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Full Length Research Paper

A systematic review of the adverse effects of tacrolimus in organ transplant patients

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Tacrolimus has been the drug of choice for prevention of graft rejection following organ transplantations. This systematic review and meta-analysis [UiTM1] was conducted to evaluate the efficacy of tacrolimus in organ transplantation. Publication in English of randomized clinical trials, which used tacrolimus to prevent graft rejection in adult patients were included in this analysis. Articles were searched from PubMed, Science Direct, Blackwell and Ovid Gateway, which were published since 1980 to 2007. The outcomes measured were biopsy-proven acute rejection at three months; graft survival at one year; post-transplant diabetes mellitus; hypertension and neurotoxicity. Seven reports, which involved 2415 participants showed that tacrolimus was associated with reduced odds of biopsy-proven acute rejections three months of post-transplantation (pooled odds ratio of 0.69; 95% CI 0.49 to 0.96) and improved graft survival at one year (pooled odds ratio of 1.11 and 95% confidence interval 0.72 to 1.71). In terms of adverse effects, tacrolimus-treated patients were significantly at high odds of developing post-transplant diabetes mellitus (pooled odds ratio of 1.90; 95% CI 1.09 to 3.30) and neurotoxicity (pooled odds ratio of 1.61; 95% CI 1.15 to 2.25) but reduced odds of developing hypertension (pooled odds ratio of 0.80; 95% CI 0.65 to 0.98). Low to moderate heterogeneity between trials existed for the incidences of biopsy-proven acute rejections, graft survival, post-transplant diabetes mellitus and incidence of hypertension; but the analysis showed a significant increment of neurotoxicity by tacrolimus.

Key words: Tacrolimus, neurotoxicity, hypertension, diabetes mellitus, efficacy.

INTRODUCTION

Tacrolimus is a calcineurin inhibitor derived from a soil fungus, *Streptomyces tsukubaensis* which was found in northern Japan in 1984 (Kelly et al., 1995). It was first approved for use to prevent graft rejection in 1994 for liver transplantation and in 1997 for kidney transplantation (Demirbas et al., 2003). Inhibition of calcineurin by tacrolimus indirectly prevents transcription of cytokines genes that encode for interleukin-2, interleukin-3, interleukin-4, granulocyte-macrophage-colony-stimulating factor, tumour necrosis factor-alpha and gamma interferon in the early phase of T-cell activation (Wingard et al., 1998).

Several meta-analyses have been conducted to investigate the efficacy of tacrolimus in prevention of graft rejection. Knoll and Bell (1999) had shown that the use of tacrolimus in preventing graft rejection was associated with a significant reduction in acute rejection in the first year (odds ratio 0.52; 95% CI 0.36 to 0.75) but the study did not show any significant effect in preventing graft loss (odds ratio 0.95; 95% CI 0.65 to 1.40). McAlister et al. (2006) reported a significant reduction in acute rejection (relative risk 0.81, 95% CI 0.75 to 0.88) and graft loss one year post-transplantation (relative risk 0.73, 95% CI 0.61 to 0.86) following liver transplantation in patients given tacrolimus. In addition, both studies reported a significant increase in prevalence of post-transplant diabetes mellitus in the tacrolimus group. However, other

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Table 1. Justification of criteria for the assessment of methodological quality of trials.

Criteria	Justification
Randomization	Adequate (score 1): The method of randomization was described in detail Unclear (score 0.5): If randomization was stated but the method was not described. Inadequate (score 0): Randomization was not stated.
Study Bias	Adequate (score 1): Inclusion exclusion criteria were stated. Inadequate (score 0): Inclusion and exclusion criteria were not described.
Sample size	Adequate (score 1): Sample size large enough, more than 50. Inadequate: Sample size very small, less than 50.
Length of study	Adequate (score 1): More than six months. Inadequate (score 0): Less than six months.
Analysis of participants	Adequate (score 1): Intention-to-treat analysis was used. Unclear (score 0.5): The method of patient's analysis was not clearly described. Inadequate (score 0): Intention-to-treat analysis was not performed.

adverse effects such as hypertension and neurotoxicity were not discussed in both studies.

Therefore, this study aims to systematically review primary research studies on the adverse effects profile, in addition to the efficacy of tacrolimus. The parameters that would be measured include post-transplant diabetes mellitus, neurological adverse effects and hypertension, incidence of acute rejection and graft survival after one year of transplantation.

METHODOLOGY

Subject recruitment

All randomized clinical trials that used tacrolimus as treatment intervention in organ transplantation were included in this systematic review. The control groups were those given other immunosuppressants such as steroid and cyclosporine. Only publications in English were selected for evaluation.

Literature search

Literature search was performed by using PubMed, Science Direct, Blackwell and Ovid Gateway. All related publications since 1980 to 2007 were searched. The keywords used were "tacrolimus", "Prograf", "FK506", "tacrolimus and clinical trials", "tacrolimus and controlled trials" and "tacrolimus and organ transplantation". Combined search of each keyword was also conducted. The lists of relevant articles were critically reviewed in search for relevant studies. Studies related to this review were retrieved and comprehensively evaluated for the inclusion and exclusion criteria.

Outcomes measurement

Parameters used for measurement of outcomes in this study include post-transplant diabetes mellitus, hypertension, neurotoxicity, acute rejection at three months and graft survival at 12 months. Post-transplant diabetes mellitus is defined as the need for insulin for more than 30 days for participants who did not require insulin at baseline; hypertension as the need for antihypertensive agents to control blood pressure; neurotoxicity as manifestation of one of the symptoms such as headache and tremor and; acute rejection as proven by biopsy.

Methodological quality of trials

The quality of each of the trial was scored. The criteria assessed for each trial were sample randomization; study bias; sample size; length of study and intention-to-treat analysis. Scores were given as follows: adequate (score 1), unclear (score 0.5) and inadequate (score 0). The justifications of each criterion are described in Table 1.

Data extraction and analysis

Data were analyzed and extracted for evaluation of the specified outcomes. Odds ratio was estimated for each outcome used. A fixed-effects model was used if heterogeneity across studies were statistically non-significant when tested with Cochran Q-test (p-value was greater than 0.05) or less than 50% when tested using I^2-test for inconsistency. A random effects model was used if significant heterogeneity was observed between individual studies (p-value of Cochran Q-test was less than 0.05 and I^2-test was more than 50%).

RESULTS

Literature search

Two hundreds and five articles were identified using PubMed (n=51), Science Direct (n=61), Blackwell (n=47) and Ovid Gateways (n=46) by using the keywords "tacrolimus", "Prograf", "FK506", "tacrolimus and clinical

Table 2. Participants' baseline characteristics.

Study name	Mean age (± SD)	Diagnosis	Tacrolimus dosage	Tacrolimus level (<3 months)	Tacrolimus level (>3 months)
Margarit et al. (2005)	57±7	End-stage liver cirrhosis	0.05 mg/kg twice daily	10-15 ng/ml	8-12 ng/ml
Margreiter et al (2002)	42.4 ± 10.4	End-stage renal disease	0.15 mg/kg twice daily	10-20 ng/ml	5-15 ng/ml
Mayer et al. (1997)	46.6 ± 25	End-stage renal disease	0.15 mg/kg twice daily	10-20 ng/ml	5-15 ng/ml
Moench et al. (2007)	53.5 ± 8.3	End-stage liver disease	0.20 mg/kg twice daily	10-15 ng/ml	5-10 ng/ml
Murphy et al. (2003)	45 ± 12	End-stage renal disease	0.10 mg/kg twice daily	8-15 ng/ml	5-10 ng/ml
O'grady et al. (2002)	52 ± 10	End-stage liver cirrhosis	0.10 mg/kg twice daily	5-15 ng/ml	5-15 ng/ml
US Multicenter (1994)	44 ± 18	End-stage liver cirrhosis	0.15 mg/kg twice daily	<0.2 or >5 ng/ml if toxicity occurred	<0.2 or >5 ng/ml if toxicity occurred

trials", "tacrolimus and controlled trials" and "tacrolimus and organ transplantation". Sixteen articles were further evaluated and assessed for suitability to be included in this review. Out of sixteen articles, seven were included and were evaluated for methodological quality.

Description of studies Included

Seven studies were included for analysis involving 2415 participants randomized into tacrolimus group (1285) and control group (1130). Five out of seven studies were single center studies and another two studies were multicenter trials. Tacrolimus was compared to cyclosporine in one trial (Mayer et al., 1997), microemulsified cyclosporine in four trials (Margreiter et al., 2002; Murphy et al., 2003; O'grady et al., 2002; The US Multicenter FK 506 Liver Study Group, 1994) and two trials compared tacrolimus to steroids (Margarit et al., 2005; Moench et al., 2007). The compared drug would be referred as "control" in this analysis.

The studies included in the analysis were evaluated based on randomization, bias avoidance, sample size, study duration and analysis of participants. In terms of appropriate randomization, five out of seven studies did not clearly describe their steps of randomization (Mayer et al., 1997; Margreiter et al., 2002; Murphy et al., 2003; The US Multicenter FK 506 Liver Study Group, 1994; Margaritet al., 2005). Only one study (Moench et al., 2007) fulfilled all the criteria of evaluation.

Four out of seven studies were conducted in patients who underwent liver transplantation, mostly due to end-stage liver cirrhosis (O'grady et al., 2002; The US Multicenter FK 506 Liver Study Group, 1994; Margaritet al., 2005; Moench et al., 2007) while three studies involved renal transplant recipients due to end-stage renal disease (Mayer et al., 1997; Margreiter et al., 2002; Murphy et al., 2003). Five trials were conducted for twelve months (Mayer et al., 1997; Murphy et al., 2003; O'grady et al., 2002; The US Multicenter FK 506 Liver Study Group, 1994; Moench et al., 2007), one trial was conducted for five years (Margarit et al., 2005) and another one trial was conducted for six months (Margreiter et al., 2002). All trials involved adults from 42 years old to 57 years old. They received varied range of tacrolimus regimen ranging from 0.10 to 0.20 mg/kg in two divided doses daily. The dose was adjusted to achieve trough level in the whole blood from 0.2 ng/ml to 15 or 20 ng/ml in the first three months and 5 to 15 ng/ml thereafter (Table 2).

Efficacy: Biopsy-proven acute rejection at three months and graft survival at 12 months

The incidence of acute rejection between tacrolimus group and control group showed no significant difference (Figure 1). Test for inconsistency (I^2 test) showed moderate heterogeneity (68.4%) between individual studies. In addition, the plot of random effects model showed that there was no difference in terms of graft survival between patients treated with tacrolimus and control (Figure 2). However, result obtained with fixed effects model showed significant difference between treatment and control group. The test for heterogeneity (I^2-test) shows moderate (68.1%) inconsistency between each study.

Adverse effects: Post-transplant diabetes mellitus, hypertension and neurotoxicity

The summaries of occurrence of adverse effects (post-transplant diabetes mellitus, hypertension and neurotoxicity) are described in Table 3.

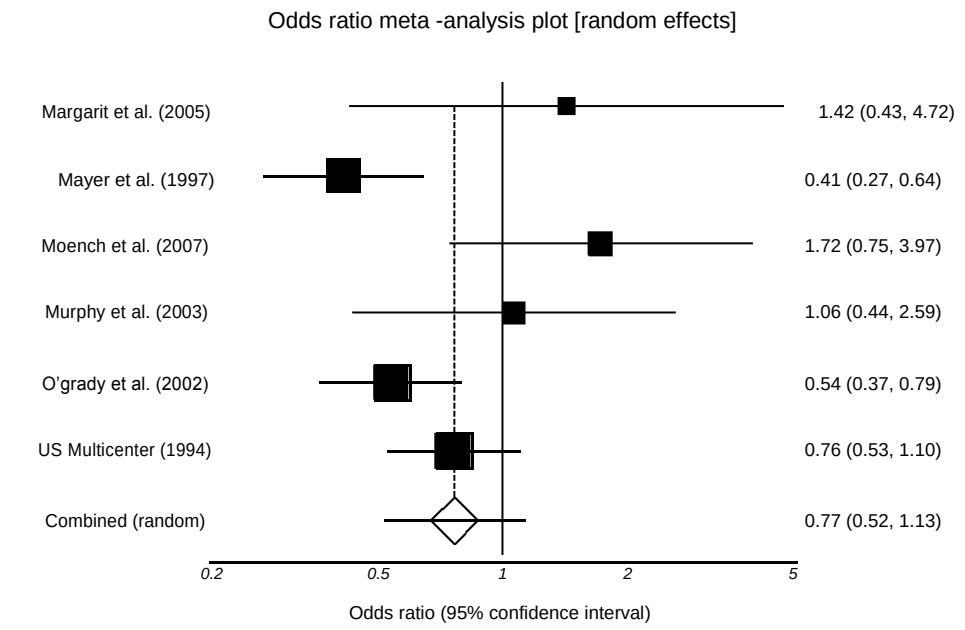

Figure 1. Incidences of biopsy-proven acute rejection.

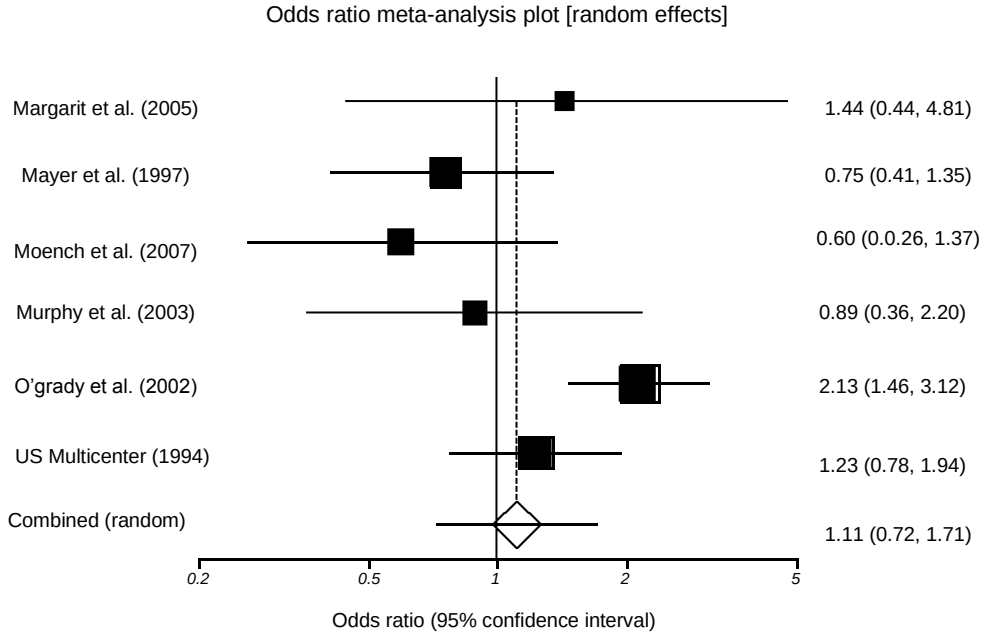

Figure 2. Graft survival at 12 months.

Results of the analysis were presented in the form of forest plot (Figures 3 to 5). Because of significant heterogeneity between studies (Cochran Q-test p-value 0.0004; I^2 is 74.5%), random-effects model was more suitable to be used. Heterogeneity might be due to the differences in defining post-transplant diabetes mellitus, the population diversity and the sample size. However, visual observation of the forest plot (Figure 3) showed that the odds of developing post-transplant diabetes mellitus favours tacrolimus-treated patients.

The incidence of hypertension was comparable between tacrolimus treated patients and control (Figure 4). The analysis showed reduced in odds of having hypertension in patients treated with tacrolimus or

Table 3. Conclusion of outcomes measured.

Study name	Odds ratio (95% confidence interval)					
	Scores for selection criteria	Acute rejection (3-months)	Graft Survival (12-months)	Hypertension	Post-transplant diabetes mellitus	Neurotoxicity
Margarit et. al. (2005)	3.5	1.42 (0.43-4.72)	1.44 (0.44-4.81)	0.36 (0.01-4.85)	0.33 (0.03-2.13)	1.04 (0.30-3.55)
Margreiter et al (2002)	4.5	-	-	0.62 (0.39-0.96)	2.53 (0.83-9.19)	3.30 (1.59-7.34)
Mayer et al. (1997)	4.5	0.41 (0.27-0.64)	0.75 (0.41-1.35)	0.87 (0.54-1.38)	4.26 (1.26-22.34)	-
Moench et al. (2007)	5	1.71 (0.75-3.97)	0.60 (0.26-1.37)	1.69 (0.74-3.86)	1.06 (0.46-2.46)	0.96 (0.12-7.52)
Murphy et al.(2003)	4	1.06 (0.44-2.59)	0.89 (0.36-2.20)	-	2.17 (0.29-24.91)	-
O'grady et al. (2002)	4.5	0.54 (0.37-0.79)	2.13 (1.46-3.12)	0.77 (0.51-1.16)	3.65 (2.57-5.18)	-
US Multicenter (1994)	4.5	0.76 (0.53-1.10)	1.23 (0.78-1.94)	0.82 (0.52-1.29)	1.46 (1.02-2.09)	1.29 (0.82-2.05)
Combined odds ratio (95% confidence interval)		0.77(0.52-1.13)	1.11 (0.72-1.71)	1.90 (1.09-3.30)	0.80 (0.65-0.98)	1.61 (1.15-2.25)
Heterogeneity (I^2- test)		68.4%	68.1%	74.5%	14.2%	49.9%

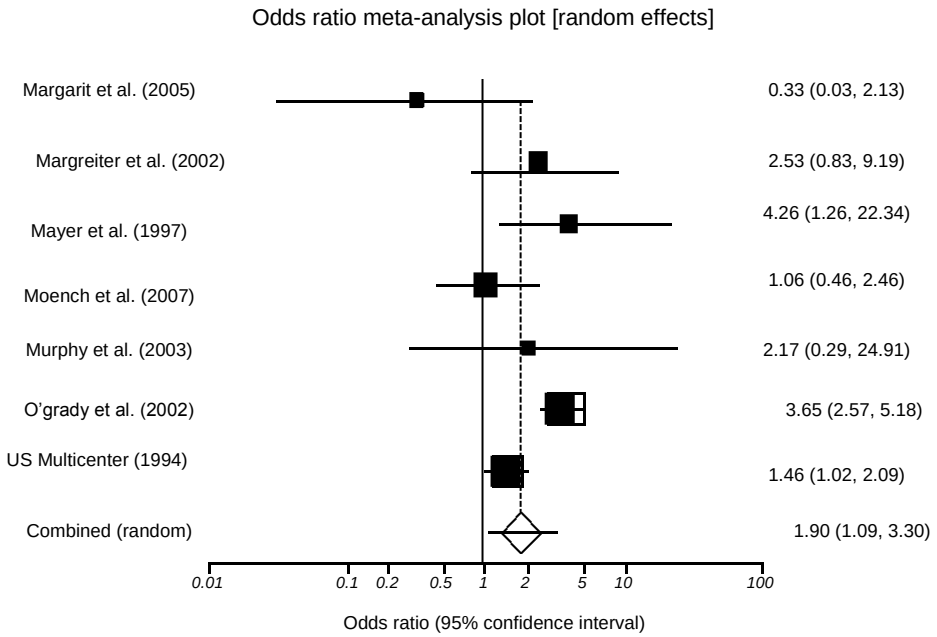

Figure 3. Adverse effect (post-transplant diabetes mellitus) among the tacrolimus-treated patients vs the controls.

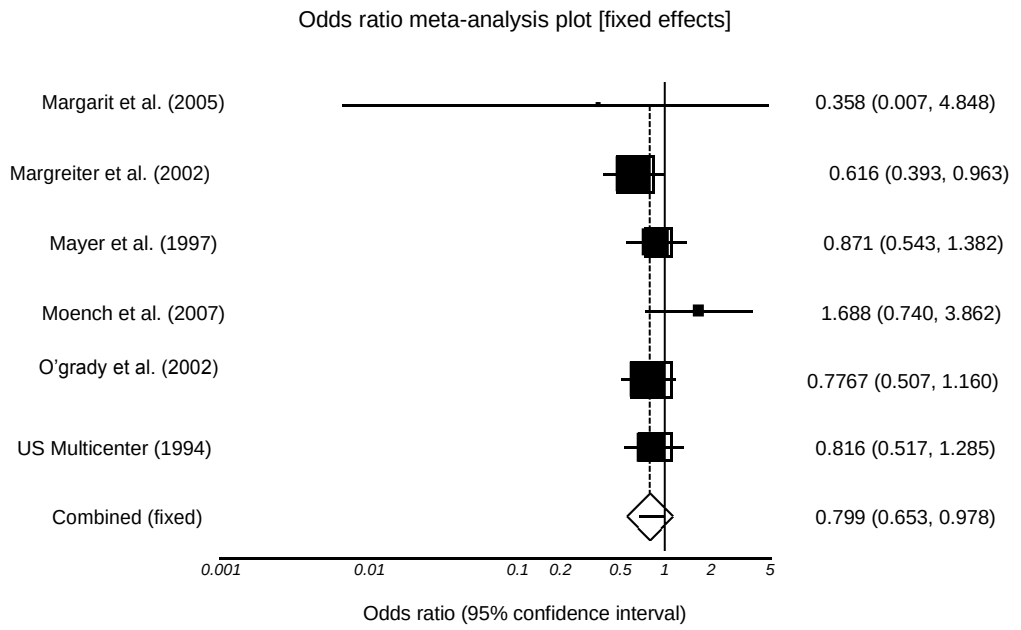

Figure 4. Adverse effect (Hypertension) among the tacrolimus-treated patients vs the controls.

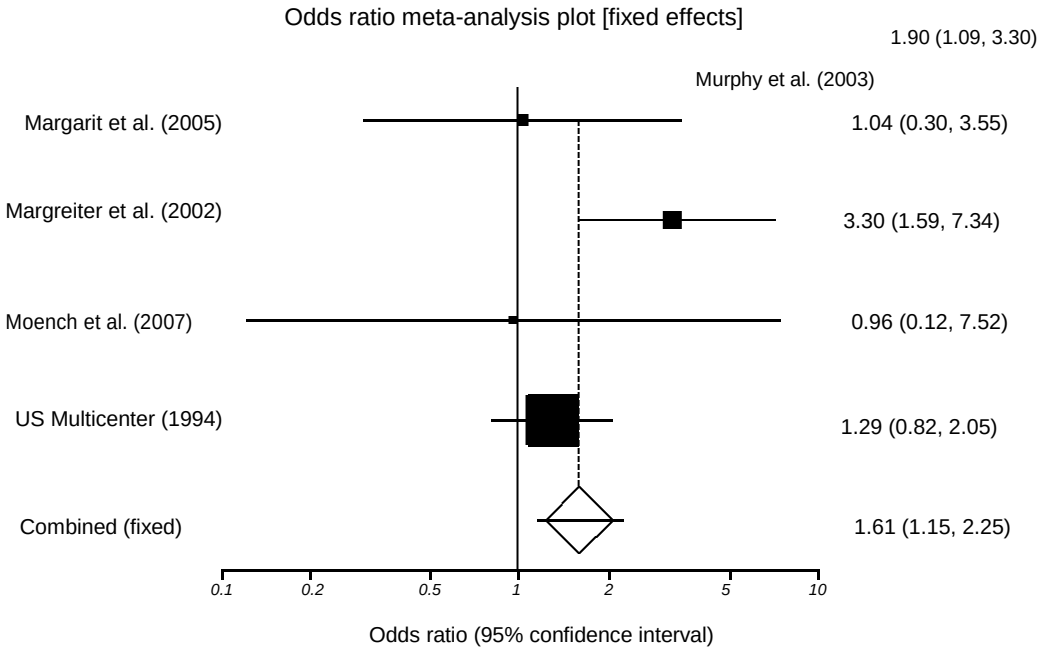

Figure 5. Adverse effect (neurotoxicity) among the tacrolimus-treated patients vs the controls.

control. Fixed-effects model was used due to low heterogeneity across studies in which Cochran Q-test showed non-significant variance across studies (p-value=0.32) and I^2-test showed low inconsistency (14.2%).

Four studies measured neurotoxic effects of tacrolimus (Margreiter et al., 2002; The US Multicenter FK 506 Liver Study Group, 1994; Margarit et al., 2005; Moenche et al., 2007); tacrolimus-treated patients had high odds of having neurotoxicity such as tremor and headache. The Cochran Q-test showed p-value of 0.11 and the I^2-test result was 49.9% which indicated low heterogeneity

among the studies.

DISCUSSION AND CONCLUSION

The use of tacrolimus in preventing graft rejection following organ transplantations was associated with both risks and benefits. In this study, separate odd ratios were presented for each studies as pooling was not justified due to differences in baseline characteristic of controls and treated groups. However, this analysis showed that the use of tacrolimus to prevent graft rejection was associated with reduction in acute rejection, graft loss and incidence of hypertension. However, its use caused an increase in the incidence of post-transplant diabetes mellitus and neurotoxicity. Even though the studies included in this review involved different comparison groups and organs transplanted, the result of this analysis had shown similar results drawn from previous meta-analyses, which were performed separately based on the types of organ transplanted and the control drugs. Other differences of this analysis compared to previous meta-analyses include addition of studies which were not included in the previous meta-analyses. For example, Murphy et al. (2003), Margarit et al. (2005) and Moench et al. (2007) had compared the use of tacrolimus against steroids in liver transplantation while Murphy et al. (2003) compared the use of tacrolimus and microemulsified cyclosporin in renal transplantation. In addition, previous meta-analyses were not evaluating the incidence of neurotoxicity and hypertension. The inclusion of these studies in this analysis provided stronger evidence regarding the superiority of tacrolimus in the prevention of graft rejection following organ transplantation.

Tacrolimus was shown to be associated with increased odds of having insulin-dependent diabetes mellitus. The mechanism on how tacrolimus causing diabetes mellitus was still uncertain. However, it was proposed due to interruption of calcium ion signalling pathways by tacrolimus that caused inhibition of insulin gene expression in the beta-cells of pancreas (Redmon et al., 1996). Nevertheless, the inhibition of insulin gene transcriptions by tacrolimus was concentration-dependent and reversible (Redmon et al., 1996).

Tacrolimus therapy is also shown to cause high odds of symptoms of neurotoxicity ranging from headache, tremor, neuralgia and agitation to motor weakness and seizures. The reason for these effects was because of the inhibition of calcineurin by tacrolimus, which was abundant in the brain. Calcineurin is involved in the regulation of various proteins in the brain which affects both basic brain functions and higher-order processes such as synaptic transmission and processing of memory respectively (Tan and Robinson, 2006). Tacrolimus-induced neurotoxicity was suggested to occur in hepatic impaired patients with reduced metabolism of this drug and thus higher concentration of tacrolimus (Jurewicz, 2003).

Reduction in odds of developing post-transplant hypertension is significant in patients treated with tacrolimus. Tacrolimus treatment has associated with a significantly better cardiovascular risk profile and superior renal function compared with cyclosporin microemulsion treatment which has been translated into improved long-term graft survival (Bottiger et al., 1999).

Almost all of the outcomes measured in this analysis are limited by the low to moderate heterogeneity across the studies except for incidence of neurotoxicity. Therefore, a firm conclusion regarding the efficacy of tacrolimus to prevent graft rejection in organ transplantation could not be made. The reasons for inconsistencies between individual studies may be due to diversity in length of study and study population, different method used to measure the effect and difference in baseline characteristics of participants.

Another limitation of this analysis is contributed by the number of studies which were small. Only seven studies were suitable to be included in the analysis. This is due to limitation of access to full text of related publications and search engines. The importance of pharmacogenotyping and the correlation of blood levels of tacrolimus with graft survival and adverse effects were however, not able to be analyzed due to lack of data even though high blood level and genetic polymorphism of CYP's on tacrolimus was believed to be strongly associated with the development of adverse effects such as post-transplant diabetes mellitus and neurotoxicity (Bottiger et al., 1999). Further study should investigate the long-term efficacy of tacrolimus intervention following organ transplantation and the correlation between genetic profiles and blood level of the drug and graft outcomes.

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