Tacrolimus Versus Cyclosporine Microemulsion for Heart Transplant Recipients: A Meta-analysis

Fan Ye, MD,[a] Xiao Ying-Bin, MD,[a] Weng Yu-Guo, MD,[b] and Roland Hetzer, MD[b]

Background: Tacrolimus and cyclosporine microemulsion are the 2 major immunosuppressants for heart transplantation. Several studies have compared these 2 drugs, but the outcomes were not consistent. This meta-analysis of randomized controlled trials compared the beneficial and harmful effects of tacrolimus and microemulsion cyclosporine for heart transplant recipients.

Methods: Electronic databases and manual bibliography searches were conducted. A meta-analysis was performed of all randomized controlled trials comparing tacrolimus with cyclosporine microemulsion as primary immunosuppression for heart transplant recipients. Data for mortality, acute rejection, withdrawals, and adverse events were extracted. The combined results of the data of the randomized controlled trials were summarized as relative risk with 95% confidence intervals.

Results: The study assessed 7 randomized controlled trials including 885 patients. There was no difference in mortality at 1 year between recipients treated with tacrolimus and cyclosporine microemulsion. Tacrolimus-treated patients had less acute rejection risk at 6 months and 1 year. Fewer patients stopped tacrolimus than cyclosporine microemulsion. The rate of new-onset diabetes mellitus requiring insulin treatment was higher with tacrolimus. More post-transplantation hypertension occurred with cyclosporine microemulsion. The groups had comparable incidences of malignancy and renal failure needing dialysis.

Conclusions: The use of tacrolimus as primary immunosuppressant for heart transplant recipients results in comparable survival and a significant reduction in acute rejection compared with cyclosporine microemulsion. J Heart Lung Transplant 2009;28:58–66.

Heart transplantation is an effective therapy for patients with end-stage heart disease and severe heart failure. The 10-year survival rate of heart transplant recipients is about 50% according to data from the International Society for Heart and Lung Transplantation (ISHLT).[1] 1 After the first heart transplantation in 1967, however, the procedure was discontinued in most centers for several decades because of sub-optimal immunosuppressive regimens. The introduction of cyclosporine into cardiac transplantation in the 1980s led to dramatic improvement in patients' outcomes and greatly increased the number of heart transplantations worldwide.

New immunosuppressants made much greater advancement in improving survival and reducing side effects. Tacrolimus, another calcineurin inhibitor, emerged as an alternative to cyclosporine during the early 1990s. Since the middle of the last decade, the original oil-based formulation of cyclosporine had been largely replaced by a microemulsion formulation (Neoral, Novartis Pharmaceutical Corp, East Hanover, NJ) that improved absorption characteristics and had less variable pharmacokinetics. In recent years, tacrolimus and cyclosporine microemulsion have become 2 major immunosuppressants for heart transplant recipients.

Several randomized controlled trials (RCTs) recently compared the efficacy and harmful effects of tacrolimus vs microemulsion cyclosporine, but these RCTs did not come to identical conclusions. Meta-analyses of cyclosporine vs tacrolimus for kidney and liver transplant patients have been performed, but few systematic reviews have compared these drugs for cardiac transplant patients.[2–4] The objective of this study was to systematically review RCTs in which tacrolimus was compared with cyclosporine microemulsion as the primary immunosuppressant for heart transplant recipients.

MATERIALS AND METHODS

Identification and Selection of Studies

Relevant studies were identified and selected by searching the databases, Medline (1966–June 2008), Embase (1980–June 2008), Cochrane Controlled Trials Register (Cochrane Library Issue 2, 2008), and PUBMED (up-

From the [a]Department of Cardiothoracic and Vascular Surgery, Chongqing Xinqiao Hospital, Third Military Medical University, Chongqing, China; and [b]Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin, Berlin, Germany.

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Reprint requests: Dr Xiao Ying-Bin, Third Military Medical University, [a]Department of Cardiothoracic and Vascular Surgery, Chongqing 86, China. Telephone: 008-623-687-74607. Fax: 008-623-687-55304. E-mail: xiao_ying_bin@yahoo.com.cn

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dated to June 2008) using the search words "tacrolimus" or "FK506," "heart" or "cardiac" as well as "randomized controlled trial" (a much wider search was also done using the words "tacrolimus" or "FK506" as well as "heart" or "cardiac," and the same RCTs that fulfilled the including criteria were found). Bibliographies in relevant articles and conference proceedings were scanned. No limitation on language, date, or patients' race or age was imposed. Authors were also contacted for supplemental data when important information was missing.

The selection criteria were:

1. RCTs;
2. trials comparing tacrolimus vs cyclosporine microemulsion as initial immunosuppressive therapy in patients undergoing heart transplantation;
3. the trials should report at least 1 of the outcomes needed;
4. a given patient population was used only once; if the same population appeared in other publications, the article that provided the most complete follow-up data was selected;
5. any trial in which participants received other solid organs in addition to a heart transplantation was excluded.

Data Extraction

Data were independently abstracted from each study with a pre-designed review form, and disagreement was resolved by consensus. Data were extracted on study characteristics, patient clinical characteristics and demographics, doses of drugs used, concomitant medications and duration of follow-up; primary outcomes including mortality at 1 year, and acute rejection at 6 months and 1 year (proven by endomyocardial biopsy or any treated rejections); additional outcomes including withdrawal of tacrolimus or cyclosporine microemulsion, new-onset diabetes requiring insulin therapy, post-transplant hypertension, malignancy (all kinds of malignant tumor), renal failure needing dialysis, and other adverse events.

Quality of Methodology

The quality of each fully published trial was assessed by the Jadad score (Table 1).[5] Any disagreement was resolved by consensus. The overall quality score was based on the number of criteria met (score range, 2–10).

Statistical Methods

The data analysis was performed using the fixed-effect model or the random-effect model (Mantel-Haenszel) with RevMan 5 software (Cochrane Collaboration). Results were expressed as relative risk (RR) with the 95% confidence interval (CI), with values of less than 1 favoring tacrolimus. The relative risk for each clinical event was considered as significant if $p \leq 0.05$ (2-sided). Heterogeneity between trials was tested by using the Cochran chi-square and I^2 tests, with $p \leq 0.1$ or $I^2 \geq 50\%$ indicating significant heterogeneity.[6] The RR for each clinical event was pooled with a fixed-effect model. If the tests for heterogeneity were significant, the analysis was also redone with a random-effect model. Publication bias was assessed using funnel plots.

Table 1. Methodologic Quality Assessment (Jadad score)

Generation of allocation sequence	
2	Computer-generated random numbers
1	Not described
Allocation concealment	
3	Central randomization
2	Sealed envelopes or similar
1	Not described or inadequate
Investigator blindness	
2	Identical placebo tablets or similar
1	Inadequate or not described
0	No double-blinding
Description of withdrawals and drop-outs	
1	Numbers and reasons are described
0	Numbers and reasons are not described
Efficacy of randomization	
2	Pre-treatment variables in tabular form
1	Balance of pre-treatment variables mentioned but not in tabular form
0	No information reported

RESULTS

Description of the Selected Studies

The search strategy generated 229 studies. From these, 22 RCTs were identified comparing tacrolimus with cyclosporine as the primary immunosuppressant in heart transplantation.[7–28] Only 7 RCTs fulfilled the criteria for consideration in the meta-analysis.[7–13] All included studies were published as peer-reviewed articles and were in English.

The meta-analysis involved 885 patients: 505 were randomized to tacrolimus and 380 to the cyclosporine microemulsion (Table 2). Two studies were multicenter trials,[11,12] and the 5 remaining studies were conducted at a single center.[7–10,13] In 5 trials the recipients were all adults, whereas the other 2 studies included children.[10,13] The daily dose of tacrolimus was 0.03 to 0.3 mg/kg, and the dose of cyclosporine microemulsion was 3 to 10 mg/kg. All studies used trough-level monitoring to guide cyclosporine microemulsion and tacrolimus dosing. The

Table 2. Baseline Characteristics of Trials Included in the Meta-analysis

Study/Year	No. taking Tac/CyA	Patient group	Dose, mg/kg/day		Concomitant medication	Definition of acute rejection	Duration, months
			Tac	mCyA			
Mhera,[7] 2002	41/22	Adults	NR	NR	Steroid, MMF	Rejection requiring treatment	12
Meiser,[8] 2004	30/30	Adults	0.03–0.1	3–8	Steroid, MMF	Grade ≥ II or grade IB requiring treatment	24
Wang,[9] 2004	11/10	Adults	0.15	6	Steroid, Aza	Grade ≥ 1B	6
Pollock-Barziv,[10] 2005	14/12	Children	0.1–0.3	6–10	Steroid, Aza	Grade ≥ 3A	15
Grimm,[11] 2006	157/157	Adults	0.075	4–6	Steroid, Aza	Grade ≥ 3A at 6 months Grade ≥ 1B at 1 year	18
Kobashigawa,[12] 2006	219/115	Adults	4–8 (mg/day)	6–10	Steroid, MMF, SRL	Grade ≥ 3A or hemodynamic compromise requiring treatment	12
Kobashigawa,[13] 2006	33/34	Adults, Children	NR	NR	Steroid, Aza	Grade ≥ 3A or treated rejection	60

Aza = azathioprine; mCyA = cyclosporine microemulsion; MMF = mycophenolate mofetil; NR = not reported; SRL= sirolimus; Tac = tacrolimus.

initial targeted concentration of tacrolimus was 10 to 20 ng/ml, and the initial concentration of cyclosporine microemulsion was 200 to 400 ng/ml. In 1 study the dosages for 3 treatment groups were tacrolimus + mycophenolate mofetil (MMF), tacrolimus + sirolimus, and cyclosporine microemulsion + MMF.[12] The other 6 trials all used the same baseline immunosuppression in both tacrolimus and cyclosporine microemulsion arms (MMF, azathioprine). Induction therapies were also comparable between these 2 groups. Definition of acute rejection varied among these trials but was the same within trials (Table 2).

Trial Quality

The method of randomization and allocation concealment was unclear or inadequate for most trials, except in 1 study that used central randomization.[11] No trials were blinded. All 7 RCTs had complete follow-up. Intention-to-treat analysis was explicitly stated in 3 studies.[11–13] Withdrawals and dropouts were clearly described in 6 studies.[8–13] All RCTs illustrated the efficacy of randomization by pre-treatment variables in tabular form except 1, in which the efficacy of randomization was mentioned but not in tabular form.[9] The total Jadad scores ranged from 4 to 8.

Outcomes

No statistical heterogeneity was evident among the studies, and only the fixed-effect model was used. The exception was the result of acute rejection at 1 year, which showed significant heterogeneity, and the random-effect model was used (Figures 1 and 2). The difference in mortality at 1 year between recipients treated with tacrolimus and cyclosporine microemulsion was not statistically significant (RR, 0.70; 95% CI, 0.45–1.08; $p = 0.11$). In our analysis, acute rejection risk was lower in tacrolimus-treated recipients at 6 months (RR, 0.61; 95% CI, 0.49–0.75; $p < 0.00001$) and 1 year (RR, 0.69; 95% CI, 0.48–0.98; $p = 0.04$). More patients stopped taking cyclosporine microemulsion than tacrolimus (RR, 0.57; 95% CI, 0.40–0.83; $p = 0.003$). A significant difference was noted in the incidence of new-onset diabetes mellitus requiring insulin treatment in the 2 groups that favored cyclosporine microemulsion (RR, 1.65; 95% CI, 1.18–2.29; $p = 0.003$). Fewer tacrolimus-treated patients had post-transplantation hypertension compared with the cyclosporine microemulsion patients (RR, 0.88; 95% CI, 0.81–0.96; $p = 0.004$). The 2 groups had comparable incidences of malignancy (RR, 0.64; 95% CI, 0.31–1.32; $p = 0.23$) and renal failure needing dialysis (RR, 1.68; 95% CI, 0.81–3.52; $p = 0.17$). A sensitivity analysis was conducted by using both random- and fixed-effects models and practically the same outcomes were found, except the result of the risk of new-onset diabetes mellitus, which showed no difference between tacrolimus and cyclosporine microemulsion when under the random-effect model (RR, 1.49; 95% CI, 0.78–2.84; $p = 0.22$). Analysis by funnel plot showed no significant publication bias.

Sensitivity and Sub-group Analysis

A sensitivity analysis included the studies of adults and excluding 2 studies that included children. No outcomes of this analysis were significantly changed after those 2 studies were excluded. A sensitivity analysis was done that only included the larger-sized studies (total number of patients ≥ 50). Two trials were excluded for their small sizes of 21 and 26 patients.[9,10] The outcomes of our analysis were not significantly altered by exclusion of those studies.

Because a confirmed observation time spot for withdrawals or adverse events was not set, another sensitivity analysis was performed that only included the

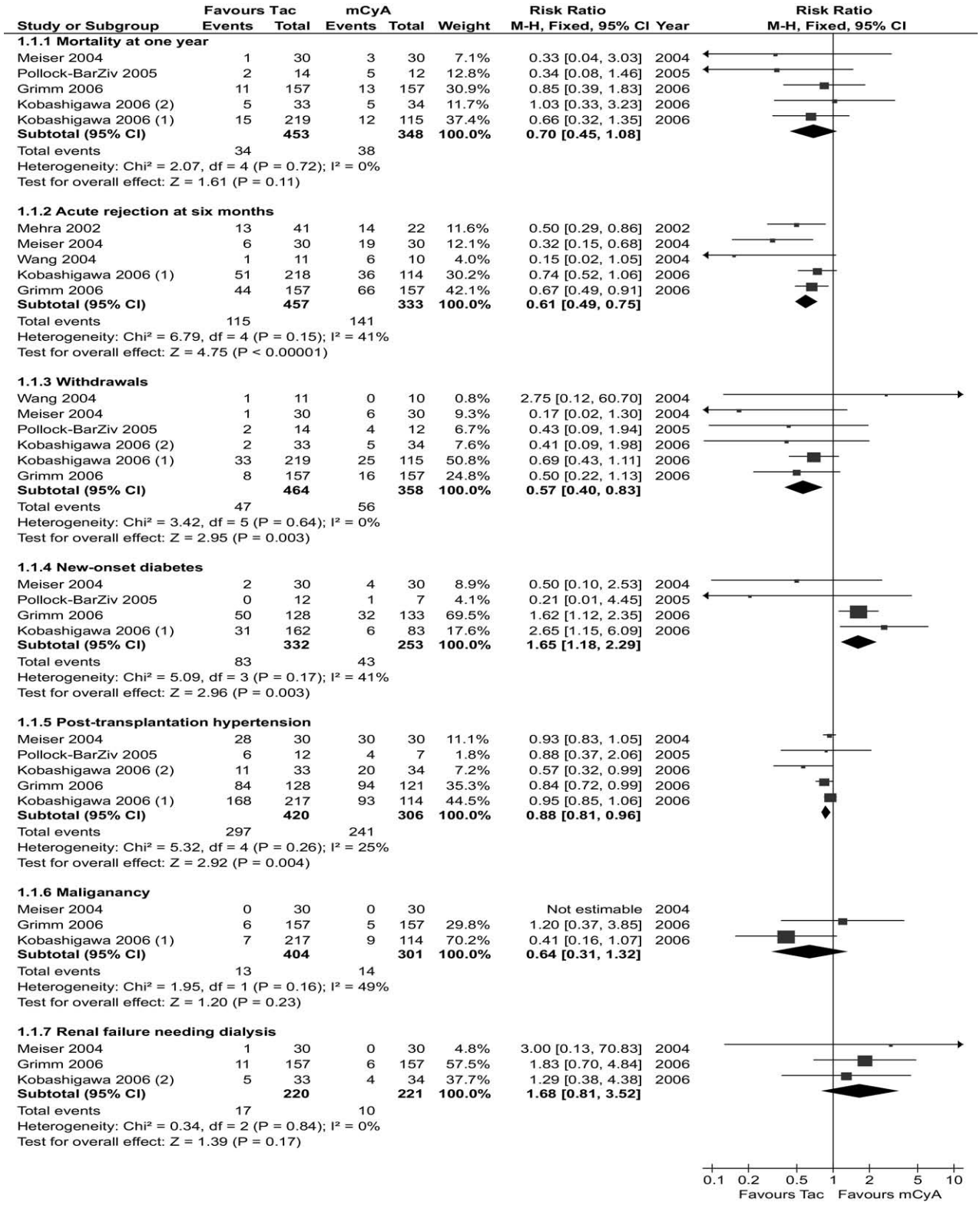

Figure 1. Meta-analysis of randomized clinical trials comparing tacrolimus (Tac) with cyclosporine microemulsion (mCyA). CI, confidence interval.

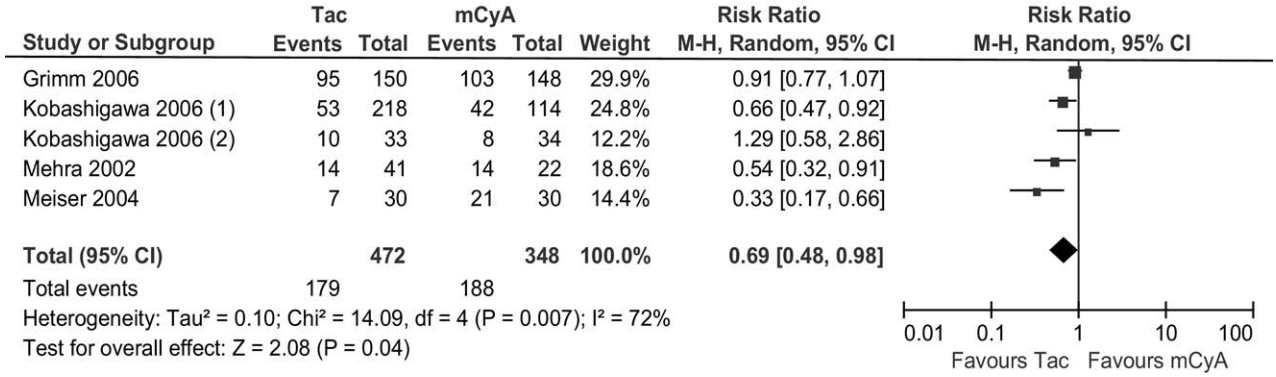

Figure 2. Meta-analysis of randomized clinical trials comparing tacrolimus (Tac) with cyclosporine microemulsion (mCyA) for acute rejection at 1 year. CI, confidence interval.

studies with durations of 12 months or longer. One trial was excluded for a short, 6-month duration of treatment.[9] However, this trial only reported the number of patients withdrawn from tacrolimus and cyclosporine microemulsion. The difference for withdrawals between the 2 groups remained statistically significant.

Cointerventions were allowed in our analysis. To control their effects on outcomes that might lead to bias, the data of the patients receiving sirolimus in the Kobashigawa et al[12] RCT were excluded (Figures 3 and 4). After the exclusion, the same baseline immunosuppressants (MMF or azathioprine) were used in both arms with equal doses in all the RCTs. The mortality rate at 1 year remained not statistically different, and other outcomes were also not significantly altered.A sub-group analysis was then done according to different concomitant medications (tacrolimus/MMF vs cyclosporine/MMF and tacrolimus/azathioprine vs cyclosporine/azathioprine) and found no relevant differences when MMF RCTs and azathioprine RCTs were independently analyzed.

COMMENT

During the past few decades, heart transplantation has evolved from a pioneering procedure with limited success to an acceptable treatment option for patients with severe cardiac failure or end-stage ischemic or non-ischemic cardiomyopathy. The use of calcineurin inhibitors has dramatically increased life expectancy of heart transplant recipients. The advantage of these drugs compared with cytotoxic immunosuppressants is that they act specifically on targeted sites in the immune system, not affecting other rapidly proliferating cells. Tacrolimus and cyclosporine, which are both calcineurin inhibitors, are now commonly used for immunosuppression after heart transplantation in combination with an anti-proliferative agent and steroids. These 2 immunosuppressants act by binding to specific proteins to form complexes that inhibit gene transcription for the expression of molecules with key roles in the immune responses, such as interleukin (IL)-2, CD154, and CD25, thereby inhibiting T-lymphocyte activation through the abrogation of cytokine production.[29] Although they have a similar main mechanism of action, tacrolimus binds to a different cytosolic-binding protein. Cyclosporine acts by binding to cyclophilins, and tacrolimus binds to FK-binding protein and has a greater binding affinity than cyclosporine. Many recent in vitro and in vivo studies also found that tacrolimus and cyclosporine had different effects on numerous factors, such as IL-10 synthesis, which may be the cause of the differences between these 2 drugs in efficacy and immunosuppressive activities.[30-32]

During the past 10 years, there has been a trend toward less use of cyclosporine and more use of tacrolimus.[33] Not surprisingly, according to the 2007 ISHLT report, tacrolimus has overtaken cyclosporine for the first time as the most commonly used calcineurin inhibitor (54% vs 40%) for heart transplant recieptents.[1] The latest ISHLT report still showed that more recipients used tacrolimus than cyclosporine (57% vs 37%).[34]

This meta-analysis identified 7 RCTs that compared the tacrolimus regimen with cyclosporine microemulsion immunosuppressive regimen in heart transplantation. The risk of death at 1 year was similar in both groups. Compared with cyclosporine microemulsion, tacrolimus significantly reduced the risk of acute rejection after heart transplantation. Treating with tacrolimus led to 39% and 31% fewer patients having acute rejection at 6 months and 1 year, respectively. This may be related to the drugs having different binding proteins and different effects on other immunologic factors. More patients stopped taking cyclosporine microemulsion than stopped tacrolimus.

New-onset diabetes mellitus after transplantation is a serious complication for heart transplant recipients. It increases patients' susceptibility to serious infection

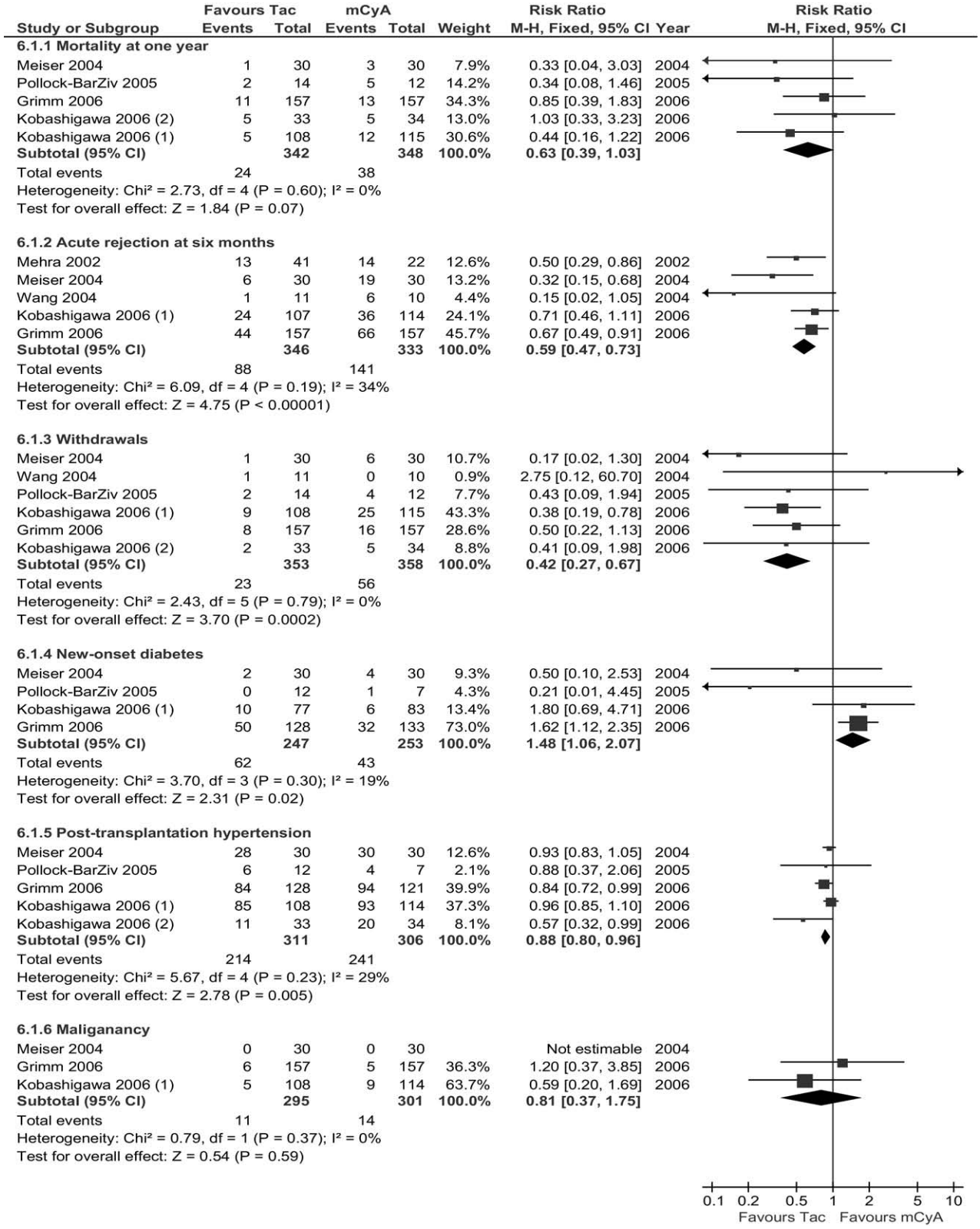

Figure 3. Sensitivity analysis with trials that used the same baseline immunosuppressants. CI, confidence interval; mCyA, cyclosporine microemulsion; Tac, tacrolimus.

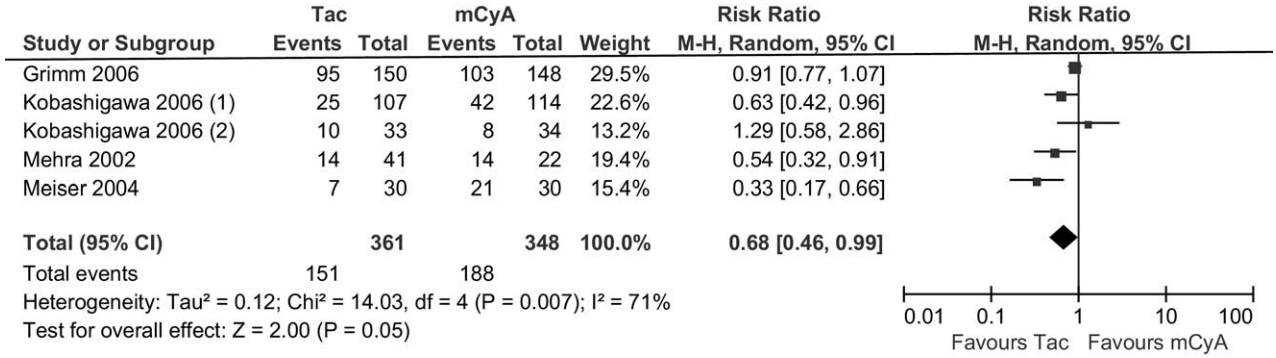

Figure 4. Sensitivity analysis with trials that used the same baseline immunosuppression for acute rejection at 1 year. CI, confidence interval; mCyA, cyclosporine microemulsion; Tac, tacrolimus.

and the incidence of cardiac allograft vasculopathy, which represents the main risk factor for long-term mortality. Immunosuppressive agents are one of the leading causes for new-onset diabetes after heart transplantation. Previous meta-analysis for kidney and liver transplantation reported that tacrolimus was more diabetogenic than cyclosporine. Similar with their results, our study found that the rate of new-onset diabetes was higher in tacrolimus-treated patients than in those receiving cyclosporine microemulsion. However, it did not reach statistical significance when using random-effect model, and the other 2 trials (one reported the rate of post-transplantation diabetes, the other described new-onset diabetes without the number of patients) also indicated the rate of diabetes between these two groups was not significantly different.[7,13]

Calcineurin inhibitors are associated with hypertension, which also contributes to the subsequent development of cardiac allograft vasculopathy. In our analysis, the incidence of post-transplant hypertension was significantly different between the 2 groups, which favored tacrolimus. The incidence of malignancy and renal failure needing dialysis were both comparable in the tacrolimus and cyclosporine microemulsion groups.

A meta-analysis of the results of other adverse events could not be done because of insufficient data. However, 5 studies reported the risk of infection in patients using tacrolimus and cyclosporine microemulsion,[7–9,11–12] and none showed any significant difference in the incidence of infection between the 2 groups. Tacrolimus treatment resulted in a lower risk of hyperlipidemia compared with cyclosporine microemulsion in all studies except 1, which showed similar incidence in both groups, whereas the number of patients included in this trial was very small.[10] White et al[35] also reported that conversion from cyclosporine microemulsion to tacrolimus resulted in decreased cholesterol and apolipoprotein B concentrations.

As mentioned, long-term survival in cardiac transplant recipients is frequently limited by the development of cardiac allograft vasculopathy. Unfortunately, a meta-analysis of this result could not be done because few trials have reported it. The costs of the different immunosuppression treatments, which are important considerations for both doctors and patients, also could not be analyzed in this study because no RCT reported this item.

The sensitivity analyses demonstrated that pooling the data on death, acute rejection, withdrawals, and adverse events did not alter the results of the analysis significantly after excluding the RCTs including children, with small size, with significantly shorter (6 months) durations, or using different baseline medication (sirolimus).

This meta-analysis has limitations. First, just like the other 2 meta-analyses comparing cyclosporine with tacrolimus,[3,4] only a few of the included RCTs were confirmed of intention to treat and described adequate allocation concealment, and none was double-blinded because of the nature of the intervention.

Second, compared with these 2 previous meta-analyses, the number of patients included in this study was a little small. However, the total number of patients receiving heart transplantation worldwide is about 80,000 (about 3,000 a year),[34] which is far fewer than the number of kidney or liver transplant recipients or patients undergoing other cardiac operations. So we thought the patients included in our analysis could represent the population of heart transplant recipients to discuss our theme.

Third, the RCTs included in this analysis used different concomitant medications: 3 used MMF, 4 used azathioprine, and 1 used sirolimus. This may result in bias. However, the sensitivity analysis excluded patients receiving sirolimus, so the same baseline concomitant medications with same doses were used in both the tacrolimus and cyclosporine microemulsion arms in each individual trial and may mitigate this bias. Outcomes were not significantly altered after excluding the data of this portion of patients. In addition, sub-group

analysis according to different concomitant medications (MMF, azathioprine) also found no relevant difference.

Fourth, this analysis showed a slight trend toward better survival in the tacrolimus group, but this did not reach statistical difference ($p = 0.11$). The lack of mortality benefit with the tacrolimus group might be related to the number of patients included, and more RCTs with large number of patients are needed. It would be much better if they also analyzed the results by gender or ethnicity.

In conclusion, no difference in mortality was noted at 1 year between patients receiving tacrolimus and cyclosporine microemulsion. Tacrolimus, with its potency to reduce incidence of acute rejection, appeared to be superior after heart transplantation. Tacrolimus was also associated with fewer withdrawals and post-transplantation hypertension, but the rate of new-onset diabetes was higher in patients treated with tacrolimus compared with those treated with cyclosporine microemulsion. The incidence rate of malignancy and renal failure needing dialysis were both comparable in these 2 groups.

REFERENCES

1. Taylor DO, Edwards LB, Boucek MM, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplantation report—2007. J Heart Lung Transplant 2007;26:769–81.
2. Knoll GA, Bell RC. Tacrolimus versus cyclosporin for immunosuppression in renal transplantation: meta-analysis of randomised trials. BMJ 1999;318:1104–7.
3. McAlister VC, Haddad E, Renouf E, et al. Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. Am J Transplant 2006;6:1578–85.
4. Webster AC, Woodroffe RC, Taylor RS, et al. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. BMJ 2005;331:810.
5. Jadad AR, Moore RA, Carroll D. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
6. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
7. Mehra MR, Uber PA, Scott RL, et al. Ethnic disparity in clinical outcome after heart transplantation is abrogated using tacrolimus and mycophenolate mofetil-based immunosuppression. Transplantation 2002;74:1568–73.
8. Meiser BM, Groetzner J, Kaczmarek I, et al. Tacrolimus or cyclosporine: which is the better partner for mycophenolate mofetil in heart transplant recipients? Transplantation 2004;78:591–8.
9. Wang CH, Ko WJ, Chou NK, et al. Efficacy and safety of tacrolimus versus cyclosporine microemulsion in primary cardiac transplant recipients: 6-month results in Taiwan. Transplant proc 2004;36:2384–5.
10. Pollock-Barziv SM, Dipchand AI, McCrindle BW, et al. Randomized clinical trial of tacrolimus- vs cyclosporine-based immunosuppression in pediatric heart transplantation: preliminary results at 15-month follow-up. J Heart Lung Transplant 2005;24:190–4.
11. Grimm M, Rinaldi M, Yonan NA, et al. Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients–a large European trial. Am J Transplant 2006;6:1387–97.
12. Kobashigawa JA, Miller LW, Russell SD, et al. Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. Am J Transplant 2006;6:1377–86.
13. Kobashigawa JA, Patel J, Furukawa H, et al. Five-year results of a randomized, single-center study of tacrolimus vs microemulsion cyclosporine in heart transplant patients. J Heart Lung Transplant 2006;25:434–9.
14. Groetzner J, Meiser BM, Schirmer J, et al. Tacrolimus or cyclosporine for immunosuppression after cardiac transplantation: which treatment reveals more side effects during long-term follow-up? Transplant Proc 2001;33:1461–4.
15. Taylor DO, Barr ML, Radovancevic B, et al. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. J Heart Lung Transplant 1999;18:336–45.
16. Reichart B, Meiser B, Vigano M, et al. European Multicenter Tacrolimus (FK506) Heart Pilot Study: one-year results–European Tacrolimus Multicenter Heart Study Group. J Heart Lung Transplant 1998;17:775–81.
17. Meiser BM, Uberfuhr P, Fuchs A, et al. Single-center randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of acute myocardial rejection. J Heart Lung Transplant 1998;17:782–8.
18. Arbustini E, Dal Bello B, Rinaldi M, et al. Acute rejection and heart infection rates in FK 506- versus cyclosporine A-treated heart transplant recipients: an endomyocardial biopsy pathologic study. J Heart Lung Transplant 1997;16:982–4.
19. Rinaldi M, Pellegrini C, Martinelli L, et al. FK506 effectiveness in reducing acute rejection after heart transplantation: a prospective randomized study. J Heart Lung Transplant 1997;16:1001–10.
20. Meiser BM, Uberfuhr P, Fuchs A, et al. Comparison between tacrolimus (FK506) and cyclosporin A (CyA) after heart transplantation: a randomised, controlled clinical study. Z Kardiol 1996;85(suppl):133.
21. Klauss V, König A, Spes C, et al. Cyclosporine versus tacrolimus (FK 506) for prevention of cardiac allograft vasculopathy. Am J Cardiol 2000;85:266–9.
22. Petrakopoulou P, Anthopoulou L, Muscholl M, et al. Coronary endothelial vasomotor function and vascular remodeling in heart transplant recipients randomized for tacrolimus or cyclosporine immunosuppression. J Am Coll Cardiol 2006;47:1622–9.
23. White M, Ross H, Haddad H, et al. Subclinical inflammation and prothrombotic state in heart transplant recipients: impact of cyclosporin microemulsion vs. tacrolimus. Transplantation 2006;82:763–70.
24. Wang CH, Ko WJ, Chou NK, et al. Therapeutic drug monitoring of tacrolimus in cardiac transplant recipients: a comparison with cyclosporine Neoral. Transplant Proc 2004;36:2386–7.
25. von Steinbüchel N, Limm H, Leopold C, et al. Assessment of health-related quality-of-life in patients after heart transplantation under therapy with tacrolimus or cyclosporine. Transplant international 2000;13(suppl 1):S609–14.
26. Mehra MR, Uber PA, Park MH, et al. A randomized comparison of an immunosuppressive strategy using tacrolimus and cyclosporine in black heart transplant recipients. Transplant Proc 2001;33:1606–7.
27. Kobashigawa JA, Miller LW, Russell SD. A randomized, prospective, multicenter comparison of tacrolimus, mycophenolate mofetil (MMF) and steroids vs cyclosporine microemulsion, MMF and

steroids vs tacrolimus, sirolimus and steroids in de novo cardiac transplant recipients - 6 month report. Presented at 3rd International Congress on Immunosuppression, San Diego, CA, Dec 8–11, 2004.
28. Kobashigawa JA, Moriguchi JD, Takemoto S, et al. First year results of a randomized trial of tacrolimus vs Neoral cyclosporine in heart transplant patients. J Heart Lung Transplant 2000;19:47.
29. Halloran P. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004;351:2715.
30. Jiang H, Wynn C, Pan F, Ebbs A, et al. Tacrolimus and cyclosporine differ in their capacity to overcome ongoing allograft rejection as a result of their differential abilities to inhibit interleukin-10 production. Transplantation 2002;73:1808–17.
31. Khanna A, Cairns V, Hosenpud J. Tacrolimus induces increased expression of transforming growth factor in mammalian lymphoid as well as non-lymphoid cells. Transplantation 1999;67:614–9.
32. Shin GT, Khanna A, Ding R, et al. In vivo expression of transforming growth factor-beta1 in humans: stimulation by cyclosporine. Transplantation 1998;65:313–8.
33. Kaufman DB, Shapiro R, Lucey MR, et al. Immunosuppression: practice and trends. Am J Transplant 2004;4(suppl 9):38–53.
34. Taylor DO, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult heart transplant report—2008. J Heart Lung Transplant 2008;27:943–6.
35. White M, Haddad H, Leblanc MH, et al. Conversion from cyclosporine microemulsion to tacrolimus-based immunoprophylaxis improves cholesterol profile in heart transplant recipients with treated but persistent dyslipidemia: the Canadian multicentre randomized trial of tacrolimus vs cyclosporine microemulsion. J Heart Lung Transplant 2005;24:798–809.