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REVIEW

Assessing the relative risk of cardiovascular disease among renal transplant patients receiving tacrolimus or cyclosporine

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Summary

Calcineurin inhibitors potentially contribute to risk of cardiovascular events through the development of new-onset diabetes mellitus, hypertension and hyperlipidemia. The exact extent to which calcineurin inhibitors affect these risk factors is difficult to establish since pre-existing renal disease and concomitant immunosuppressive agents (such as steroids or TOR inhibitors) also exert an effect. Clinical trials have consistently shown a higher incidence of new-onset diabetes mellitus with tacrolimus, which has been borne out in large-scale registry analyses. However, the risk of hypertension is approximately 5% higher with cyclosporine than tacrolimus, as is the risk of hyperlipidemia. Statin therapy is effective in treating dyslipidemia and has significant benefits in renal transplant patients. An individualized approach to choice of calcineurin inhibitor, by which cyclosporine or tacrolimus are selected based on the patient's particular risk profile, may thus help to reduce the toll of cardiovascular mortality among renal transplant recipients in the future.

The burden of cardiovascular disease in the renal transplant population

Premature cardiovascular disease (CVD) is common after renal transplantation, accounting for up to 50% of deaths [1,2]. Cardiovascular events are at least twice as frequent in renal transplant recipients as in the general population [3] with a corresponding increase in cardiovascular mortality. Renal transplant patients with diabetes are at particularly high relative risk of a cardiovascular event [1]. As renal allograft survival improves [4], death with a functioning graft due to cardiovascular disease is also likely to become a more important cause of graft loss. Prevention of premature cardiovascular disease is thus an important target to prolong graft and patient survival following transplantation.

Risk factors for cardiovascular disease in the renal transplant population

The high incidence of cardiovascular disease seen in renal transplant patients can be attributed to three categories of risk factors. Firstly, there are conventional risk factors such as age, gender, family history, smoking and hypertension, at least some of which may be more heavily represented in the transplant population when compared to the general population. Secondly, there may be additional risk factors associated with deterioration of renal function, either due to recurrence of the original disease, genetic predisposition to progression of renal failure, or to abnormalities occurring secondary to renal dysfunction such as anemia and hypertension. Thirdly, there are cardiovascular risk factors specifically related to transplantation, most notably those that occur secondary to immunosuppressive therapy, but also acute rejection (and its treatment) and viral infections such as cytomegalovirus.

An analysis of risk factors for major ischemic heart disease (IHD) events has been carried out by Kasiske and colleagues in 1,124 renal transplant recipients who had a functioning graft for more than 1 year [5], in whom the observed risk was compared to that estimated from the Framingham study risk factors. Type 1 and 2 diabetes, increasing age, smoking, and

low HDL-cholesterol in women were all independently related to the risk of IHD following renal transplantation. A diagnosis of 'hypertension' was not associated with increased risk although higher blood pressures were associated with high cardiovascular event rates. In terms of transplant-specific risk factors, the following were found to be predictive of IHD: new-onset diabetes mellitus after transplant, transplantation prior to 1992, two or more episodes of rejection, bilateral nephrectomy, serum albumin <4.0 mg/dl and proteinuria. This analysis showed that some risk factors identified in the Framingham analysis are disproportionately predictive of IHD in renal transplant recipients, and may thus merit additional attention when attempting to reduce cardiovascular risk following transplantation. Specifically, the relative risk of IHD associated with diabetes mellitus was 2.78 in male transplant patients compared to 1.53 in men within the general population, and 5.40 in women compared to 1.82 in the nontransplant population (Fig. 1) [5]. The impact of blood pressure was less than that predicted by the Framingham Study in the general population equation.

Calcineurin inhibition-related risk factors for cardiovascular disease

Three adverse effects of calcineurin inhibition merit consideration as potential risk factors for CVD after renal transplantation: new-onset diabetes mellitus, hypertension and lipid dysregulation. Each of these is associated with both commercially available calcineurin inhibitors, cyclosporine (CsA) and tacrolimus, but to differing degrees [6]. Inevitably, the risk of these occurring is influenced by a host of other factors, such as genetic susceptibility, pre-existing subclinical disease, concomitant medications such as steroids, and the extent of drug exposure. Nevertheless, there is sufficient evidence to evaluate the comparative risk of new-onset diabetes mellitus, raised blood pressure and hyperlipidemia with CsA and tacrolimus, and the likely impact that the differences may exert in terms of cardiovascular events.

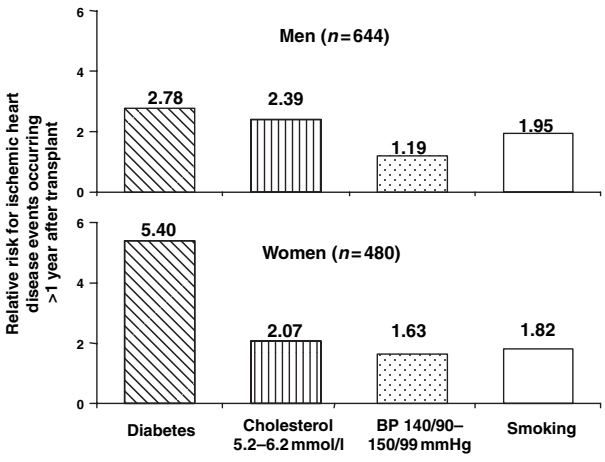

Figure 1 Relative risk of ischemic heart disease associated with modifiable risk factors among renal transplant recipients >1 year post-transplant [5].

Relative diabetogenic effect of tacrolimus and CsA

In the study by Kasiske, new-onset diabetes increased the risk of death by 87% (RR 1.87, 95% CI 1.60–2.18, $P < 0.0001$) in renal transplant patients. As in the general population, the risk of diabetes is affected by demographic and metabolic variables such as age, race, male gender and body mass index. However, renal transplant recipients bear the additional burden of diabetogenic immunosuppression [7]. A meta-analysis of 19 studies in solid organ transplantation, based on a total of 3,611 patients, reported that the type of immunosuppression accounted for 74% of the variability in incidence of new-onset diabetes mellitus [8].

Three comparative clinical trials have reported the incidence of diabetes in renal patients who were not diabetic at time of transplant (although we have no data on the prevalence of impaired glucose tolerance). Two of these were the registration studies for tacrolimus, that compared tacrolimus versus the Sandimmune formulation of CsA. The US study reported that 19.9% of tacrolimus-treated patients and 4.0% of CsA-treated patients required insulin for 30 days during the first year following transplantation ($P < 0.001$) [9]. Similarly, there was a higher incidence of new-onset diabetes using tacrolimus in the European study (8.3% vs. 2.2%) [10]. The absolute differences in the incidence of new-onset diabetes between these studies reflects the susceptibility of blacks to diabetes and the higher proportion of blacks in the North American study. However, both trials showed a 4–5-fold increase in the incidence of new-onset diabetes with tacrolimus at the doses used in these studies. The only published large-scale comparative trial of tacrolimus and CsA (Neoral) reported a 4.5% incidence of new-onset diabetes with tacrolimus and 2.0% with CsA over 6 months (n.s.) and a significantly higher mean blood glucose in the tacrolimus cohort [11]. A meta-analysis of clinical studies has found a 5-fold increase in incidence of diabetes mellitus after transplantation with tacrolimus [12] when compared to CsA.

The relative risk of new-onset diabetes has also been evaluated in two studies of renal registry databases. The first assessed data from 1996 to 2000 on 11,659 patients who were not diabetic at time of transplant, and used

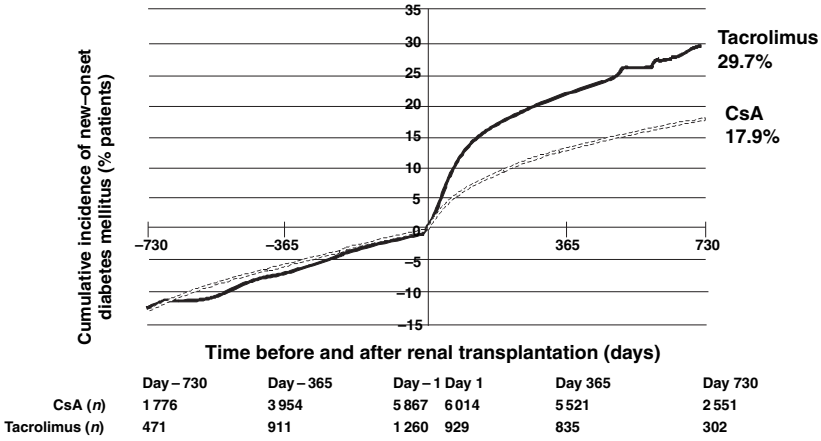

Figure 2 Incremental incidence of new-onset diabetes mellitus to 2 years post-transplant among renal transplant recipients receiving CsA or tacrolimus who were not diabetic at time of transplantation. Incremental incidence refers to total incidence minus the expected incidence if transplantation had not occurred. Adapted from Woodward *et al*. [13].

Cox proportional hazards analysis to show that use of tacrolimus as initial maintenance immunosuppression increased the risk of developing diabetes by 53% (RR 1.53, 95% CI 1.29–1.81, $P < 0.001$) [7]. A separate analysis of almost 7,000 patients, transplanted between 1994 and 1998, reported that the incidence of new-onset diabetes at 2 years post-transplant was 29.7% in the tacrolimus-treated patients compared to 17.9% in the CsA cohort (Fig. 2) [13]. The authors commented that patients receiving tacrolimus, but not those on CsA, continue to develop new-onset diabetes at an increased rate after the first year following transplantation.

For patients who develop new-onset diabetes while receiving tacrolimus, switch to CsA may be considered, particularly if blood glucose levels are not readily controlled by oral hypoglycemic agents or insulin is required [14]. In patients who develop diabetes while receiving CsA, it may be effective to minimise CsA by the addition of, or increasing the dose of, a proliferation inhibitor.

Hypertension in the CNI-treated renal transplant recipient

Over half of all renal transplant patients have systolic blood pressure >140 mm Hg (Fig. 3) [15], despite antihypertensive treatment. With such a high prevalence it can be hard to determine the relative hypertensive effect of immunosuppressive agents accurately. It is known that both CsA and tacrolimus therapy are associated with reduced nitric oxide production [16,17] and impaired endothelial function [18,19], contributing to impaired vasodilation and hypertension. Forearm blood flow response to carbachol, an endothelium-dependent vasodilator, is reduced in patients receiving CsA [16] and high-resolution ultrasound has demonstrated inhibited endothelium-dependent vasodilation with tacrolimus and, particularly, CsA [20]. Three large-scale prospective studies have reported the relative incidence of 'hypertension' with tacrolimus and CsA, albeit without a clear definition or reporting of absolute blood pressures or usage of antihypertensive medication. Two of these, using CsA (Sandimmune) and higher tacrolimus dosing regimens than are generally used today, found no significant difference in the proportion of patients developing 'hypertension' [9,10]. A more recent study, in which tacrolimus was compared to CsA (Neoral) and tacrolimus dosing was more representative of current practice, found a 5% difference in incidence of hypertension (tacrolimus 15.7%, CsA 23.2%, $P < 0.05$) [11]. Given the impact of renal dysfunction on blood pressure, it is also interesting to consider the relative hypertensive effect of the two agents in liver transplantation. For the two large-scale trials of tacrolimus versus CsA (Neoral) published in the literature, one found no difference in use of antihypertensive agents (occurrence of hypertension or blood pressure levels were not reported) [21], and the other showed a

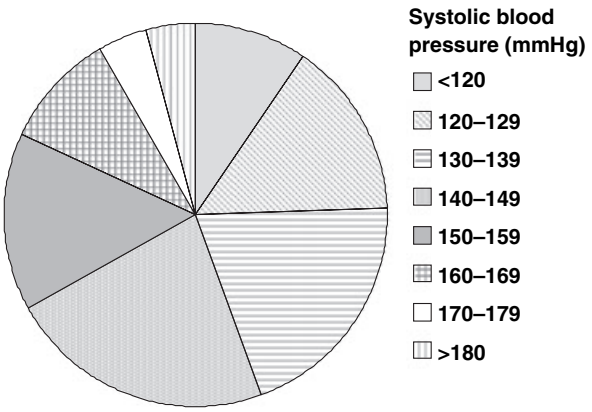

Figure 3 Incidence of hypertension among cadaveric renal transplant recipients with a functioning graft at 1 year registered with the Collaborative Transplant Study [15].

significantly lower incidence of 'hypertension' with tacrolimus (24% vs. 31%, $P < 0.01$) [22]. In a direct comparative study of 499 liver transplant patients, there was no significant difference in incidence of hypertension at 6 months between tacrolimus and patients managed by C_2 monitoring of Neoral [23].

There is no consensus on therapeutic approaches to hypertension in this population, nor appropriate targets. The choice of individual agents may be restricted by comorbid disease (e.g. angina or peripheral vascular disease) and current practice still favours the use of beta blockers and calcium antagonists, rather than angiotensin converting enzyme inhibition or angiotensin II blockade, although the latter are more effective. Most patients require two or more agents.

Dyslipidemia in CNI-treated renal transplant recipients

Approximately 60% of renal transplant recipients have raised total cholesterol or LDL-cholesterol, and 35% have hypertriglyceridemia [24]. Lipid dysregulation has a complex aetiology and in the renal transplant population there is a high incidence of disposing factors such as age, obesity, diabetes and ethnicity. Superimposed on these, is the additional risk related to renal dysfunction and proteinuria, as well as the polypharmacy that is typical of renal transplant recipients, including use of diuretics, beta blockers, steroids, TOR inhibitors and calcineurin inhibitors.

Raised total cholesterol is a predictor of IHD, but does not appear to increase risk of cerebrovascular or peripheral vascular disease in renal transplant patients [25]. Relative risk of IHD has been reported to increase 2-fold if total cholesterol exceeds 6.2 mmol/l in male recipients of a renal transplant or exceeds 5.2 mmol/l in female recipients [5]. There is also evidence to suggest that hyperlipidemia may have an effect on risk of chronic rejection in some patient types. An analysis of 442 renal transplant patients with a functioning graft at 1 year has reported that although hypercholesterolemia (>6.5 mmol/l) had no effect on graft loss over the following 10 years in patients who remained rejection-free, male patients (but not females) who had experienced rejection showed a significant association between hypercholesterolemia and risk of graft loss. Another trial has reported that the association between cholesterol levels and graft outcome is only significant in younger recipients [26]. Most published studies, however, have reported no impact of hypercholesterolemia on graft survival [27,28].

Although both tacrolimus and CsA are hyperlipidemic, CsA has a more pronounced effect. In a randomised 6-month trial of tacrolimus and CsA (Neoral) in 560 patients, the incidence of 'hyperlipidemia' (as defined by the investigator) was 8.9% with CsA and 4.2% with tacrolimus ($P < 0.05$) [11]. Mean total cholesterol was 5.9 mmol/l in the CsA group at 6 months compared to 5.4 mmol/l with tacrolimus ($P < 0.0001$), similar to previous findings in a registration study of tacrolimus versus Sandimmune [9]. A registry analysis of 8,952 renal transplant patients who did not have hyperlipidemia at time of transplantation, has shown the incidence of new-onset hyperlipidemia at 2 years post-transplant was 4.6% higher with CsA compared to tacrolimus [29].

Some authors have proposed switching patients with stable renal allograft function from CsA to tacrolimus if total cholesterol level is >6.2 mmol/l [30]. However, administration of low-dose statin therapy appears to achieve greater reduction in lipid levels than switch to tacrolimus [31]. Statin therapy is as effective in treating hyperlipidemia in the renal transplant population as in the general population [32], and achieves a comparable reduction in the incidence of myocardial infarction and cardiac death. The recent ALERT study, in which over 2000 renal transplant patients (all more than 6 months post-transplant) were randomised to receive fluvastatin or placebo, reported significantly fewer cardiovascular deaths or non-fatal myocardial infarctions in the fluvastatin group (70 vs. 140, $P = 0.005$) [33]. A survival benefit with statin therapy has been reported elsewhere [34], albeit not in the setting of a randomised trial. It may be appropriate to offer statin therapy routinely to all transplant recipients in view of their heightened cardiovascular risk and it certainly provides an effective means of correcting hyperlipidemia secondary to immunosuppression.

Conclusions

Assessing the overall cardiovascular risk related to an individual drug is necessarily complex due to the multitude of risk factors involved, particularly in renal transplant recipients. A multivariate analysis of patients transplanted between 1963 and 1997 has shown no difference between CsA and tacrolimus on risk of IHD [5]. Recently, an attempt was made to quantify the risk for coronary artery disease associated with CsA and tacrolimus in a 6-month prospective study of 557 renal transplant recipients [35]. This reported significantly lower serum cholesterol and blood pressure with tacrolimus, but significantly higher blood glucose. The authors used the Framingham risk algorithm to assign 10-year risk of coronary heart disease based on these data, and found a significantly lower risk in men treated with tacrolimus but not in women. However, since the weighting according to diabetes and hypertension by the Framingham algorithm may not be applicable to renal transplant patients [5], this methodology may be inappropriate.

In terms of the three main factors to consider when studying cardiovascular risk associated with calcineurin inhibitors, the relative risk is becoming better defined. The risk of hypertension is approximately 5% higher with CsA than tacrolimus [11], and can be difficult to control even with polypharmacy. However, hypertension may carry less risk for IHD in renal transplant patients than in the general population [5], possibly because hypertension is endemic in renal transplant recipients. New-onset diabetes, which occurs at least twice as frequently in tacrolimus-treated patients compared to CsA-treated patients, is associated with a 2.5-fold increased risk of IHD in renal transplant patients [5], and a comparable increased risk of death [7]. In contrast, hyperlipidemia is seen in 5% more CsA-treated patients than those receiving tacrolimus [30]. Although this will affect cardiovascular risk, it is readily reduced by statins, which recent evidence suggests should be used in the vast majority of transplant recipients.

In the absence of a long-term, large-scale prospective study, it is reasonable to assume that overall cardiovascular risk is relatively similar for both CsA and tacrolimus. Given the shift to individualized immunosuppression, avoidance of tacrolimus in patients with, or at risk of developing, new-onset diabetes may help to avoid excessive cardiovascular risk. Similarly, patients with moderate or severe dyslipidemia that remains unresponsive to statin therapy may be more appropriate for tacrolimus therapy than CsA. A selective approach to choice of calcineurin inhibitor may thus help to reduce the toll of cardiovascular mortality among renal transplant recipients in the future.

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