RESEARCH ARTICLE

Sirolimus and Non-melanoma Skin Cancer Prevention after Kidney Transplantation: A Meta-analysis

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Abstract

Background: Whether sirolimus is useful in the prevention of non-melanoma skin cancer (NMSC) remains unclear and we therefore performed this meta-analysis of randomized controlled trials to test the hypothesis that Sirolimus-based immunosuppression is associated with a decrease in NMSC. Methods: The main outcomes were NMSC, squamous-cell carcinoma and basal-cell carcinoma. The pooled risk ratio (RR) with its 95% confidence interval (95%CI) were used to assess the effects. Results: 5 randomized trials involving a total of 1499 patients receiving kidney transplantation were included. Patients undergoing Sirolimus-based immunosuppression had much lower risk of NMSC (RR = 0.49, 95%CI 0.32-0.76, P = 0.001). Subgroup analyses by tumor type showed that Sirolimus-based immunosuppression significantly decreased risk of both squamous-cell carcinoma (RR = 0.58, 95%CI 0.43-0.78, P < 0.001) and basal-cell carcinoma (RR = 0.56, 95%CI 0.37-0.85, P = 0.006). The quality of evidence was high for NMSC, and moderate for squamous-cell carcinoma and basal-cell carcinoma. No evidence of publication bias was observed. Conclusion: High quality evidence suggests that Sirolimus-based immunosuppression decreases risk of non-melanoma skin cancer, and Sirolimus has an antitumoral effect among kidney-transplant recipients.

Keywords: Sirolimus - non-melanoma skin cancer - kidney transplantation - meta-analysis

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Introduction

For patients with end-stage renal disease, kidney transplantation is the treatment of choice to improve quality of life and increase life expec¬tancy (Meguid El Nahas et al., 2005). The growing and aging of the end-stage kidney disease population have increased the number of patients receiving and living with kidney transplants who are at risk for the long-term complications of transplantation (Nankivell et al., 2011). Besides, the manipulation of the alloim¬mune response is crucial for a successful renal transplantation, but many adverse events associated with the administration of immunosuppressive drugs affect the long-term outcomes of transplant recipients (Dantal et al., 2005; Nankivell et al., 2010). Skin cancers affect more than half of organ-transplant recipients during their long-term course, and previous studies have shown that after a first cutaneous squamous-cell carcinoma, multiple subsequent skin cancers develop in 60 to 80% of kidney-transplant recipients within 3 years (Sun et al., 2011; Yunus et al., 2012).

A few studies have reported a lower rate of skin cancer in transplant recipients who were treated with Sirolimus than in those treated with calcineurin inhibitors, but the available evidence from those studies was weak, owing to sparseness of data or disagreements among studies (Salgo et al., 2010; Flechner et al., 2011; Campbell et al., 2012; Euvrard et al., 2012). Those studies with relative sample size have insufficient power and could inevitably increase the risk of chance responsible for their conclusions, while combining data from all eligible studies by meta-analysis has the advantage of reducing random error and obtaining precise estimates for clinical interventions (Petitti, 2000). Thus, whether Sirolimus was useful in the prevention of non-melanoma skin cancer (NMSC) has not been assessed and we perform this meta-analysis of randomized controlled trials to test the hypothesis that Sirolimus-based immunosuppression is associated with a decrease in NMSC.

Materials and Methods

Search Strategy and Inclusion Criteria.

We searched for publications in Pubmed, Embase, and Web of Science databases through May 28, 2012 without restriction on the publication status or the language of publication. We combined database-specific search terms for Sirolimus, renal transplantation (kidney transplantation or renal transplantation) and randomized controlled studies (randomized or randomized). A hand search of relevant journals and annual meetings was also conducted. Authors of relevant abstracts were contacted to obtain any unpublished data (if available). All reference sections of eligible studies and pertinent reviews were

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hand-reviewed for potential studies. All prospective randomized controlled studies in which Sirolimus-based immunosuppression in renal transplant recipients was compared with common immunosuppression and reported data on the incidence of NMSC were included into this meta-analysis.

Outcome Measures and Data extraction

All available data for the described outcome measures were extracted from individual trials. In studies where 1-year follow-up was not available even after correspondence with the principal investigator, those outcomes that are available at the nearest time point to 1 year were included in the general and subgroup analyses. Furthermore, completeness of follow-up was defined as the number of patients that were not lost to follow-up. The following information was extracted from each study: the first author, publication year, number of patients, study design, and outcomes. The primary outcomes analyzed were NMSC, and the other outcomes assessed were squamous-cell carcinoma and basal-cell carcinoma.

Quality assessment and Evidence assessment

Quality of studies was assessed independently by two reviewers. The Cochrane Risk of Bias Tool was used to the risk of bias in the included studies. The risk of bias tool covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias (Higgins et al., 2011). We used principles from the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group to summarize the quality of the evidence overall for each factor as low, moderate, or high, reflecting the confidence that the estimate of effect is correct (Guyatt et al., 2008). These ratings may be modified by detailed study design, consistency, dose-response effect, directness, precision, and whether all plausible confounding would reduce a demonstrated effect (Guyatt et al., 2008).

Meta-analysis

For each trial, risk ratio (RR) with their 95% confidence interval (95% CI) of those outcomes was calculated or derived. In our study, two models for dichotomous outcomes were conducted: the random-effects model and the fixed-effects model (Mantel et al., 1959; DerSimonian et al., 1986). The random-effects model was conducted using the DerSimonian and Laird's method, which assumed that studies were taken from populations with varying effect sizes and calculated the study weights both from in-study and between-study variances (DerSimonian et al., 1986). The fixed-effects model was conducted using the Mantel-Haenszel's method, which assumed that studies were sampled from populations with the same effect size and made an adjustment to the study weights according to the in-study variance (Mantel et al., 1959). To assess the between-study heterogeneity more precisely, both the chi-square based Q statistic test (Cochran's Q statistic) to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation due to heterogeneity were calculated (Cochran, 1954; Higgins et al., 2003). Besides, to validate the credibility of outcomes in this meta-analysis, a sensitivity analysis was performed by sequential omission of individual studies. Publication bias in this meta-analysis was assessed using funnel plot, in which the standard error of logor of each study was plotted against its logor, and an asymmetric plot suggested possible publication bias. Statistical analyses were performed with the software Stata program (version 12.0). All p values were two-sided and a P value of less than 0.05 was deemed statistically significant.

Results

Trials selection and methodology quality

Our search yielded a total of 180 studies, and after reviewing tiles and abstracts, 7 randomized controlled trials were preliminarily identified (Campistol et al., 2006; Schena et al., 2009; Salgo et al., 2010; Alberu et al., 2011; Flechner et al., 2011; Campbell et al., 2012; Euvrard et al., 2012). After screening original full-texts and extracting data, two studies were excluded: one was for lack of necessary data (Flechner et al., 2011), and one was for containing overlapping data (Schena et al., 2009). Thus, five randomized controlled trials involving a total of 1499 patients revived kidney transplantation were finally included into this meta-analysis (Campistol et al., 2006; Salgo et al., 2010; Alberu et al., 2011; Campbell et al., 2012; Euvrard et al., 2012). The main characteristics of these included 5 studies were summarized in Table 1 (Table 1). Reporting bias was assessed using the Cochrane risk of bias tool, and the risk of bias was low in all five randomized controlled trials.

Table 1. Baseline Characteristics of 5 Randomized Trials Included in the Meta-analysis

Study [Reference]	Treatment Arms	Patients	Mean Age (Mean ± SD, year)	Gender (Male, %)	Primary End Point	Follow-up
Euvrard S 2012 (Euvrard et al., 2012)	Sirolimus	64	48.0±13.0	47 (73%)	NMSC; SCC; BCC	2 years
	Calcineurin inhibitors	56	48.8±12.8	45 (80%)		
Campbell SB 2012 (Campbell et al., 2012)	Sirolimus	39	47.3±13.4	31 (80%)	NMSC; SCC; BCC	2 years
	Calcineurin inhibitors	47	47.0±10.6	34 (72%)		
Alberu J 2011 (Alberu et al., 2011)	Sirolimus	555	38.9±4.2	385 (69%)	NMSC	2 year
	Calcineurin inhibitors	275	40.8±4.4	194 (70%)		
Salgo R 2010 (Salgo et al., 2010)	Sirolimus	16	44.5± 3.1	12 (75%)	NMSC	2 year
	Calcineurin inhibitors	17	40.0±3.7	13 (76%)		
Campistol JM 2006 (Campistol et al., 2006)	Sirolimus	215	51±12	NG	NMSC; SCC; BCC	5 years
	Sirolimus/cyclosporine A	215	49±13	NG		

NG, not given; SD, standard deviation; NMSC, nonmelanoma skin cancer; SCC, Squamous-cell carcinoma; BCC, Basal-cell carcinoma

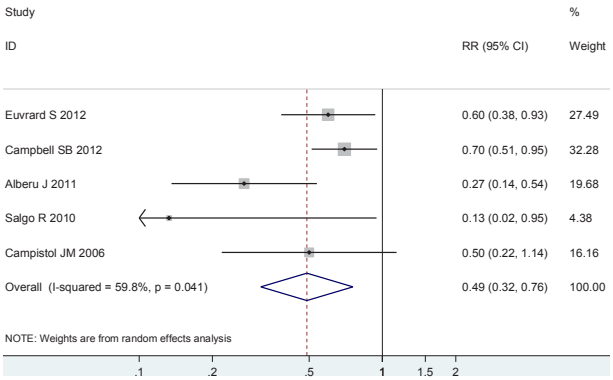

Figure 1. Forest Plot for the Meta-analysis of Sirolimus in Non-melanoma Skin Cancer Prevention

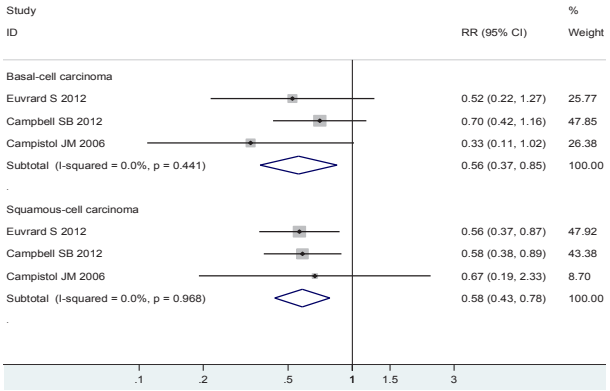

Figure 2. Forest Plot for the Meta-analysis of Sirolimus in Non-melanoma Skin Cancer Prevention by Histological Type

Meta-analysis

Five trials all reported relevant data on the NMSC (Campistol et al., 2006; Salgo et al., 2010; Alberu et al., 2011; Campbell et al., 2012; Euvrard et al., 2012), and there was obvious heterogeneity among those trials (I^2 = 59.8%), thus the random-effects model was used to pool those data. Meta-analysis showed patients who received Sirolimus-based immunosuppression had much lower risk of NMSC (RR = 0.49, 95%CI 0.32-0.76, P = 0.001) (Figure 1). Sensitivity analyses by sequential omission of individual studies did not materially alter the overall pooled RR, suggesting the pooled RR was valid and credible.

Subgroup analyses were further performed by the histological type of skin cancer. Three trials reported relevant data on the basal-cell carcinoma (Campistol et al., 2006; Campbell et al., 2012; Euvrard et al., 2012), and there was no heterogeneity among those trials (I^2 =0.0%), thus the fixed-effects model was used to pool those data. Meta-analysis showed patients who received Sirolimus-based immunosuppression had lower risk of basal-cell carcinoma (RR = 0.56, 95%CI 0.37-0.85, P = 0.006) (Figure 2). Three trials reported relevant data on the squamous-cell carcinoma (Campistol et al., 2006; Campbell et al., 2012; Euvrard et al., 2012), and there was obvious heterogeneity among those trials (I^2 = 0.0%), thus the fixed-effects model was used to pool those data. Meta-analysis showed patients who received Sirolimus-based immunosuppression had lower risk of squamous-cell carcinoma (RR = 0.58, 95%CI 0.43-0.78, P < 0.001) (Figure 2).

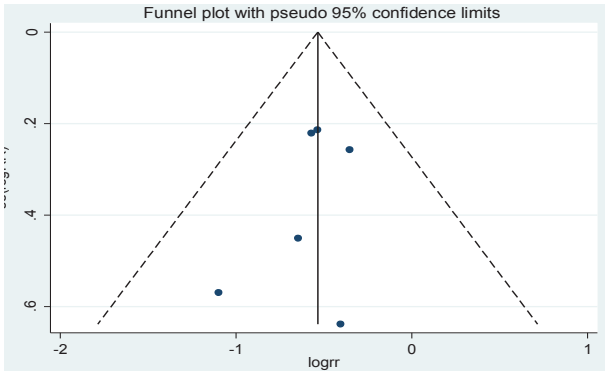

Figure 3. Funnel Plot for Assessing Publication bias in this Meta-analysis

According to the GRADE system, the quality of evidence was high for NMSC, and moderate for squamous-cell carcinoma and basal-cell carcinoma.

Publication bias

Funnel plot was used to assess the publication bias in this meta-analysis. The symmetry of funnel plot' shape suggested the publication bias was not evident in this meta-analysis (Figure 3). Thus, no evidence of publication bias was observed.

Discussion

Renal transplantation confers increased survival with improvement of immune suppressive drugs, but posttransplant malignancies can arise as secondary complications (Dantal et al., 2005; Yunus et al., 2012). Many factors can contribute to high susceptibility to posttransplant malignancies, such age at transplantation, certain types of viral infections, chronic usage of immune suppressive agents, and type of immune suppressive drugs, and ethnic characteristics (Dantal et al., 2005; Yunus et al., 2012). Because transplant recipients share common risk factors with the nonimmunosuppressed population, the specific tumor burden of posttransplant malignancies is linked to the immunosuppressive medications used (Wu et al., 2011). Among those posttransplant malignancies, NMSC is the most common cancer found in patients (Traywick et al., 2005). Skin cancers may result from both a decrease in immunosurveillance and drug-specific properties (Euvrard et al., 2003; Wisgerhof et al., 2010). Calcineurin inhibitors (cyclosporine and tacrolimus) may enhance tumor development through mechanisms independent of host immunity (De Masson et al., 2011), while mTOR inhibitors, including Sirolimus and Everolimus, are newer immunosuppressants that have antineoplastic properties (Halloran, 2004).

Long-term immunosuppression imposes increased malignancy risk in renal allograft recipients, significantly contributing to mortality. Whether Sirolimus was useful in the prevention of NMSC has not been assessed and we perform this meta-analysis of randomized controlled trials to test the hypothesis that Sirolimus-based immunosuppression is associated with a decreased risk in NMSC. Finally, 5 randomized trials involving a total of 1499 patients revived kidney transplantation were

included into this meta-analysis. Patients who received Sirolimus-based immunosuppression had lower risk of NMSC (RR = 0.49, 95%CI 0.32-0.76, P = 0.001). Subgroup analyses by tumor type showed that Sirolimus-based immunosuppression significantly decreased risk of both squamous-cell carcinoma (RR = 0.58, 95%CI 0.43-0.78, P < 0.001) and basal-cell carcinoma (RR = 0.56, 95%CI 0.37-0.85, P = 0.006). The quality of evidence was high for NMSC, and moderate for squamous-cell carcinoma and basal-cell carcinoma. Thus, there is a high quality evidence suggests that Sirolimus-based immunosuppression decreases risk of non-melanoma skin cancer, and Sirolimus has an antitumoral effect among kidney-transplant recipients.

There may be a specific antineoplastic activity of Sirolimus that explains the decrease in new skin cancers rather than a lower amount of immunosuppression (Euvrard et al., 2012). The effects of mTOR inhibitors have been extensively studied in animal models and assessed in clinical studies both in patients who were not undergoing organ transplantation and in those with cancer (Serra et al., 2010). Sirolimu interrupts the PI3K-AKT pathway, which plays a critical role in the regulation of cell proliferation, survival, mobility, and angiogenesis (De Luca et al., 2012). In addition, mTOR inhibitors also inhibit the growth of endothelial cells and the progression of tumor neovascularization at serum concentrations that correspond to the target levels for transplant recipients, both through a decrease of synthesis and a signaling inhibition of vascular endothelial growth factor (Guba et al., 2004). Furthermore, Sirolimus had a better effect on the progression of ultraviolet radiation (UV)-induced tumors than on the initiation of such tumors (de Gruijl et al., 2010). Thus, there are obvious evidences for the specific antineoplastic activity of Sirolimus in the prevention of skin cancer.

The eligibility criteria for inclusion of patients revived kidney transplantation differed for each study, which might influence the obvious consistency of effects across the included studies. Besides, a meta-analysis of updated individual patient data should be done because this provides the least biased and most reliable means of addressing questions that have not been satisfactorily resolved by individual clinical trials (Simmonds et al., 2005). Besides, cost-effectiveness analysis was not studied in present study. Cost-effectiveness analysis can provide important information for the allocation of health care resources across a broad range of conditions and interventions (Russell et al., 1996). Further studies can analyze the cost-effectiveness of Sirolimus in non-melanoma skin cancer prevention for patients with kidney transplantation.

In conclusion, there is high quality evidence suggests that Sirolimus-based immunosuppression decreases risk of non-melanoma skin cancer, and Sirolimus has an antitumoral effect among kidney-transplant recipients.

Acknowledgements

The author(s) declare that they have no competing interests.

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