting for possible heterogeneity between the studies, we fitted random effects models to derive pooled estimators of the natural logarithms of the OR using the restricted maximum-likelihood estimator.<sup>13</sup> Standard errors were estimated using incidences and number of patients per group. All calculations were performed using the *meta* and *metafor* package in the statistical software package R (version 3.5.1). *P* values below .05 were considered significant, and all confidence limits were on the 95% level.

### 2.4 | Data extraction and methodological quality

The following data were extracted from eligible articles by two reviewers (S.W., J.A.): type of transplanted organ, induction therapy, number of patients per treatment arm, mTOR-I dose, start of mTOR-I treatment post transplantation, biopsy-proven acute rejection (BPAR), patient and graft survival, trough levels, follow-up period, description, type and incidence of events of post-transplant infections, and statistical analysis of the post-transplant infections under mTOR-Is and CNIs both alone and in combination.

"Overall infections" included all documented infections up to 12 months after transplantation. To get more specific information on the infections, we collected data on viral, bacterial, fungal, BKV, HSV, CMV, respiratory, and urogenital infections.

Methodological quality was assessed by three reviewers (S.W., J.A., M.L.) using the Cochrane Collaboration's tool and ITT analysis.<sup>14,15</sup>

### 3 | RESULTS

#### 3.1 | Included studies

The literature search produced 954 studies, of which 19 met the inclusion criteria. Thus, a total number of  $n = 9861$  patients could be included (Figure 1). The trials compared mTOR-I + CNI with CNI treatment ( $n = 9$ ) (Table S2) and mTOR-I without CNI vs CNI ( $n = 8$ ) (Table S1). There were two trials containing three different treatment arms, mTOR-I, mTOR-I with CNI, and CNI (Table S3). Of these 19 trials, 11 RCTs used sirolimus (SRL) and eight everolimus (ERL) as

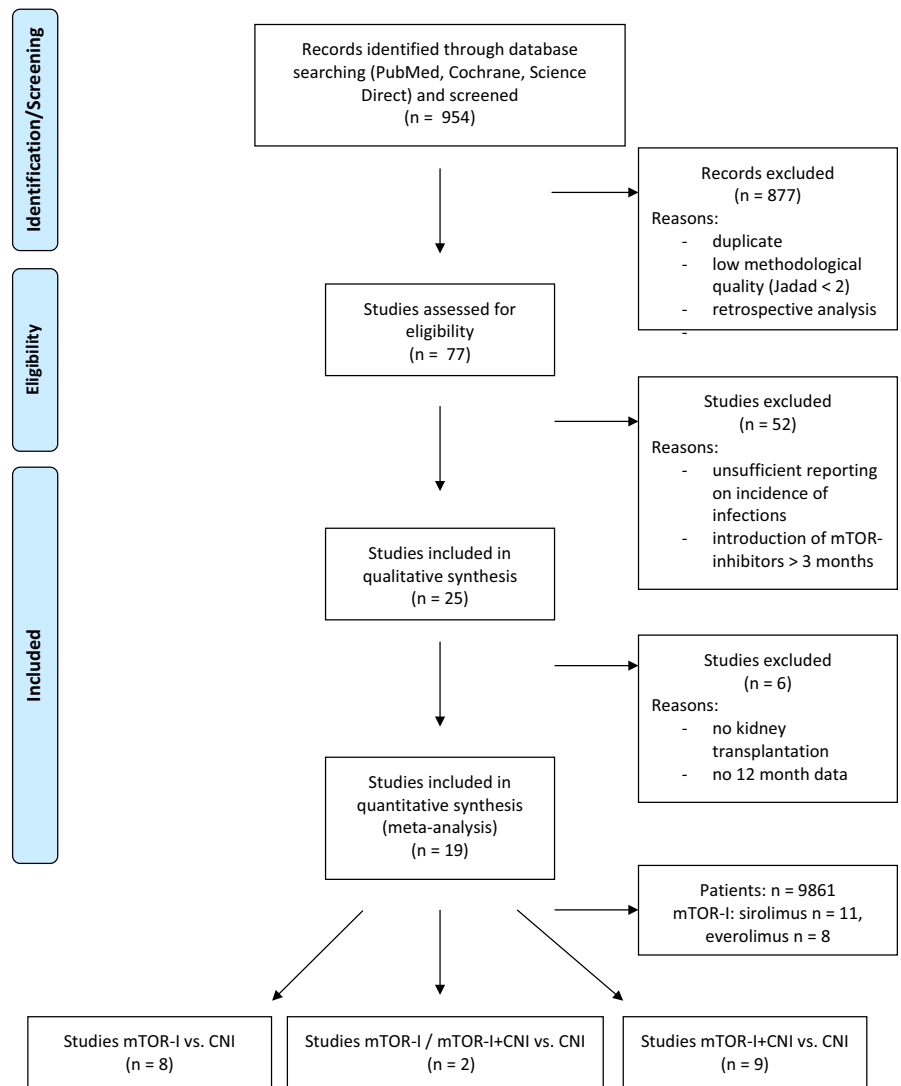
the mTOR inhibitor. We only included studies with introduction of the mTOR-I within 3 months after the transplantation. Mostly, the mTOR-I was introduced de novo or very early (within the first month;  $n = 17, 89\%$ ). The majority used either monoclonal or polyclonal antibodies as induction therapy ( $n = 16, 84\%$ ).

All of these trials delivered data on the incidence of infections as well as patient and graft survival 12 months post transplantation.

#### 3.2 | Methodological quality

All of the 19 RCTs were considered to be of good methodological quality according to the Cochrane Collaboration's tool (Figures S1-S3).

Almost all of the RCTs used intention to treat (ITT) to analyze the data (90%).



**FIGURE 1** Flowchart of the selection of articles

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

### 3.3 | Incidence of infections 12 months post transplantation

There was no significant difference for the incidence of overall infections under mTOR-I (n = 6, SIR = 4, ERL = 2) compared to CNI treatment (OR 0.97, CI 0.82-1.14, P = .68; Figure 2). The funnel plot did not reveal asymmetry (P = .50). Also, there was no indication of a significant heterogeneity between the trials (I<sup>2</sup> = 0.00%, Q test for heterogeneity: P = .76).

When the mTOR-I was combined with a CNI (n = 9, SIR = 4, ERL = 5), there was a significantly reduced odds ratio for overall infections compared to CNI treatment (OR 0.76, CI 0.68-0.85, P < .001, Figure 3). There was no indication of publication bias in the funnel plot as indicated by the regression test showing no significance for the asymmetry (P = .87). There was also no significant heterogeneity between the studies (I<sup>2</sup> = 0.00%, Q test for heterogeneity: P = .86).

### 3.4 | Incidence of pneumonia 12 months post transplantation

There were seven RCTs (SIR = 5, ERL = 2) describing the incidence of pneumonia. The odds ratio for pneumonia was significantly

increased under an mTOR-I therapy without a CNI compared to a CNI treatment (OR 2.09, CI 1.41-3.12, P < .001; Figure 4A). When the mTOR-I was combined with a CNI (n = 3, SIR = 2, ERL = 1), there was no significant difference compared to the CNI treatment alone (OR 1.42, CI 0.60-3.35, P = .42; Figure 4B).

There was no indication of publication bias in the funnel plot as indicated by the regression test showing no significance for the asymmetry in the analyses for the combination vs CNI therapy (P = .77). A significant asymmetry was seen for the analysis of mTOR-I vs CNI (P = .018). There was no significant heterogeneity between the studies in both analyses (mTOR-I vs CNI: I<sup>2</sup> = 0.00%, Q test for heterogeneity: P = .54, mTOR-I + CNI vs CNI: I<sup>2</sup> = 0.00%, Q test for heterogeneity: P = 1.00).

### 3.5 | Incidence of urinary tract infections (UTI) 12 months post transplantation

Six RCTs (SIR = 4, ERL = 2) with mTOR-I vs CNI treatment showed data on UTIs. There was no difference for the incidence of UTIs between the treatment groups (OR 0.86, CI 0.71-1.05, P = .14; Figure 5A). Comparable results were seen when the mTOR-I was combined with a CNI (n = 4, SIR = 2, ERL = 2, OR 0.89, CI 0.71-1.12, P = .33; Figure 5B).

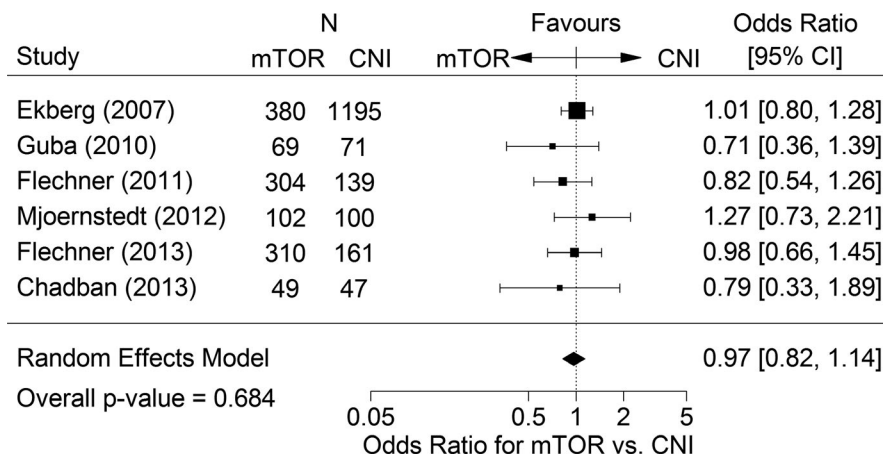


FIGURE 2 Forest plot indicating the odds ratios of the occurrence of infections on mTOR-I vs CNI treatment post transplantation

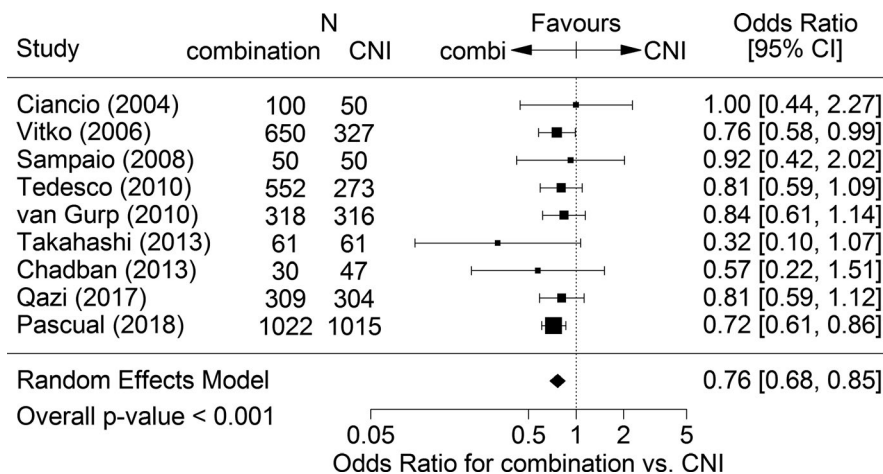
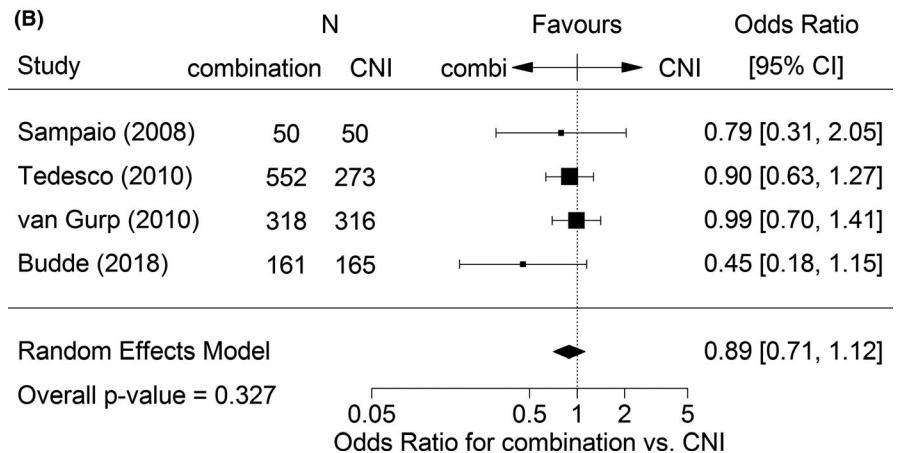
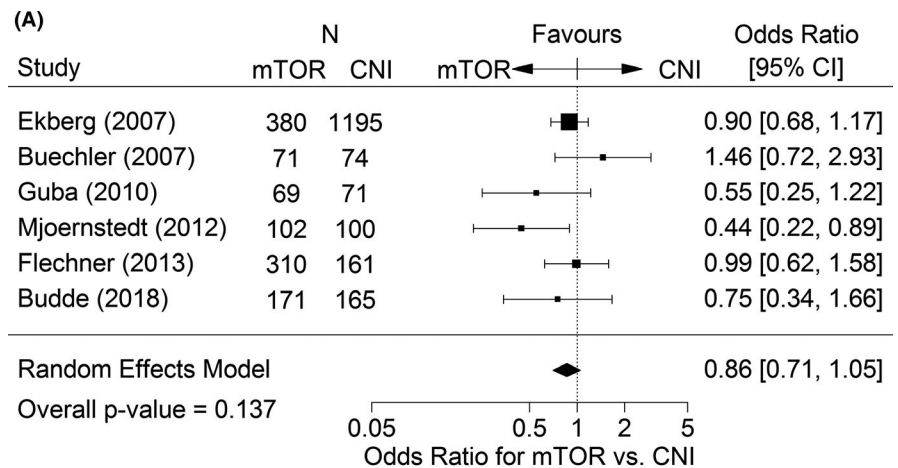
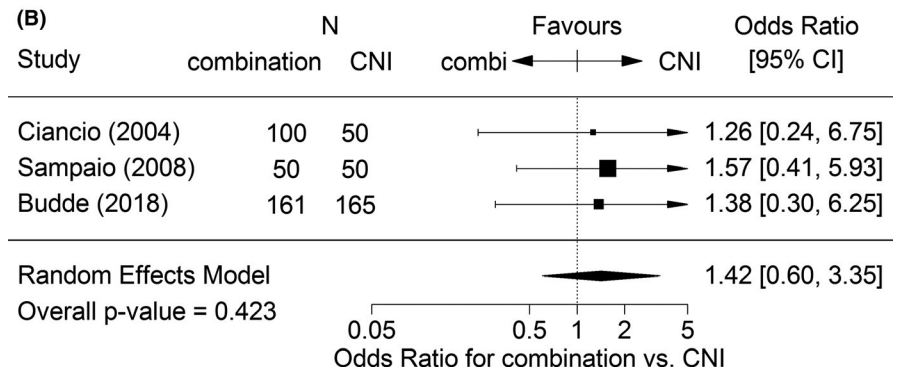
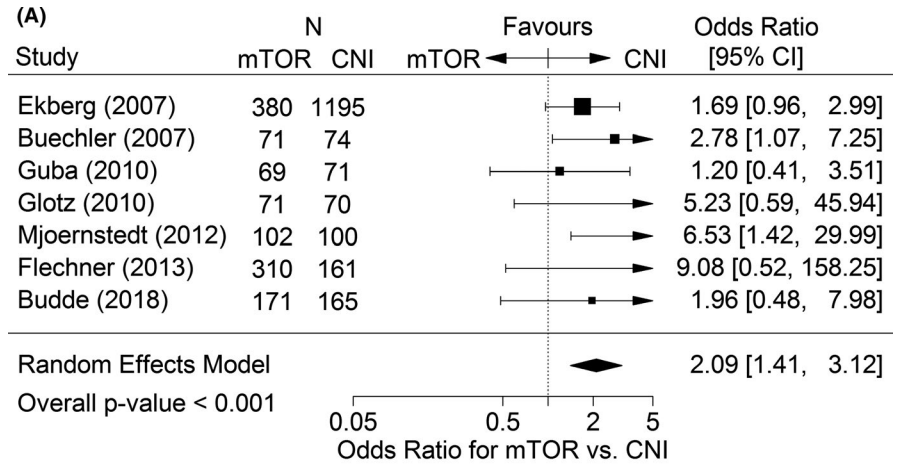


FIGURE 3 Forest plot indicating the odds ratios of the occurrence of infections on mTOR-I + CNI vs CNI treatment post transplantation

**FIGURE 4** Incidence of pneumonia post transplantation. A, Forest plot indicating the odds ratios of the occurrence of pneumonia on mTOR-I vs CNI treatment post transplantation. B, Forest plot indicating the odds ratios of the occurrence of pneumonia on mTOR-I + CNI vs CNI treatment post transplantation



**FIGURE 5** Incidence of urinary tract infections post transplantation. A, Forest plot indicating the odds ratios of the occurrence of urinary tract infections on mTOR-I vs CNI treatment post transplantation. B, Forest plot indicating the odds ratios of the occurrence of urinary tract infections on mTOR-I + CNI vs CNI treatment post transplantation

There was no indication of publication bias in the funnel plot as indicated by the regression test showing no significance for the asymmetry (mTOR-I vs CNI:  $P = .46$ , mTOR-I + CNI vs CNI:  $P = .21$ ). There was also no significant heterogeneity between the studies (mTOR-I vs CNI:  $I^2 = 32.20\%$ , Q test for heterogeneity:  $P = .19$ ; mTOR-I + CNI vs CNI:  $I^2 = 0.00\%$ , Q test for heterogeneity:  $P = .49$ ).

### 3.6 | Incidence of CMV infections 12 months post transplantation

Four RCTs (SIR = 2, ERL = 2) on mTOR-I w/o CNI vs CNI were included. The meta-analysis showed a significant benefit for the mTOR-I (OR 0.46, CI 0.32-0.66,  $P < .001$ ; Figure 6A). This beneficial anti-CMV effect was also present under the combination of mTOR-I + CNI ( $n = 9$ , SIR = 4, ERL = 5, OR 0.30, CI 0.17-0.51,  $P < .001$ ; Figure 6B).

There was no indication of publication bias in the funnel plot as indicated by the regression test showing no significance for the asymmetry (mTOR-I vs CNI:  $P = .66$ , mTOR-I + CNI vs CNI:  $P = .47$ ). There was also no significant heterogeneity between mTOR-I vs CNI

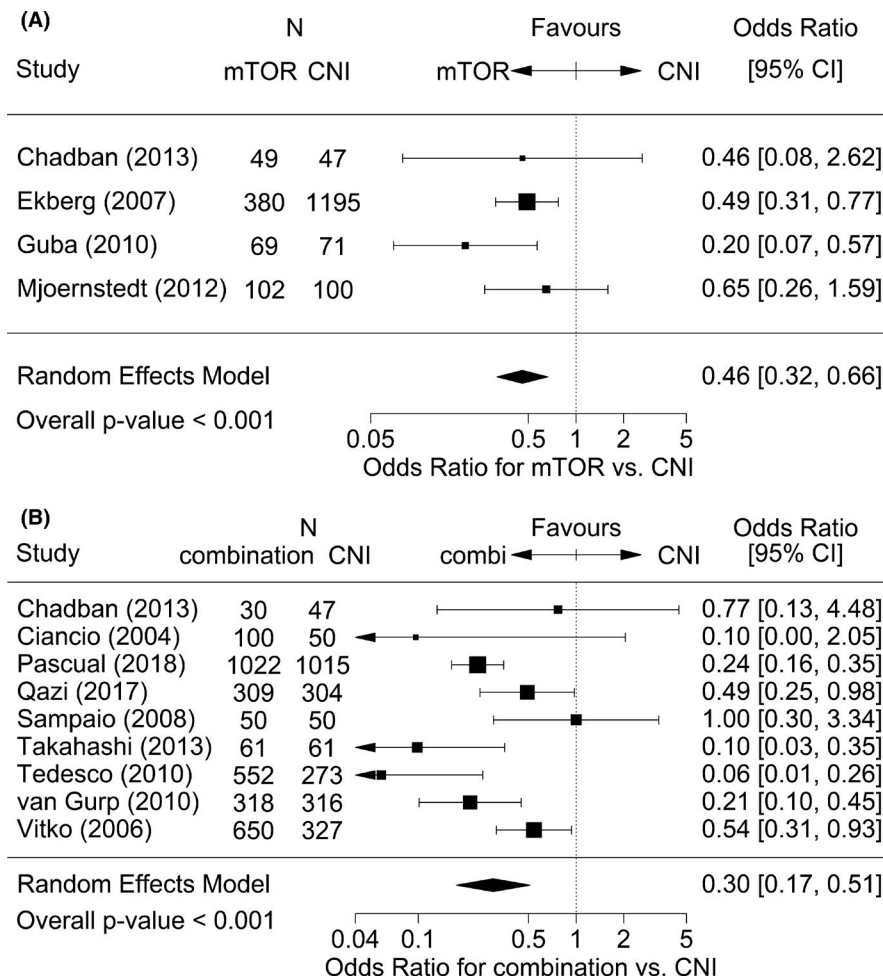
studies ( $I^2 = 2.7\%$ , Q test for heterogeneity:  $P = .38$ ). The heterogeneity was significant for mTOR-I + CNI vs CNI therapy ( $I^2 = 63.6\%$ , Q test for heterogeneity:  $P = .005$ ).

### 3.7 | Graft survival (censored for death) 12 months post transplantation

There were seven RCTs included in this analysis comparing mTOR-I with CNI treatment. SIR was the mTOR-I used in four RCTs and ERL in three RCTs. The ensuing analysis implied a higher risk for graft loss and therefore a negative effect for graft survival under mTOR-I therapy (OR 1.52, CI 1.05-2.19,  $P = .026$ ; Figure 7A). The regression test for funnel plot asymmetry was not significant ( $P = .80$ ). There was no heterogeneity between the RCTs ( $I^2 = 0.00\%$ , Q test for heterogeneity:  $P = .71$ ).

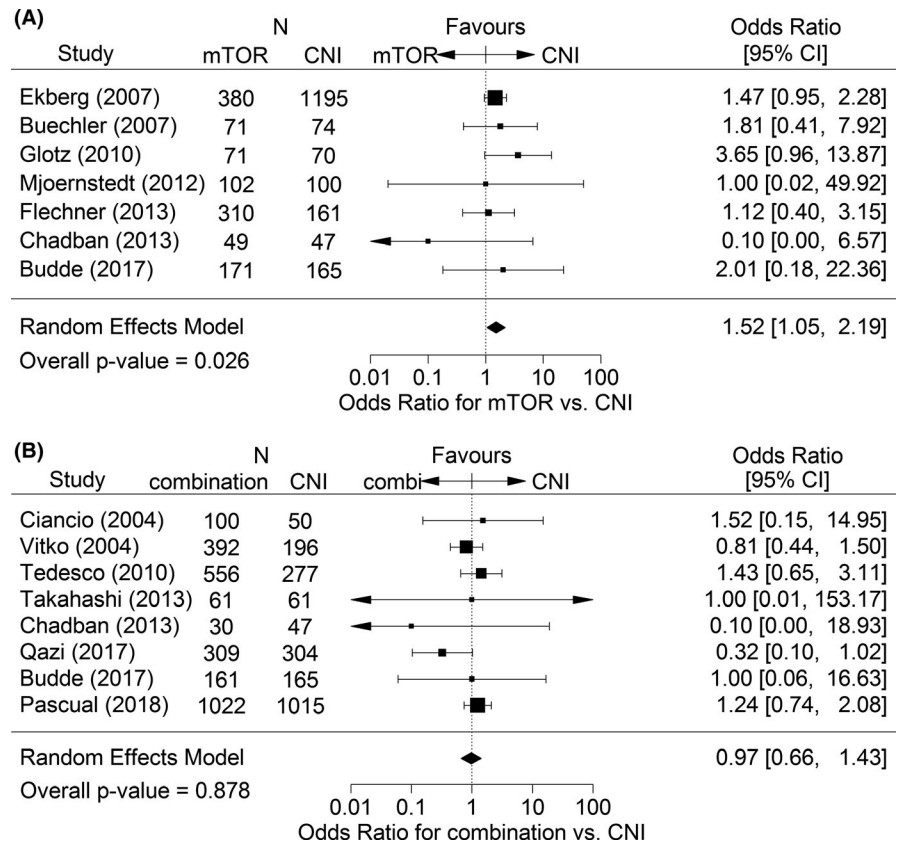
Eight RCTs (SIR = 1, ERL = 7) showed results on graft survival comparing mTOR-I with CNI and CNI. There was no significant difference for graft loss and survival between treatment groups (OR 0.97, CI 0.66-1.43,  $P = .88$ ; Figure 7B).

The regression test for funnel plot asymmetry was not significant ( $P = .46$ ). There was no heterogeneity between the RCTs ( $I^2 = 12.36\%$ , Q test for heterogeneity:  $P = .48$ ).



**FIGURE 6** Incidence of CMV infections post transplantation. A, Forest plot indicating the odds ratios of the occurrence of CMV infections on mTOR-I vs CNI treatment post transplantation. B, Forest plot indicating the odds ratios of the occurrence of CMV infections on mTOR-I + CNI vs CNI treatment post transplantation

**FIGURE 7** Graft survival censored for death post transplantation. A, Forest plot indicating the graft survival censored for death on mTOR-I vs CNI treatment. B, Forest plot indicating the graft survival censored for death on mTOR-I + CNI vs CNI



### 3.8 | Patient survival 12 months post transplantation

There were 10 RCTs included in this analysis comparing mTOR-I with CNI treatment. SIR was the mTOR-I used in seven RCTs and ERL in three RCTs. There was no significant difference for patient survival between mTOR-I and CNI therapy (OR 1.22, CI 0.77-1.95,  $P = .4$ ; Figure 8A).

The regression test for funnel plot asymmetry was not significant ( $P = .92$ ). There was no heterogeneity between the RCTs ( $I^2 = 0.00\%$ , Q test for heterogeneity:  $P = .93$ ).

There was also no difference for the patient survival between treatment groups if the mTOR-I was combined with a CNI ( $n = 12$ , SIR = 4, ERL = 8, OR 0.86, CI 0.59-1.27,  $P = .45$ ; Figure 8B).

The regression test for funnel plot asymmetry was not significant ( $P = .70$ ). There was no heterogeneity between the RCTs ( $I^2 = 8.04\%$ , Q test for heterogeneity:  $P = .72$ ).

## 4 | DISCUSSION

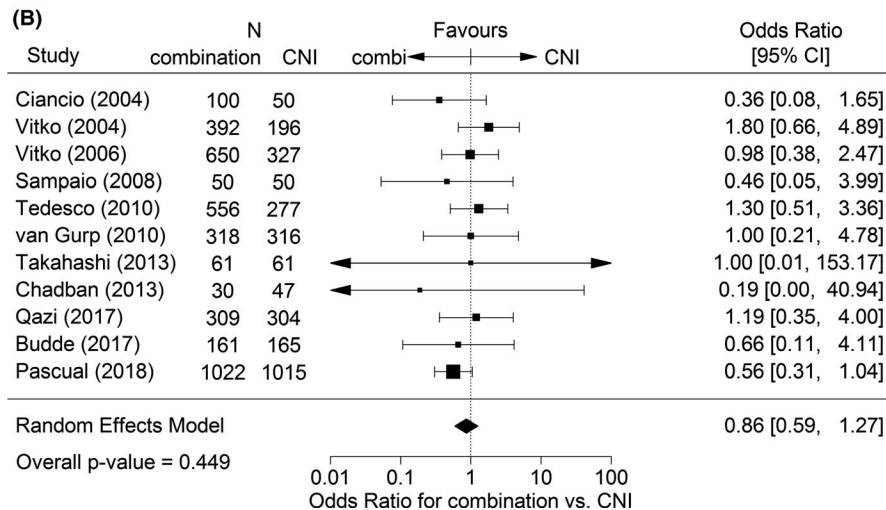
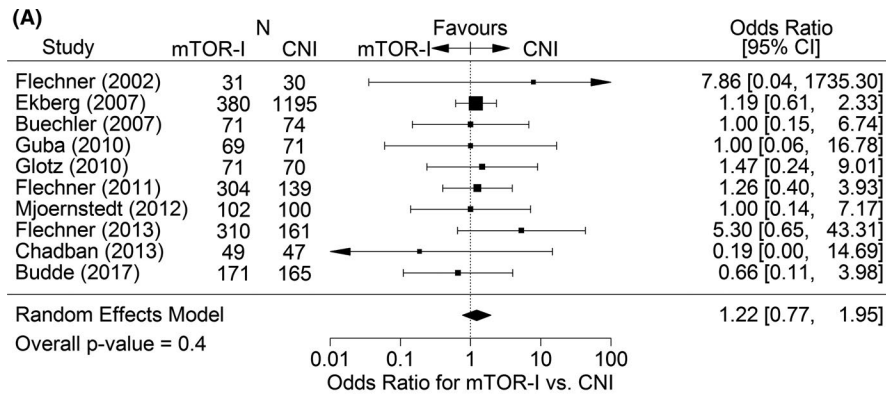
This is a systematic review analyzing the impact of mTOR-I vs CNIs on infections following renal transplantation. Analyses were performed on "overall infections" and infection subtypes as urogenital, respiratory and CMV infections. Data of 19 RCTs with  $n = 9861$  patients were included, making this analysis to the largest of its kind on this topic. Infections occur most often in the early post-transplant

period when multiple immunosuppressive drugs at high concentrations are administered. Therefore, only those RCTs were included which had the mTOR-I introduced de novo or up to 3 months.

Infections are responsible for morbidity and mortality in the immunosuppressed patients following renal transplantation.<sup>16</sup> Most common are operative and perioperative nosocomial bacterial and fungal infections, the reactivation of latent infections, and also invasive fungal as well as donor-derived infections.<sup>17</sup>

In the early phase <1 month after transplantation, infections are mostly related to surgical complications.<sup>2</sup> It is widely accepted that mTOR-I are associated with surgical wound complications and prolonged wound healing after surgery.<sup>18-20</sup> This may have contributed to our data. The trials had introduced the mTOR-I within the first 3 months after transplantation. More specifically, six of the included trials (75%) on mTOR-I without an additional CNI vs CNI started the mTOR-I de novo, 89% within the first month after the transplantation. Unfortunately, the trials most often did not distinguish between non-infectious wound complications (wound dehiscence, incisional hernia, etc) and actual wound infections. Neither was there enough information to draw a subtle conclusion between wound and "other" infections.

We found that there is no significant difference for the incidence of overall infections for an mTOR-I monotherapy in comparison with standard CNI regimen within 12 months post transplantation. Our data compare well with a longitudinal cohort study from Australia and New Zealand with 9353 patients that showed no significant difference for de novo mTOR-I vs CNI treatment regarding infections



**FIGURE 8** Patient survival post transplantation. A, Forest plot indicating the patient survival on mTOR-I vs CNI treatment. B, Forest plot indicating the patient survival on mTOR-I + CNI vs CNI

causing death (13% vs 16%),<sup>9</sup> and another report where the overall infection rate was not significantly different under SRL (sirolimus) compared to CsA (17.4% vs 21.8%).<sup>10</sup>

Unexpectedly, our data indicated that infections occur significantly less often when the mTOR-I is combined with a CNI compared to a regular CNI therapy. This was surprising, since the combination of these two substance classes was thought to have rather an additive immunosuppressive effect.

The incidence of CMV infections was significantly reduced in accordance to previously published reports.<sup>5,21-23</sup> This may also hold true for BK virus infections.<sup>24,25</sup> BK viremia in patients who were changed from tacrolimus to sirolimus after detection of BKVAN decreased by more than 50% in the first 2 months after mTOR-I initiation and was almost undetectable at 19 months after the conversion.<sup>25</sup> A meta-analysis primarily on CMV and BKV infections comparing mTOR-I with CNIs described an 8% increase of overall infections (viral, bacterial, and fungal) under mTOR-I monotherapy (OR 1.08, CI 1.02-1.15) but no difference when the mTOR-I was combined with a CNI. CMV infections were significantly reduced under mTOR-I in comparison with CNI therapy, whereas no such effect was seen for BKV infections. Trial composition was substantially different to our analysis. There was no information presented on the time of mTOR-I initiation. Follow-up ranged from 6 months to 5 years, and studies were not confined to kidney transplantation.<sup>26</sup>

The following scenarios may serve as potential explanations for our findings: Using the combination, mTOR-I and CNI trough levels are substantially reduced. Nonetheless, the beneficial antiviral effect is still present as we and others could show.<sup>5</sup> Maybe, the positive antiviral effect of the mTOR-I even under the reduced dose simply outweighs the additional immunosuppression of the combination therapy.<sup>27,28</sup> Another explanation may be that mTOR-I is known not only to suppress but also enhance certain immune reactions as memory T-cell functions,<sup>23</sup> quantity and quality of virus-specific CD8 T cells and memory precursor cells.<sup>23</sup> Furthermore, SRL was shown to enhance the effector to memory T-cell transition.<sup>23</sup> Another immune-stimulatory effect caused by the inhibition of mTOR is an increase of proinflammatory cytokines such as IL-12 and IL-1beta, while the anti-inflammatory cytokine IL-10 is suppressed.<sup>29</sup> In addition, increased MHC antigen presentation via autophagy in monocytes/macrophages and dendritic cells and counteracting immunosuppressive effects of steroids have been reported.<sup>29,30</sup>

Which of these effects is responsible for the lower incidence of infections under the combination therapy remains speculative and cannot be answered by this analysis.

The manuscripts were also screened for bacterial, fungal, and community-acquired infections. Unfortunately, to these data presentation had been incomplete. Pneumonia and urinary tract infections were the only "other" more specific sites of infection rendering enough data for statistically sound analyses.



Pneumonia is an important risk factor for morbidity and mortality in transplanted patients. A retrospective analysis on 406 kidney transplant recipients showed that 20% of the transplanted patients suffered from pneumonia, which were mostly caused by bacterial infections.<sup>31</sup>

We found a significantly increased risk for pneumonia in transplanted patients treated with an mTOR-I compared to a CNI. This effect was alleviated and no longer significant when mTOR-I was combined with CNIs.

Non-infectious pneumonitis, which can be mistaken for infectious pneumonitis, may be a potential explanation for these data. Non-infectious pneumonitis is rare. There exists a dose-response relationship—especially under high concentrations, which are preferably used in the oncological field, in which pneumonitis is a well-recognized problem. It is observed in about a third of all cancer patients, although only around 10% will have symptoms necessitating treatment.<sup>32</sup> Therefore, it is more likely to occur under a mTOR-I therapy without a CNI, when the mTOR-concentration used is higher than in combination therapy. On pulmonary CT scan, non-infectious pneumonitis commonly presents with an organizing pneumonia-like pattern, a nonspecific interstitial pneumonitis-like pattern, or both.<sup>33</sup> A recent randomized controlled trial, the “3C study,” came to similar results, with raised pulmonary infections under SIR based therapy, which were explained by possible misclassification (attribution of symptoms to an infective cause rather than to a direct drug effect).<sup>34</sup>

Urogenital infections (UTI) are also a major problem and represent with more than 30% the most common infection after kidney transplantation. Etiology is mostly attributed to *Escherichia coli* in more than 35%, *Enterobacter sp* in about 20%, *Klebsiella pneumoniae* in 11%, and to *Pseudomonas aeruginosa* in 6%.<sup>35</sup>

In our analyses, there was no difference for the incidence of UTI neither for mTOR-I monotherapy nor the combination therapy with CNI vs a standard CNI treatment. This is in line with another meta-analysis which showed similar results with an OR of 1.00 for urogenital infections comparing mTOR-I + CNI with CNI treatment.<sup>36</sup>

We included trials using ATG as well as Daclizumab/Basiliximab induction. There exists evidence from >15 years ago that ATG induction may cause more infections than IL-2R antibodies following renal transplantation.<sup>37</sup> Advances in the immunosuppressive protocols as well as anti-infectious therapy/prophylaxis most likely have contributed to the data of more recent trials which could not confirm a significant difference between poly- and monoclonal antibodies as induction therapy.<sup>38,39</sup>

As a secondary outcome of this study, we also analyzed patient and graft survival. Graft survival censored for death was not different under the combination of mTOR-I and CNI compared to a CNI therapy. When the mTOR-I was administered without a CNI, however, graft survival was significantly worse compared to a CNI therapy. It has been repetitively shown that a de novo or an early “monotherapy” with an mTOR-I results in a higher percentage of BPARs and a high number of therapy dropouts.<sup>40-43</sup>

We did not find a significant difference concerning patient survival between the groups regardless of whether mTOR-I was administered with or without a CNI. This confirms the findings of a previous large meta-analysis and the most recent prospective randomized trials (ZEUS, TRANSFORM, HERAKLES).<sup>44-47</sup> However, data have also been published which show a worse survival under mTOR-I. Especially, registry data from ANZDATA<sup>9</sup> and SRTR<sup>48</sup> showed an inferior outcome. Registry data seem not suitable for this comparison since many transplant patients are changed onto an mTOR-I whenever malignancy or deteriorating transplant function occurs—both situations for which an earlier death would be expected. Furthermore, many patients had been included in earlier years when higher doses of mTOR-I were standard. The only trial to date that used randomized controlled data and showed a worse survival under mTOR-I was the meta-analysis by Knoll et al.<sup>49</sup> Trial composition had been substantially different using many trials from a very early era (five of 21 trials were published before 2002) when the experience with the mTOR-I was low and extraordinary high loading and maintenance doses of SRL de novo were used (76% of the selected RCTs). Importantly, mortality under “low-dose” SRL, as is preferably used nowadays in transplantation, was not increased.

Our study has some limitations. Naturally, the primary endpoint in the included RCTs was on survival and BPAR and not infection. Also, there was not a general definition for infection and most of the trials did not record or show detailed information on the infections that occurred. This made more specific analyses impossible. Most studies did not allow calculating hazard ratios, which would be the primary choice for this type of data. However, given the relatively short observation time of 12 months, we do not expect to have introduced a large bias.

Following renal transplantation, the overall incidence of infections is not increased under mTOR-I vs CNIs. The combination of mTOR-I with CNI even reduces the incidence of infections. This may primarily be explained by the powerful anti-CMV effect of mTOR-I as we could not find beneficial effects of mTOR-I over CNIs on other infections.

Lung affections may be more often under mTOR-I without CNIs. This could be related to the difficulty to differentiate between infectious and non-infectious pneumonitis. Incidence of urogenital infections under mTOR-I vs CNIs is not different. Mortality is not increased with an mTOR-I therapy, and best protection against graft loss is provided by a combination therapy of an mTOR-I and a CNI.

Future randomized trials should deliver more detailed information on post-transplant infections to allow for more subtle analyses.

## CONFLICT OF INTEREST

All authors declare no conflict of interest.

## AUTHORS' CONTRIBUTIONS

S.W., M.L. and J.A. contributed to research design, data acquisition and analysis and writing of the paper. M.L. performed the statistics.

All authors contributed to critical review and revision of the paper and approved it for publication.

## ORCID

Sebastian Wolf  <https://orcid.org/0000-0001-5298-8901>

## REFERENCES

- Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med.* 2007;357:2601-2614.
- Fishman JA. Practice ASTIDCo: introduction: infection in solid organ transplant recipients. *Am J Transplant.* 2009;9(Suppl 4):S3-S6.
- Fishman JA, Issa NC. Infection in organ transplantation: risk factors and evolving patterns of infection. *Infect Dis Clin North Am.* 2010;24:273-283.
- Weikert BC, Blumberg EA. Viral infection after renal transplantation: surveillance and management. *Clin J Am Soc Nephrol.* 2008;3(Suppl 2):S76-S86.
- Andrassy J, Hoffmann VS, Rentsch M, et al. Is cytomegalovirus prophylaxis dispensable in patients receiving an mTOR inhibitor-based immunosuppression? A systematic review and meta-analysis. *Transplantation.* 2012;94:1208-1217.
- Jouve T, Rostaing L, Malvezzi P. Place of mTOR inhibitors in management of BKV infection after kidney transplantation. *J Nephropathol.* 2016;5:1-7.
- Suwelack B, Malyar V, Koch M, Sester M, Sommerer C. The influence of immunosuppressive agents on BK virus risk following kidney transplantation, and implications for choice of regimen. *Transplant Rev (Orlando).* 2012;26:201-211.
- Siddiqui AS, Zimmerman JL. Everolimus associated interstitial pneumonitis in a liver transplant patient. *Respir Med Case Rep.* 2016;19:15-17.
- Badve SV, Pascoe EM, Burke M, et al. Mammalian target of rapamycin inhibitors and clinical outcomes in adult kidney transplant recipients. *Clin J Am Soc Nephrol.* 2016;11:1845-1855.
- Cravedi P, Ruggenenti P, Remuzzi G. Sirolimus for calcineurin inhibitors in organ transplantation: contra. *Kidney Int.* 2010;78:1068-1074.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629-634.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21:1539-1558.
- Viechtbauer W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat.* 2005;30:261-293.
- Doug Altman DA, Bender R, Bunce C, et al. Chapter 16: Special topics in statistics. *Cochrane Handbook for Systematic Reviews of Interventions* Version 510 (updated March 2011). The Cochrane Collaboration. Edited by Julian PT Higgins JDaDGAobotCSMG. 2011.
- Pengel LH, Barcena L, Morris PJ. The quality of reporting of randomized controlled trials in solid organ transplantation. *Transplant Int.* 2009;22:377-384.
- Martin-Gandul C, Mueller NJ, Pascual M, Manuel O. The impact of infection on chronic allograft dysfunction and allograft survival after solid organ transplantation. *Am J Transplant.* 2015;15:3024-3040.
- Chelala L, Kovacs CS, Taeye AJ, Hanouneh IA. Common infectious complications of liver transplant. *Cleve Clin J Med.* 2015;82:773-784.
- Kuppahally S, Al-Khaldi A, Weisshaar D, et al. Wound healing complications with de novo sirolimus versus mycophenolate mofetil-based regimen in cardiac transplant recipients. *Am J Transplant.* 2006;6:986-992.
- Dean PG, Lund WJ, Larson TS, et al. Wound-healing complications after kidney transplantation: a prospective, randomized comparison of sirolimus and tacrolimus. *Transplantation.* 2004;77:1555-1561.
- Zuckermann A, Barten MJ. Surgical wound complications after heart transplantation. *Transplant Int.* 2011;24:627-636.
- Frascaroli G, Varani S, Blankenhorn N, et al. Human cytomegalovirus paralyzes macrophage motility through down-regulation of chemokine receptors, reorganization of the cytoskeleton, and release of macrophage migration inhibitory factor. *J Immunol.* 2009;182:477-488.
- Moorman NJ, Shenk T. Rapamycin-resistant mTORC1 kinase activity is required for herpesvirus replication. *J Virol.* 2010;84:5260-5269.
- Araki K, Turner AP, Shaffer VO, et al. mTOR regulates memory CD8 T-cell differentiation. *Nature.* 2009;460:108-112.
- Dharnidharka VR, Cherikh WS, Abbott KC. An OPTN analysis of national registry data on treatment of BK virus allograft nephropathy in the United States. *Transplantation.* 2009;87:1019-1026.
- Wali RK, Drachenberg C, Hirsch HH, et al. BK virus-associated nephropathy in renal allograft recipients: rescue therapy by sirolimus-based immunosuppression. *Transplantation.* 2004;78:1069-1073.
- Mallat SG, Tanios BY, Itani HS, et al. CMV and BKPyV infections in renal transplant recipients receiving an mTOR inhibitor-based regimen versus a CNI-based regimen: a systematic review and meta-analysis of randomized, controlled trials. *Clin J Am Soc Nephrol.* 2017;12:1321-1336.
- Nashan B. Maximizing the clinical outcome with mTOR inhibitors in the renal transplant recipient: defining the role of calcineurin inhibitors. *Transplant Int.* 2004;17:279-285.
- de Jonge H, Naesens M, Kuypers DR. New insights into the pharmacokinetics and pharmacodynamics of the calcineurin inhibitors and mycophenolic acid: possible consequences for therapeutic drug monitoring in solid organ transplantation. *Ther Drug Monit.* 2009;31:416-435.
- Saemann MD, Haidinger M, Hecking M, Horl WH, Weichhart T. The multifunctional role of mTOR in innate immunity: implications for transplant immunity. *Am J Transplant.* 2009;9:2655-2661.
- Weichhart T, Haidinger M, Katholnig K, et al. Inhibition of mTOR blocks the anti-inflammatory effects of glucocorticoids in myeloid immune cells. *Blood.* 2011;117(16):4273-4283.
- Dizdar OS, Ersoy A, Akalin H. Pneumonia after kidney transplant: incidence, risk factors, and mortality. *Exp Clin Transplant.* 2014;12:205-211.
- Duran I, Goebell PJ, Papazisis K, et al. Drug-induced pneumonitis in cancer patients treated with mTOR inhibitors: management and insights into possible mechanisms. *Expert Opin Drug Saf.* 2014;13:361-372.
- Baas MC, Struijk GH, Moes DJ, et al. Interstitial pneumonitis caused by everolimus: a case-cohort study in renal transplant recipients. *Transplant Int.* 2014;27:428-436.
- Haynes R, Baigent C, Harden P, et al. Campath, calcineurin inhibitor reduction and chronic allograft nephropathy (3C) study: background, rationale, and study protocol. *Transplant Res.* 2013;2:7.
- Sousa SR, Galante NZ, Barbosa DA, Pestana JO. Incidence of infectious complications and their risk factors in the first year after renal transplantation. *J Bras Nefrol.* 2010;32:75-82.
- Xie X, Jiang Y, Lai X, Xiang S, Shou Z, Chen J. mTOR inhibitor versus mycophenolic acid as the primary immunosuppression regime combined with calcineurin inhibitor for kidney transplant recipients: a meta-analysis. *BMC Nephrol.* 2015;16:91.
- Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D, Thymoglobulin Induction Study Group. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med.* 2006;355:1967-1977.
- Hellemans R, Hazzan M, Durand D, et al. Daclizumab versus rabbit antithymocyte globulin in high-risk renal transplants: five-year follow-up of a randomized study. *Am J Transplant.* 2015;15:1923-1932.
- Pilch NA, Taber DJ, Moussa O, et al. Prospective randomized controlled trial of rabbit antithymocyte globulin compared with IL-2

- receptor antagonist induction therapy in kidney transplantation. *Ann Surg*. 2014;259:888-893.
40. Buchler M, Caillard S, Barbier S, et al. Sirolimus versus cyclosporine in kidney recipients receiving thymoglobulin, mycophenolate mofetil and a 6-month course of steroids. *Am J Transplant*. 2007;7:2522-2531.
  41. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Study EL-S: reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med*. 2007;357:2562-2575.
  42. Flechner SM, Glyda M, Cockfield S, et al. The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. *Am J Transplant*. 2011;11:1633-1644.
  43. Silva HT Jr, Felipe CR, Garcia VD, et al. Planned randomized conversion from tacrolimus to sirolimus-based immunosuppressive regimen in de novo kidney transplant recipients. *Am J Transplant*. 2013;13:3155-3163.
  44. Wolf S, Hoffmann VS, Habicht A, et al. Effects of mTOR-Is on malignancy and survival following renal transplantation: a systematic review and meta-analysis of randomized trials with a minimum follow-up of 24 months. *PLoS ONE*. 2018;13:e0194975.
  45. Budde K, Becker T, Arns W, et al. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. *Lancet*. 2011;377:837-847.
  46. Lehner F, Budde K, Zeier M, et al. Efficacy and safety of conversion from cyclosporine to everolimus in living-donor kidney transplant recipients: an analysis from the ZEUS study. *Transplant Int*. 2014;27:1192-1204.
  47. Pascual J, Berger SP, Witzke O, et al. Everolimus with reduced calcineurin inhibitor exposure in renal transplantation. *J Am Soc Nephrol*. 2018;29:1979-1991.
  48. Santos AH Jr, Casey MJ, Xuerong W, Womer KL. Association of baseline viral serology and sirolimus regimens with kidney transplant outcomes: a 14-year registry-based cohort study in the United States. *Transplantation*. 2017;101:377-386.
  49. Knoll GA, Kokolo MB, Mallick R, et al. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. *BMJ*. 2014;349:g6679.

#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Wolf S, Lauseker M, Schiergens T, et al. Infections after kidney transplantation: A comparison of mTOR-Is and CNIs as basic immunosuppressants. A systematic review and meta-analysis. *Transpl Infect Dis*. 2020;22:e13267. <https://doi.org/10.1111/tid.13267>