**Aims** This comparative prospective multi-centre study evaluated efficacy and safety of cyclosporine A downtitration in heart transplant recipients with chronic renal dysfunction potentially attributable to cyclosporine (n = 161).

**Methods** In the intervention arm (n = 109, recruited from 9 centres), mycophenolate mofetil was introduced de novo or substituting azathioprine, followed by cyclosporine reduction (target trough levels 2–4 µg/ml and 50 ng/ml, respectively). In controls (n = 52, recruited from 1 centre), immunosuppression remained unchanged. Renal function was recorded twelve, six, and three months before, and throughout the eight-month study period.
Introduction

Introduction of cyclosporine has markedly improved the success of organ transplantation. However, side-effects, particularly nephrotoxicity, may diminish long-term benefits of this agent. In 5–10% of heart transplant recipients, long-term use (5–10 years) of cyclosporine has resulted in end-stage renal failure.1–4

Mycophenolate mofetil is a non-nephrotoxic immunosuppressant specific for T and B-cells. Its non-immunological side-effects are different from those of cyclosporine.5 Compared with azathioprine, superior safety and efficacy of mycophenolate mofetil has been demonstrated in heart transplant recipients with improved one-year survival and lower rejection incidence.6–8 In kidney and liver transplant recipients, the use of mycophenolate mofetil with lower cyclosporine dosages has been reported to improve renal function while maintaining adequate immunosuppression.9–13 In heart transplant recipients, comparable protocols have so far not been tested in controlled clinical studies, but preliminary reports have been encouraging.14–16

This investigator-initiated prospective comparative multi-centre study was designed to assess whether introduction of mycophenolate mofetil, followed by reduction of cyclosporine, ameliorates progressive renal dysfunction after heart transplantation (IMPROVED Study: Is introduction of mycophenolate mofetil and reduction of cyclosporine valuable in renal dysfunction after heart transplantation?). The study hypothesis was that decreasing cyclosporine trough levels to 50 ng/ml after introduction of mycophenolate mofetil would reduce chronic renal dysfunction. In addition, the impact of factors potentially modulating the effects of this treatment strategy, such as the degree of renal impairment at study entry and co-morbidity with diabetes mellitus, were studied.

Methods

Patients

Adult patients at least 6 months post-heart transplant surgery suffering from chronic renal dysfunction were eligible. Renal dysfunction was defined as serum creatinine concentrations of ≥ 150 μmol/l (1.7 mg/dl) repeatedly confirmed over a period of at least 3 months. All patients received cyclosporine, azathioprine, and – optionally – steroids as immunosuppressants throughout the entire post-transplant period. Heart transplant recipients not on long-term cyclosporine or with a history of acute allograft rejection within the past six months were not eligible. Other exclusion criteria included renal artery stenosis, renal parenchymal disease, active duodenal or gastric ulcer, malignancy, intolerance to mycophenolate mofetil, acute overdose of cyclosporine (excluded on grounds of stable daily cyclosporine dosages and repeat whole blood trough levels within the therapeutic range prior to study entry), and pregnancy, breast feeding or lack of adequate contraception in women. The study was approved by the local Ethical Review Board of each participating centre and all patients gave written informed consent.

Study design

We chose an open label, parallel group, prospective multi-centre approach and compared an intervention arm with a control arm representing the natural course of the disease. Randomisation was not feasible due to distinct preferences of several centres to use mycophenolate mofetil in their patients and of one centre to maintain a regular-dose cyclosporine regimen in all patients. To minimise bias potentially arising from the non-randomised study design, centres were asked prior to inclusion of their first patient to decide on one of the two arms. Contribution of one centre to both arms was not permitted. In the end, one large centre (KP) recruited the total number of controls, whereas the nine other centres included patients in the intervention arm. Study duration was eight months. The primary endpoint was improvement in renal function in the intervention arm as determined by a decline in serum creatinine. Secondary endpoints were the change of reciprocal serum creatinine over...
the study period in the intervention arm. Another secondary endpoint was the difference between the two study arms (intervention vs. control arm) regarding the changes in reciprocal creatinine throughout and in the 12 months preceding the study. Reciprocal creatinine was selected because it corresponds more closely than serum creatinine to the creatinine clearance and has been shown to predict development of terminal renal failure reliably. Further secondary endpoints were the change in creatinine clearance calculated according to Cockcroft and Gault, effects of the intervention on blood pressure, left ventricular septal hypertrophy and renal parenchymal thickness measured by ultrasound, and safety and tolerability of the intervention strategy.

Study protocol

All study participants received the same cyclosporine preparation (Sandimmun Optoral, Novartis Pharma GmbH, Nürnberg, Germany). The study protocol did not specify any systematic changes in immunosuppression in the control arm. In the intervention arm, prednisolone was given from study initiation in a dosage of 7.5 mg/day irrespective of whether or not patients were on steroids prior to inclusion. Mycophenolate mofetil was introduced either as an additional immunosuppressant (89% of participants) or as a substitute for azathioprine (11%). In a run-in period of variable duration, mycophenolate mofetil was titrated in a step-wise fashion beginning with 250 mg bid in the first week followed by increases of 500 mg/day every two weeks, until the target whole blood trough levels of 2–4 μg/ml were reached. If mycophenolate mofetil was tolerated at trough levels, cyclosporine dosage was reduced every two weeks in steps of 20 mg/day aiming at whole blood trough levels of 50 ng/ml. The EMIT 2000 assay (Dade Behring, Linderbach, Germany) was used for drug monitoring. Myocardial biopsies were performed, and dosages of immunosuppressants, co-medication, and adverse events were recorded. In the intervention arm, patients were monitored fortnightly in the titration phase, and adverse events were recorded. In the intervention arm received at least one dose of mycophenolate mofetil, as applicable. A physical examination including Riva-Rocci blood pressure measurement, ECG, and echocardiogram was performed, and dosages of immunosuppressants, co-medication, and adverse events were recorded. In the intervention arm, patients were monitored fortnightly in the titration phase and monthly thereafter; in the control arm, patients were seen at study entry and at 3, 7, and 8 months.

Data analysis

Sample size calculation was based on detection of a 17.7 ± 44.0 μmol/l (0.2 ± 0.5 mg/dl) decrease in mean serum creatinine at study end compared to baseline in the intervention arm, with a power of 0.95 and a significance level of 0.05. A drop out rate of 20% was anticipated. Accordingly, 109 patients were to be included in the intervention arm. The main analysis was a last-value-carried-forward (LVCF) analysis conducted on all participants who started the cyclosporine downtitration protocol in the intervention arm (n = 92), in analogy to the intention-to-treat analysis in randomised trials. Comparisons within and between study arms were made using non-parametric tests, as appropriate. As only one primary endpoint was evaluated, P-values were not corrected for multiple testing.

A multiple linear regression analysis was performed with percentage change in creatinine as the dependent variable, which adjusted for potential confounding factors as listed in Tables 1 and 2 using backward selection (P \leq 0.15). The assumption of normality and constant variance was checked by inspection of residual plots. Three sensitivity analyses were conducted to examine the robustness of the main analysis. First, we added a quadratic and cubic term to the continuous variables in the regression models to assess non-linearity. Second, we made use of a dataset in which absent/missing values had been imputed by utilising all available information in the incomplete dataset without disturbing the relationship between the variables as observed in the data. Third, the analysis was conducted on all patients in both arms who had completed the study per protocol.

Response to the intervention was pre-defined as a reduction of serum creatinine of more than 17.7 μmol/dl (0.2 mg/dl) and was applied to the LVCF population. This cut-off value was selected empirically since a change of that magnitude would be considered clinically relevant. Mean changes in reciprocal creatinine over time were derived from individual slopes within each study arm based on linear regression analyses across measurements over time. Slopes were compared using non-parametric testing as appropriate. Fisher’s exact test was used to assess differences in adverse events in study arms. All P-values are reported two-sided.

Role of the funding source

Hoffmann-La Roche AG (Grenzach-Wyhlen, Germany) facilitated printing of case report forms, biochemical analyses, data monitoring, and generation of the data base. The authors collected, analysed and interpreted the data, and wrote this paper without involvement of Hoffmann-La Roche AG.

Results

Patient characteristics

One hundred and nine patients allocated to the intervention arm received at least one dose of mycophenolate mofetil. Of these, 17 patients had to be excluded in the run-in phase of the study prior to cyclosporine down titration for reasons stated in Fig. 1. Of the 52 patients of the control arm, 2 were excluded immediately after baseline. Thus, the main analysis was performed on 92 patients in the intervention arm in whom cyclosporine down titration was initiated and 50 patients in the control arm. Their characteristics are listed in Table 1. During the study, 16 patients (15%) of the intervention arm and 3 controls (4%) terminated the study prematurely (Fig. 1). Both arms were comparable for most demographic characteristics, co-morbidity, risk factors and steroid therapy before the start of the study. However, controls had a longer post-transplant period and were more intensely medically treated (Table 1). Patients in...
the intervention arm who terminated the study prematurely were not different from patients finishing per protocol (Table 1). Renal function and cyclosporine burden were similar between study arms in the first year post-transplant, in the year preceding the study, and at study entry (Table 2).

**Immunosuppression**

Introduction of mycophenolate mofetil yielded adequate trough levels of $2.7 \pm 1.4 \, \mu g/ml$ after 5 weeks, at a mean dose of $1.3 \pm 0.6 \, g/day$. Mycophenolate mofetil

## Table 1: General characteristics of participants in the intervention arm (evaluated patients and drop-outs) and controls

<table>
<thead>
<tr>
<th></th>
<th>Intervention arm</th>
<th>Controls</th>
<th>(P^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Evaluated (n = 92)</td>
<td>59 (8)</td>
<td>Drop-out (n = 16)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>Evaluated (n = 92)</td>
<td>7 (8)</td>
<td>Drop-out (n = 16)</td>
</tr>
<tr>
<td>Primary cardiac disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD, n (%)</td>
<td>Evaluated (n = 92)</td>
<td>26 (28)</td>
<td>Drop-out (n = 16)</td>
</tr>
<tr>
<td>DCM, n (%)</td>
<td>Evaluated (n = 92)</td>
<td>58 (63)</td>
<td>Drop-out (n = 16)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>Evaluated (n = 92)</td>
<td>8 (9)</td>
<td>Drop-out (n = 16)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>Evaluated (n = 92)</td>
<td>28.2 (4.5)</td>
<td>Drop-out (n = 16)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>Evaluated (n = 92)</td>
<td>136 (15)</td>
<td>Drop-out (n = 16)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>Evaluated (n = 92)</td>
<td>85 (9)</td>
<td>Drop-out (n = 16)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>Evaluated (n = 92)</td>
<td>6 (7)</td>
<td>Drop-out (n = 16)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>Evaluated (n = 92)</td>
<td>22 (24)</td>
<td>Drop-out (n = 16)</td>
</tr>
<tr>
<td>Time since transplantation, years</td>
<td>Evaluated (n = 92)</td>
<td>5.3 (3.2)</td>
<td>Drop-out (n = 16)</td>
</tr>
</tbody>
</table>

Data are means (SD) or absolute numbers (percent), as indicated. IHD: ischaemic heart disease; DCM: dilated cardiomyopathy; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; LDL: low density lipoprotein; HDL: high density lipoprotein.

\(a\) \(P\) for comparison between evaluated patients of the intervention arm (n = 92) and controls (n = 50).

## Table 2: Temporal development of renal failure after heart transplantation (intervention arm, n = 92; controls, n = 50), and cyclosporine trough levels and dosages

<table>
<thead>
<tr>
<th>Time since transplantation</th>
<th>Serum creatinine, (\mu \text{mol/l})</th>
<th>Cyclosporine trough level, (\text{ng/ml})</th>
<th>Cyclosporine dosage, (\text{mg/day})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
</tr>
<tr>
<td>1 month after transplant</td>
<td>114.9 (44.2)</td>
<td>114.9 (44.2)</td>
<td>327 (240)</td>
</tr>
<tr>
<td>3 months after transplant</td>
<td>132.6 (44.2)</td>
<td>132.8 (35.4)</td>
<td>259 (145)</td>
</tr>
<tr>
<td>6 months after transplant</td>
<td>150.3 (53.0)</td>
<td>141.4 (35.4)</td>
<td>252 (143)</td>
</tr>
<tr>
<td>12 months after transplant</td>
<td>168.0 (44.2)</td>
<td>141.4 (26.5)</td>
<td>226 (128)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

Reduction of cyclosporine after introduction of mycophenolate mofetil 1629
target levels were maintained throughout the study. Cyclosporine trough levels below 70 ng/ml in the intervention arm were reached 8–10 weeks after study start and were maintained throughout the study at mean doses of 126 ± 36 mg/day. The mean cyclosporine level at study end was 57 ± 24 ng/ml in the intervention arm, and 116 ± 36 ng/ml in controls. In the intervention arm, steroids were obligatory in the initial phase of the study. After exclusion of rejection by endomyocardial biopsy at cyclosporine and mycophenolate mofetil target levels steroid dosing was left to the discretion of the local investigator. At the end of the study, 60 of 92 patients (65%) in the intervention arm were free of steroids; in the remaining 32, the mean daily prednisolone dosage was 5.4 ± 1.4 mg. In control subjects, 49 of 50 patients were treated with steroids (mean prednisolone dosage 6.4 ± 1.5 mg/day at study entry and 6.4 ± 1.4 mg/day at the final visit). Thus, compared to controls, patients in the intervention arm received significantly less steroids at the end of the study (P = 0.004).

Renal function

The main effect of cyclosporine downtitration on renal function during the study course of 8 months is shown in Table 3. In the LVCF analysis, in the intervention arm, serum creatinine decreased from 210.2 ± 65.1 to 186.8 ± 86.4 μmol/l (P < 0.0001), but remained unchanged in controls (195.8 ± 50.9 and 203.1 ± 72.1 μmol/l, respectively; P = 0.992). This resulted in a change of −23.3 ± 50.7 μmol/l in the intervention arm vs. +7.3 ± 46.9 μmol/l in controls during the 8 month study period (P = 0.0001 for comparison between groups). Similarly, calculated creatinine clearance increased by 7.6 ± 10.9 ml/min in the intervention arm, but was unchanged in controls (P < 0.001 for comparison between groups). These findings were corroborated in analyses with imputed data and per protocol, with the largest effects seen in the per protocol analysis (Table 3). In the intervention arm, 57% of patients showed reductions in serum creatinine of at least 17.7 μmol/l, compared with 32% in controls (P = 0.008 for comparison between groups). If the response criterion was set to a creatinine reduction of at least 20%, patients in the intervention arm had also fared better (35% vs. 4%, P < 0.0001).

In the 12 months preceding the study, a negative regression slope of serial reciprocal creatinine values indicated significant deterioration of renal function over time in both study arms (Fig. 2). This negative trend stopped and stabilised during the study among controls, whereas in the intervention arm the slope became positive, indicating renal improvement (P = 0.047 and P < 0.0001, respectively, for differences in slopes within study arms). Consistently, the change in slope was more pronounced in the intervention arm than in the control arm (P = 0.005). Serum creatinine, creatinine clearance,
and reciprocal creatinine slopes decreased to a similar extent in diabetics and non-diabetics, and in strata of different serum creatinine levels at the start of the study, except in the highest stratum of creatinine >309 µmol/l (>3.5 mg/dl; Table 4).

To evaluate the impact of potential confounding on the intervention effect, a multiple linear regression model was built with percentage change in creatinine as the dependent variable. The following factors (regression co-efficients \( b \) with 95% confidence intervals) were identified: intervention (\(-11.71, -18.56 \) to \(-4.86, \) \( P < 0.001 \)), baseline cyclosporine trough level per ng/ml (\(-0.16, -0.24 \) to \(-0.07, \) \( P < 0.001 \)), baseline diastolic blood pressure per mmHg (0.53, 0.21–0.86; \( P = 0.002 \)), and beta-blocker therapy (10.85, 1.65–20.05; \( P = 0.021 \)). These co-efficients were robust if the level of adjustment was expanded to the full list of baseline criteria (data not shown). Assessment of non-linearity showed no significant non-linear terms (i.e., the assumption of linearity was satisfied).

Blood pressure, echocardiography, and renal ultrasound

Sitting systolic/diastolic blood pressure remained unchanged in controls (both \( P > 0.70 \)) but decreased during the study in the intervention arm by \(-3 \pm 18/ -4 \pm 14\) mmHg (\( P = 0.070/0.014 \)) exhibiting a significant change for comparison between groups (\( P = 0.033 \)). Systolic/diastolic 24 h blood pressure values at study end had improved by \(-5 \pm 15/-5 \pm 14\) mmHg (\( P = 0.005/0.001 \)) for day averages and by \(-5 \pm 18/-5 \pm 14\) mmHg (\( P = 0.008/0.010 \)) for night averages, respectively. Changes in myocardial septal thickness, renal parenchymal thickness, and kidney length were not different in both study arms (data not shown).

Safety

Serious adverse events were observed in 9% in the intervention arm and in 11% of controls (\( P = 0.563 \)). All but one of the serious adverse events were consequences of hospitalisations for various reasons (intervention arm/controls): death (0/1), pathological finding at myocardial biopsy (1/0), suicidal tendencies (0/1), infection (5/2), orthostatic fainting (1/0), tertiary hyperparathyroidism (1/0), hip surgery (1/2), abdominal surgery (1/1), cardiology surgery (0/1). A causal relationship between serious adverse event and intervention was classified as 'likely' in 17%, 'possible' in 25%, and 'unlikely' in 58%. The intensity of serious adverse events in cases with 'likely' relationship to intervention was classified moderate in all cases. Adverse and serious adverse events occurring before cyclosporine downtitration and the reasons leading to premature discontinuation of the study are given in detail in Fig. 1. In total, adverse events were observed in 61% of the intervention arm and in 80% of controls (\( P = 0.024 \)). A causal relationship between adverse event and intervention was classified as 'likely' in 24%, 'possible' in 41%, and 'unlikely' in 35%. The intensity of adverse events in cases with 'likely' relationship to intervention was severe in 43%, moderate in 47%,
Incidence of infections and need of antibiotic therapy was similar between study arms. One case of early CMV reactivation occurred in the intervention arm. Myocardial biopsies showed 3 rejections grade 1B, 1 rejection grade 2, and 3 rejections grade 3A, the latter without haemodynamic compromise and histologically reversible with therapy.

Discussion

The principal finding of this comparative multi-centre study was that cyclosporine downtitration to mean trough levels of 57 ng/ml after introduction of mycophenolate mofetil lowered serum creatinine in long-term survivors of heart transplantation with chronic renal dysfunction, regardless of the presence of diabetes. A consistent effect of this intervention strategy was observed in all analyses. Although in new heart transplant recipients alternative immunosuppressive regimes with less unfavourable effects on renal function are increasingly used, the majority of patients in the chronic post-operative phase are still treated with cyclosporine. Our findings should contribute to improved management of this patient population, since no other means are known to slow or stop progression to end stage renal failure. In those who tolerate the switch to mycophenolate mofetil this regimen appears safe, but graft monitoring is recommended in the first months.

Clinical relevance and generalizability of results

To the best of our knowledge, this is the first study in heart transplant recipients which demonstrated, in a controlled study design, that chronic cyclosporine-associated nephrotoxicity is partially reversible. Until recent preliminary reports from case series suggested that cyclosporine downtitration might beneficially affect renal function, renal damage due to long-term cyclosporine therapy was considered irreversible. The present study observed an improvement in serum creatinine strata ranging from 150 to 310 µmol/l (1.7–3.5 mg/dl) in subjects suffering from progressive renal failure documented over several months prior to study entry. It remains to be shown whether the benefit of cyclosporine downtitration is limited to this creatinine range since numbers in the stra-

Table 4 Change in serum creatinine and creatinine clearance in patients who ended the study per protocol according to predefined subgroups

<table>
<thead>
<tr>
<th>Change in serum creatinine, µmol/l</th>
<th>P</th>
<th>Change in calculated creatinine clearance, ml/min</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention (n = 76)</td>
<td></td>
<td>Control (n = 47)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine at study start</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150–203 µmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>204–255 µmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>256–310 µmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;310 µmol/l</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Values are means (SD). Reported P-values refer to comparison between study arms.

a P > 0.5 for comparison within study arm.
b Corresponding to cut-off values of 1.7–2.2, 2.3–2.8, 2.9–3.5, and >3.5 mg/dl.
tum with creatinine above 310 \(\mu\)mol/l (3.5 mg/dl) were too small \((n = 8)\). At the same time, we may speculate that cyclosporine reduction should be initiated early in renal failure. Importantly, our findings extend to patients with diabetes (28% of study cohort) who form per se a high risk group for developing end stage renal failure. Higher baseline cyclosporine trough levels were associated with better response to intervention, and higher baseline diastolic blood pressure levels and beta-blocker therapy were associated with a poorer response. Our study was not powered to study the effects in these subgroups but it is biologically plausible that patients with the highest cyclosporine levels respond best to downtitration. Similarly, high diastolic blood pressure, regardless of concomitant treatment, may be an indicator of more advanced renal parenchymal damage and, therefore, worse response to cyclosporine downtitration. Beta-blockade is not given in heart transplant recipients on a routine basis. Hence, the negative association with the intervention strategy was unexpected, may be a chance finding, and needs further evaluation in larger trials. Cyclosporine downtitration reduced mean 24-h and sitting blood pressure levels by 4–5 mmHg, an effect comparable to that of introduction of an anti-hypertensive agent. This is important because hypertension is among the strongest predictors for the development of end-stage renal failure in this patient group.2–4

At study entry, subjects of the control arm were longer post-transplant (7.9 vs. 5.3 years). This might have contributed to a more 'fixed' state of compromised kidney function in control subjects. However, creatinine levels in control subjects during the pre-study period were, if anything, lower than in the intervention arm, and the slope of renal deterioration was similar in both groups. Even more importantly, renal deterioration during the study period was also attenuated in controls (Fig. 2). This is in accordance with the widely acknowledged beneficial effects of study participation per se and underscores the importance of a control group when studying intervention strategies.

Safety

Switching the immunosuppressive therapy appeared to be safe as judged by the incidence of adverse and seriously adverse events. While in the initial phase of the study steroid therapy was obligatory for safety reasons, investigators apparently felt confident to not only reduce but discontinue prednisolone in the majority of patients on this immunosuppressive regimen thus also avoiding the unwanted long-term effects of steroids. In about 18% of eligible heart transplant recipients, introduction of and maintenance on mycophenolate mofetil was precluded by side-effects of this drug, predominantly gastrointestinal toxicity, inability to reach therapeutic mycophenolate mofetil levels, or a number of rarer side-effects. This somewhat limits the clinical applicability of such a strategy since it is not possible to predict which individual will tolerate the switch in immunosuppression. Myocardial histology was only available in the intervention arm, where graft rejections grade 3A were observed at an incidence of 0.04 per patient year, were all subclinical, and resolved after intensified treatment. A causal relationship between these findings and the switch in immunosuppression remains as speculative as the clinical relevance of these findings, as the same incidence of histological abnormalities indicating graft rejection \(\geq 3A\) was observed in 133 long-term survivors 5–10 years after heart transplantation, was associated with a benign prognosis, and resolved spontaneously even without intensified immunosuppression.24

Limitations

The reasons for choosing an observational cohort study design rather than a randomised trial were discussed above. Since all controls were recruited by a single centre, a treatment effect could not be distinguished from a centre effect. However, considering the comparable gradual decline in renal function observed in both the control and the intervention arm in the 12 month period preceding the study and the immediate improvement of renal function in patients from nine different centres in whom immunosuppression was switched according to the study protocol, a true treatment effect appears likely. To further ascertain this main finding of the study, a randomised multi-centre trial would be required. Baseline characteristics were not identical in both study arms, representing mainly centre-specific treatment preferences and their effects on blood pressure and lipid profiles. However, in multivariate regression, the crude intervention effect appeared robust after adjustment for baseline characteristics. We thus consider it unlikely that the intervention effect can be explained by confounding. It cannot be excluded that patients terminating the study prematurely were different in certain unmeasured aspects to those successfully completing the study although we were unable to identify such a difference. Therefore, a differential drop-out biasing our results is unlikely. Data collection was not entirely symmetric in both study arms, with more visits to the clinic and additional safety measures in participants of the intervention arm. The higher number of follow-up visits might have influenced reciprocal creatinine slopes since these were based on multiple creatinine measurements. It is unlikely, however, that this would have affected the main analysis of changes in creatinine levels from study start to end. Finally, \(P\)-values resulting from analyses of secondary endpoints should be interpreted with caution because multiple secondary research questions were investigated and statistically tested.

Conclusions

Cyclosporine downtitration to trough levels of 50–60 ng/ml after introduction of mycophenolate mofetil was shown to be a safe and effective strategy to improve chronic renal dysfunction in diabetic and non-diabetic heart transplant recipients across a wide range of creatinine levels. A modest but consistent effect on serum creatinine levels was found after 8 months. Graft monitoring is recommended after switching the immunosuppressive regimen. The benefit of this strategy in
postponing or preventing end-stage renal failure in this patient population would have to be assessed in longer term clinical trials.

Acknowledgements

The authors thank Nini Win, MD, Renate Beckmann, MPH, and Sigrid Balser, PhD, for their help in designing the case report forms, monitoring of the study and structuring of the data base. The support of all medical and nursing staff of the participating centres in completing the data acquisition is deeply appreciated.

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