Long-term cardiovascular risk in transplantation—insights from the use of everolimus in heart transplantation

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Abstract

Everolimus is a potent immunosuppressive agent that has anti-proliferative activity. The benefits of everolimus vs azathioprine in de novo heart transplant recipients were assessed in a randomized, double-blind study. Patients (n = 634) were randomized to receive everolimus (1.5 mg/day or 3.0 mg/day) or azathioprine; all patients received steroids and full-dose ciclosporin (CsA). The primary endpoint was the incidence of efficacy failure [biopsy-proven acute rejection (BPAR), graft loss, death or loss to follow-up]. The incidence of cardiac allograft vasculopathy (CAV) was assessed by intravascular ultrasound. The incidence and hospitalization costs of major adverse cardiac events (MACE) were assessed after 4 years. The incidence of efficacy failure was significantly reduced with everolimus compared with azathioprine at 12, 24 and 48 months (P < 0.05), largely because of a lower incidence of BPAR. An increase in serum creatinine levels was seen with everolimus compared with azathioprine at 12, 24 and 48 months (P < 0.05), largely because of a lower incidence of BPAR. An increase in serum creatinine levels was seen with everolimus compared with azathioprine, likely attributed to CsA nephrotoxicity. There was a significantly larger increase in vascular intimal thickness with azathioprine than with everolimus (P ≤ 0.01), which was accompanied by a significantly lower incidence of CAV in the everolimus groups. After 4 years, the incidence of MACE was higher with azathioprine than with either dose of everolimus. MACE-related treatment costs were estimated at $431,428 for azathioprine, $136,664 for everolimus 1.5 mg/day (68% saving) and $191,957 for everolimus 3.0 mg/day (56% saving). Everolimus is significantly more effective than azathioprine in preventing efficacy failure in de novo heart transplant recipients and is also associated with reduced incidence and severity of CAV and MACE at 4 years post-transplant. The reduced 4-year incidence of MACE is likely to lead to substantially reduced hospitalization costs. Since cardiovascular morbidity and mortality are important factors in the long-term survival of renal transplant recipients, applying lessons from the use of everolimus in heart transplantation may further improve the understanding of managing cardiovascular risk in renal transplantation.

Keywords: azathioprine; cardiac allograft vasculopathy; everolimus; heart transplantation; MACE; renal transplantation

Introduction

Everolimus (Certican®, Novartis Pharma AG, Basel, Switzerland) is a potent immunosuppressant that also has important anti-proliferative properties; both of these effects are related to its action as a proliferation signal inhibitor. Growth factors, such as interleukin 2, that are secreted by T-cells are important in promoting clonal lymphocyte expansion. While calcineurin inhibitors (CNIs) prevent the production of such growth factors, everolimus acts further downstream to prevent antigen-driven T-cell proliferation [1]. Everolimus also differs from mycophenolic acid-based agents, which inhibit the de novo pathway of purine synthesis. Importantly, the anti-proliferative actions of everolimus are not limited to the immune system, but also act to reduce vascular smooth muscle proliferation [2] and prevent vascular remodelling [3], which is known to be a key component of progressive allograft dysfunction [4]. The use of everolimus in de novo heart transplant recipients has significant benefits in reducing the incidence of cardiac allograft vasculopathy (CAV) [5–7] and associated major adverse cardiac events (MACE) [8]. Given that cardiovascular morbidity and mortality have a major impact on the long-term survival of renal transplant recipients, the implications of these studies may be relevant in renal transplantation.
Efficacy of everolimus in de novo heart transplant recipients

The everolimus B253 study was a randomized, double-blind trial comparing everolimus (1.5 mg/day or 3.0 mg/day) with azathioprine (1–3 mg/kg/day) in 634 de novo heart transplant recipients [5–7]. The primary objective of the study was to assess the efficacy of everolimus in terms of a composite efficacy failure endpoint consisting of the incidence of biopsy-proven acute rejection (BPAR) of at least grade 3A (or any rejection associated with haemodynamic compromise), graft loss, death or loss to follow-up. Secondary endpoints included the individual components of the composite endpoint, as well as the incidence of CAV, assessed by intravascular ultrasound (IVUS). Safety assessments included adverse events, infections and laboratory parameters. Patients were randomized to treatment within 72 h after transplantation, and all the patients received full-dose ciclosporin (CsA) microemulsion (maintaining trough blood levels of 250–400 ng/ml) and steroids (0.5–1.0 mg/kg/day) in addition to the study medication. The initial study period was 2 years, and this was followed by a 4 year extension [7].

After 12 months of treatment, the incidence of efficacy failure was significantly reduced with both doses of everolimus compared with azathioprine \((P < 0.05; \text{Figure 1})\) [5]. Subsequent follow-up has shown that the superior efficacy of everolimus was maintained at 24 and 48 months (Figure 1) [6,7]. Analysis of secondary endpoints revealed that the increased incidence of efficacy failure in the azathioprine group was largely the result of an increased incidence of BPAR. At 24 months, the incidence of BPAR in the azathioprine group was 48.1% compared with 34.9% and 22.7% in the everolimus 1.5 mg/day and 3.0 mg/day groups, respectively \((P < 0.05)\) [6].

Over the first 12 months of treatment, everolimus was associated with an increase in serum creatinine levels compared with azathioprine, which is likely to be related to potentiation of the nephrotoxic effects of CsA [5]. A significant difference between the azathioprine and everolimus groups with regard to serum creatinine continued to be evident up to 48 months [7], although the creatinine level stabilized after month 12 as the result of a protocol amendment stating that CsA trough blood levels should be maintained at a lower level of 100 ng/ml, while everolimus trough blood levels remain within the recommended target level (i.e. more than 3 ng/ml) [5,6]. In light of these observations, the CsA dose should be reduced early post-transplant; this approach has been proven to maintain immunosuppressive efficacy in clinical experience [9–11].

Assessment of cardiac allograft vasculopathy by intravascular ultrasound

The main component of post-transplant vasculopathy is intimal thickening as a result of smooth muscle cell proliferation [12], and thus the condition can be considered as a proliferative disease. IVUS is an important technique for the assessment of CAV, as it is the only available technique that allows simultaneous assessment of lumen size and vessel wall morphology. This provides an important advantage over coronary angiography, which simply outlines the vessel lumen with contrast dye. Thus, a vessel which appears normal on a coronary angiogram may reveal significant amounts of atherosclerosis or intimal thickening using IVUS [13]. Moreover, an IVUS validation study in 125 primary heart transplant recipients suggested that the incidence of CAV (defined as progression of intimal thickening by more than 0.5 mm) in the first year after transplantation is a reliable surrogate marker for subsequent mortality and non-fatal MACE within 5 years after heart transplantation [14].

In the everolimus B253 study, CAV was assessed by IVUS in a subgroup of patients, with the first assessment carried out at baseline (i.e. during the first week after transplantation), and follow-up evaluations after 1 and 2 years post-transplantation. After 1 year of treatment, the average increase in intimal thickness was significantly larger (0.10 mm) with azathioprine than with everolimus 1.5 mg/day (0.04 mm; \(P = 0.01\)) or 3.0 mg/day (0.03 mm; \(P = 0.003\)) [5]. This was accompanied by a significantly lower incidence of CAV in the everolimus 1.5 mg/day (35.7%; \(P = 0.045\)) and 3.0 mg/day (30.4%; \(P = 0.01\)) groups compared with the azathioprine group (52.8%). Results from the 24 month analysis show that these benefits on IVUS parameters and incidence of CAV are maintained (Table 1) [6].
Major adverse cardiac events in heart transplant recipients

Patients who had an IVUS measurement at baseline and at 1 year in the B253 study were eligible for a 4 year evaluation of MACE [defined as acute myocardial infarction, congestive heart failure, percutaneous cardiac intervention (PCI), coronary artery bypass grafting (CABG), implantable cardiac defibrillator (ICD), cerebrovascular accident or peripheral vascular disease] [8]. This evaluation included 211 patients (azathioprine, n=72; everolimus 1.5 mg/day, n=70; everolimus 3.0 mg/day, n=69), with all the incidences of MACE occurring after the first month of treatment included in the analysis.

Similarly to the incidence of CAV, at 4 years post-transplant, the total incidence of MACE was higher with azathioprine than with either dose of everolimus (Figure 2) [8]. The majority of occurrences of MACE comprised congestive heart failure, with no incidences of CABG or ICD reported in the 4 years of follow-up. Notably, the reduced incidence of MACE in the everolimus groups was largely accounted for by a reduced incidence of PCI (mainly angioplasty), with six incidences of PCI in the azathioprine group compared with one in the everolimus 3.0 mg/day group. There were no incidences of PCI in the everolimus 1.5 mg/day group. Two deaths, as a result of MACE were reported during the study, both of which occurred in azathioprine-treated patients with CAV. One patient died as a result of coronary heart failure and one due to coronary artery occlusion.

To calculate the treatment costs of MACE, data for the mean costs of hospitalization were obtained from the US Healthcare Cost and Utilization Project, in which costs ranged from $70 618 for a CABG to $20 600 for congestive heart failure [15]. Overall, the total treatment costs for MACE were estimated at $431 428 for azathioprine, $136 664 for everolimus 1.5 mg/day and $191 957 for everolimus 3.0 mg/day (Table 2), representing economic savings of 68.3% for everolimus 1.5 mg/day and 55.5% for everolimus 3.0 mg/day vs azathioprine [8].

Discussion

The results of the B253 study have a number of important implications for renal transplant recipients.

Patients who receive a renal transplant are at a significantly increased risk of cardiovascular disease [16–18]. This is, in turn, is associated with a substantially increased risk of cardiovascular mortality [18]. Therefore, it is critical that immunosuppressive regimens are chosen that combine optimum efficacy with minimal risk of cardiovascular disease. The results of the B253 study show that the use of everolimus in heart transplant recipients can significantly reduce the incidence of cardiovascular disease compared with azathioprine, with the potential to reduce healthcare costs, and it seems likely that similar results will be seen in renal transplant recipients. Indeed, reports of everolimus use in renal transplant recipients suggest that it may be beneficial for cardiovascular risk factors such as hypertension (see case report by Pascual in this supplement). In clinical studies, everolimus has been associated with an increased risk of dyslipidaemia [19], although this can easily be managed with statin therapy [20]. Notably, when combined with reduced-dose CsA therapy, everolimus 1.5 mg/day is associated with a lower incidence of hypertension, hypercholesterolaemia and hypertriglyceridaemia compared with either everolimus plus full-dose CsA or mycophenolate mofetil (MMF) plus full-dose CsA [21].

Results from the B253 study also confirm the effects of concomitant administration of everolimus

<table>
<thead>
<tr>
<th>IVUS measurement: change from baseline</th>
<th>Everolimus 1.5 mg/day (n=45/209)</th>
<th>Everolimus 3.0 mg/day (n=44/211)</th>
<th>Azathioprine (n=60/214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum intimal thickness (mm)</td>
<td>0.07*</td>
<td>0.06**</td>
<td>0.15</td>
</tr>
<tr>
<td>Intimal area (mm²)</td>
<td>0.79**</td>
<td>0.83**</td>
<td>1.52</td>
</tr>
<tr>
<td>Intimal volume (mm³)</td>
<td>13.21</td>
<td>12.54**</td>
<td>20.25</td>
</tr>
<tr>
<td>Incidence of vasculopathy (%)</td>
<td>33.3*</td>
<td>45.5</td>
<td>58.3</td>
</tr>
</tbody>
</table>

*P < 0.05 vs azathioprine; **P < 0.01 vs azathioprine.
plus full-dose CsA on renal function, with significantly higher serum creatinine levels reported in the everolimus groups compared with the azathioprine group after 12 months of treatment [5]. Studies in renal transplant recipients have shown similar results for everolimus and full-dose CsA in comparison with MMF [22,23], however, this effect is unlikely to be the result of a direct effect of everolimus to induce renal dysfunction, and is instead related to the potentiation of CsA-related nephrotoxicity. Thus, in the B253 study, a reduction in trough blood levels of CsA led to the stabilization of serum creatinine [5,7]. Clinical experience with everolimus and low-dose CNI in heart transplantation also suggests that this is an efficacious regimen leading to preservation of renal function [24]. Furthermore, it has also been shown that de novo renal transplant recipients who receive everolimus plus a reduced exposure to CsA achieve comparable efficacy with those receiving full-dose CsA, with improved renal function [25,26]. Use of everolimus has been found to enable a 57% reduction in the dose of CsA; this was associated with improvements in serum creatinine levels and creatinine clearance over 6 and 12 months [21,25].

Conclusions

Heart transplant recipients receiving everolimus in combination with CsA and steroids experience a significantly lower incidence of treatment failure 4 years post-transplant compared with azathioprine, largely as a result of a reduced risk of BPAR. Importantly, despite increased lipid levels in patients receiving everolimus, there are substantial cardiovascular benefits in these patients, including significant reductions in the incidence and severity of CAV, and a reduced incidence of MACE at 4 years after transplantation. Renal transplant recipients may experience similar benefits on cardiovascular disease, as these patients are known to be at a high risk of cardiovascular morbidity and mortality. Optimization of CsA levels is required to provide the maximum level of graft protection and tolerability.

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