Effect of different immunosuppressive regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study

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Abstract

Background. The metabolic syndrome (MS) is an important risk factor for graft dysfunction and patient death after renal transplantation. The aim of this sub-analysis of the Symphony study was to assess the progression of the laboratory parameters associated with MS in the first year after transplantation.

Methods. Data collected from the Symphony study were used; 1645 patients were randomized to receive standard-dose cyclosporine (Stand-CsA), low-dose cyclosporine (Low-CsA), tacrolimus (Low-Tac) or sirolimus (Low-SRL), in addition to mycophenolate mofetil (MMF) and corticosteroids. Data were collected for levels and progression over the first year post-transplantation of systolic and diastolic blood pressure, uric acid, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and fasting glucose levels by treatment arm.

Results. The low-SRL group had significantly higher levels of triglycerides and LDL. The two CsA arms were associated with the highest uric acid levels at each time point. There were no significant differences in overall levels or changes in glucose or HDL. Patients in the standard-CsA arm had significantly higher diastolic blood pressure than those in the Low-SRL and Low-Tac arms. Systolic blood pressure was higher in the Low-CsA arm than in the Low-Tac arm. The use of antihypertensive and antidiabetic agents was similar between the treatment arms. In the Low-SRL arm, more patients were treated with lipid-lowering therapy. Mean daily steroid doses were the highest in the Low-SRL arm.

Conclusions. This sub-analysis demonstrates that there is a difference in metabolic parameters between immunosuppressive groups. CsA therapy was associated with the highest values of uric acid and systolic and diastolic blood pressure. Patients on SRL therapy had the worst lipaemic control. A possible effect of Tac on new-onset diabetes could not be excluded.

Keywords: calcineurin inhibitor; metabolic parameters; renal transplantation; Symphony study

Introduction

In contrast to the short-term survival, the long-term outcome of both transplant recipients and their grafts has not improved. Therefore, optimization of long-term outcome has become increasingly important. Leading causes of graft loss in the renal transplant population are patient death, which is often related to cardiovascular disease, and chronic graft dysfunction. Chronic renal graft dysfunction is the result of both immunological and non-immunological insults. Some non-immunological factors associated with chronic renal graft dysfunction are high donor age, calcineurin inhibitor toxicity, obesity, dyslipidaemia, arterial hypertension and new-onset hyperglycaemia after transplantation. These non-immunological risk factors constitute the metabolic syndrome (MS). There is increasing evidence that presence of MS induces a prominent risk for chronic graft dysfunction, graft loss, new-onset diabetes after transplantation (NODAT) and patient death [1]. However, all components of MS do not appear to contribute equally to chronic graft dysfunction. Systolic blood pressure and hypertriglyceridaemia are independently associated with impaired renal allograft function beyond the first year after transplantation [2, 3].

It is well known that immunosuppressive therapy plays an important role in the development of metabolic complications after transplantation. The prevalence of hypertension, glucose intolerance and hyperlipidaemia after transplantation is high. Evidence from comparative and conversion trials suggests that blood pressure, hyperlipidaemia and hyperglycaemia may be differentially affected by different types of immunosuppressive drugs. Cyclosporine A (CsA), and to a lesser extent tacrolimus (Tac), is associated with...
defined as having MS: obesity (BMI > 30 kg/m²), triglycerides > 150 mg/dL, high-density lipoprotein (HDL) < 40 mg/dL in men or < 50 mg/dL in women, blood pressure > 130/85 mmHg, and fasting blood glucose > 100 mg/dL. The proportion of patients classified with MS was based only on patients without any missing values for the applicable parameters within each follow-up period. These proportions were also estimated based on interpolated values based on measurements at other time periods for individual patients. New onset of MS was considered to be the presence of the syndrome at 12 months but absence at baseline. We also calculated the proportion of patients who had MS at baseline who did not qualify at the completion of the study. Medication information was reported throughout the study period. Medications were classified as lipid lowering, blood pressure lowering and insulin/oral antidiabetics. We reported the proportion of patients within each study arm who used any medication within these classes at any point during the study period. We then tested for any association between use of medication within each class and treatment arm. Differences between numbers of antihypertensive medications were evaluated using Poisson regression.

The graphical representation of the progression of parameters over time was depicted using spline functions, with the mean levels by treatment arm at the applicable follow-up intervals. Analysis of variance models were used to detect any significant difference in 1-year levels of parameters between treatment arms. For models that were statistically significant, individual mean levels of treatment arms were compared and P-values were adjusted for multiple comparisons by the Tukey method. Comparisons of proportions were conducted with chi-squared tests. All analyses were conducted with SAS v.9.2 software (SAS Inc., Cary, NC).

Results

Baseline characteristics

Table 1 demonstrates the baseline characteristics of the four different immunosuppressive groups. There were no significant between-group differences with respect to clinical, demographic and donor-recipient characteristics.

Blood pressure

Figure 1a shows the mean systolic blood pressure of patients according to immunosuppressive regimen. A significant difference in mean systolic blood pressure at 1 year was evident between patients in the Low-CsA and the Low-Tac treatment arms, with an average level that was 4 mmHg lower in Low-Tac patients (n = 1327). Additional comparisons were not statistically significant between treatment arms. Mean levels were similar when restricting the analysis to patients who were on treatment at 1 year; however, with the smaller number of patients, none of the comparisons between treatment arms were statistically significantly different.

The progression of mean diastolic blood pressure levels according to immunosuppressive regimen is shown in Figure 1b (n = 1325). Patients in the Stand-CsA arm had significantly higher diastolic blood pressure at 1 year than patients in the Low-CsA and Low-Tac treatment arms. In addition, patients in the Low-Tac arm had significantly lower diastolic blood pressure than patients in the Low-CsA arm. Mean levels in the Low-Tac and Low-SRL treatment arms remained statistically significantly lower than in the Stand-CsA arm when restricting the analysis to patients who remained on treatment at 1 year; however, there was no longer a significant difference between Low-CsA and Low-Tac.

Body mass index (BMI)

There was no significant difference in mean BMI at 1 year in the different treatment arms (n = 1285). Mean levels at 1 year were as follows: Stand-CsA = 25.8 kg/m², Low-CsA = 26.0 kg/m², Low-Tac = 25.4 kg/m² and Low-SRL = 25.3 kg/m². Levels were similar when the analysis was restricted to patients who were on treatment, and differences between treatment arms remained non-significant at 12 months.

Glucose

Fasting glucose levels were not significantly different at 1 year in the different treatment arms (n = 1310). Mean levels at 1 year were as follows: Stand-CsA = 100 mg/dL, Low-CsA = 102 mg/dL, Low-Tac = 101 mg/dL and Low-SRL =

Methods

The study population included 1645 renal transplant recipients enrolled in the Symphony study. The study design and main efficacy data have been published elsewhere [5]. Briefly, patients were randomized to receive one of four baseline MMF-based immunosuppressive regimens denoted (i) Stand-CsA (for standard dose CsA) (n = 390), (ii) Low-CsA (n = 399), (iii) Low-Tac (n = 401) and (iv) Low-SRL (n = 399) (for low doses of CsA, Tac or SRL) in conjunction with MMF, 1 g twice daily, and corticosteroids. In addition, five doses of daclizumab were given to all patients except those in the Stand-CsA group. CsA, SRL and Tac were administered orally within 24 h before or after transplantation. Stand-CsA was defined as a target trough concentration of 150–300 ng/mL for the first 3 months and 100–200 ng/mL thereafter, and Low-CsA was defined as a target trough concentration of 50–100 ng/mL. Target trough concentrations for Low-Tac and Low-SRL were 3–7 and 4–8 ng/mL, respectively.

Inclusion criteria for the study were adult recipients of a solitary kidney transplant from a living or a deceased donor. Major exclusion criteria were history of malignancy, panel-reactive antibody >20% or transplants of kidneys with >30 h of cold ischaemia.

We categorized patients with or without MS based on the criteria defined by the 2001 National Cholesterol Education Program Adult Treatment Panel (ATP III), updated in 2005 [6, 7]. Because information on waist circumference was not available, BMI was used as a surrogate. Patients who fulfilled three or more of the following characteristics were defined as having MS: obesity (BMI > 30 kg/m²), triglycerides >150 mg/dL, high-density lipoprotein (HDL) ≤40 mg/dL in men or ≤50 mg/dL in women, blood pressure >130/85 mmHg, and fasting blood glucose >100 mg/dL. The proportion of patients classified with MS was based only on patients without any missing values for the applicable parameters within each follow-up period. These proportions were also estimated based on interpolated values based on measurements at other time periods for individual patients. New onset of MS was considered to be the presence of the syndrome at 12 months but absence at baseline. We also calculated the proportion of patients who had MS at baseline who did not qualify at the completion of the study. Medication information was reported throughout the study period. Medications were classified as lipid lowering, blood pressure lowering and insulin/oral antidiabetics. We reported the proportion of patients within each study arm who used any medication within these classes at any point during the study period. We then tested for any association between use of medication within each class and treatment arm. Differences between numbers of antihypertensive medications were evaluated using Poisson regression.
shown in Figure 2 (n = 1052). Patients in the Low-SRL treatment arm had the highest LDL levels at 1 year; these were significantly elevated as compared to patients in the Low-Tac arm. In addition, patients in the Low-Tac arm had significantly lower LDL levels than patients in the Low-CsA arm at 1 year. Results were consistent between patients on treatment at 1 year, with the exception that Low-SRL patients also had significantly higher levels than patients in the Stand-CsA arm.

Comparing patients in the different treatment arms, there were no significant differences in HDL levels at 1 year (n = 1112). Mean levels for the treatment arms were as follows: Stand-CsA = 55 mg/dL, Low-CsA = 55 mg/dL, Low-Tac = 53 mg/dL and Low-SRL = 55 mg/dL. There were also no significant differences between the study arms when we restricted comparisons to patients who were on treatment at 1 year (P = 0.11).

Triglycerides

The mean triglyceride levels of patients according to immunosuppressive regimen are shown in Figure 3 (n = 1245). As indicated, mean levels at 1 year were significantly higher in the Low-SRL treatment arm than in the Low-CsA and in the Low-Tac treatment arms. When we restricted the analysis to patients who were on treatment at 1 year, the mean level in patients in the Low-SRL treatment arm was significantly higher than for patients in all other treatment arms, including the Stand-CsA arm. The mean level in Low-SRL patients who remained on treatment was 220 mg/dL; the levels in the remaining treatment arms were not significantly altered by restricting the analysis to patients on treatment.

Uric acid

Mean uric acid levels at 1 year, according to treatment, were as follows: Stand-CsA = 7.2 mg/dL, Low-CsA = 6.7, Low-Tac = 6.6 and Low-SRL = 6.0. The levels were statistically significantly higher in the Stand-CsA arm than in the other treatment arms. In addition, the Low-SRL arm had significantly lower mean levels than the Low-CsA and the Low-Tac treatment arms. The results were consistent when the analysis was limited to patients who were on treatment at 1 year (P < 0.0001).

Incidence of the MS

The proportion of patients who were classified as having MS at the time of transplantation was 15%. This proportion at baseline was not significantly different between treatment arms nor was there a difference in incidence of MS at 12 months. However, the proportion was significantly higher at baseline in males than in females (P < 0.001), in recipients aged 50 years and older than in younger recipients (P = 0.003) and in recipients transplanted with a kidney from an expanded criteria donor (P = 0.02). These differences were consistent at 12 months. The proportion of patients with new onset of MS was 8%. New onset of MS was also significantly more common in males and in older transplant recipients. Among the patients who had MS at baseline and also had available information (n = 739) for parameters at 12 months, only 31% still had the syndrome at 12 months. The percentage of missing data was not significantly different between the different immunosuppressive agents.

Use of medication

Over the study period, 33% of patients used at least one lipid-lowering medication, 77% used at least one blood pressure-lowering medication and 13% used insulin or hypoglycaemia control medication (Table 2). The use of lipid-lowering medications was higher in the Low-dose SRL arm (39%) relative to the other study arms, and the association between use and study arm was statistically significant (P = 0.007). Use of blood pressure medications was very similar in the different study arms (P = 0.61), as was the use of antidiabetic agents (P = 0.42). There were no significant differences in average and median number of antihypertensive agents over the four immunosuppressive groups (P = 0.10). Mean daily doses of corticosteroids were 15.1 ± 11.7 mg in the Stand-CsA group, 13.7 ± 14.2 mg in the Low-CsA arm, 13.2 ± 9.8 mg in the Low-Tac and 17 ± 13.8 mg in the low-SRL arm. These doses were higher in the Low-SRL group than in the Stand-CsA, Low-CsA and Low-Tac arm (P = 0.0017, P < 0.0001.

Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard-dose CsA</th>
<th>Low-dose CsA</th>
<th>Low-dose Tac</th>
<th>Low-dose SRL</th>
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<tr>
<td>Age (year)</td>
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<td>47.2</td>
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<td>92</td>
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<td>21</td>
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<tr>
<td>HLA-DR (% 2 MM)</td>
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<td>18</td>
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<tr>
<td>Donor type (% living)</td>
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<td>37</td>
<td>36</td>
<td>0.96</td>
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<tr>
<td>Donor age (year)</td>
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<td>46.2</td>
<td>45.2</td>
<td>46</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*MM: mismatches.

bChi-squared test for independence of study arm or Wilcoxon rank sum.

98 mg/dL. The levels were similar when the analysis was restricted to patients who remained on treatment (P = 0.47), and differences between treatment arms were not statistically significant at 12 months.
and \( P < 0.0001 \), respectively) and higher in the Stand-CsA group than in the Low-Tac group \( (P = 0.0071) \).

**Discussion**

This sub-analysis of the Symphony study is the first report in a very large patient cohort on the influence of different immunosuppressive regimens on the evolution of parameters comprising MS.

We found significant differences in several metabolic parameters according to treatment group. Diastolic blood pressure control was more adequate in patients who received Low-Tac/MMF or Low-SRL/MMF than in those who received CsA/MMF during the first year after transplantation. The Low-SRL group showed the highest levels and the highest changes in triglycerides and LDL levels. There were no significant differences in BMI, fasting glucose levels and prevalence of MS at 12 months. This study largely corroborates findings from previous studies but it is the first study to prospectively collect these data in a large patient cohort.
With the introduction of calcineurin inhibitors, the incidence of post-transplant hypertension rapidly increased [8, 9]. The association of specific immunosuppressive regimens with blood pressure control has mixed empirical evidence. In some trials [10–12], but not all [13–17], a greater incidence of hypertension has been found in recipients treated with CsA than in those treated with Tac. Conversion from CsA to Tac may reduce both systolic and diastolic blood pressure [3, 18]. There are no data to indicate that SRL plays a role in occurrence of
hypertension after transplantation. Here, we found that blood pressure control was most adequate in patients receiving Low-TAC or Low-SRL. Patients in the Stand-CsA arm had significantly higher diastolic blood pressure at 1 year than patients in the Low-SRL and Low-Tac treatment arms. In addition, patients in the Low-Tac arm had significantly lower diastolic blood pressure than patients in the Low-CsA arm. It is striking that similar blood pressure control was obtained in both the Low-Tac and Low-SRL groups, indicating that low-dose Tac has a limited effect on the occurrence of hypertension, as already demonstrated by Larson et al. [19].

Transplant-associated hyperglycaemia (TAH) is a well-recognized complication after transplantation [20]. Although numerous factors including obesity, family history of diabetes, ethnic origin, donor source, hepatitis C infection, acute rejection and age may contribute to post-operative metabolic disturbances, immunosuppressive agents play an important role [21]. There are controversial data on the impact of SRL on the clinical occurrence of post-transplant hyperglycaemia [22–26]. Compared to CsA-based immunosuppression, Tac appears to be associated with more pronounced glucose intolerance after renal transplantation [27–29]. The Diabetes Incidence after Renal Transplantation trial showed that CsA is associated with a significantly lower incidence of NODAT and TAH than Tac at 6 months after renal transplantation [30]. The negative effect of Tac on glucose tolerance may be reversible, however, by reduction of drug exposure [20, 31]. It should also be noted that in the DIRECT trial, there was no standardization of the use of corticosteroids. Adjunctive use of MMF permits Tac and steroid sparing and may reduce the risk of TAH [32]. Moreover, recent conversion trials showed mostly unaffected glucose levels [3, 18, 33, 34]. We found no significant difference in fasting glucose levels between treatment groups at 1 year. Furthermore, there was no difference between treatment arms regarding usage of antidiabetic agents. Since the Low-Tac arm was associated with the lowest rate of acute rejection and the lowest mean daily dose of corticosteroid use, this may be one reason for the absence of a difference in glycaemia levels at 1 year. As previously reported [5], the incidence of new-onset diabetes mellitus, based on adverse event reports, was 10.6% in the Low-Tac arm and 4.7–7.8% (P = 0.02) in the other arms. Three months after the reported event, only 2.7% of patients in the Low-Tac arm and 1.0–1.5% (P = 0.37) in the other arms used any antidiabetic medication.

This sub-analysis is in agreement with recent studies comparing CsA with SRL, showing lower uric acid levels in the SRL group indicating that SRL has substantially less effect on uric acid metabolism in patients undergoing renal transplantation. This difference cannot be explained by differences in renal function [35, 36]. We found significantly higher uric acid levels in the Stand-CsA arm than in the Low-CsA arm, indicating a dose effect of CsA-induced hyperuricaemia.

In the evaluation of serum lipids, we found that patients in the Low-Tac arm had significantly lower LDL levels than patients in the Low-CsA arm at 1 year. Mean levels of triglycerides at 1 year were significantly higher in the Low-SRL treatment arm than in the Low-CsA and the Low-Tac treatment arms. Margreiter et al. [10] and Charpentier et al. [15] have already demonstrated that hypercholesterolaemia occurs more frequently during treatment with CsA than during treatment with Tac. Moreover, conversion from CsA to Tac reduces LDL cholesterol [3, 37] and triglyceride levels [18]. Dyslipidaemia associated with SRL is a serious clinical problem, with a high incidence of both hypercholesterolaemia and hypertriglyceridaemia [38]. This side effect is dose-dependent, but although Kreis and Flechner [26, 39] could not demonstrate any difference in the lipid profiles or in the use of lipid-lowering medication between SRL- and CsA-treated patients, we found significantly higher levels of triglycerides and LDL in the SRL arm—even with low trough levels and higher usage of lipid-lowering therapy. Interestingly, we found no difference in HDL-cholesterol levels. This is consistent with previous studies [26, 40] in which it is demonstrated that the increases in cholesterol and triglycerides are likely due to increases in LDL, very low-density lipoprotein (VLDL) and non-HDL cholesterol. The exact mechanism is yet to be unravelled but Morrissett et al. demonstrated that sirolimus alters the insulin signalling pathway with an increase in hepatic synthesis of triglycerides, VLDL and increased hypertriglyceridaemia [41].

The results concerning the use of general medication appear to corroborate the general associations reported in the study. In particular, there was no significant difference in the use of antihypertensive agents or in the use of antidiabetics in the different study arms, and it is unlikely that this would confound the main differences in the results. The limitation of this measurement is that some patients may have been on multiple agents or may have had a long duration of treatment, while others may have been on single agents or for a short duration.
There were no significant differences in mean BMI or in the proportion of MS between the different treatment arms. The percentage of new onset of MS was rather low. This might be partly due to racial and geographical differences and to the use of lower doses of immunosuppressive drugs. In the population of the Symphony study, <2% of individuals were black and only 8% were diabetic, which is also not consistent with the current population on the waiting list in the USA. On the other hand, the use of modified ATP III criteria with the use of BMI instead of waist circumference is another limitation considering the fact that recent data show that BMI post-transplantation correlates poorly with central obesity post-transplantation [42].

Another limitation of this study is the lack of data on a steroid-free protocol since this was not part of the study design. Current data on the effect of prolonged use of corticosteroids demonstrate a worse metabolic profile, which might be more important than differences between other immunosuppressive agents [43–45]. A recent meta-analysis by Knight demonstrated that the incidence of hypertension, NODAT and hypercholesterolaemia is reduced significantly by steroid avoidance or withdrawal [43]. Furthermore, we found significant differences in steroid dose between the treatment arms which as a consequence might be partially responsible for the differences in metabolic outcome.

However, the major limitation of this study is the fact that it was not powered for the secondary end points thereby implying that absence of significance should not be interpreted as definitive lack of difference between the different immunosuppressive regimens.

In summary, this sub-analysis of the Symphony study population demonstrates a clear difference in metabolic parameters among immunosuppressive groups. CsA therapy was associated with the highest values of systolic and diastolic blood pressure. There was no significant difference in BMI between the four groups. SRL had the worst lipaemic control. In addition to better allograft survival and less acute rejection as demonstrated by the Symphony study, the low-dose Tac regimen gave the best control of blood pressure and lipids. Although the main study has demonstrated that the incidence of NODAT was significantly higher in the Low-Tac group, permanent antidiabetic treatment was not, and here, we did not find any differences in blood glucose levels at 1 year. In any event, the potentially negative effect on glucose tolerance by tacrolimus indicates that close follow-up is required to evaluate whether or not the beneficial cardiovascular profile of low-dose Tac is offset by the development of diabetes.

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