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

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

[1]Department of General-, Visceral- and Transplantation-Surgery, University Hospital Augsburg, Augsburg, Germany

[2]IBE, Ludwig-Maximilian's University Munich, Munich, Germany

[3]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

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.

1 | INTRODUCTION

Side effect profile of a continuous immunosuppression following renal transplantation is well known.[1]

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.[2] 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.[3,4] Recently, mTOR-Is either in combination with or instead of CNI's have been shown to reduce the incidence of CMV infections significantly.[5] The use of mTOR-Is may also be beneficial against BK virus infections.[6,7] On the contrary, affections of the lung, that is, pneumonitis have been known to be increased under mTOR-Is.[8]

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.[9,10] 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) 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.[11] Between-study heterogeneity was examined using Q test for heterogeneity and the I^2 statistic.[12] 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.[13] 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.[14,15]

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).

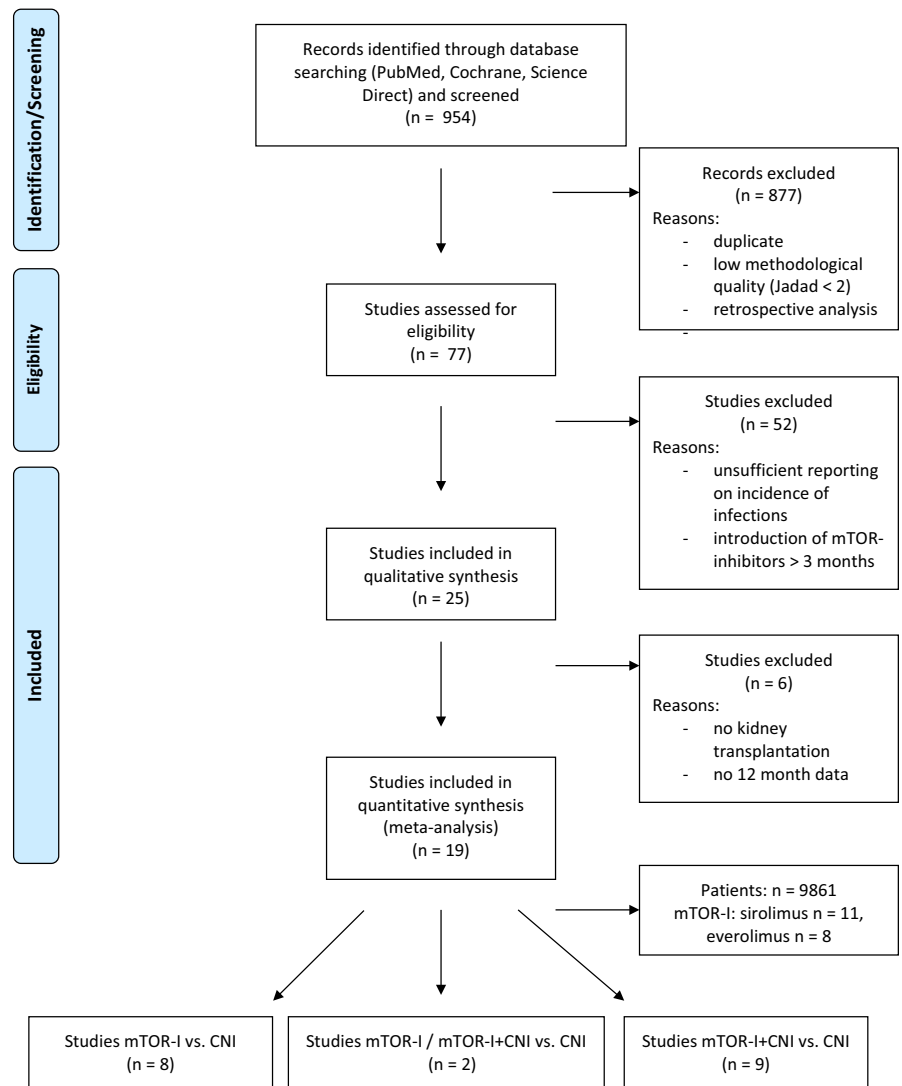Almost all of the RCTs used intention to treat (ITT) to analyze the data (90%).

FIGURE 1 Flowchart of the selection of articles

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^2 = 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^2 = 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^2 = 0.00%, Q test for heterogeneity: P = .54, mTOR-I + CNI vs CNI: I^2 = 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).
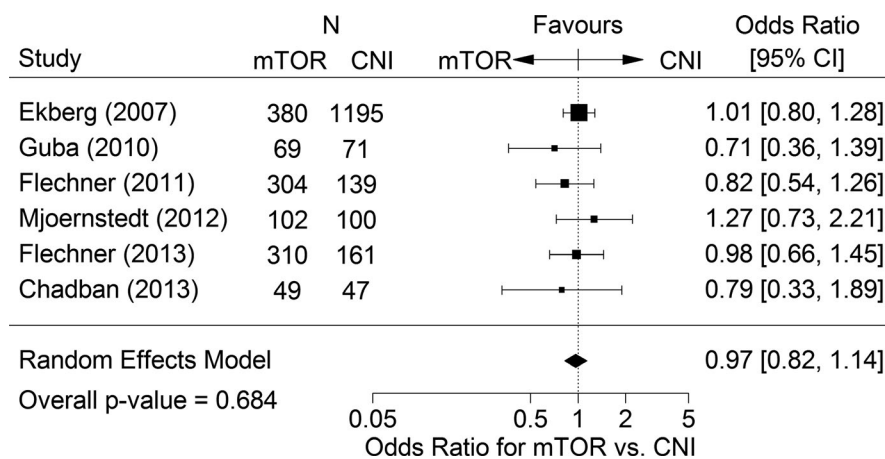

FIGURE 2 Forest plot indicating the odds ratios of the occurrence of infections on mTOR-I vs CNI treatment post transplantation
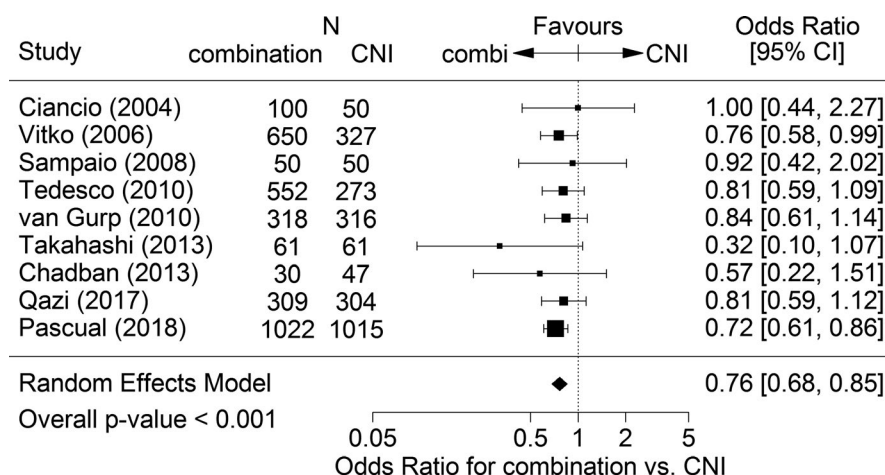

FIGURE 3 Forest plot indicating the odds ratios of the occurrence of infections on mTOR-I + CNI vs CNI treatment post transplantation

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

(A)

Study	N mTOR	N CNI	Favours	Odds Ratio [95% CI]
Ekberg (2007)	380	1195		1.69 [0.96, 2.99]
Buechler (2007)	71	74		2.78 [1.07, 7.25]
Guba (2010)	69	71		1.20 [0.41, 3.51]
Glotz (2010)	71	70		5.23 [0.59, 45.94]
Mjoernstedt (2012)	102	100		6.53 [1.42, 29.99]
Flechner (2013)	310	161		9.08 [0.52, 158.25]
Budde (2018)	171	165		1.96 [0.48, 7.98]
Random Effects Model				2.09 [1.41, 3.12]
Overall p-value < 0.001				

Odds Ratio for mTOR vs. CNI

(B)

Study	N combination	N CNI	Favours	Odds Ratio [95% CI]
Ciancio (2004)	100	50		1.26 [0.24, 6.75]
Sampaio (2008)	50	50		1.57 [0.41, 5.93]
Budde (2018)	161	165		1.38 [0.30, 6.25]
Random Effects Model				1.42 [0.60, 3.35]
Overall p-value = 0.423				

Odds Ratio for combination vs. CNI

(A)

Study	N mTOR	N CNI	Favours	Odds Ratio [95% CI]
Ekberg (2007)	380	1195		0.90 [0.68, 1.17]
Buechler (2007)	71	74		1.46 [0.72, 2.93]
Guba (2010)	69	71		0.55 [0.25, 1.22]
Mjoernstedt (2012)	102	100		0.44 [0.22, 0.89]
Flechner (2013)	310	161		0.99 [0.62, 1.58]
Budde (2018)	171	165		0.75 [0.34, 1.66]
Random Effects Model				0.86 [0.71, 1.05]
Overall p-value = 0.137				

Odds Ratio for mTOR vs. CNI

(B)

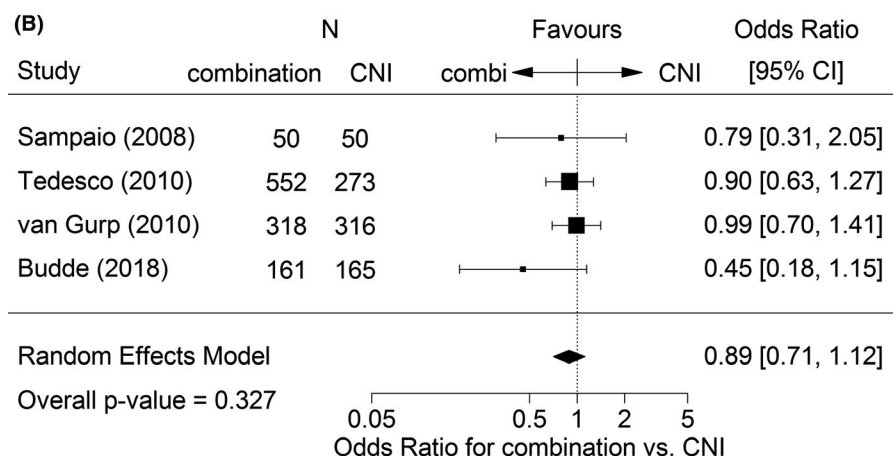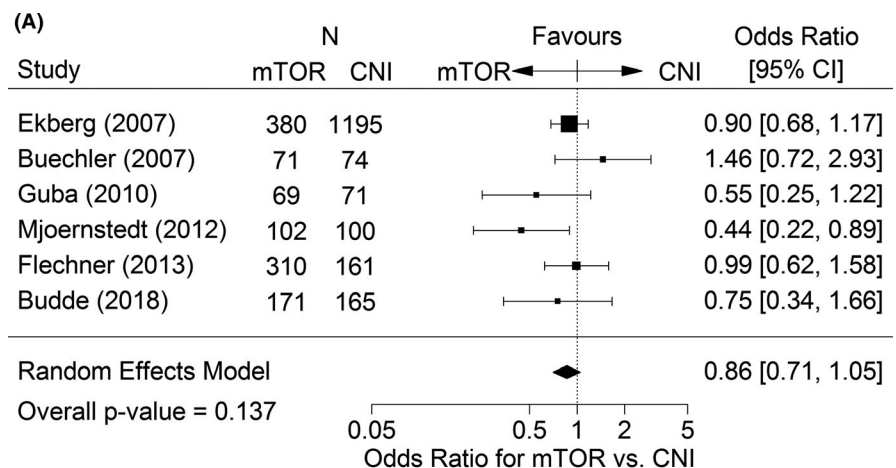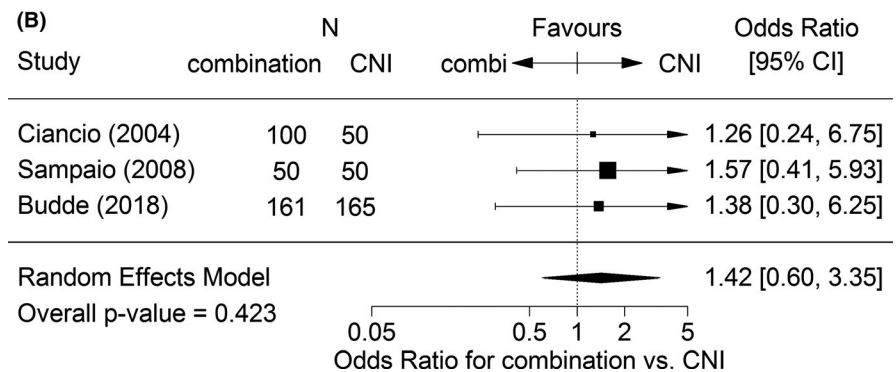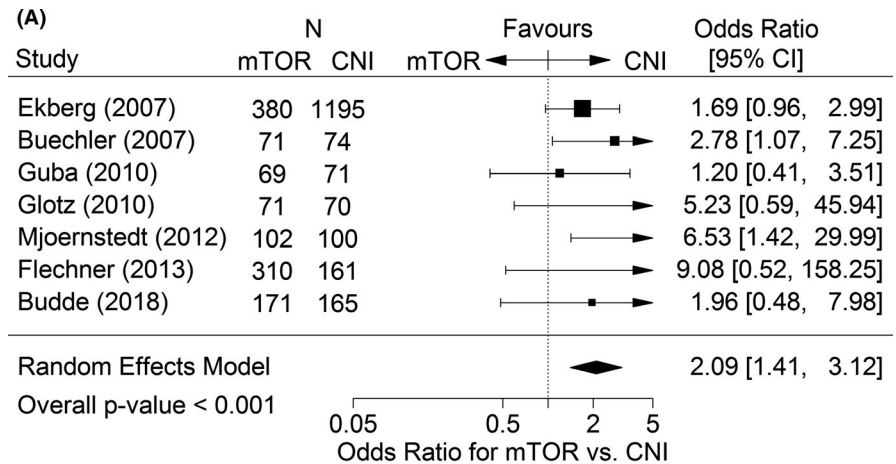| Study	N combination	N CNI	Favours	Odds Ratio [95% CI]
Sampaio (2008)	50	50		0.79 [0.31, 2.05]
Tedesco (2010)	552	273		0.90 [0.63, 1.27]
van Gurp (2010)	318	316		0.99 [0.70, 1.41]
Budde (2018)	161	165		0.45 [0.18, 1.15]
Random Effects Model				0.89 [0.71, 1.12]
Overall p-value = 0.327				

Odds Ratio for combination vs. CNI

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: $P = .48$).

(A)

Study	N mTOR	CNI	Favours mTOR ← → CNI	Odds Ratio [95% CI]
Chadban (2013)	49	47		0.46 [0.08, 2.62]
Ekberg (2007)	380	1195		0.49 [0.31, 0.77]
Guba (2010)	69	71		0.20 [0.07, 0.57]
Mjoernstedt (2012)	102	100		0.65 [0.26, 1.59]
Random Effects Model				0.46 [0.32, 0.66]

Overall p-value < 0.001

Odds Ratio for mTOR vs. CNI

(B)

Study	N combination	CNI	Favours combi ← → CNI	Odds Ratio [95% CI]
Chadban (2013)	30	47		0.77 [0.13, 4.48]
Ciancio (2004)	100	50		0.10 [0.00, 2.05]
Pascual (2018)	1022	1015		0.24 [0.16, 0.35]
Qazi (2017)	309	304		0.49 [0.25, 0.98]
Sampaio (2008)	50	50		1.00 [0.30, 3.34]
Takahashi (2013)	61	61		0.10 [0.03, 0.35]
Tedesco (2010)	552	273		0.06 [0.01, 0.26]
van Gurp (2010)	318	316		0.21 [0.10, 0.45]
Vitko (2006)	650	327		0.54 [0.31, 0.93]
Random Effects Model				0.30 [0.17, 0.51]

Overall p-value < 0.001
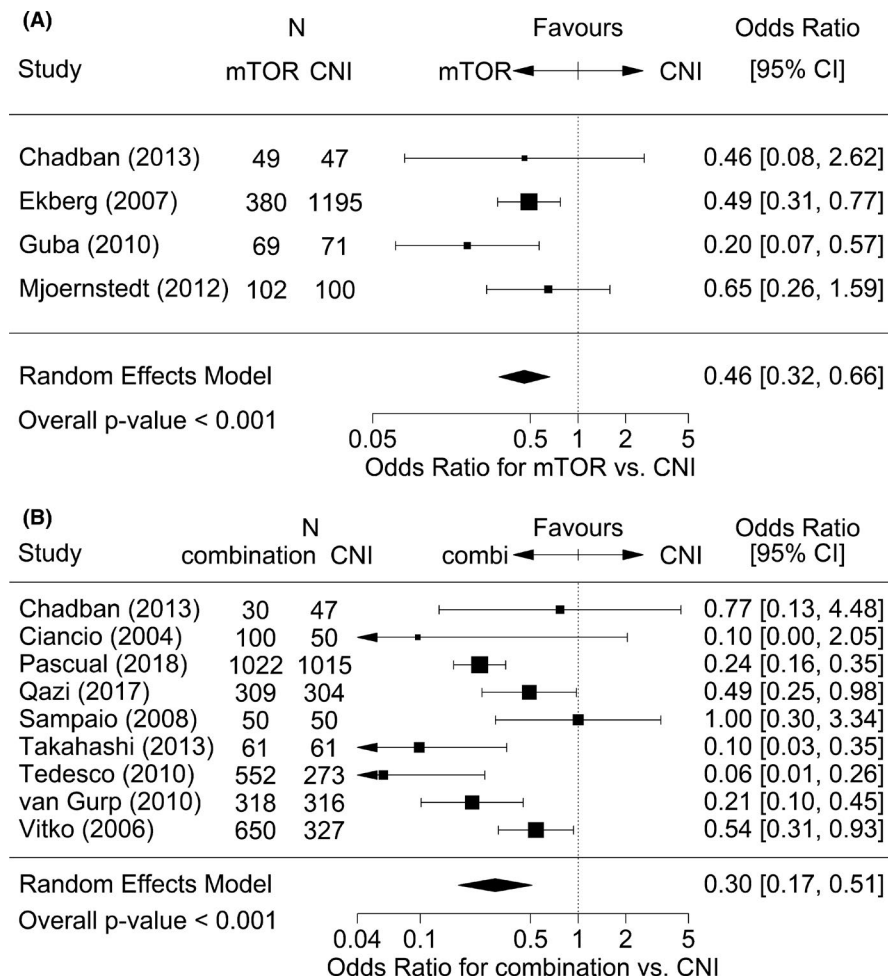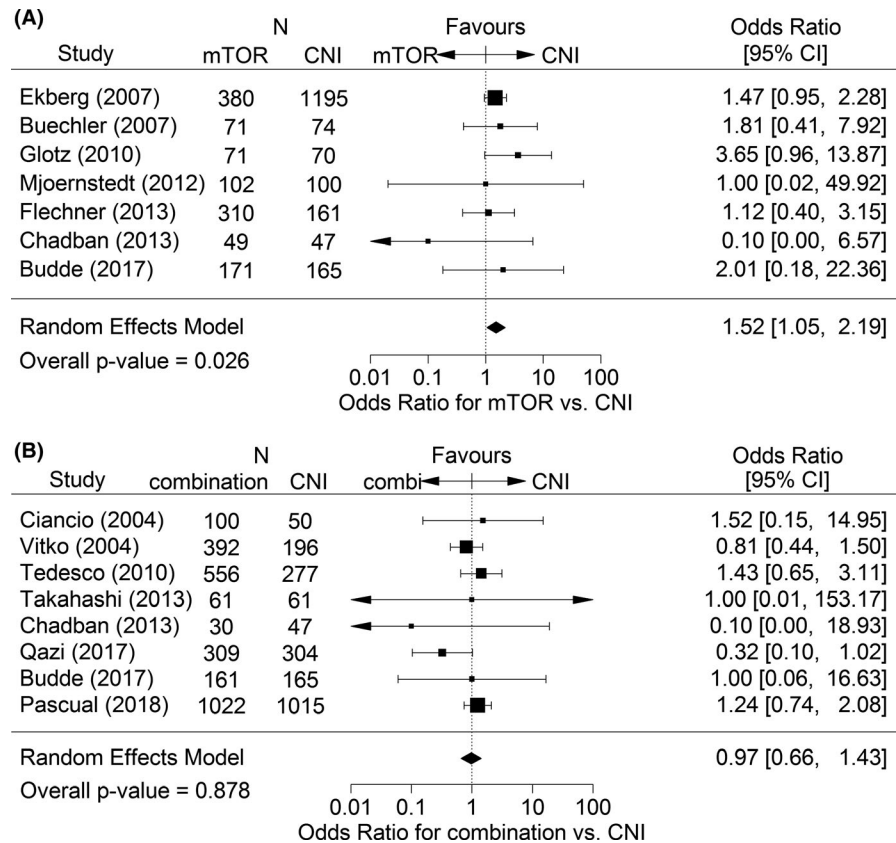
Odds Ratio for combination vs. CNI

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

(A)

Study	N mTOR	N CNI	Favours mTOR ← → CNI	Odds Ratio [95% CI]
Ekberg (2007)	380	1195		1.47 [0.95, 2.28]
Buechler (2007)	71	74		1.81 [0.41, 7.92]
Glotz (2010)	71	70		3.65 [0.96, 13.87]
Mjoernstedt (2012)	102	100		1.00 [0.02, 49.92]
Flechner (2013)	310	161		1.12 [0.40, 3.15]
Chadban (2013)	49	47		0.10 [0.00, 6.57]
Budde (2017)	171	165		2.01 [0.18, 22.36]
Random Effects Model				1.52 [1.05, 2.19]

Overall p-value = 0.026

Odds Ratio for mTOR vs. CNI

(B)

Study	N combination	N CNI	Favours combi ← → CNI	Odds Ratio [95% CI]
Ciancio (2004)	100	50		1.52 [0.15, 14.95]
Vitko (2004)	392	196		0.81 [0.44, 1.50]
Tedesco (2010)	556	277		1.43 [0.65, 3.11]
Takahashi (2013)	61	61		1.00 [0.01, 153.17]
Chadban (2013)	30	47		0.10 [0.00, 18.93]
Qazi (2017)	309	304		0.32 [0.10, 1.02]
Budde (2017)	161	165		1.00 [0.06, 16.63]
Pascual (2018)	1022	1015		1.24 [0.74, 2.08]
Random Effects Model				0.97 [0.66, 1.43]

Overall p-value = 0.878

Odds Ratio for combination 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-Is 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.[16] 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.[17]

In the early phase <1 month after transplantation, infections are mostly related to surgical complications.[2] It is widely accepted that mTOR-Is are associated with surgical wound complications and prolonged wound healing after surgery.[18-20] 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
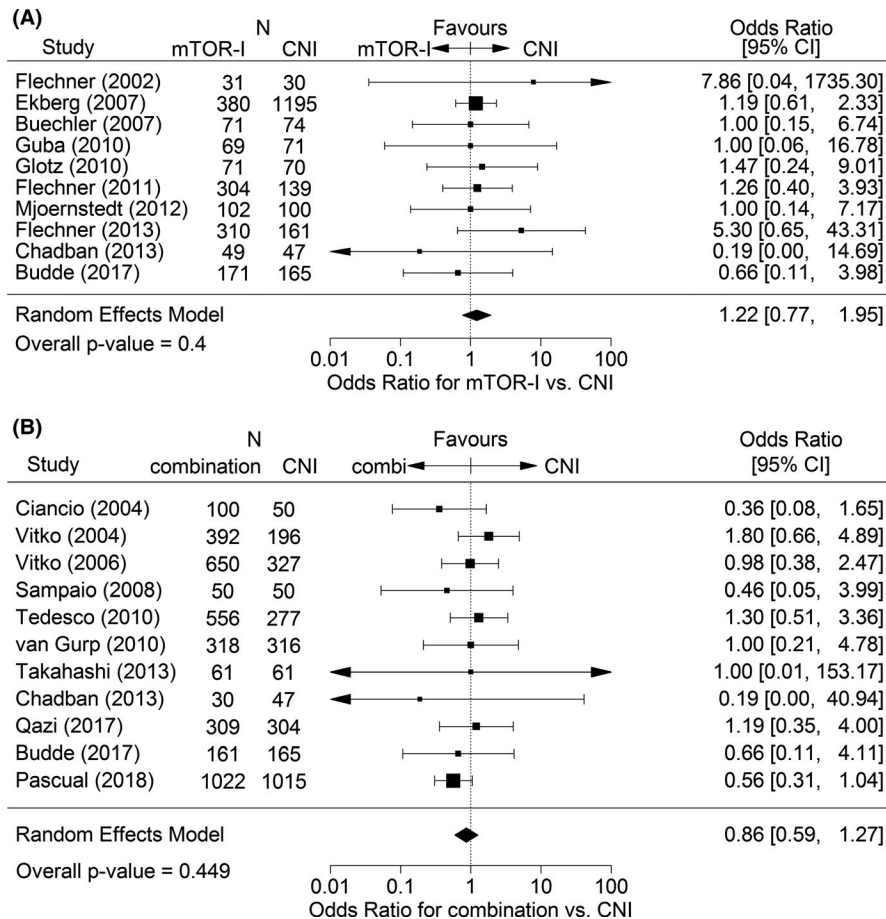
(A)

Study	N mTOR-I	N CNI	Favours mTOR-I ◄——► CNI	Odds Ratio [95% CI]
Flechner (2002)	31	30		7.86 [0.04, 1735.30]
Ekberg (2007)	380	1195		1.19 [0.61, 2.33]
Buechler (2007)	71	74		1.00 [0.15, 6.74]
Guba (2010)	69	71		1.00 [0.06, 16.78]
Glotz (2010)	71	70		1.47 [0.24, 9.01]
Flechner (2011)	304	139		1.26 [0.40, 3.93]
Mjoernstedt (2012)	102	100		1.00 [0.14, 7.17]
Flechner (2013)	310	161		5.30 [0.65, 43.31]
Chadban (2013)	49	47		0.19 [0.00, 14.69]
Budde (2017)	171	165		0.66 [0.11, 3.98]
Random Effects Model				1.22 [0.77, 1.95]

Overall p-value = 0.4

0.01 0.1 1 10 100
Odds Ratio for mTOR-I vs. CNI

(B)

Study	N combination	N CNI	Favours combi ◄——► CNI	Odds Ratio [95% CI]
Ciancio (2004)	100	50		0.36 [0.08, 1.65]
Vitko (2004)	392	196		1.80 [0.66, 4.89]
Vitko (2006)	650	327		0.98 [0.38, 2.47]
Sampaio (2008)	50	50		0.46 [0.05, 3.99]
Tedesco (2010)	556	277		1.30 [0.51, 3.36]
van Gurp (2010)	318	316		1.00 [0.21, 4.78]
Takahashi (2013)	61	61		1.00 [0.01, 153.17]
Chadban (2013)	30	47		0.19 [0.00, 40.94]
Qazi (2017)	309	304		1.19 [0.35, 4.00]
Budde (2017)	161	165		0.66 [0.11, 4.11]
Pascual (2018)	1022	1015		0.56 [0.31, 1.04]
Random Effects Model				0.86 [0.59, 1.27]

Overall p-value = 0.449

0.01 0.1 1 10 100
Odds Ratio for combination vs. CNI

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%),[9] and another report where the overall infection rate was not significantly different under SRL (sirolimus) compared to CsA (17.4% vs 21.8%).[10]

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.[5,21-23] This may also hold true for BK virus infections.[24,25] 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.[25] A meta-analysis primarily on CMV and BKV infections comparing mTOR-Is 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-Is 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.[26]

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.[5] Maybe, the positive antiviral effect of the mTOR-Is even under the reduced dose simply outweighs the additional immunosuppression of the combination therapy.[27,28] Another explanation may be that mTOR-Is are known not only to suppress but also enhance certain immune reactions as memory T-cell functions,[23] quantity and quality of virus-specific CD8 T cells and memory precursor cells.[23] Furthermore, SRL was shown to enhance the effector to memory T-cell transition.[23] 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.[29] In addition, increased MHC antigen presentation via autophagy in monocytes/macrophages and dendritic cells and counteracting immunosuppressive effects of steroids have been reported.[29,30]

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.[31]

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-Is were 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.[32] 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.[33] 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).[34]

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%.[35]

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.[36]

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.[37] Advances in the immunosuppressive protocols as well as anti-infective 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.[38,39]

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.[40-43]

We did not find a significant difference concerning patient survival between the groups regardless of whether mTOR-Is were 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).[44-47] However, data have also been published which show a worse survival under mTOR-Is. Especially, registry data from ANZDATA[9] and SRTR[48] 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-Is were standard. The only trial to date that used randomized controlled data and showed a worse survival under mTOR-Is was the meta-analysis by Knoll et al.[49] 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-Is 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-Is 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-Is as we could not find beneficial effects of mTOR-Is over CNIs on other infections.

Lung affections may be more often under mTOR-Is without CNIs. This could be related to the difficulty to differentiate between infectious and non-infectious pneumonitis. Incidence of urogenital infections under mTOR-Is 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.

ORCID

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

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SUPPORTING INFORMATION

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