Review

Safety and Efficacy of Two Different Doses of Everolimus in Kidney Transplantation

A Systematic Review and Meta-Analysis

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Introduction. The aim of this systematic review and meta-analysis was to evaluate the efficacy-related events and adverse events of 2 different doses of everolimus in kidney transplant recipients.
Materials and Methods. The Cochrane, PubMed, and Google Scholar databases were searched for randomized controlled trials published by the end of 2015 on the use of everolimus in kidney transplant recipients at doses of 1.5 mg/d and 3 mg/d. Two independent reviewers assessed the studies for quality and eligibility and extracted the data. The relative risk (RR) and 95% confidence interval (CI) for treated efficacy-related events and adverse events were collected to calculate pooled measures.
Results. A total of 8 articles describing 7 randomized controlled trials (n = 2148 participants) were included in this study. The overall RR in adverse event outcomes was significantly in favor of the lower dose of everolimus (RR, 0.96; 0.95% CI, 0.93 to 0.99; $P < .001$). The overall risk of graft loss was lower with 1.5 mg/d of everolimus (RR, 0.76; 0.95% CI, 0.59 to 0.99; $P = .04$, $I^2 = 25.0\%$). There was no relationship between the rates of efficacy failure, biopsy-proven acute rejection, death, or loss to follow up outcomes in all the three follow-up times between the two doses of everolimus.
Conclusions. The result of this systematic review and meta-analysis showed that the overall outcomes in adverse events and graft loss were better with everolimus, 1.5 mg/d, than with everolimus, 3 mg/d, when combined with other kidney transplantation medications.

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INTRODUCTION

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease.[1,2] To reduce the risk of rejection, different regimens of immunosuppressive drugs are used.[3,4] Calcineurin inhibitors are linked to nephrotoxicity, hypertension, hyperlipidemia, and new-onset diabetes mellitus.[5,6] Thus, current efforts are focused on nonnephrotoxic immunosuppressive regimens that can reduce exposure to calcineurin inhibitors, while maintaining low rates of acute rejections.[2] Everolimus is a member of the mammalian target of rapamycin inhibitor class with comparable efficacy to mycophenolate mofetil when used with corticosteroids and standard-dose cyclosporine A.[7,8] Everolimus is a mammalian target of rapamycin inhibitor that is structurally similar to sirolimus,[3,4] but with a number of important pharmacokinetic differences, including a shorter half-life and time to steady state.[6,9].

Everolimus was previously approved in Europe for use in adult kidney and heart transplant recipients and in the United States in combination with reduced-dose calcineurin inhibitors and

steroids for adult recipients at low-to-moderate risk in 2010.[9] A number of randomized controlled trials (RCTs) have investigated the efficacy and safety of different doses of everolimus in combination with other drugs for de novo kidney transplantation,[10-15] and some of these studies have claimed that using high doses of everolimus is associated with increased side effects and severe adverse events. The reason of doing this systematic review was to help clinical experts in taking best evidence-based option in this field. In this study, we evaluated the efficacy-related event and adverse events of 2 different doses of everolimus (1.5 mg/d versus 3 mg/d) when used as the primary immunosuppressive regimen for kidney transplant recipients.

MATERIALS AND METHODS

Study Design

This systematic review was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[16]

Eligibility Criteria and Study Selection

All RCTs and quasi-RCTs where drug regimens containing everolimus in 2 doses were compared in the posttransplant period in any time of follow-up were included in this analysis. There was no restriction by time and language of trial report. The intervention was everolimus in combination with any other immunosuppressive agents, at any stage of the posttransplant period. Those RCTs that compared everolimus with other drug regimens were not included. Two main groups of outcomes were assessed at all-time points after transplantation. The 1st group of outcomes was adverse events (any adverse events, any infections, anemia, hypertension, constipation, proteinuria, hypercholesterolemia, hyperlipidemia, lymphocele, viral infections, cytomegalovirus infections, fungal infections, urinary tract infection, edema, peripheral edema, hyperkalemia, diarrhea, pneumonia, malignancy, leucopenia, thrombocytopenia, acne, and diabetes mellitus) and the 2nd group was the efficacy-related events including efficacy failure, biopsy-proven acute rejection, graft loss, death, and loss to follow up. Studies were excluded if they did not evaluate adverse events and efficacy related events; presented pharmacokinetics or pharmacodynamics results; were single-arm studies; were nonrandomized controlled trials; were placebo-controlled studies; and had less than 6 months of follow-up.

Search Strategy

The PubMed, Cochrane Database, and Google Scholar were searched using related terms including "everolimus," "Certican," "Zortress," "kidney transplantation," and "renal transplantation" up to November 2015, without language restriction. We also performed a manual search of references that were included in the identified studies (Supplement Table 1). Two reviewers (MA and EH) searched databases based on the keywords. Differences over selection of articles were discussed until consensus was reached.

Selection of Studies and Data Collection

All the three phase of the study, screening of titles, abstracts, and full texts, were performed by 2 reviewers independently. Discrepancies were resolved via consultation with a 3rd researcher. After scrupulous reading of all included articles, data were extracted and collected using specially-designed hard copy and electronic forms. The Cochrane Review Manager Software, RevMan 5.3 (Winter Tree Software Inc, Ontario, Canada) was used for analysis of data. The overall adverse events and efficacy-related outcomes were collected to extract those most prevalent among them. The data were collected in terms of the number of patients who presented an explicit outcome.

Quality Assessment

The study quality was assessed by 2 reviewers independently, and any disagreements were resolved by consensus. The selected RCTs were appraised using the Cochrane Collaboration Tool,[17,18] considering the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Given the seven items for quality appraisal, a score of 3 and less was considered weak; 4 to 5, moderate; and higher than 5, good quality.

Data Synthesis and Data Analysis

Outcomes were meta-analysed if they were reported in at least two articles, within the same

treatment arm and at the same time of follow-up. Fixed effect models were employed to estimate the pooled effect sizes across studies.[19,20] The results are expressed as the pooled relative risk (RR), and 95% confidence interval (CI) were reported for dichotomous data. A *P* value less than .05 was considered significant.

To assess heterogeneity I^2 were used. Values for I^2 between zero and 25% indicated that heterogeneity might not be important; values between 25% and 50% indicated moderate inconsistency; values of 50% to 75% indicated substantial heterogeneity; and values between 75% and 100% indicated considerable inconsistency.[21,22] Publication bias was accessed with the Egger test using funnel plots. All analyses was conducted using the RevMan 5.3. The result of single-arm trials combined with two-arm trials in this field were considered subject of another study to be published separately.

RESULTS

Study Characteristics

A PRISMA flow diagram describing the literature screening process and the reasons for exclusion is shown in Figure 1. A total of 663 citations identified by the databases search, and 32 additional articles were identified from other sources. Twenty-seven articles were excluded in full-text screening phase because of study designed other than RCT, not providing enough data, or ineligible intervention and outcomes.[4,6,8,10-12,14,20,23-41] Finally, 8 articles from 7 studies met the inclusion criteria.[42-49] Two articles were different reports of different follow-up time from the same RCT.[46,47] The characteristics of the included studies are detailed in Table 1. All studies were in English language. Six RCTs were multicenter studies, with the number of centers ranging from 2 to 44 and 1 RCT was single center. The follow-up time of the included studies were different from 6 to 36 months. A total of 2148 participants were included in these RCTs (1051 receiving everolimus, 1.5 mg/d, and 1097 receiving everolimus, 3 mg/d). The majority of the studies had been conducted in European countries. A total of 23 adverse events and 5 efficacy-related events were reported in these 8 articles. Seven studies had declared sponsorship or support by Novartis Pharmaceuticals.

Quality of Included Studies

Of 8 RCTs, 3 were assessed as having a good quality, 4 moderate quality, and 1 weak quality (37.5%, 50%, and 12.5% respectively). All of the RCTs reported adequate sequence generation and most RCTs did not report the allocation concealment clearly (75%). Risk of bias graph and risk of bias summary are shown in Figures 2 and 3, respectively. Publication bias was not likely to have much effect on the results because the studies were evenly distributed symmetrically on both sides of the RR for posttransplant adverse events (Figure 4).

Outcomes

All 8 articles reported some adverse events and efficacy-related events. We collected all adverse

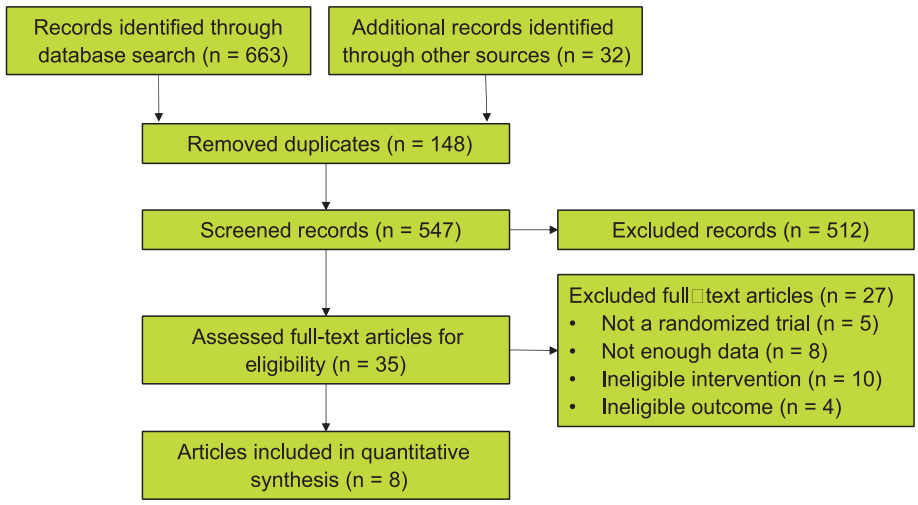

Figure 1. The PRISMA Flow diagram of literature search process.

Table 1. Characteristics of Included Studies

Study	Sites	Follow-up, mo	Other Medications		Number of Participants		Quality (Score)
			Everolimus 1.5 mg/d	Everolimus 3 mg/d	Everolimus 1.5 mg/d	Everolimus 3 mg/d	
Lorber et al[42] 2005	Multicenter	12, 36	Steroids Cyclosporine Prednisone	Steroids Cyclosporine Prednisone	193	194	Good (6)
Salvadori et al[44] 2009	Single-center	6, 12	Cyclosporine Basiliximab Methylprednisolone Prednisone	Cyclosporine Basiliximab Methylprednisolone Prednisone	143	142	Weak (3)
Silva Jr et al[45] 2010	Multicenter	12	RD-Cyclosporine Corticosteroid Basiliximab	RD-Cyclosporine Corticosteroid Basiliximab	277	279	Moderate (4)
Vitko et al[46] 2005	Multicenter	36	Cyclosporine Prednisone Corticosteroid	Cyclosporine Prednisone Corticosteroid	194	198	Good (6)
Pascual et al[43] 2010	Multicenter	6	TAK Corticosteroid Methylprednisolone Prednisone	TAK Corticosteroid Methylprednisolone Prednisone	15	20	Moderate (4)
Vítko et al[47] 2004	Multicenter	6, 12	Cyclosporine Prednisone Corticosteroid	Cyclosporine Prednisone Corticosteroid	194	198	Good (7)
Curtis et al[48] 2001	Multicenter	6	Without Basiliximab	With Basiliximab	117	139	Moderate (4)
Vítko et al[49] 2001	Multicenter	6	Without Basiliximab	With Basiliximab	112	125	Moderate (5)

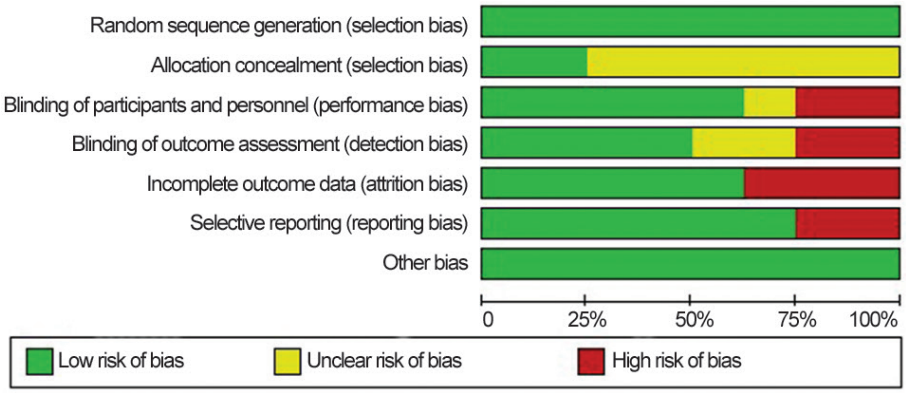

Figure 2. Risk of bias.

events and efficacy-related events that reported in the included studies, and the most prevalent events were included in the meta-analysis. The adverse events reported in these studies included any adverse events, any infections, anemia, hypertension, constipation, proteinuria, hypercholesterolemia, hyperlipidemia, lymphocele, viral infections, cytomegalovirus infections, fungal infections, urinary tract infection, edema, peripheral edema, hyperkalemia, diarrhea, pneumonia, malignancy, leucopenia, thrombocytopenia, acne, and diabetes mellitus. The efficacy-related events reported in these studies included efficacy failure, biopsy-proven acute rejection, graft loss, death, and loss to follow-up. Most reported adverse events in these studies were anemia, lymphocele and cytomegalovirus infections in 7 studies; hypertension, constipation, and urinary tract infections in 6 studies; and diarrhea in 4 studies. The comparable events in each study were classified for data analysis (Supplement Tables 2 and 3). Efficacy-related events meta-analysis were prepared in three subgroups for 3 follow-up durations (6, 12, and 36 months).

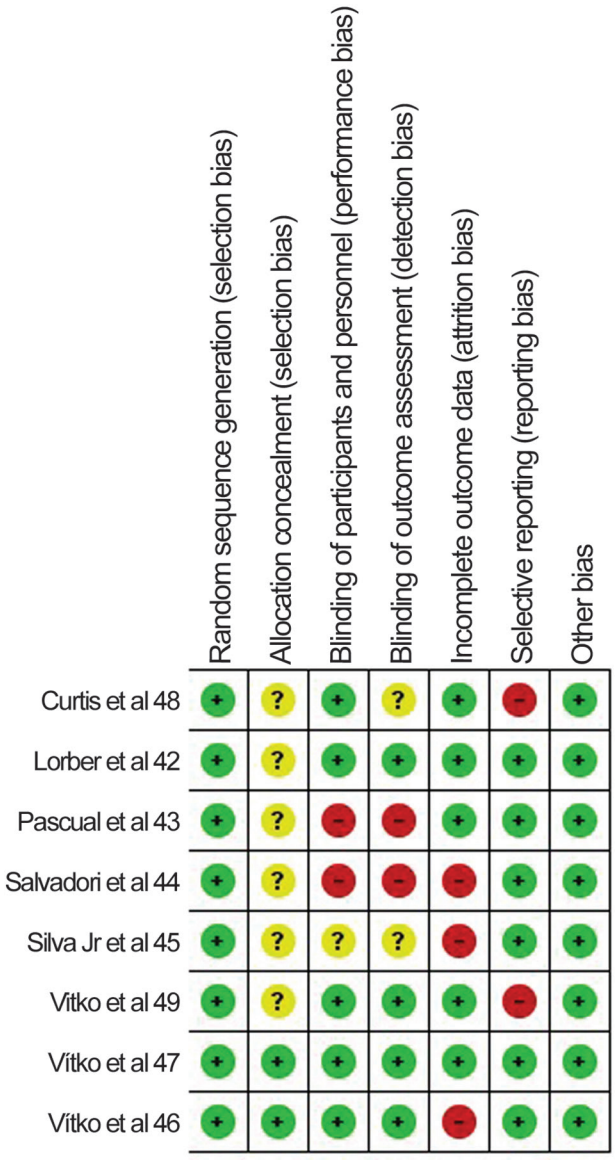

Figure 3. Risk of bias summary.

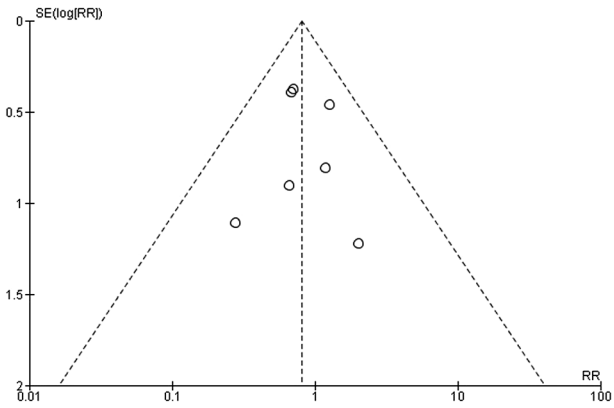

Figure 4. Funnel plot with cytomegalovirus infections. SE indicates standard error and RR, relative risk.

Adverse Events

All 8 articles that compared 1.5 mg/d and 3 mg/d of everolimus were included in this analysis. Every one of articles reported adverse events data related to everolimus in the two different doses. The numbers of studies reporting each adverse event were different because not all trials provided a complete report about everolimus adverse events. Heterogeneity was substantial for constipation and moderate for proteinuria, lymphocele, and leukopenia with I^2 varying between 32% and 56% (Table 2).

The pooled results indicated that everolimus 3, mg/d, was associated with an increased risk for anemia, viral infections, and diabetes mellitus, and the other outcomes had no statistical significance in the pooled results. This association was significant in favor of everolimus, 1.5 mg/d, at pooled analysis for overall adverse events. The risk of overall adverse event was reduced in the 1.5-mg/d regimen (n = 2148; RR, 0.96; 95% CI, 0.93 to 0.99; $P < .001$), but substantial heterogeneity was observed ($I^2 = 68\%$; Table 2). However, sensitivity analysis confirmed stability in this set of outcomes. The results of 7 studies were meta-analyzed and are displayed in Table 2 and Figure 5.

Efficacy-related Events

All 7 RCTs that compared 1.5 mg/d and 3 mg/d of everolimus were included in this analysis. Not all trials provided a complete report about everolimus efficacy-related events during a same time of follow-up. Three studies reported efficacy-related events only for 6 months of follow-up. Two studies reported it for 6 and 12 months of follow-up, 1 study reported events after 12 months, 1 study reported events after 36 months, and 1 study reported events after 12 to 36 months. For these events we use subgroup analysis. Meta-analysis conducted for 5 efficacy-related events in 3 durations of follow-up (6, 12, and 36 months after transplant). Only in 1 efficacy-related event, graft loss, there was a significant difference between the two doses of everolimus within 6 months of follow-up data (Figure 6). Subgroup analysis demonstrated that everolimus, 1.5 mg/d, significantly decreased graft loss (RR, 0.76; 0.95% CI, 0.59 to 0.99; $P = .04$, $I^2 = 25.0\%$; Figure 6). The pooled data for all 4 remaining events were not significantly different between the two doses of

Table 2. Meta-analysis Result of Adverse Events Reported by Studies Comparing Everolimus at 1.5 mg/d Versus 3 mg/d

Adverse Event	Number of Trials	Other Medications		Risk Factor	95% Confidence Interval	*P*	I2 (%)
		Everolimus 1.5 mg/d	Everolimus 1.5 mg/d				
Anemia	7	1230	1275	0.86	0.77 to 0.96	.009	0
Hypertension	6	1036	1077	0.98	0.85 to 1.13	.79	0
Constipation	6	1036	1077	1.01	0.82 to 1.23	.87	56
Proteinuria	2	470	473	0.89	0.64 to 1.23	.47	46
Hypercholesterolemia	3	530	534	1.02	0.84 to 1.25	.81	0
Hyperlipidemia	3	664	671	0.97	0.80 to 1.17	.74	0
Lymphocele	7	1051	1097	0.87	0.70 to 1.10	.24	43
Viral infections	2	388	396	0.66	0.47 to 0.92	.01	0
CMV infections	7	1230	1275	0.80	0.53 to 1.21	.29	0
Fungal infections	2	388	396	0.78	0.50 to 1.20	.26	0
Urinary tract infections	6	857	899	1.12	0.96 to 1.30	.15	0
Edema	2	387	392	1.01	0.80 to 1.28	.92	0
Peripheral edema	4	807	813	1.07	0.94 to 1.21	.31	0
Hyperkalemia	2	470	473	0.89	0.68 to 1.16	.38	0
Any adverse effect	7	1051	1097	1.00	0.97 to 1.02	.84	0
Any infections	6	858	889	0.95	0.88 to 1.02	.19	0
Diarrhea	5	759	784	1.07	0.88 to 1.30	.48	18
Pneumonia	3	372	392	0.71	0.29 to 1.71	.44	0
Malignancy	3	423	448	0.96	0.44 to 2.07	.91	0
Leucopenia	3	423	448	0.71	0.45 to 1.11	.13	32
Thrombocytopenia	3	423	448	0.71	0.45 to 1.13	.15	0
Acne	3	422	444	1.02	0.73 to 1.41	.92	0
Diabetes mellitus	3	614	619	0.52	0.34 to 0.82	.004	0
Overall	7	1051	1097	0.96	0.93 to 0.99	< .001	68

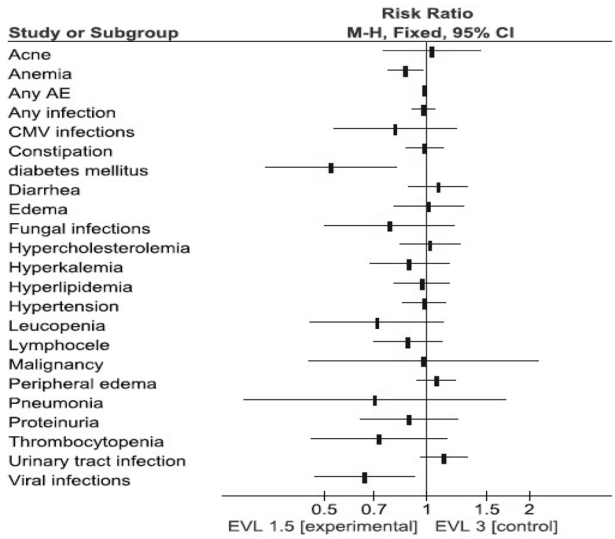

Figure 5. Meta-analysis of randomized controlled trials comparing the adverse effect events of everolimus at 2 different doses (1.5 mg/d versus 3 mg/d) at 3 follow-up times.

everolimus (Figures 7 to 10). A subgroup analysis by follow-up time showed that different periods of follow-up made no difference to efficacy-related outcomes.

DISCUSSION

Nowadays, immunosuppressive therapy for kidney transplantation is focused on regimens with calcineurin inhibitor minimization or elimination that can promote long-term graft function without increasing rejection rates.[3] Everolimus shows synergistic immunosuppressive activity with calcineurin inhibitor and may permit calcineurin inhibitor reduction,[7] then considering optimal doses of this drug is very important to support evidence for better decision making in terms of immunosuppressive therapy. Accordingly, we conducted this systematic review and meta-analysis to describe the impact of everolimus-based regimens on kidney transplant recipients.

Two different doses of everolimus were evaluated and compared in this meta-analysis. Evaluating the adverse events of immunosuppressive drugs in kidney transplantation because of use of concurrent multiple drug therapy is difficult.[50] Based on the formal parameters mentioned in the Cochrane Handbook,[17,18] the quality of the majority of studies was good and only 1 study

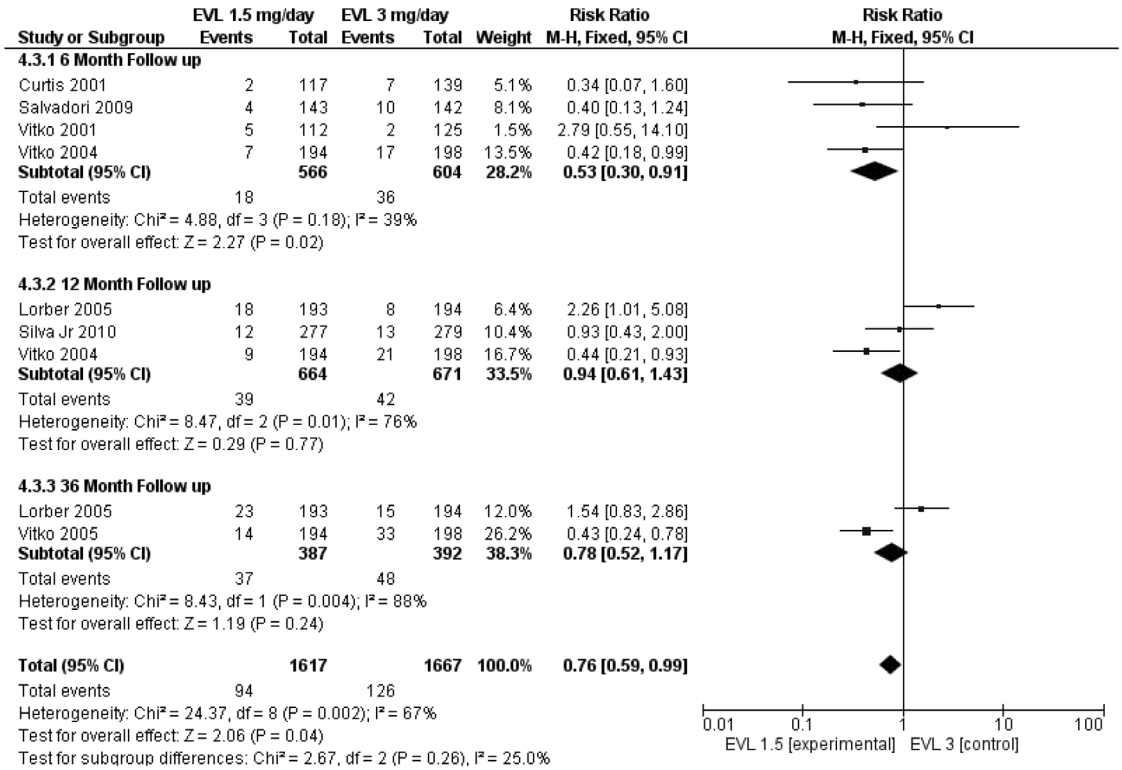

Figure 6. Meta-analysis of randomized controlled trials comparing the overall graft loss of everolimus at 2 different doses (1.5 mg/d versus 3 mg/d) at 3 follow-up times.

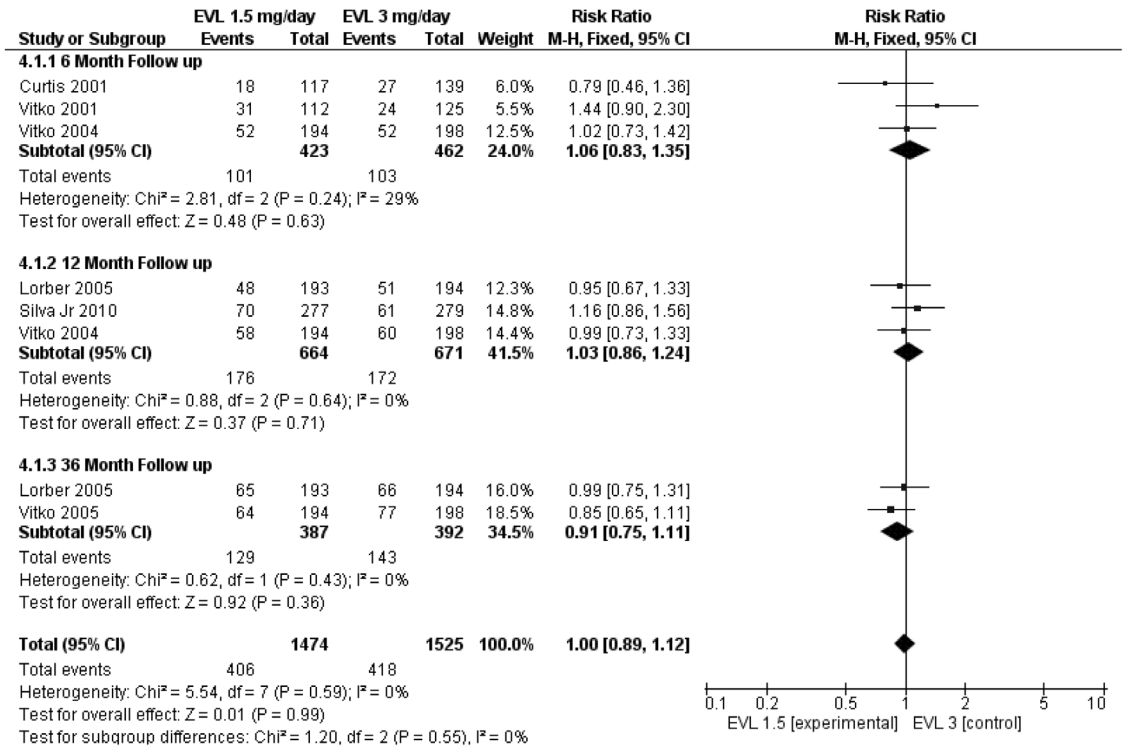

Figure 7. Meta-analysis of randomized controlled trials comparing the overall efficacy failure of everolimus at 2 different doses (1.5 mg/d versus 3 mg/d) at 3 follow-up times.

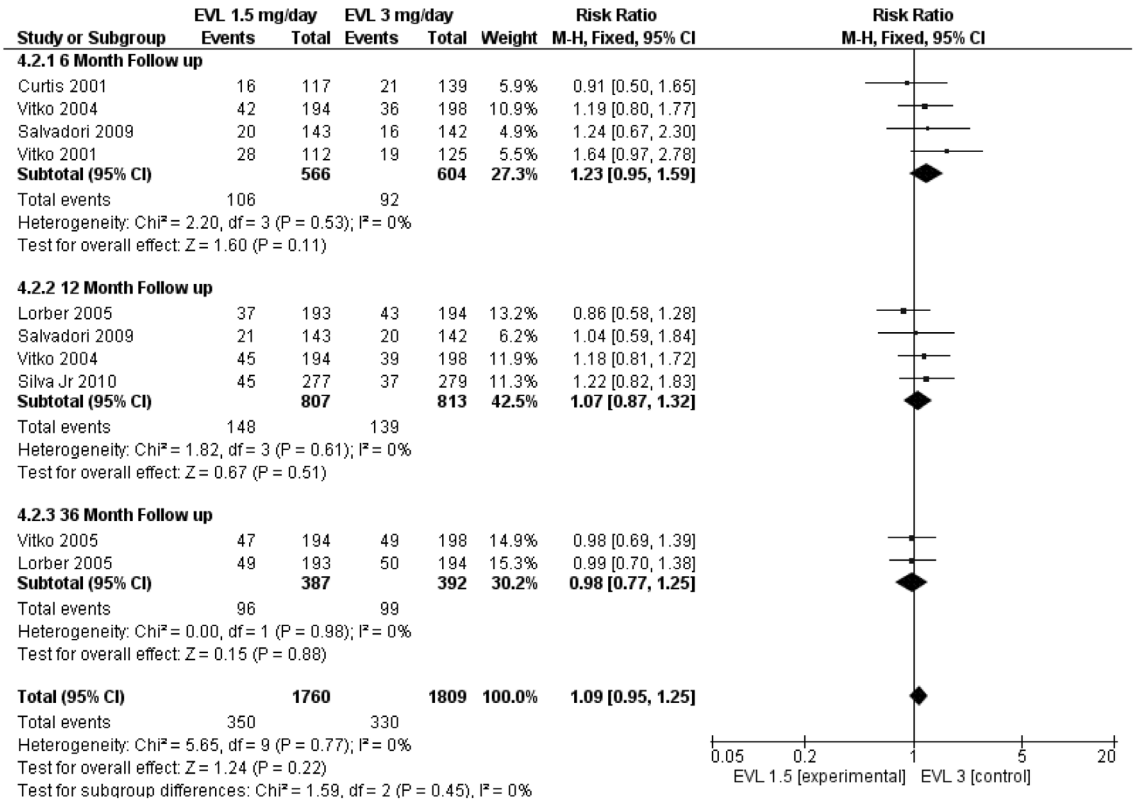

Figure 8. Meta-analysis of randomized controlled trials comparing the overall biopsy-proven acute rejection of everolimus at 2 different doses (1.5 mg/d versus 3 mg/d) at 3 follow-up times.

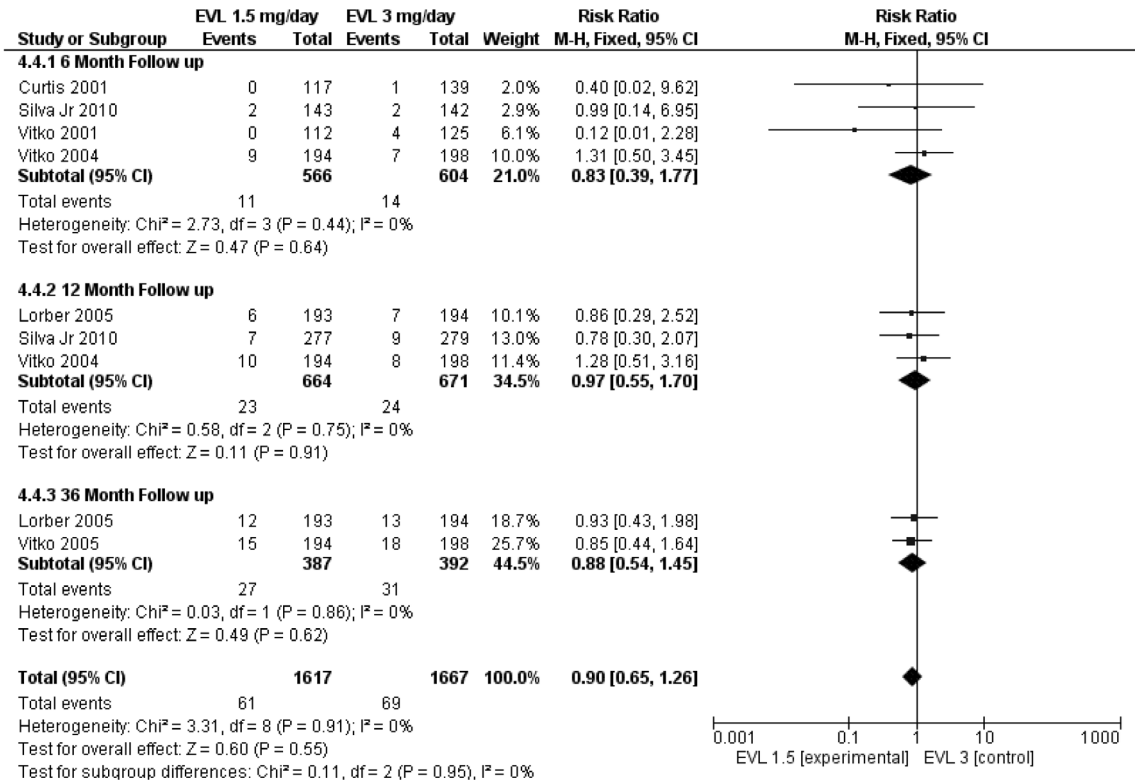

Figure 9. Meta-analysis of randomized controlled trials comparing the overall death of everolimus at 2 different doses (1.5 mg/d versus 3 mg/d) at 3 follow-up times.

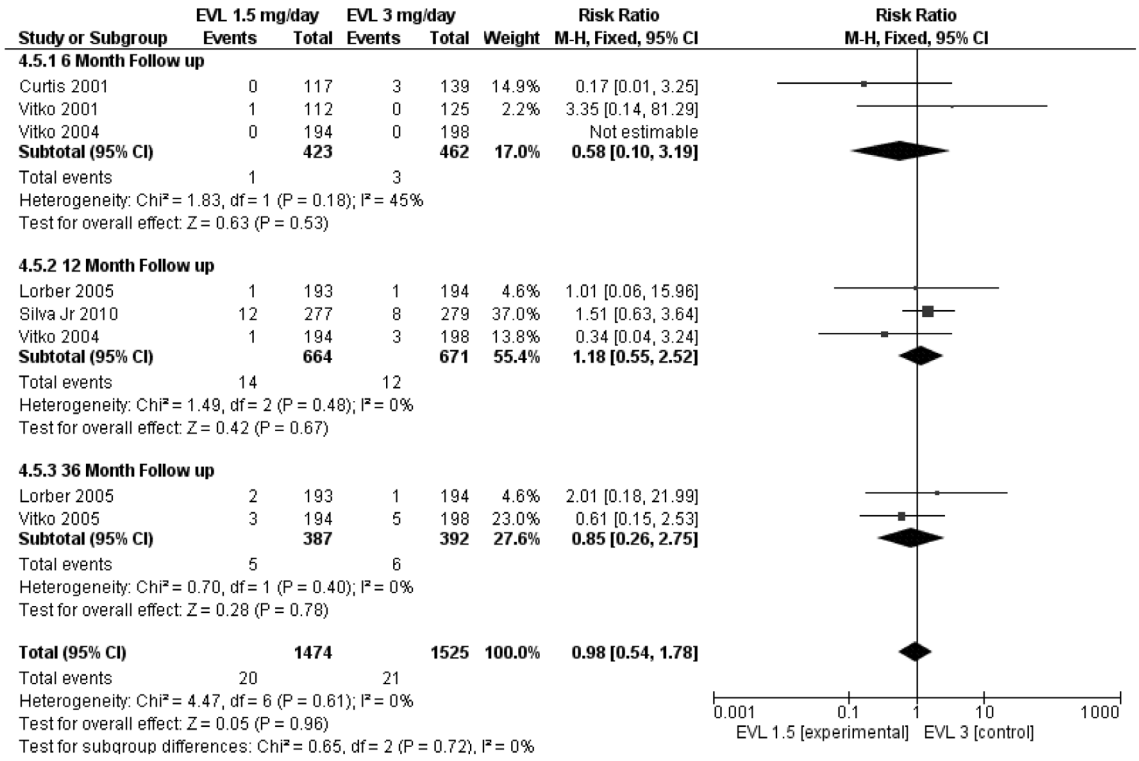

Figure 10. Meta-analysis of randomized controlled trials comparing the overall loss to follow up of everolimus at 2 different doses (1.5 mg/d versus 3 mg/d) at 3 follow-up times.

revealed a high risk of bias.[44] Some studies had a lack of sufficient information to judge allocation concealment, detection bias, and performance bias. Overall, the heterogeneity of efficacy-related event and adverse event results was low, representing small inter-study variability.

Our results suggested that 1.5 mg/d of everolimus regimens were associated with significantly decreased incidence of adverse events, and also, significantly decreased graft loss as one of the most important efficacy-related outcomes over a short follow-up period of 6 months or longer follow-up durations (12 and 36 months). There was a reduced risk of viral infections and anemia with 1.5 mg/d of everolimus, with a comparable risk of other adverse events. In addition, 1.5 mg/d of everolimus-based regimens were associated with a lower risk of diabetes mellitus as compared to patients on a 3-mg/d dose.

Some limitations of the data should be taken into account when using the results from the present meta-analysis. The definition of adverse events varied between the included studies from which the data were pooled, and all events were self-reported by the individual centers. Consequently, the reported frequencies of the adverse events are possibly biased. Although, a reporting bias would not be projected to be different between the everolimus, 1.5 mg/d, and everolimus, 3 mg/d, within each of the studies. On the other hand, the number of RCTs that reported the efficacy-related events after 36 months of follow-up was very low—only 2 studies—and the analysis in this period of time may be not valuable.

CONCLUSIONS

This meta-analysis demonstrated that using 1.5 mg/d of everolimus in combination therapy was associated with significantly decreased graft loss without any differences in efficacy failure, biopsy-proven acute rejection, death, or loss to follow-up. There was a reduced risk of viral infections, anemia, and diabetes mellitus with 1.5 mg/d of everolimus. With respect to good safety and efficacy of everolimus in a low dose (1.5 mg/d) and as well as the low cost,[51-53] (better cost-effectiveness), use of everolimus in the lower dose may be a good option in terms of best decision making for treatment in kidney transplant recipients.

CONFLICT OF INTEREST

None declared.

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