Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Do wound complications or lymphoceles occur more often in solid organ transplant recipients on mTOR inhibitors? A systematic review of randomized controlled trials

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Keywords
lymphoceles, mTOR inhibitors, randomized controlled trials, solid organ transplantation, systematic review, wound complications.

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Conflicts of Interest
PJM chairs a data safety committee for Bristol-Meyers Squibb and has in the past received lecture fees from Novartis, Astellas, Roche and Genzyme.

Received: 9 June 2011
Revision requested: 6 July 2011
Accepted: 30 August 2011
Published online: 29 September 2011

doi:10.1111/j.1432-2277.2011.01357.x

Summary

mTOR inhibitors have been associated with wound complications and lymphoceles. We systematically reviewed randomized controlled trials (RCTs) to compare these outcomes for solid organ transplant recipients. Relevant medical databases were searched to identify RCTs in solid organ transplantation comparing mTOR inhibitors with an alternative therapy reporting on wound complications and/or lymphoceles. Methodological quality of RCTs was assessed. Pooled analyses were performed to calculate odds ratios (OR) and 95% confidence intervals (CI). Thirty-seven RCTs in kidney, heart, simultaneous pancreas-kidney and liver transplantation were included. Pooled analyses showed a higher incidence of wound complications (OR 1.77, CI 1.31–2.37) and lymphoceles (OR 2.07, CI 1.62–2.65) for kidney transplant recipients on mTOR inhibitors together with calcineurin inhibitors (CNIs). There was also a higher incidence of wound complications (OR 3.00, CI 1.61–5.59) and lymphoceles (OR 2.13, CI 1.57–2.90) for kidney transplant recipients on mTOR inhibitors together with antimetabolites. Heart transplant patients receiving mTOR inhibitors together with CNIs also reported more wound complications (OR 1.82, CI 1.15–2.87). We found a higher incidence of wound complications and lymphoceles after kidney transplantation and a higher incidence of wound complications after heart transplantation for immunosuppressive regimens that included mTOR inhibitors from the time of transplantation.

Introduction

The introduction of calcineurin inhibitors (CNIs) has significantly improved the outcome of solid organ transplantation. However, CNIs have been associated with nephrotoxicity and other side-effects [1]. One alternative to CNIs is a new class of immunosuppressants, sirolimus (SRL) and everolimus (EVL) that inhibit the mammalian target of rapamycin (mTOR inhibitors). Quite early after the introduction of mTOR inhibitors into immunosuppressive regimens, it became apparent that the antiproliferative actions of mTOR inhibitors might have an effect on healing as evident by poor wound healing and the occurrence of lymphoceles after renal transplantation [2–4]. This antiproliferative effect on fibroblasts in the healing wound is likely to be the explanation for complications of healing [5]. In particular, tracheal dehiscence was noted after lung transplantation [6].

In 2006, a Cochrane review by Webster *et al.* [7] evaluated the efficacy and safety of mTOR inhibitors for kidney transplant recipients in the immediate post-transplant period. The authors found that patients treated with mTOR inhibitors showed an increased risk of developing lymphoceles when compared with patients treated with CNIs or antimetabolites. They did not find an increased risk for developing wound complications nor did they find a difference when comparing lower versus higher dose mTOR inhibitors or when comparing lower dose

mTOR inhibitors plus standard CNIs versus higher dose mTOR inhibitors plus lower dose CNIs. Their literature search was done up to July 2005 and since then some of the included conference abstracts have been published as full articles and a number of additional, large RCTs have been published that report on wound complications or lymphoceles.

Therefore, the primary aim of the study was to evaluate the occurrence of wound complications and lymphoceles in solid organ transplant recipients receiving mTOR inhibitors from the time of transplantation compared with patients not receiving mTOR inhibitors. We tested the null hypothesis that wound complications and lymphoceles do not occur more commonly in patients receiving mTOR inhibitors than in patients who do not receive mTOR inhibitors.

As it has been suggested that steroid avoidance may reduce the negative impact of mTOR inhibitors on wound healing and lymphocele formation, a secondary analysis was planned to review the effects of mTOR inhibitors plus steroids versus mTOR inhibitors without steroids on these outcomes [8,9].

Methods

Inclusion criteria

For the primary analysis, eligible studies included randomized controlled trials (RCTs) in solid organ transplantation that compared mTOR inhibitors given from the time of transplantation with at least one alternative non-mTOR inhibitor intervention arm. For the secondary analysis, we included RCTs with mTOR inhibitors in both arms and at least one steroid arm and one steroid-free arm. Studies had to report on wound complications or lymphoceles. Wound complications included (superficial or deep) wound infection, (superficial) wound dehiscence, fascial dehiscence, wound debridement, delayed/slow wound healing, abnormal wound healing, partial wound healing, haematoma, seroma, wound inflammation, increased wound drainage, wound haemorrhage, wound secretion or incisional hernia. Studies only reporting on peripheral oedema, fluid overload and oedema were excluded.

Identification of studies

Full reports of RCTs were identified through searches of the Transplant Library, Medline, Embase and the Cochrane Central Register of Controlled Trials up to 24 March 2011 without language restrictions. Search terms in Medline and Cochrane included all MeSH terms for solid organ transplantation and other generic transplantation MeSH terms. The Cochrane highly sensitive search strategy was used to identify RCTs in Medline. Other specific search terms included sirolimus, rapamycin, rapamune, everolimus, ay 22-989, SDZ RAD and Certican. When there was more than one report of the same trial, all reports that reported on wound complications or lymphoceles were included in the review. The reference lists of identified RCTs or reviews were inspected for additional references. Conference abstracts were not included.

Data extractions and methodological quality

The following data were extracted from eligible articles by one reviewer: type of organ, intervention arms, induction therapy, mTOR inhibitor dose, steroid dose, number of participants, follow-up period, description and incidence of wound complications and/or lymphoceles. Methodological quality was assessed independently by two reviewers using both the Jadad score and the items allocation concealment and intention to treat [10,11]. The Jadad score addresses the items randomization, blinding and description of withdrawals and dropouts. The total Jadad score ranges from 0 to 5 with RCTs scoring at least 3 of 5 being considered to be consistent with sound methodological quality. However, also the use of allocation concealment and intention to treat were part of the overall assessment of quality. Intention to treat was defined as an analysis including all randomized participants, that was based on the groups to which participants were originally randomly assigned regardless of whether they satisfied the entry criteria, the treatment actually received and subsequent withdrawal or deviation from the protocol.

Analysis

The RCTs were analysed according to organ and concomitant therapy, i.e. mTOR inhibitors together with CNIs or antimetabolites. If there was more than one RCT with similar interventions, a meta-analysis was performed for the incidence of wound complications or lymphoceles. Data were extracted by two reviewers using a spreadsheet. Review Manager (RevMan) [Computer program] version 5.1.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used to pool the incidence of wound complications or lymphoceles among studies. We pooled all data irrespective of the length of follow-up, as most complications would develop within the first few months after transplantation. A subgroup analysis was also performed for studies considered to be of good methodological quality, i.e. studies that used adequate allocation concealment or scored at least 3 points on the Jadad scale. The Mantel–Haenszel random effects model was used to calculate

odds ratios (OR). For trials with more than two arms, the incidences of wound complications or lymphoceles for the mTOR inhibitor or control arms were grouped and compared collectively with the comparator. If there were no events in both arms, the RCT was excluded from the quantitative analysis. Statistical heterogeneity was tested using the I^2 statistic. A secondary analysis was performed to assess whether complications occur more commonly in patients receiving concomitant steroids compared with no steroids. To assess possible publication bias, funnel plots were created for comparisons that included at least 10 trials [12].

Results

Included studies

The literature search identified a total of 518 unique references of which 37 RCTs met the inclusion criteria for the qualitative analysis (Fig. 1). One study was omitted from the quantitative primary and secondary analyses, as it was reported that no events occurred in either study arms [13]. Thirty-one RCTs evaluated sirolimus whereas six RCTs evaluated everolimus. For the primary quantitative analysis, a total of 28 RCTs were published on kidney transplantation reporting on 8916 patients

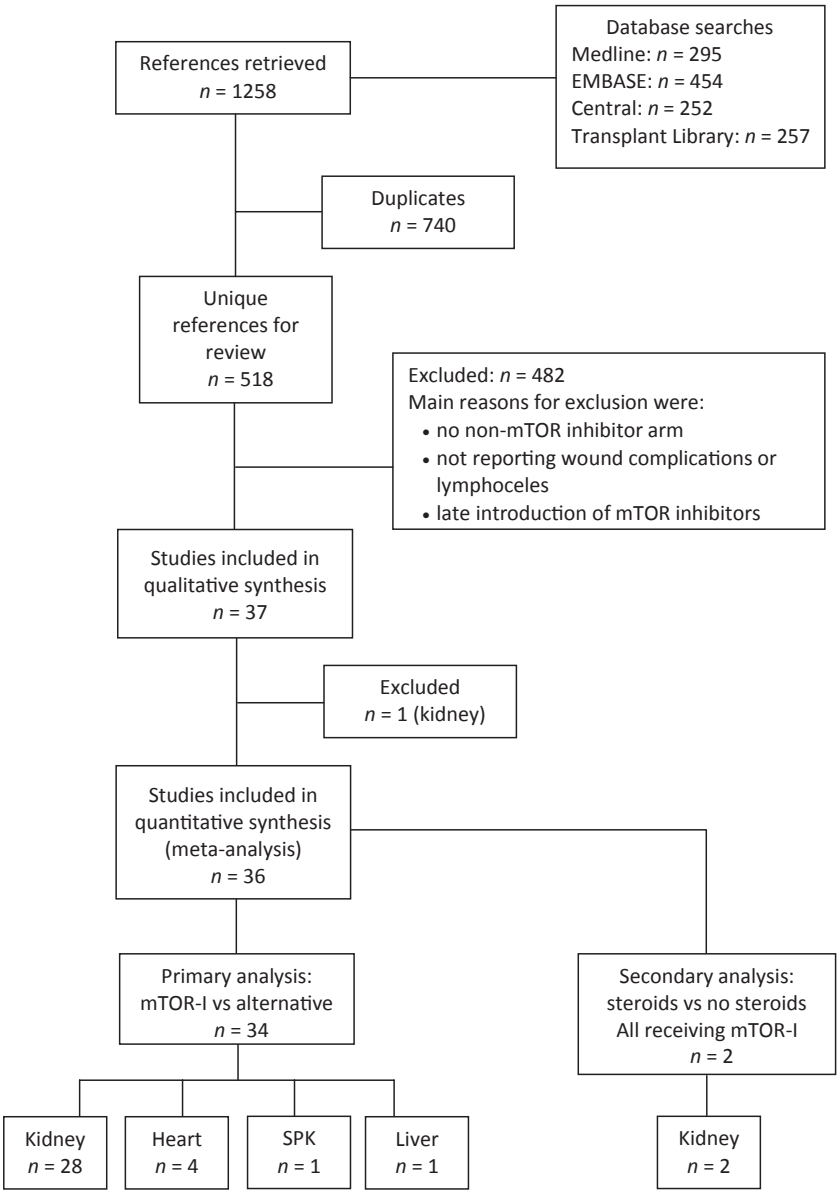

Figure 1 Flowchart of the selection of articles. SPK, simultaneous pancreas-kidney; mTOR-I, mTOR inhibitors.

(Tables 1 and 2, Table S1), [13–43] four RCTs were published on heart transplantation reporting on 1289 patients (Table S2), [44–47] one RCT [48] was published on liver transplantation reporting on 78 patients (Table S3) and one RCT [49] was published on simultaneous kidney and pancreas transplantation reporting on 123 patients (Table S4). In kidney transplantation, 14 RCTs evaluated mTOR inhibitors together with CNIs, 13 RCTs evaluated mTOR inhibitors together with antimetabolites and 1 RCT evaluated an mTOR inhibitor together with belatacept. For all RCTs in heart transplantation, mTOR inhibitors were given together with CNIs. For the secondary quantitative analysis, i.e. evaluation of the possible impact of mTOR inhibitors combined with steroids versus no steroids, two RCTs on kidney transplantation were identified (Table S5) [50,51]. Most trials on kidney transplantation reported on both wound complications and lymphoceles (Table S6).

Methodological quality

For the primary analysis, nearly half of all RCTs (46%) were considered to be of good methodological quality according to the Jadad scale. Of the 35 RCTs, 14 trials described an appropriate method to generate the randomization sequence. Five trials were double-blinded, four of which adequately described the method of double-blinding. An adequate description of withdrawals and dropouts was given for 31 of 35 trials. More than half of all RCTs (63%) used intention to treat to analyse data and about one-third (37%) of trials adequately described allocation concealment. For the secondary analysis, the Jadad score of the two trials was inadequate. Only Montagnino *et al.* [50] adequately described allocation concealment and analysed the data according to intention to treat.

Wound complications and lymphoceles

Kidney transplantation

Pooled analyses showed that kidney transplant patients receiving mTOR inhibitors together with CNIs reported more wound complications (12 trials, $n = 4787$; OR 1.77, 95% confidence interval (CI) 1.31–2.37) and more lymphoceles (11 trials, $n = 5370$; OR 2.07, CI 1.62–2.65) than patients not receiving mTOR inhibitors (Figs 2 and 3). The heterogeneity was minimal ($I^2 = 0\%$ for both analyses). A subgroup analysis of RCTs considered to be of good methodological quality also showed a higher incidence of wound complications and lymphoceles for patients on mTOR inhibitors (Table S7). The funnel plot for both analyses showed asymmetry suggesting that smaller studies with and without significant effects could have remained unpublished.

Kidney transplant patients receiving mTOR inhibitors together with antimetabolites reported more wound complications (13 trials, $n = 2757$; OR 3.00, CI 1.61–5.59) and lymphoceles (8 trials, $n = 2372$; OR 2.13, CI 1.57–2.90) than patients not receiving mTOR inhibitors (Figs 3 and 4 & Figure S1). The heterogeneity for the incidence of wound complications was substantial ($I^2 = 59\%$) but not for the incidence of lymphoceles ($I^2 = 0\%$). The subgroup analysis of RCTs considered to be of good methodological quality also showed a higher incidence of wound complications for patients on mTOR inhibitors (Table S7). The substantial heterogeneity of 60% was thereby reduced to 0% in the subgroup analysis indicating that heterogeneity could have been due to differences in methodological quality. The subgroup analysis for the incidence of lymphoceles found a higher incidence for patients on mTOR inhibitors when the Jadad score was at least 3, however, this was not found for studies using concealed allocation. The funnel plot for the analysis of wound complications showed asymmetry suggesting that small studies without significant effects could have remained unpublished.

For both the analyses, i.e. mTORs together with either CNIs or antimetabolites, there was no increase or decrease of the incidence of wound complications or lymphoceles over time.

One RCT evaluated wound complications and lymphoceles in 89 kidney transplant recipients comparing mTOR inhibitors together with belatacept versus belatacept and MMF versus tacrolimus and MMF [43]. There were no cases of wound dehiscence in the mTOR group versus three cases of wound dehiscence in the non-mTOR groups and one case of lymphoceles in the mTOR group versus one case of lymphoceles in the non-mTOR groups.

Heart transplantation

Heart transplant patients receiving mTOR inhibitors together with CNIs reported more wound complications (four trials, $n = 1278$; OR 1.82, CI 1.15–2.87) than patients not receiving mTOR inhibitors (Supplemental Figure S2) [44–46]. Heterogeneity was minimal ($I^2 = 5\%$).

Liver transplantation

One RCT evaluated wound complications in 78 liver transplantation receiving either everolimus with early CsA withdrawal versus standard CsA and MMF [48]. Forty-six per cent of patients in the everolimus arm versus 27% of patients in the CsA arm experienced incisional hernias ($P = 0.16$) and 21% versus 31% experienced biliary complications ($P = 0.51$).

Table 1. Studies evaluating mTOR inhibitors plus calcineurin inhibitors for kidney transplantation (n = 15).

				mTOR-I dose					Methodological Quality		
Reference	*n*	Comparison	Induction	Loading dose	Maintenance	Pred maintenance dose	Study period	Outcomes	Jadad (0–5)	AC	ITT
Van Gurp [40]	659	I. SRL, Tac, pred II. Tac, MMF, pred	None	6 mg	2 mg/day for 28 days, 1 mg thereafter	125 mg bolus on day 1. From day 2 20 mg/day tapered to 5 mg/day by day 90. Discontinued thereafter.	6 months	Wound complications, lymphoceles*	2	Yes	No
Tedesco Silva [39]	833	I: 1.5 mg everolimus, reduced CsA, pred II. 3 mg everolimus, reduced CsA, pred III. MPA, standard CsA, pred	Basiliximab	None	I: 3–8 ng/ml II: 6–12 ng/ml	According to local practice.	12 months	Wound complications, lymphoceles	3	Yes	Yes
Sampaio [38]	100	I. SRL, Tac, pred II. MMF, Tac, pred	None	15 mg	2 mg/day	Started at 30 mg/day with target of 10 mg/day by 3 months; target of 5 mg/day at 6 months.	12 months	Wound complications, lymphoceles	3	No	Yes
Anil Kumar [15]	200	I. CsA, MMF II. CsA, SRL III. Tac, MMF IV. Tac, SRL	Basiliximab, methylprednisolone	None	Initiated on day 4 at 2 mg/day. Target was 5–10 ng/ml	None	5 years	Wound complications	3	No	Yes
Vitko [42]	977	I. 0.5 mg SRL, Tac, pred II. 2 mg SRL, Tac, pred III. MMF, Tac, pred	None	I: 1.5 mg; II: 6 mg	I: 0.5 mg; II: 2 mg	Day 1: 125 mg; subsequently tapered to 20 mg/day (day 14), 15 mg/day (day 28), 10 mg/day (day 42); 5 mg/day thereafter.	6 months	Wound complications, lymphoceles	2	Yes	Yes
Vitko [41]	588	I: 1.5 mg everolimus, CsA, pred II. 3 mg everolimus, CsA, pred III. MMF, CsA, pred	None	None	I: 0.75 mg everolimus b.i.d; II 1.5 mg everolimus b.i.d.	Tapered from 20 mg/day on day 1 to ≥5 mg/day at 6 months.	3 years	Lymphoceles	3	No	Yes

Table 1. continued

Reference	*n*	Comparison	Induction	mTOR-I dose		Pred maintenance dose	Study period	Outcomes	Methodological Quality		
				Loading dose	Maintenance				Jadad (0–5)	AC	ITT
Lorber [33]	583	I: 1.5 mg everolimus, CsA, pred II. 3 mg everolimus, CsA, pred III. MMF, CsA, pred	None	None	I: 0.75 mg everolimus b.i.d; II 1.5 mg everolimus b.i.d.	Day 1: 500 mg. Tapered to 20 mg/day by day 30 and ≥5 mg/day for at least 6 months.	3 years	Lymphoceles	3	No	Yes
Kandaswamy [31]	239	I. CsA, MMF, pred (0–5 days) II. High Tac, low SRL, pred (0–5 days) III. Low Tac, high SRL, pred (0–5 days)	Thymoglobulin	10 mg/None†	I: 3–7 ng/ml; II: 8–12 ng/ml	Day 1: 1 mg/kg; days 2–3 0.5 mg/kg; day 4–5 0.25 mg/kg. Discontinued thereafter.	Mean 16 months	Wound complications	2	Yes	Yes
Anil Kumar [14]	150	I: Tac, MMF II: Tac, SRL	Basiliximab/ methylprednisolone	None	Initiated on day 4 at 2 mg/day. Target was 6–10 ng/ml	None	Median 400 days	Wound complications, lymphoceles	3	No	No
Machado [35]	70	I: SRL, CsA, pred II. AZA, CsA, pred	None	6 mg	2 mg/day	0–30 days: 0.5 mg/kg/day (max. 30 mg/day). Tapered to 20 mg/day by 2 months and 10 mg/day between 3–6 months.	12 months	Wound complications, lymphoceles	1	No	Yes
Ciancio [18]	150	I. SRL, Tac, pred II. SRL, CsA, pred III. MMF, Tac, pred	Daclizumab	4 mg	8 ng/ml	Days 1–3: 500 mg/day. Tapered to 0.3 mg/kg at 1 month and 0.15 mg/kg at 3 months.	12 months	Wound complications, lymphoceles	2	No	Yes
Van Hooff [13]	104	I: Tac, pred II: 0.5 mg SRL, Tac, pred‡ III: 1 mg SRL, Tac, pred‡ IV: 2 mg SRL, Tac, pred‡	None	I: 1.5 mg; II: 3 mg; III: 6 mg	I: 0.5 mg; II: 1 mg; III: 2 mg	Day 1: 125 mg; subsequently tapered to 20 mg/day (day 14), 15 mg/day (day 28), 10 mg/day (day 42); 5 mg/day thereafter.	6 months	Lymphoceles§	2	No	No

Table 1. continued

Reference	*n*	Comparison	Induction	mTOR-I dose		Pred maintenance dose	Study period	Outcomes	Methodological Quality		
				Loading dose	Maintenance				Jadad (0–5)	AC	ITT
MacDonald [28,29,34]	576	I: 2 mg/day SRL, CsA, pred II: 5 mg/day SRL, CsA, pred III: placebo, CsA, pred	None	I: 6 mg; II: 15 mg	I: 2 mg/day; II: 5 mg/day	Day 0: 250 mg. Tapered to 30 mg/day by day 7, 10 mg/day by month 6 and 5–10 mg/day thereafter.	12 months	Wound complications, lymphoceles	5	Yes	Yes
Kahan [27]	719	I. 2 mg SRL, CsA, Pred II. 5 mg SRL, CsA, Pred III: AZA, CsA, Pred	None	6 ml	2 mg/day; 5 mg/day	Day 0: 500 mg. Tapered to 30 mg/day by day 6, 10 mg/day by month 6, 5–10 mg/day thereafter.	12 months	Wound complications, lymphoceles	5	Yes	Yes
Kahan [30]	149	I. 1 mg/m^2/day SRL, high CsA, pred II. 3 mg/m^2/day SRL, high CsA, pred III. 1 mg/m^2/day SRL, low CsA, pred IV. 3 mg/m^2/day SRL, low CsA, pred V. 5 mg/m^2/day SRL, low CsA, pred VI. high CsA, pred	None	3 times the study dose	I. 1 mg/m^2/day II. 3 mg/m^2/day III. 1 mg/m^2/day IV. 3 mg/m^2/day V. 5 mg/m^2/day	Day 0 500 mg. Tapered to 40 mg/day by day 6, 20–30 mg/day for weeks 1–6 and ≤10 mg/day thereafter.	12 months	Wound complications	2	No	No

SRL, sirolimus; Tac, tacrolimus; CsA, cyclosporine A; MMF, mycophenolate mofetil; MPA, mycophenolic acid; AZA, azathioprine; Pred, prednisolone; AC, allocation concealment; ITT, intention to treat.

*Data regarding wound complications and lymphoceles were not included in the article but were provided by the author upon request. All wound complications were reported as serious adverse events.

†For the first 21 months of this trial, a loading dose of 10 mg was given. Thereafter, no loading dose was given.

‡SRL groups were randomized a second time (1:1) after 3 months to discontinue SRL at either the end of month 3 or the end of month 5.

§It was stated that there were no reports for lymphoceles and therefore the study was excluded from the quantitative meta-analysis.

Table 2. Studies evaluating mTOR inhibitors plus antimetabolites for kidney transplantation (n = 13).

				mTOR-I dose					Methodological Quality		
Reference	n	Comparison (n)	Induction	Loading	Maintenance	Pred maintenance dose	Study period	Outcomes	Jadad (0–5)	AC	ITT
Franz [23]	127	I. SRL, MMF, pred II. CsA, MMF, pred	None	30 mg/day for 3 days	Started at 16 mg to reach 10–20 ng/ml during months 1–3; months 4–6: 8–15 ng/ml	1000, 500, 250 mg on days 0, 1, 2 respectively. Then 0.5 mg/kg/day, tapered every other week by 5 mg to 15 mg, then tapered by 2.5 mg to 7.5 mg	6 months	Wound complications, lymphoceles	2	No	Yes
Glotz [24]	141	I. SRL, MMF, pred II. Tac, MMF, pred	Group I: ATG	15 mg/day for 2 days	Started at 10 mg/day for 5 days. Target 12–20 ng/ml from day 8 to 1 year	250 mg on day 0. Days 1–10: 0.3–0.5 mg/kg/day, days 11–30: 0.15–0.3 mg/kg/day, days 31–90: 0.1–0.15 mg/kg/day, 0.1 mg/kg/day thereafter	12 months	Wound complications, lymphoceles	2	No	Yes
Guba [26]	141	I. SRL, MMF, pred II. CsA, MMF, pred	ATG	0.1 mg/kg	Started at 2–4 mg/day. Target 8–12 ng/ml for months 0–3 and 5–10 ng/ml thereafter	Day 0: 500 mg. Maintenance according to centre practice. Minimum 20 mg for weeks 0–2, 15 mg for weeks 3–8, 10 mg for months 2–4 and 2 mg thereafter	12 months	Wound complications, lymphoceles	3	Yes	Yes
Durrbach [20]	72	I. SRL, MMF, pred II. CsA, MMF, pred	ATG	30 mg/day for 2 days	Started at 10 mg/day to reach 10–20 ng/ml	According to centre practice	6 months	Wound complications, lymphoceles	2	Yes	No
Pescovitz [37]	60	I. SRL, MMF, pred II. CsA, MMF, pred	Daclizumab	15 mg/day for 3 days	0–2 months: 10–25 ng/ml; 8–15 ng/ml thereafter	According to centre practice.	6 months	Wound complications	2	No	Yes
Ekberg [21]	1645	I: low dose SRL, MMF, pred II: standard CsA, MMF, pred III: low dose CsA, MMF, pred IV: low dose Tac, MMF, pred	Groups I, III, IV: Daclizumab 0–2 months post-transplant	9 mg/day for 3 days	4–8 ng/ml	According to centre practice. Minimum at 0–2 weeks: 20 mg, 3–8 weeks: 15 mg, 2–4 months: 10 mg, 5 mg thereafter	12 months	Wound complications, lymphoceles	3	Yes	No

Table 2. continued

Reference	*n*	Comparison (*n*)	Induction	mTOR-I dose		Pred maintenance dose	Study period	Outcomes	Methodological Quality		
				Loading	Maintenance				Jadad (0–5)	AC	ITT
Barsoum [16]	113	I. Pred, CsA (0–3 mo), MMF (from 3 mo), SRL II. Pred, CsA, MMF	None	9 mg	0–3 months: 5–10 ng/ml; 10–15 ng/ml thereafter	0–1 month: 20–50 mg/day; 1–3 months: 10–20 mg/day; 3–6 months:10 mg/day; 6–12 months:5–10 mg/day; 12–24 months 0–5 mg/day	24 months	Wound complications, lymphoceles	0	No	No
Büchler [17]	145	I. SRL, MMF, pred II: CsA, MMF, pred	ATG	15 mg for 2 days	10–15 ng/ml	Day 0: 500 mg. Day 1–7: 1 mg/kg/day; days 8–14: 0.5 mg/kg/day. From day 14 progressive decrease to complete discontinuation at end of month 5	12 months	Wound complications, lymphoceles	3	No	Yes
Flechner [22]	61	I.: SRL, MMF, pred II. CsA,, MMF, pred	Basiliximab	15 mg	0–6 months: 10–12 ng/ml; 5–10 ng/ml thereafter	500 mg/day for 3 days. Tapered from 120 mg to 30 mg by day 8, 27.5 mg by day 21 and 25 mg by day 30. Then tapered by 2.5 mg/month to 7.5 mg daily	5 years	Wound complications, lymphoceles	3	No	Yes
Martinez-Mier [36]	41	I. SRL, MMF, pred II. CsA, MMF, pred	Basiliximab if HLA match was less than three.	10 mg	0–6 months: 10–15 ng/ml; 5–10 ng/ml thereafter	Started at 1 g intraoperatively. Tapered to 20 mg/day by day 6 and 5 mg/day at 6 months	12 months	Wound complications	2	No	Yes
Dean [19]	123	I. SRL, MMF, pred II. Tac, MMF, pred	ATG	Started on day 4: 10 mg/day for 2 days	Started at 5 mg/day to target trough levels of 15–20 ng/ml during months 0–4. 10–15 ng/ml thereafter	Day 0: 500 mg. 0–1 month: 20 mg/day, from 3 months 5 mg/day	Mean 21 months	Wound complications	2	No	No
Kreis [32]	78	I. SRL, MMF (0–6 months), pred II. CsA, MMF (0–6 months), pred	None	24 mg/m^2 for days 0–3	0–2 months: 30 ng/ml, 15 ng/ml thereafter	Day 0: 500 mg. Day 1: 200 mg/day, tapered to 30 mg/day by day 7 and 10 mg/day by month 6; 6–12 months: 5–10 mg/day	12 months	Wound complications	2	No	Yes

Table 2. continued

Reference	*n*	Comparison (*n*)	mTOR-I dose			Pred maintenance dose	Study period	Outcomes	Methodological Quality		
			Induction	Loading	Maintenance				Jadad (0–5)	AC	ITT
Groth [25]	83	I. SRL, AZA, pred II: CsA, AZA, pred	None	16–24 mg/m^2/day	Started at 8–12 mg/m^2/day. Adjusted to reach 30 ng/ml during months 0–2; 15 ng/ml thereafter	Day 0: 500 mg. From day 1: 200 mg/day. Tapered to 30 mg/day by day 7 and 10 mg/day by month 6	12 months	Wound complications	3	Yes	Yes

ATG, antithymocyte globulin; MMF, mycophenolate mofetil; SLR, sirolimus; AZA, azathioprine; Tac, tacrolimus; Pred, prednisolone; AC, allocation concealment; ITT, intention to treat.

SPK transplantation

One trial evaluated wound complications in 123 SPK transplant patients receiving sirolimus together with tacrolimus versus MMF together with tacrolimus [49]. Impaired wound healing occurred in 13 patients of the sirolimus group versus 10 patients in the MMF group. There were four cases of lymphoceles in the sirolimus group versus three cases of lymphoceles in the MMF group.

Subgroup analysis: Steroid avoidance

Sandrini *et al.* [51] compared early steroid withdrawal at day 5 with late steroid withdrawal at month 6. Montagnino *et al.* [50] compared early steroid withdrawal at day 7 with continued low dose steroid use. Sandrini *et al.* found a higher incidence of wound healing complications in the late steroid withdrawal group compared with the early steroid withdrawal group (21% vs. 4%, $P = 0.02$). A pooled analysis of the two RCTs for the incidence of lymphoceles showed that patients in the early steroid withdrawal groups experienced less lymphoceles compared with the late steroid withdrawal and continued low dose steroid groups ($n = 229$; OR 0.19, CI 0.04–0.88). Heterogeneity was minimal ($I^2 = 0\%$).

Discussion

Meta-analysis of the available data showed a higher incidence of wound complications and lymphoceles after kidney transplantation and a higher incidence of wound complications after heart transplantation for immunosuppressive regimens that included mTOR inhibitors versus regimens that did not include mTOR inhibitors from the time of transplantation.

Wound complications and lymphoceles typically appear within the first few months after transplantation and thus, mTOR inhibitors should be avoided from the time of transplantation for probably 3 months to prevent such problems. However, one RCT comparing immediate introduction of everolimus with delayed introduction after 4 weeks in kidney transplantation found no differences in wound healing complications at 3 months or 12 months [52,53]. A number of RCTs have evaluated the late conversion to sirolimus at 3 months post-transplant but none of these studies report on the occurrence of wound complications or lymphoceles possibly because these problems are unlikely to occur after such time period [54–56].

As a result of its anti-inflammatory effect, steroid use can lead to poor wound healing [57]. This systematic review identified one RCT that showed a higher incidence of poor wound healing for late steroid withdrawal compared with early steroid withdrawal in

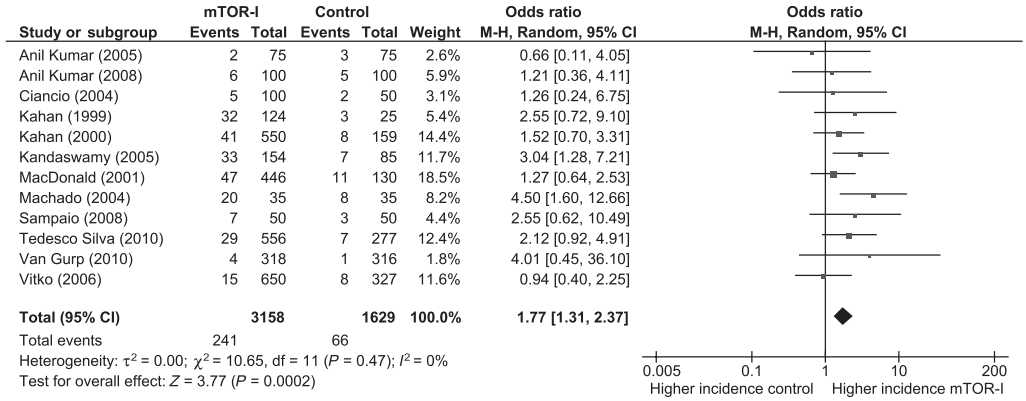

Figure 2 Forest plot indicating the odds ratio of the occurrence of wound complications in kidney transplant recipients on mTOR inhibitors plus calcineurin inhibitors.

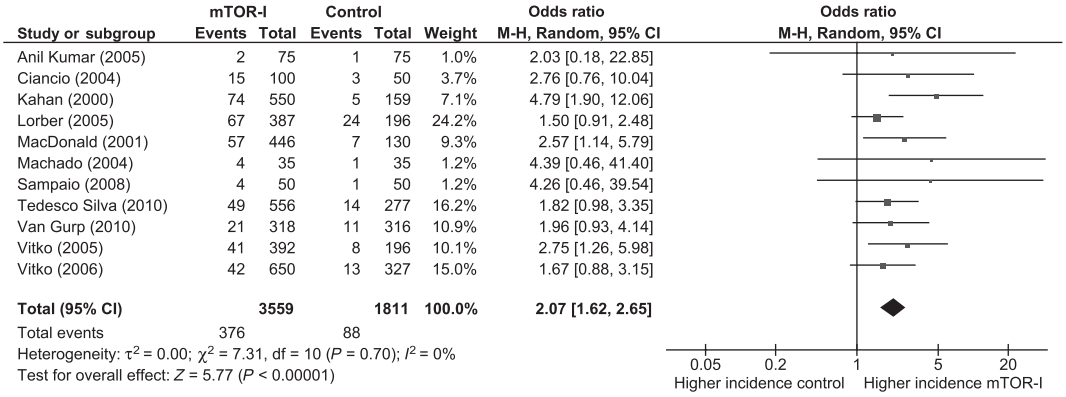

Figure 3 Forest plot indicating the odds ratio of the occurrence of lymphoceles in kidney transplant recipients on mTOR inhibitors plus calcineurin inhibitors.

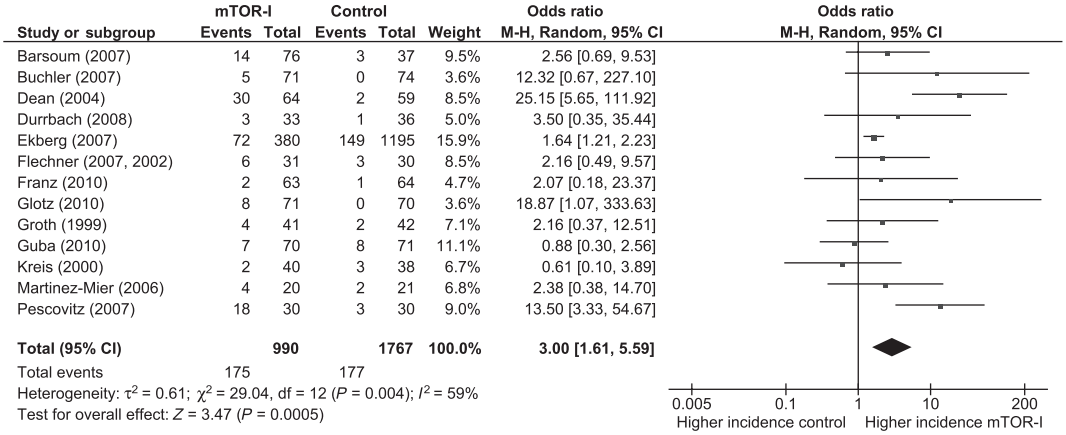

Figure 4 Forest plot indicating the odds ratio of the occurrence of wound complications in kidney transplant recipients on mTOR inhibitors plus antimetabolites.

kidney transplantation. A pooled analysis of two RCTs showed less lymphoceles for early steroid withdrawal compared with late steroid withdrawal or continued use of low dose steroids in kidney transplantation. A non-randomized study on kidney transplantation comparing sirolimus without steroids with historical controls on long-term maintenance steroids also showed a lower incidence of lymphoceles for the steroid avoidance group but no differences between groups for wound hernia or wound dehiscence [8]. However, because of insufficient level 1 evidence, we cannot draw a definitive conclusion regarding the impact of steroids on wound healing and lymphoceles.

Several studies have evaluated risk factors for impaired wound healing. Knight *et al.* [58] conducted a retrospective review of wound complications in kidney transplantation. They found that older recipient age, obesity, Caucasian race, thymoglobulin induction and cumulative use of at least 35 mg sirolimus within 4 days post-transplant were independent risk factors for wound complications, which also included lymphoceles. Flechner *et al.* [59] divided a cohort of 513 consecutive patients into three groups according to their immunosuppression. Multivariate analysis showed that body mass index (BMI) and delayed graft function were risk factors for wound complications. Tiong *et al.* [60] aimed to develop a systematic approach to reduce wound complications in sirolimus-treated kidney transplant recipients. They concluded that for wound complications or wound complications needing surgery, a BMI > 32 was the strongest independent predictor. For lymphocele formation and lymphoceles needing treatment, a BMI > 32 and acute rejection were independent risk factors. Thus, even though none of these risk factors were identified from randomized controlled trials, these studies indicate that patient characteristics could also contribute to wound complications and lymphocele formation.

In conclusion, immediate use of mTOR inhibitors leads to a higher incidence of wound complications and lymphoceles. Therefore, mTOR inhibitors should be avoided in the first few months after transplantation.

Authorship

LHMP: designed the study, rated methodological quality, extracted and analysed data and wrote the paper. LL: extracted data and rated methodological quality. PJM: designed the study, analysed data and wrote the paper.

Funding sources

No funding was received for this study.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Forest plot indicating the odds ratio of the occurrence of lymphoceles in kidney transplant recipients on mTOR inhibitors plus antimetabolites.
Figure S2 Forest plot indicating the odds ratio of the occurrence of wound complications in heart transplant recipients on mTOR inhibitors plus CNIs.
Table S1. mTOR inhibitors plus belatacept in kidney transplantation ($n = 1$).
Table S2. mTor inhibitors plus CNIs for heart transplantation ($n = 4$).
Table S3. mTOR inhibitors in liver transplantation ($n = 1$).
Table S4. mTor inhibitors in simultaneous pancreas kidney transplantation ($n = 1$).
Table S5. RCTs that investigated mTOR inhibitors combined with steroids versus no steroids in kidney transplantation ($n = 2$).
Table S6. Description of wound-related events and whether lymphoceles were reported for each RCT included in the systematic review.
Table S7. Subgroup analysis for RCTs of good methodological quality, i.e., adequate allocation concealment or a total Jadad score of at least three for RCTs in kidney transplantation. The number of trials refers to the number of RCTs that were of good methodological quality according to each of the quality criteria including the total number of patients included in the analysis.

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