Systematic Review and Meta-Analysis

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Alemtuzumab versus antithymocyte globulin induction therapies in kidney transplantation patients

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Alemtuzumab (ALEM) is widely used as an induction therapy for organ transplantation, and numerous randomized controlled trials (RCTs) have been published to evaluate its efficacy and safety in kidney transplantation as compared with antithymocyte globulin (ATG). The purpose of this study was to compare the benefits and safety of ALEM with those of ATG for induction therapy.

A systematic literature search in three electronic databases, including PubMed, EmBase, and Cochrane Library, since inception through October 2016, was conducted to identify potential RCTs for inclusion. Trials that investigated the risk of biopsy-proven acute rejection (BPAR), mortality, graft failure, delayed graft function (DGF), chronic allograft nephropathy (CAN), infections, cytomegalovirus (CMV) infections, new-onset diabetes mellitus after transplant (NODAT), and granulocyte colony stimulation factor (GCSF) use in kidney transplant recipients who received ALEM or ATG as an induction therapy were included. Relative risk (RR) and 95% confidence intervals (CIs) were calculated using a random-effects model.

Six RCTs involving 446 kidney transplantation patients were included in this meta-analysis. The effects of ALEM therapy were not significantly different from those of ATG therapy, including the incidence of BPAR (RR: 0.77; 95% CI: 0.51–1.18; $P = .229$), mortality (RR: 0.64; 95% CI: 0.30–1.39; $P = .263$), graft failure (RR: 0.81; 95% CI: 0.49–1.33; $P = .411$), DGF (RR: 1.00; 95% CI: 0.60–1.67; $P = .999$), CAN (RR: 1.42; 95% CI: 0.44–4.57; $P = .556$), infections (RR: 1.00; 95% CI: 0.74–1.35; $P = .989$), CMV infections (RR: 0.70; 95% CI: 0.38–1.30; $P = .263$), NODAT (RR: 0.50; 95% CI: 0.18–1.36; $P = .174$), and GCSF use (RR: 1.16; 95% CI: 0.81–1.66; $P = .413$). Sensitivity analyses were consistent with the overall analysis for all effects except CAN, suggesting that the risk of CAN might be higher with ALEM therapy than ATG therapy (RR: 2.45; 95% CI: 1.02–5.94; $P = .046$).

The findings of this study suggest that the beneficial effects of ALEM therapy are greater than those of ATG therapy in kidney transplantation patients; however, the effects were not statistically significant because of the limited number of trials. Further large-scale RCTs are needed to verify the treatment effects of ALEM.

Abbreviations: ALEM = alemtuzumab, ATG = antithymocyte globulin, BPAR = biopsy-proven acute rejection, CAN = chronic allograft nephropathy, CIs = confidence intervals, CMV = cytomegalovirus, DGF = delayed graft function, ESRD = end-stage renal disease, GCSF = granulocyte colony stimulation factor, NODAT = new-onset diabetes mellitus after transplant, rATG = rabbit antithymocyte globulin, RCTs = randomized controlled trials.

Keywords: alemtuzumab, antithymocyte globulin, kidney transplantation

1. Introduction

End-stage renal disease (ESRD) is characterized by a long-term irreversible decline in kidney function that requires renal replacement therapy. Chronic kidney disease progresses to ESRD over the course of 5.5 years in the United Kingdom.[1] Currently, kidney transplantation is the treatment of choice to improve survival and quality of life of ESRD patients.[2,3] However, major clinical concerns including acute kidney rejection and graft loss[4] have been noted; further, immunosuppressive therapy is necessary to reduce the risk of kidney rejection and to prolong survival of the graft.[5,6]

Previous studies have illustrated induction therapy, both intraoperatively and immediately postoperatively, to be associated with lower overall doses of maintenance immunosuppressive regimens.[7,8] Currently, the main types of induction therapy include alemtuzuman (ALEM), rabbit antithymocyte globulin (rATG), basiliximab, and conventional immunosuppressive agents containing cyclosporine, mycophenolate, and methyl prednisolone that are always combined with other therapy regimens.[9–12] In low-risk patients, Oliaei et al[11] found that the combination of rATG with conventional agents is associated with a lower incidence of posttransplantation problems such as signs of rejection, rise of creatinine, graft losses, and delayed graft function. Further, the rate

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of acute rejection in low-risk patients receiving ALEM was lower than in patients receiving rATG; however, no significant differences were observed between ALEM and rATG in high-risk patients.[13] Consequently, the inconsistent results regarding the treatment effects in patients receiving ALEM and rATG require verification. Therefore, we attempted a comprehensive examination of the available RCTs to determine the efficacy and safety of ALEM versus ATG in kidney transplantation patients.

2. Methods

2.1. Data sources, search strategy, and selection criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Checklist S1).[14]

The ethical approval and written consent are not necessary for the meta-analysis, because the data of meta-analysis are collected from published literature.

Any RCT that evaluated the efficacy and safety of ALEM versus ATG was eligible for inclusion in this meta-analysis. Further, language and publication status were not restricted. Three electronic databases, including PubMed, EmBase, and the Cochrane Library were searched through October 2016. Core keywords included ("alemtuzumab" OR "campath" OR "mab-campath" OR "lemtrada") AND "antithymocyte globulin" AND "kidney transplant." Ongoing RCTs that have been completed but are not published were also identified from the Meta-register of Controlled Trials and the http://clinicaltrials.gov/website. We also conducted manual searches of reference lists from all relevant original and review articles to identify additional eligible studies.

The literature search was independently undertaken by two authors using a standardized approach. Any inconsistencies between the results obtained by these two authors were settled by the corresponding author until a consensus was reached. The meta-analysis was restricted to RCTs as observational studies are susceptible to confounding factors. Studies were eligible for inclusion if the following criteria were met: (1) patients underwent kidney transplantation; (2) the study had an RCT design; (3) patients received ALEM or ATG therapy; and (4) at least one of the following outcomes were reported: biopsy-proven acute rejection (BPAR), mortality, graft failure, delayed graft function (DGF), chronic allograft nephropathy (CAN), infections, cytomegalovirus (CMV) infections, new-onset diabetes mellitus after transplant (NODAT), and granulocyte colony stimulation factor (GCSF) use. Exclusion criteria were as follows: (1) studies that studied patients with diseases other than ESRD, (2) studies that included patients with inappropriate disease control, (3) studies without an RCT design, and (4) studies in which the data could not be extracted.

2.2. Data collection and quality assessment

A standardized protocol was adopted by two authors to extract all the data from included trials. The collected data included the first author's name, publication year, country, sample size, mean age of recipient, percentage of male patients, history of diabetes, percentage of retransplant patients, immunologic risk, percentage of CMV infections, mean age of donor, interventions, controls, and the duration of follow-up periods. The Jadad scale, which is quite comprehensive and has been partially validated for evaluating the quality of RCTs in meta-analyses, was employed to assess methodological quality.[15] The Jadad scale is based on randomization, blinding, allocation concealment, withdrawals and dropouts, and use of intention-to-treat analysis; scores range from 0 to 5.

2.3. Statistical analysis

The results of individual RCTs were considered dichotomy data; relative risks (RRs) and 95% confidence intervals (CIs) from each study were calculated from events and nonevents in each group. The summary RRs and 95% CIs for ALEM versus ATG were calculated using a random-effects model.[16,17] Furthermore, RRs with 95% CIs were calculated for BPAR, mortality, graft failure, DGF, CAN, infections, CMV infections, NODAT, and GCSF use. Heterogeneity between studies was investigated using the Q statistic, and we considered $P < .10$ as indicative of significant heterogeneity.[18,19] We performed sensitivity analyses by removing each individual study from the meta-analysis.[20] Subgroup analyses were performed for BPAR based on sample size, percentage of males, immunologic risk, percentage of cytomegalovirus cases, ALEM doses, and control. Egger[21] and Begg[22] tests were also used to statistically assess publication bias for interesting outcomes. All reported P values are two-sided, and $P < .05$ were considered statistically significant for all included studies. Statistical analyses were performed using STATA software (version 12.0; Stata Corporation, College Station, TX).

3. Results

3.1. Literature search

Results of the study selection process are shown in Figure 1. We identified 258 articles in our initial electronic search, of which 244 were excluded after duplicates and irrelevant studies were identified. Fourteen potentially eligible studies were chosen. After detailed evaluations, 6 RCTs were selected for the final meta-analysis.[13,23–27] A manual search of the reference lists from these studies did not yield any new eligible studies. The general characteristics of the included studies are presented in Table 1.[13,23–27]

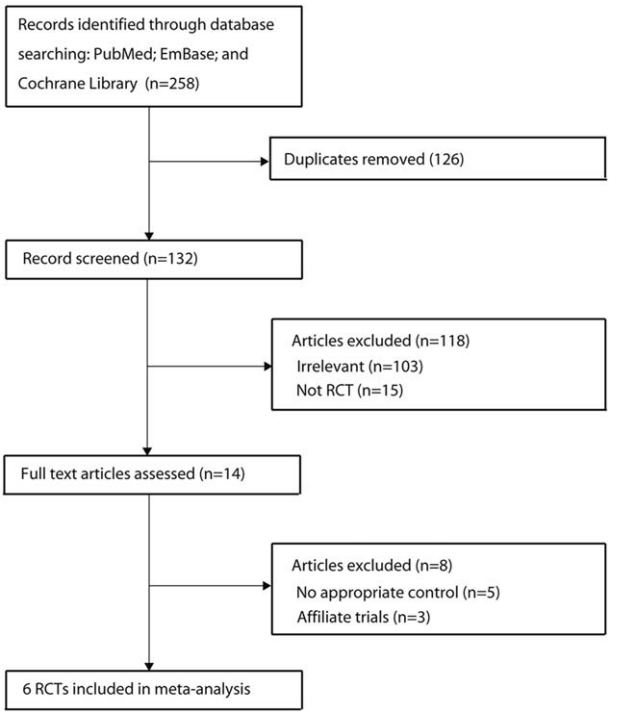

Figure 1. Study selection process.

Table 1

Baseline characteristics of studies included in the systematic review and meta-analysis.[13,23–27]

Study	Publication year	Country	Sample size	Mean age (yr)	Percentage male (%)	History of diabetes (%)	Retransplant (%)	Immunologic risk	Cytomegalovirus (%)	Donor age (yr)	Intervention (induction)	Intervention (maintenance)	Control (induction)	Control (maintenance)	Duration of follow up (yr)	Jadad score
Thomas[23]	2007	US	19	45.02	42.11	NA	52.63	High	94.74	NA	ALEM (30 mg)	Tacrolimus	Thymoglobulin (1.5 mg/kg), with	Tacrolimus, mycophenolate, and steroids	1.0	1
Farney[27]	2009	US	180	49.94	58.11	44.14	10.36	High and low	22.52	41.47	ALEM (30 mg)	Tacrolimus/cyclosporin, mycophenolate mofetil, mycophenolic acid and steroids	rATG (1.5 mg/kg, 3–7 total doses)	Tacrolimus/cyclosporin, mycophenolate mofetil, mycophenolic acid and steroids	2.0	2
Ciancio[24]	2010	US	26	42.25	73.08	7.70	NA	High and low	NA	NA	ALEM (0.3 mg/kg)	Methylprednis olone	Thymoglobulin (1 mg/kg/d)	Methylprednis olone	3.0	2
Ciancio[25]	2008	US	60	49.75	63.33	25.00	NA	High and low	NA	34.65	ALEM (0.3 mg/kg)	Methylprednisolone	Thymoglobulin (1 mg/kg/d)	Methylprednisolone	2.0	2
Lu[26]	2011	China	22	39.95	40.91	NA	50.00	High	86.36	NA	ALEM (15 mg) and another dosage of ALEM (15 mg)	Acetaminophen, diphenhydramine, and 40 mg methylprednisolone	rATG (9.0 mg/kg)	Methylprednisolone	1.0	1
Hanaway[13]	2011	US	139	46.59	54.68	NA	17.27	High	23.74	35.29	ALEM (30 mg)	Tacrolimus, mycophenolate mofetil, mycophenolic acid and steroids	rATG in four intravenous doses of 1.5 mg/kg, given on day 0, day 1, and day 2, as well as either day 3 or day 4.	Tacrolimus, mycophenolate mofetil, mycophenolic acid and steroids	3.0	3

ALEM = alemtuzumab, rATG = rabbit antithymocyte globulin.

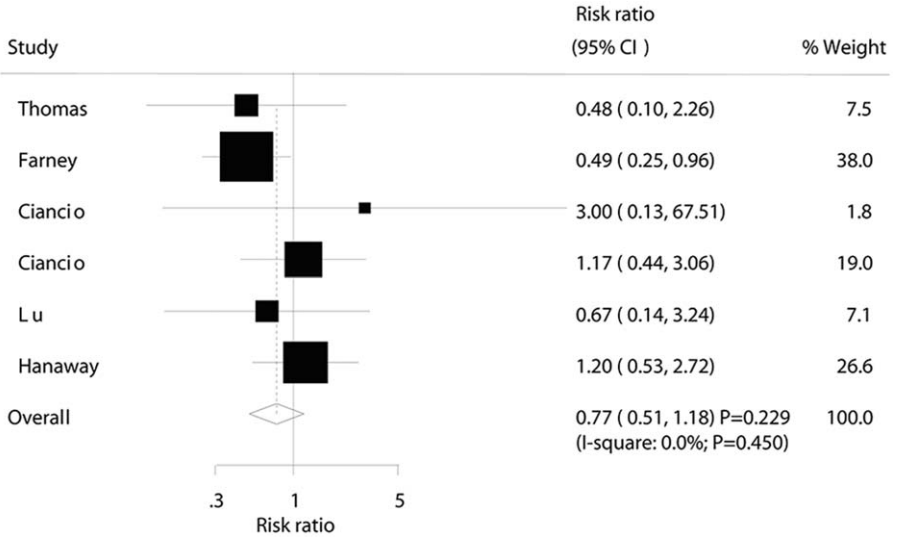

Figure 2. Forest plot of ALEM versus ATG on BPAR.

3.2. Study characteristics

The meta-analysis includes 6 trials with a total of 446 kidney transplantation patients. The follow up for patients was 1.0 to 3.0 years, with 19 to 180 patients included in each trial. Five studies were conducted in the United States,[13,23–25,27] and the remaining 1 study was conducted in China.[26] The mean recipient age ranged from 39.95 to 49.94 years, and the percentage of male patients ranged from 40.91% to 73.08%. Three trials included patients at high immunologic risk,[13,23,26] one trial included both high and low immunologic risk patients,[27] and the remaining two trials did not provide recipient characteristics.[24,25] The quality of studies was evaluated by the Jadad scale; 1,[13] 3,[24,25,27] and the remaining 2[23,26] had scores of 3, 2, and 1, respectively.

3.3. Summary of results

Data relating the effects of ALEM versus ATG on BPAR were collected from 6 trials. The summary RRs indicate the risk of BPAR was reduced by 23% in patients receiving ALEM; however, this result did not reach statistical significance (RR: 0.77; 95% CI: 0.51–1.18; $P=.229$; Fig. 2). Further, no heterogeneity was observed among the included trials ($I^2=0.0\%$; $P=.450$). Sensitivity analyses were performed to evaluate the influence of individual trials and confirmed that the study outcomes were not affected by the exclusion of any specific trial (Table 2). Subgroup analysis for BPAR was performed, and ALEM had little or no significant effect on BPAR in the various populations (Table 3).

The number of trials with information available for mortality and graft failure was 6 and 5, respectively. The pooled results for mortality and graft failure indicate no significant differences between outcomes for ALEM and ATG therapy (mortality: RR, 0.64, 95% CI: 0.30–1.39, $P=.263$; graft failure: RR, 0.81, 95% CI: 0.49–1.33, $P=.411$; Fig. 3). There was no heterogeneity across the trials included in the study (mortality: $I^2=0.0\%$, $P=.634$; graft failure: $I^2=0.0\%$, $P=.616$). The results of the sensitivity analyses were consistent with the overall analysis (Table 2).

The number of trials with information available for DGR and CAN was 5 and 3, respectively. No significant differences in DGF and CAN were observed between patients treated with ALEM and ATG (DGF: RR, 1.00, 95% CI: 0.60–1.67, $P=.999$; CAN: RR, 1.42, 95% CI: 0.44–4.57, $P=.556$; Fig. 4). Substantial heterogeneity was observed for CAN ($I^2=73.7\%$; $P=.022$), whereas no evidence of heterogeneity was noted for DGF ($I^2=0.0\%$; $P=.514$). The results of sensitivity analyses for DGF were consistent with the overall analysis. However, based on the sensitivity analysis for CAN, we excluded the study by Farney et al,[27] which included patients undergoing renal and pancreas transplantation; this may have affected the incidence rate of CAN in each group. After this exclusion, we concluded that the risk of CAN is 145% higher in patients receiving ALEM therapy than that of patients receiving ATG therapy (RR: 2.45; 95% CI: 1.02–5.94; $P=.046$; with no evidence of heterogeneity; Table 2).

The number of trials with information available for infections and CMV was 6 and 3, respectively. The summary RRs suggest little or no significant effects on the risk of infection (RR: 1.00; 95% CI: 0.74–1.35; $P=.989$; Fig. 5) or CMV infections (RR: 0.70; 95% CI: 0.38–1.30; $P=.263$; Fig. 5) in patients receiving ALEM. Unimportant heterogeneity was detected for infections and CMV infections (infections: $I^2=25.4\%$, $P=.243$; CMV infections: $I^2=10.2\%$, $P=.328$), and results from the sensitivity analyses were consistent with the overall analysis (Table 2).

The number of trials with information available for NODAT and GCSF use was 3 and 2, respectively. We noted ALEM was not associated with the incidence of NODAT (RR: 0.50; 95% CI: 0.18–1.36; $P=.174$; Fig. 6) or GCSF use (RR: 1.16; 95% CI: 0.81–1.66; $P=.413$; Fig. 6). Heterogeneity was not detected across included trials for NODAT and GCSF use, and results of the sensitivity analyses were consistent with the corresponding overall analysis (Table 2).

3.4. Publication bias

The Egger[21] and Begg[22] test results are presented in Table 4. We noted no evidence of publication bias for BPAR, mortality, graft failure, DGF, CAN, CMV infections, and NODAT. Although the Egger[21] test showed no evidence of publication bias for infections ($P=.147$), the Begg[22] test showed potential evidence of publication bias ($P=.060$). The conclusions were not

Table 2

Sensitivity analyses.

Outcomes	Excluding study	RR and 95% CI	*P*	Heterogeneity (%)	*P* for heterogeneity
BPAR	Thomas	0.81 (0.51–1.30)	.390	8.0	.361
	Farney	1.03 (0.60–1.75)	.924	0.0	.759
	Ciancio	0.75 (0.49–1.15)	.191	0.0	.408
	Ciancio	0.70 (0.44–1.12)	.137	0.0	.425
	Lu	0.80 (0.49–1.31)	.372	14.7	.320
	Hanaway	0.66 (0.40–1.07)	.094	0.0	.529
Death	Thomas	0.68 (0.31–1.52)	.353	0.0	.549
	Farney	0.58 (0.22–1.53)	.269	0.0	.507
	Ciancio	0.58 (0.26–1.29)	.182	0.0	.654
	Ciancio	0.55 (0.22–1.35)	.193	0.0	.562
	Lu	0.66 (0.29–1.51)	.331	0.0	.495
	Hanaway	0.80 (0.35–1.83)	.595	0.0	.828
Graft failure	Thomas	0.85 (0.51–1.41)	.523	0.0	.545
	Farney	0.72 (0.37–1.40)	.333	0.0	.498
	Ciancio	0.71 (0.41–1.23)	.217	0.0	.718
	Lu	0.83 (0.50–1.38)	.480	0.0	.480
	Hanaway	0.95 (0.53–1.71)	.872	0.0	.653
DGF	Farney	0.84 (0.34–2.08)	.702	1.9	.383
	Ciancio	1.05 (0.63–1.76)	.850	0.0	.557
	Ciancio	1.08 (0.63–1.85)	.780	0.0	.478
	Lu	1.04 (0.62–1.75)	.887	0.0	.410
	Hanaway	0.89 (0.51–1.55)	.687	0.0	.543
CAN	Farney	2.45 (1.02–5.94)	.046	0.0	.442
	Ciancio	1.12 (0.35–3.62)	.850	81.4	.020
	Ciancio	1.40 (0.16–12.59)	.764	62.1	.104
Infection	Thomas	0.93 (0.83–1.05)	.263	0.0	.774
	Farney	1.21 (0.68–2.17)	.516	33.8	.196
	Ciancio	0.97 (0.73–1.28)	.822	24.0	.261
	Ciancio	1.05 (0.70–1.56)	.825	40.2	.153
	Lu	1.00 (0.70–1.42)	.999	36.2	.180
	Hanaway	1.25 (0.71–2.21)	.437	45.4	.119
CMV infection	Farney	1.08 (0.46–2.56)	.855	0.0	.582
	Ciancio	0.66 (0.33–1.31)	.233	27.7	.240
	Hanaway	0.63 (0.21–1.84)	.394	21.9	.258
NODMAT	Ciancio	0.56 (0.18–1.74)	.317	0.0	.816
	Ciancio	0.50 (0.13–1.94)	.315	0.0	.630
	Hanaway	0.44 (0.13–1.48)	.184	0.0	.759
GCSF use	Farney	1.31 (0.48–3.59)	.594	–	–
	Hanaway	1.14 (0.78–1.67)	.501	–	–

BPAR = biopsy-proven acute rejection, CAN = chronic allograft nephropathy, CMV = cytomegalovirus, DGF = delayed graft function, ESRD = end-stage renal disease, GCSF = granulocyte colony stimulation factor, NODAT = new-onset diabetes mellitus after transplant.

Table 3

Subgroup analysis for BPAR.

Fctors	Subsets	RR and 95% CI	*P*	Heterogeneity (I^2)	*P* for heterogeneity
Sample size	≥100	0.74 (0.31–1.78)	.506	63.6	.097
	<100	0.91 (0.45–1.85)	.797	0.0	.657
Percentage male	≥50.0	0.86 (0.48–1.54)	.613	29.5	.235
	<50.0	0.57 (0.19–1.71)	.314	0.0	.768
Immunologic risk	High	0.92 (0.48–1.78)	.805	0.0	.540
	High and low	0.76 (0.35–1.64)	.485	32.9	.225
Percentage of cytomegalovirus	≥80.0	0.57 (0.19–1.71)	.314	0.0	.768
	<80.0	0.74 (0.31–1.78)	.506	63.6	.097
ALEM doses	30 mg	0.69 (0.36–1.30)	.249	32.3	.228
	15 mg or 0.3 mg/kg	1.08 (0.49–2.39)	.855	0.0	.673
Control	rATG	0.72 (0.39–1.33)	.290	27.3	.253
	Thymoglobulin	0.99 (0.44–2.19)	.972	0.0	.490

ALEM = alemtuzumab, CI = confidence interval, rATG = rabbit antithymocyte globulin, RR.

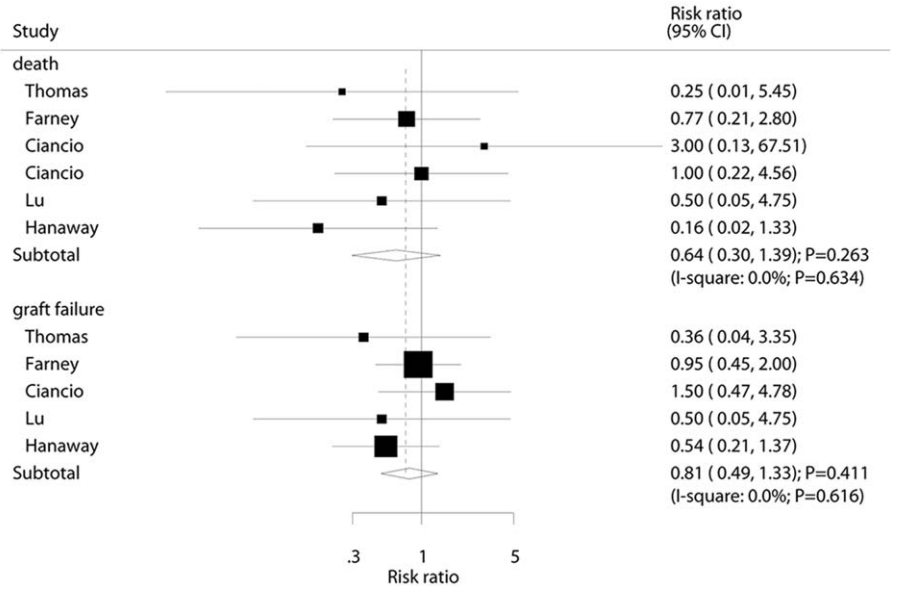

Figure 3. Forest plots of ALEM versus ATG on mortality and graft failure.

changed after adjusting for publication bias using the trim and fill method.[28]

4. Discussion

This meta-analysis was based on RCTs and we evaluated the potential efficacy and safety of ALEM versus ATG in treatment of kidney transplantation patients. Our study included 446 patients from six RCTs across a broad range of populations. The findings suggest no significant differences between ALEM and ATG for BPAR, mortality, graft failure, DGF, CAN, infections, CMV infections, NODAT, and GCSF use. Sensitivity analyses indicated that ALEM might increase the risk of CAN; however, future large-scale RCTs are needed to verity this result.

A previous meta-analysis suggested that the risk of BPAR is significantly lower in patients receiving ALEM induction therapy than those receiving interleukin-2 receptor antibodies, whereas similar effects were observed for BPAR, graft loss, DGF, and mortality between patients receiving ALEM and rATG therapy.[29] Zhang et al[30] indicated that ALEM induction therapy for kidney transplantation patients is superior to traditional antibody therapy for preventing acute rejection; however, in patients at high immunologic risk, no statistically significant differences were observed. Further, the authors indicated no significant differences for graft survival and patient survival rates. Finally, Hao et al[31] conducted a meta-analysis comparing the efficacy and safety of ALEM, ATG, and daclizumab for induction therapy in organ transplantation patients, suggesting that ALEM

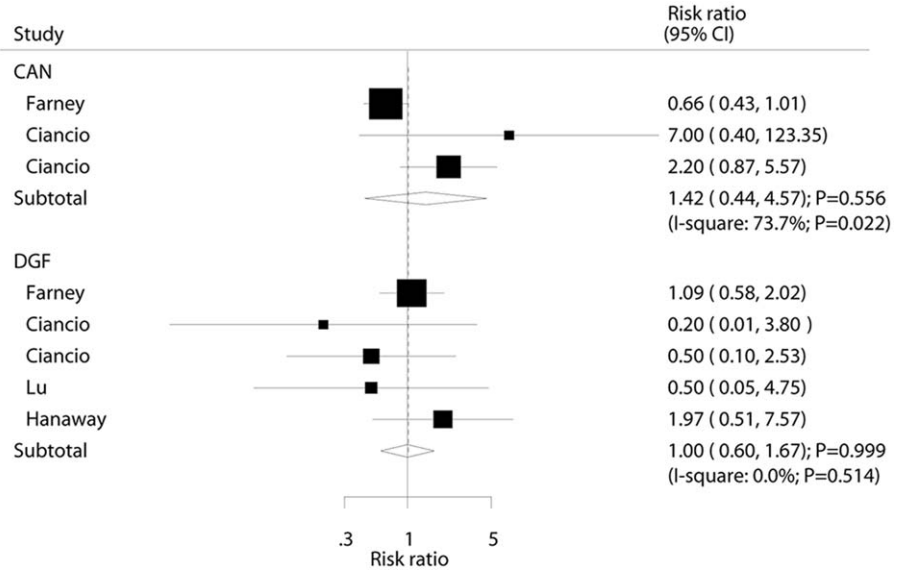

Figure 4. Forest plots of ALEM versus ATG on DGR and CAN.

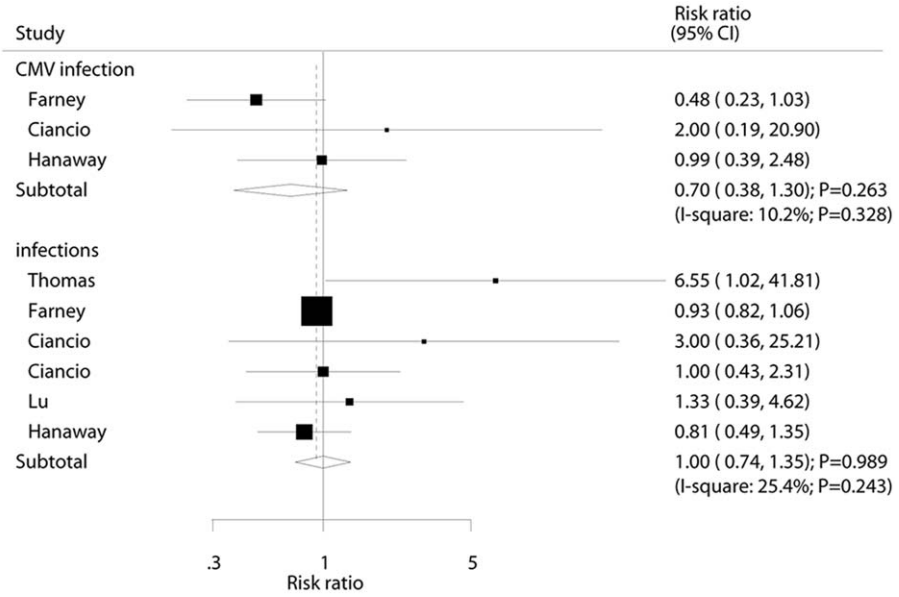

Figure 5. Forest plots of ALEM versus ATG on infections and CMV.

and daclizumab are as effective as ATG for induction therapy in kidney transplantation after 24 months. Further, the risk of infection was significantly lower after 36 months in patients receiving ALEM than those receiving ATG. The studies by Zhang et al[30] and Hao et al[31] did not directly compare the efficacy and safety of ALEM and ATG, which is an inherent limitation of the data. Further, the potential influence of a single trial in the meta-analysis by Morgan et al was not evaluated.[29] Finally, because of the small number of trials included in this study, event rates were lower than expected. Consequently, although the summary results were consistent, no statistically significant differences between ALEM and ATG were noted. Therefore, we performed a meta-analysis based on RCTs to evaluate the treatment effects of ALEM versus ATG in kidney transplantation patients.

There were no significant differences in the risk of BPAR between ALEM and ATG. However, the study conducted by Farney et al[27] reported inconsistent results, suggesting that ALEM significantly reduces the risk of BPAR with similar adverse events to those observed for rATG induction therapies. These results are likely attributable to the large sample size, which allowed higher statistical power to detect small differences between ALEM and ATG. Further, the number of patients at low immunologic risk included in this study may have contributed to this significant difference.[13] In addition, the results of individual trials were consistent with the overall analysis of other outcomes, likely attributable to the sample size being smaller than expected; further, these trials were designed to evaluate BPAR or renal function levels as the primary endpoint. Hence, clinically

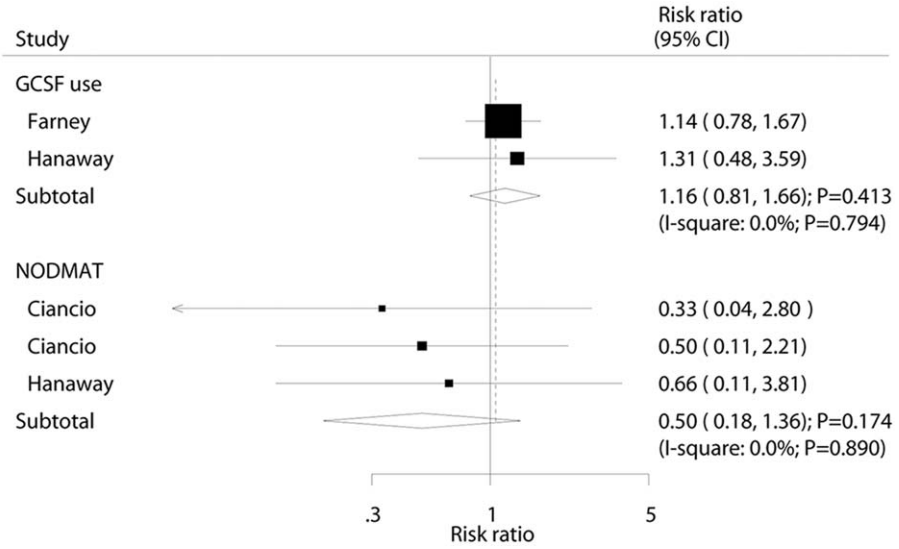

Figure 6. Forest plots of ALEM versus ATG on NODAT and GCSF.

Table 4

Publication bias.[21,22]

Outcomes	*P* for Egger[21]	*P* for Begg[22]
BPAR	.556	1.000
Death	.711	1.000
Graft failure	.508	1.000
DGF	.276	.221
CAN	.295	1.000
Infection	.147	.060
CMV infection	.439	1.000
NODMAT	.636	1.000

significant differences in individual trials were not found, and the summary results for these outcomes may be unreliable because of low statistical power. Finally, subgroup analysis revealed ALEM had no significant effect on BPAR in any subpopulations, possibly because of the small number of trials included in each subset. Therefore, the summary results provide relative results and a synthetic review.

There are several limitations of this study. First, the number of included trials was small and event rates were low. Therefore, stratified analyses not detecting significant differences might be because of the low statistical power. Second, publication bias might exist. In this study, 5 of the included trials were conducted in the United States and only 1 in China. The treatment effects might be a trend in US patients. Third, several important characteristics and individual data were not available, which restricted our ability to perform a more detailed relevant analysis. Fourth, although stratification based on induction therapy doses and control drugs have already conducted, the impact of maintenance therapies could not be ruled out, and might affect the treatment effect of different induction therapies. Finally, in the planning stages, we intend to evaluate the changes of CMV prophylaxis among the included trials; such results were not available in the above trials.

In conclusion, the findings of this study indicate there are no significant differences between ALEM and ATG for the outcomes of BPAR, mortality, graft failure, DGF, CAN, infections, CMV infections, NODAT, and GCSF use. Future large-scale trials should be conducted to verify the treatment of ALEM in kidney transplantation, and a network meta-analysis should be conducted to summarize the direct and indirect comparisons of the best treatment regimens.

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