Renal recovery after conversion to a calcineurin inhibitor-free immunosuppression in late cardiac transplant recipients

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Abstract

Objective: Calcineurin inhibitor (CNI)-related renal failure is a common problem after cardiac transplantation (HTx). The aim of this prospective study was to evaluate the safety and efficacy of a completely CNI-free immunosuppressive regimen [mycophenolate mofetil (MMF) and sirolimus (Sir)] in HTx-recipients with late post-transplant renal impairment. Methods: Since 2001, 30 HTx-patients (25 men, 6 women; 0.2–14.2 years after transplantation) with CNI-based immunosuppression and a serum creatinine > 1.9 mg/dl were included in the study. Creatinine and cystatin levels were monitored to detect renal function. Conversion was started with 6 mg Sir or 500 mg MMF according to the pre-existing regimen and was continued with the dose adjusted to achieve target trough levels between 8 and 14 ng/ml (Sir) or 1.5 and 4 µg/ml (mycophenolate). Subsequently, the CNIs were tapered down and stopped. Clinical follow-up included endomyocardial biopsies, echocardiography and laboratory studies. Additionally, every HTx-patient treated at our centre between 1996 and 2001 due to chronic renal failure without immunosuppressive conversion and fulfilling the inclusion criteria were retrospectively analysed and acted as control group. Results: Patient demographics and 1-year survival [93 (conversion) vs 90% (control)] were compared. No acute rejection episode was detected in either group. Renal function improved significantly in the conversion group (creatinine: 3.18 ± 0.71 vs 2.22 ± 0.79 mg/dl, \( P = 0.001 \)); cystatin pre- vs post-conversion: 2.95 ± 1.06 vs 2.02 ± 1.1 mg/l, \( P = 0.01 \)). In three patients haemodialysis therapy was stopped completely after conversion. In the control group renal impairment was deteriorating, creatinine increased from 2.44 ± 0.8 to 3.28 ± 1 mg/dl (\( P = 0.01 \)). In 10 out of 33 patients chronic haemodialysis had to be initiated within 1 year. Although side effects of CNI-free immunosuppression were common (76%), no patient had to be excluded due to adverse effects.

Conclusions: Conversion from CNI-based immunosuppression to MMF and Sir in HTx-patients with chronic renal failure was safe, preserved graft function and improved renal function.

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Keywords: Cardiac transplantation; Sirolimus; Mycophenolate mofetil; Renal failure; Conversion

1. Introduction

The development of new immunosuppressive regimens resulted in better prevention of acute rejection and infection after thoracic organ transplantation. In cardiac transplantation (HTx) with potent immunosuppression being mandatory, calcineurin inhibitors (CNIs) like cyclosporine or tacrolimus are the common base of immunosuppression [1]. In the past, CNIs reduced acute rejection and infection and significantly improved survival [2]. Prolonging survival allows more time for side effects to manifest, which contributes to the increasing proportion of CNI-induced morbidity in patients [3–5].

Chronic renal failure is one cause of morbidity after HTx; 5–11% of all the annual 3000–4000 HTx-recipients worldwide develop endstage renal failure and undergo chronic haemodialysis with reduced quality of life and decreased life expectancy [1,3,6]. Recently, data from a multi-institutional approach (>24 000 HTx-recipients) showed that chronic renal failure was associated with
a significantly higher risk for death (relative risk 4.55) [7]. Main factors triggering the development of renal failure are chronic pre-operative renal hypoperfusion caused by heart failure and post-transplant nephrotoxicity from CNIs [7,8]. CNIs cause specific alterations of the afferent arterioles and less specific glomerular sclerosis, tubular atrophy and interstitial fibrosis in HTx-patients. These agents play a key role in the development of chronic renal impairment [9]; thus therapeutic strategies have to focus on alternative, less nephrotoxic immunosuppressive medications.

Mycophenolate mofetil (MMF) inhibits purine synthesis especially in T- and B-cells with a different side effect profile from CNI, which includes no nephrotoxicity. The efficacy of MMF for HTx has been proven in combination with CNI, particularly, if therapy was guided by mycophenolic acid trough monitoring [10].

Sirolimus (Sir) is a macrocyclic lactone with a potent immunosuppressive activity, but a different mechanism of action than CNIs. Sir does not affect calcineurin and reduces T-cell activation at a later stage in the cell cycle by inhibiting cytokine-induced signal transduction pathways resulting in the suppression of IL-2 or IL-4 driven lymphocyte proliferation.

In combination with reduced levels of CNIs, Sir showed an excellent immunosuppressive efficacy and safety in de novo HTx-patients [11]. While Sir itself is not nephrotoxic, the addition of CNI resulted in pronounced CNI-nephrotoxicity. The combination of MMF and Sir might have the potential to provide comparable immunosuppression without the nephrotoxic downside. This combination showed a synergistic immunosuppressive effect after HTx in a rat model[12]. In de novo renal transplant patients MMF and Sir showed comparable low rejection rates and incidence of infections and experienced significantly better renal function compared to cyclosporine-treated patients [21]. This combination has not been used after thoracic organ transplantation to date. A retrospective case analysis [13], however, suggested that Sir-based immunosuppression is safe and associated with renal recovery.

The aim of this prospective study was to evaluate the safety and efficacy of a completely CNI-free immunosuppressive regimen consisting of MMF and Sir in HTx-recipients, who developed chronic renal failure under CNI-based immunosuppression.

2. Methods

In this prospective, controlled treatment study patients admitted to our hospital for renal failure after HTx since 2001 were evaluated for inclusion. Formal local ethic committee approval for this non-randomized study was obtained first, and each patient enrolled gave written informed consent. The study was supported by a research grant from Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany.

Inclusion criteria were patient age >18 years with a CNI-associated chronic renal impairment, serum creatinine >1.9 mg/dl for >3 months and a creatinine increase over 3 months of >30% (to include only patients with severe chronic and progressive renal failure). Prior conversion all patients were on a ‘renal sparing approach’; Sir or MMF was added as secondary immunosuppressants allowing lower CNI-target trough levels [tacrolimus 7–10 ng/ml in combination with MMF (n = 18) or Sir (n = 3); cyclosporine 80–250 ng/ml in combination with MMF] dependant on the interval after transplantation. Steroids had been routinely tapered down and stopped 6 months after transplantation, so all but two patients (2 and 5 months post-HTx) were steroid-free during and after conversion. ACE-inhibitors were reduced or stopped; calcium channel blockers were continued. Additional inclusion criteria were a white cell count of >4.0 × 10^9/l, haemoglobin >70 g/l, platelets >150 × 10^9/l and fasting cholesterol <240 mg/dl.

Renal failure of origine other than CNI-induced nephropathy (renal artery stenosis, renal cysts, ureter obstruction, abuse of other nephrotoxic drugs, etc.) was excluded with ultrasound and Doppler examination, laboratory testing and detailed clinical history. Routine renal biopsies were declined by nephrologists because of the risk of bleeding, infection and further renal parenchymal destruction.

Patients were not eligible for the study, if they had evidence of infection, active liver disease, insulin-dependant diabetes mellitus (to exclude patients with diabetic nephropathy), unstable disease state (i.e. hypertension, acute rejection), history of malignancies or active gastrointestinal disorder.

Immunosuppressive conversion was conducted over a 3-week period in the outpatient clinic. Either MMF (Cellcept®, Hoffmann-La Roche AG, Grenzach, Germany) or Sir (Rapamune®, Wyeth-Aerst Pharmaceuticals, Collegeville, USA) was added, depending on the pre-existing immunosuppressive regimen. CNI dosage was simultaneously reduced by 20% (Fig. 1). The initial MMF-dosage was 500 mg/day and was continued according to fasting MPA trough levels (1st year post-HTx, 2–4 mg/l; ≥2nd year post-HTx, 1.5–4 mg/l). Sir was given at a loading dose of 6 mg/day and continued with 2 mg/day until target trough levels were reached (1st year post-HTx, 10–14 ng/ml; >2nd year post-HTx, 8–12 ng/ml). After a mean time of 2.8 ± 0.4 weeks MPA and Sir trough levels were in the target range and CNIs were completely stopped. Then patients underwent their first clinical follow-up examination after complete immunosuppressive conversion. Further follow-ups occurred at 1 and 3 months as well as every 3 months thereafter. Measurements included echocardiography, blood pressure and laboratory values: creatinine, urea, cystatin (an endogenous protease inhibitor, which indicates impaired glomerular filtration, when elevated), uric acid, cholesterol, triglycerides, blood count (all performed by automated...
routine methods) and trough levels. Creatinine clearance was calculated using the Cockroft–Gault method [14].

Sir whole blood concentrations were determined by use of liquid chromatography tandem-mass spectrometry with on-line solid phase extraction [15]. Plasma concentrations of mycophenolic acid (MPA) were quantified by the use of an automated heterogeneous immunoassay (Emit®2000 Mycophenolic Acid Assay, DADE-Behring, Marburg, Germany). Initially trough levels were measured weekly twice, and after the third month weekly. Endomyocardial biopsies (using histological ISHLT-criteria) were performed routinely 1 and 3 months after conversion and if acute rejection was suspected. Further maintenance biopsies were performed in patients within a time range of < 2 years after transplantation according to the local clinical routine follow-up schedule.

In a parallel approach, a retrospective analysis was performed of all HTx-patients with chronic renal failure admitted to our hospital before the conversion study started (1996–2001). These patients were included into a historical control group, if they had met the study criteria for conversion. Each of these patients received tacrolimus or cyclosporine and MMF was added and CNI-trough levels were mildly reduced (Table 1). All other comedication with potential nephrotoxicity were stopped.

For statistical analysis paired Wilcoxon-test was used to calculate differences between parametric data prior and after conversion. A general linear model for repeated measures was used for repeated paired comparisons for laboratory parameters and creatinine clearance in the clinical follow-up and between the groups. A P < 0.05 was considered significant. Data are displayed as mean ± SD or percent, where appropriate. The statistical software package SPSS was used for all analyses.

### 3. Results

#### 3.1. Baseline data

Thirty HTx-patients, admitted to our institution due to chronic renal failure were enrolled to the conversion study since 2001. Two patients were excluded prior study entry, one patient suffered from idiopathic leucopenia and the other from recurrent psychosis. Retrospective analysis

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient data prior immunosuppressive conversion or inclusion as control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMF/Sir</td>
</tr>
<tr>
<td>Patient no. (n)</td>
<td>30</td>
</tr>
<tr>
<td>Patient gender (f/m)</td>
<td>5/25</td>
</tr>
<tr>
<td>Mean patient age (years)</td>
<td>55 ± 12.8</td>
</tr>
<tr>
<td>Mean follow-up after transplantation (at conversion) (years)</td>
<td>3.9 ± 3.2</td>
</tr>
<tr>
<td>Mean follow-up after conversion or possible inclusion (months)</td>
<td>15.8 ± 7</td>
</tr>
<tr>
<td>Number of acute rejections/patient prior conversion</td>
<td></td>
</tr>
<tr>
<td>Mild (&lt;3a ISHLT)</td>
<td>0.5</td>
</tr>
<tr>
<td>Severe (≥3a ISHLT)</td>
<td>0.2</td>
</tr>
<tr>
<td>Primary immunosuppressant prior conversion</td>
<td></td>
</tr>
<tr>
<td>CsA (%)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Tac (%)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Patients on chronic haemodialysis (n) prior conversion</td>
<td>3</td>
</tr>
</tbody>
</table>
revealed that between 1996 and 2001, 33 HTx-recipients were admitted to our department due to renal failure and met the inclusion criteria for the conversion study. In those patients CNI-treatment was continued as before due to the fact that the combination of MMF and Sir was not available. There were no significant difference in patient’s demographics and baseline characteristics (Table 1).

Survival was 93% after a mean follow-up of 15.8 ± 7 months (conversion) and 90% after 1 year (P = 0.78) and 73% after an overall follow-up of 41.1 ± 18.2 months in the control group. Causes of death were pre-existing severe graft vessel disease (GVD; two patients in the conversion group and five patients in the control group) and infections (four patients in the control group). Immunosuppression prior study entry was mainly tacrolimus-based (Table 1). In addition most of the conversion-patients received MMF (n = 28) while two received Sir prior study entry. In the control group 26 patients had MMF and 5 had azathioprine. Only three of all patients in the first 6 months after HTx were on steroid medication at the time of conversion. No patient had undergone induction therapy.

3.2. Renal function

All mean kidney parameters such as creatinine, creatinine clearance, urea and cystatin improved significantly after conversion (Table 2, Figs. 1 and 2). During the conversion period and especially after complete CNI-withdrawal, creatinine clearance did significantly increase (Figs. 2 and 3). After this initial recovery renal parameters remained mildly impaired but stable. Three patients, who already started chronic haemodialysis therapy (mean time 1.2 ± 0.7 months), could be weaned after conversion and haemodialysis could be stopped completely (Fig. 4). In one patient renal replacement therapy had to be started 14 months after conversion. Overall, in four of the 30 conversion-patients renal function did not improve (Fig. 3).

In the control group renal impairment could not be improved. Creatinine clearance decreased steadily from 38.76 ± 11.3 to 27.5 ± 9.3 ml/min (P = 0.06) and 10 of the 33 control patients, who were haemodialysis-free, when renal saving therapy without conversion started, were on renal replacement therapy after 1 year (Fig. 4).

Table 2

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Study entry (mean ± SD)</th>
<th>After 1 month (mean ± SD)</th>
<th>After 6 months (mean ± SD)</th>
<th>After 12 months (mean ± SD)</th>
<th>P-value (study entry vs 12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF/sirolimus conversion</td>
<td>3.15 ± 0.81</td>
<td>2.11 ± 0.89</td>
<td>2.23 ± 0.76</td>
<td>2.20 ± 0.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Control group</td>
<td>2.45 ± 0.88</td>
<td>2.49 ± 0.63</td>
<td>2.84 ± 0.91</td>
<td>3.31 ± 0.81</td>
<td>0.02</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF/sirolimus conversion</td>
<td>124 ± 33</td>
<td>80 ± 31</td>
<td>85 ± 33</td>
<td>78 ± 22</td>
<td>0.001</td>
</tr>
<tr>
<td>Control group</td>
<td>106 ± 51</td>
<td>109 ± 49</td>
<td>117 ± 34</td>
<td>129 ± 23</td>
<td>0.02</td>
</tr>
<tr>
<td>Cystatin (mg/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MMF/sirolimus conversion</td>
<td>2.82 ± 0.95</td>
<td>1.88 ± 0.45</td>
<td>2.12 ± 0.46</td>
<td>2.09 ± 0.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Control group</td>
<td>2.61 ± 0.42</td>
<td>2.62 ± 0.42</td>
<td>3.24 ± 0.32</td>
<td>3.72 ± 0.22</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
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<tr>
<td>MMF/sirolimus conversion</td>
<td>138 ± 13</td>
<td>125 ± 12</td>
<td>130 ± 8</td>
<td>125 ± 16</td>
<td>0.04</td>
</tr>
<tr>
<td>Control group</td>
<td>134 ± 22</td>
<td>134 ± 21</td>
<td>138 ± 22</td>
<td>139 ± 19</td>
<td>0.1</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>MMF/sirolimus conversion</td>
<td>85 ± 60</td>
<td>75 ± 8</td>
<td>81 ± 9</td>
<td>74 ± 7</td>
<td>0.02</td>
</tr>
<tr>
<td>Control group</td>
<td>86 ± 71</td>
<td>87 ± 52</td>
<td>84 ± 61</td>
<td>89 ± 71</td>
<td>0.59</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>MMF/sirolimus conversion</td>
<td>180 ± 40</td>
<td>201 ± 42</td>
<td>213 ± 70</td>
<td>216 ± 39</td>
<td>0.04</td>
</tr>
<tr>
<td>Control group</td>
<td>177 ± 42</td>
<td>173 ± 42</td>
<td>183 ± 37</td>
<td>186 ± 56</td>
<td>0.13</td>
</tr>
<tr>
<td>Leukocytes (G/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MMF/sirolimus conversion</td>
<td>6.65 ± 3.48</td>
<td>6.38 ± 3.48</td>
<td>6.31 ± 2.4</td>
<td>6.09 ± 2.64</td>
<td>0.10</td>
</tr>
<tr>
<td>Control group</td>
<td>7.01 ± 2.29</td>
<td>6.89 ± 2.61</td>
<td>6.92 ± 2.56</td>
<td>6.82 ± 2.81</td>
<td>0.27</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF/sirolimus conversion</td>
<td>11 ± 2.96</td>
<td>10.39 ± 2.77</td>
<td>10.2 ± 2.45</td>
<td>10.91 ± 2.79</td>
<td>0.81</td>
</tr>
<tr>
<td>Control group</td>
<td>10.1 ± 3.01</td>
<td>9.78 ± 2.76</td>
<td>9.1 ± 2.1</td>
<td>8.9 ± 2.01</td>
<td>0.06</td>
</tr>
</tbody>
</table>

For renal and bone marrow function and lipid metabolism prior and in the follow-up after conversion to sirolimus and MMF and blood pressure: serum creatinine (mg/dl), serum urea (mg/dl), serum cystatin (mg/l), serum uric acid (mg/dl), white blood count (G/l), haemoglobin (G/l), cholesterol (mg/dl), triglycerides (mg/dl) and systolic and diastolic arterial blood pressure (mmHg).
Each of the patients in the control group who died during follow-up was on renal replacement therapy.

### 3.3. Cardiovascular and graft function

No clinical or histological signs of acute rejection were detected during the study period. None of the 69 endomyocardial biopsies performed in the conversion-group showed histological signs of acute rejection (≥°1b ISHLT). All patients underwent biopsies after 1 and 3 months (ISHLT°0, n = 46; ISHLT°1a, n = 14). Five additional biopsies were done due to a higher risk of rejection (conversion within the first year after transplantation) or due to non-specific clinical signs of rejection (ISHLT°0, n = 2; ISHLT°1a, n = 3). Left ventricular fractional shortening remained stable (prior conversion vs after conversion, 36.9 ± 6 vs 36.4 ± 6%; P = 0.42). GVD was evident in nine patients prior conversion and was progressive in two patients: both died (sudden cardiac death) due to rapid progression 5 and 9 months after GVD was diagnosed and the patient had been converted. Overall no new onset of GVD was detected in the routine annual coronary angiographies.

In the control group no acute rejection was detected within the first year of follow-up and therefore left ventricular fractional shortening remained stable (prior conversion vs after conversion, 35.2 ± 7 vs 31.4 ± 8%; P = 0.13). GVD was detected in seven patients, when renal failure occurred. Three patients died due to rapid progressive GVD. In four patients a new onset of GVD was detected within the first year of follow-up.

Blood pressure dropped significantly after conversion and antihypertensive medication (calcium antagonists) could be reduced in six patients (20%). In the control group blood pressure remained unchanged (Table 2).

Mean cholesterol levels and triglycerides, however, increased after conversion (Table 2) and remained stable in the control-group. New onset of hypercholesteremia (> 240 mg/dl) was seen in seven conversion-patients and in five control-patients in spite of the fact that all patients were on routine statin treatment.

### 3.4. Adverse effects

The incidence of infections after conversion was 0.2 ± 0.08 infections per 100 patient-days and was
comparable to the control group (0.3 ± 0.1 infections per 100 patient-days). No difference was seen in the spectrum of infective pathogens before or after conversion. Infection rate was 52% due to bacteria (Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella, Enterococcus). Viruses (CMV, Herpes simplex) and fungi (Candida albicans, Aspergillus fumigatus) were equally distributed, each causing 23% of infection. The most common sites were the respiratory tract (52%) and the gastro-intestinal tract (26%).

Sir- or MMF-related adverse effects were seen in 21 patients (70%; Fig. 5), most commonly a transient facial acne—well known as a Sir side effect [12] which occurred in the first 3–6 weeks after conversion and disappeared without further treatment in 74% of these patients. Other common side effects were wound healing problems (aphthous ulcers), changes in all blood count and gastrointestinal disorders (diarrhea, nausea).

Aphthous ulcers (10%) were treated with topical panthenol emulsions and recovered within 2 weeks in all cases. Blood count did not show significant changes in mean platelet and white blood count. Although platelets were low in 17% of the patients (<150 000 G/l), it did not have any clinical or therapeutic impact. In one patient severe leukopenia occurred (white blood count 1.9 G/l) and MMF and Sir was intermittently reduced to subtherapeutic trough levels (MPA 1.5 mg/l; Sir 6.9 ng/ml), while the patient was kept under surveillance in hospital for acute rejection. After recovery, trough levels were readjusted to target levels. Haemoglobin values decreased after conversion, but no severe anaemia (<8 G/l) was noted and no transfusion or erythropoetin administration was necessary. In most cases of adverse effects (73%) Sir trough levels were above the target range and lowered, when side effects occurred. Gastrointestinal side effects were particularly associated with elevated MPA trough levels (mean MPA during gastrointestinal events, 6.1 ± 0.9 mg/l) and Sir levels (13.4 ± 2.7 ng/ml). Therefore, MMF treatment was stopped intermittently in six patients. Fortunately all patients recovered within 2 weeks and Sir treatment did not have to be stopped in any patient. No patient left the conversion study because of side effects.

3.5. Immunosuppressive therapy

Mean Sir trough levels of 11.21 ± 1.44 ng/ml were achieved within the clinical follow-up by administering a mean of 2.62 ± 1.62 mg of Sir. After complete conversion to Sir, patients who had received CsA prior conversion...
needed less MMF after conversion (MMF dosage prior conversion vs post-conversion, 3578 ± 1404 vs 3011 ± 1265 mg; P = 0.06) to achieve comparable MPA trough levels (2.72 ± 1.1 vs 3.01 ± 0.7 mg/l; P = 0.12). In contrast, there were no significant changes in MMF dosage in patients, who had been on Tac/MMF prior conversion (MMF dosage prior conversion vs post-conversion: 1829 ± 717 vs 2092 ± 975 mg, P = 0.54; MPA trough levels prior conversion vs post-conversion: 3.03 ± 1.4 vs 2.76 ± 0.5 mg/l, P = 0.11). During the whole study period, an average of 2392 ± 1050 mg MMF was needed to achieve a mean of 2.83 ± 0.8 mg/l MPA.

In the control group mean cyclosporine trough levels were reduced from 144 ± 54 to 103 ± 46 ng/ml (P = 0.08) and tacrolimus levels were reduced from 10.7 ± 2.9 to 8.7 ± 2.8 ng/ml (P = 0.19). MPA trough levels were 3.02 ± 0.9 mg/l.

4. Discussion

This study is the first prospective study assessing the efficacy and safety of an immunosuppressive conversion to a CNI-free regimen based on MMF and Sir in HTx. Although the study was not randomized, the results indicate that kidney function—as assessed by creatinine clearance, creatinine, urea and cystatin—significantly improved after CNIs were completely stopped and replaced by MMF and Sir. CNI withdrawal was possible in all patients, and three patients were successfully weaned from haemodialysis after conversion and remained haemodialysis-free. It is important to understand that patients in this study were not new to immunosuppression or renal failure. The post-operative time for patients in this study averaged almost 4 years. Chronic renal failure averaged for >3 months prior conversion. Causes other than CNI-induced renal impairment were non-invasively excluded and the fact that significant renal recovery only occurred, when CNIs were completely stopped, indicates CNI nephrotoxicity as the main cause of renal failure in our patients. The fate of patients with renal failure and ongoing CNI-based immunosuppression in our institution was demonstrated by a historical control group. Creatinine clearance decreased steadily resulting in chronic renal replacement therapy for 30% of the patients after 1 year.

Chronical CNI use causes structural alterations in the kidney, which have usually been described as mainly irreversible [7]. Creatinine and cystatin values in this study remained clearly elevated, but renal function significantly recovered soon after conversion. Therefore, an element of acute CNI nephrotoxicity as postulated by Snell, seems to be reversible following the withdrawal of the toxic agent and seems to play an important part. The great clinical success of this study is based on this reversible CNI nephrotoxicity, which was successfully eliminated. After the initial recovery directly after conversion, renal parameters remained stable. This is suggestive of some level of irreversible renal damage. To date, it is not possible to identify any clinical or laboratory parameter, that has a predictive value for the degree of reversibility of renal failure. Therefore we could not identify risk factors for non-responding patients. Fortunately, most of the patients did respond (80%) by renal recovery.

Given the number of successful outcomes and the low risks associated with the conversion, a switch to MMF and Sir may be confidently recommended to patients demonstrating CNI toxicity.

Besides the positive effect of CNI withdrawal on renal function, conversion to MMF and Sir as alternative immunosuppression had a striking effect on other, though not all side effects of these drugs.

Hypertension was significantly reduced after CNI withdrawal and antihypertensive calcium antagonist medication could be reduced. The beneficial effect on blood pressure in this study was more pronounced than in other studies, that reduced CNI after adding MMF as second immunosuppressant [16,17]. Only in studies with complete CNI withdrawal more extensive beneficial effects were seen [18,19]. To date, complete replacement of CNI by MMF with an acceptable incidence of acute rejections has only been demonstrated in renal or liver transplant recipients. After thoracic transplantation requiring higher levels of immunosuppression, CNI-free immunosuppression consisting of MMF and steroids was associated with a substantial loss of immunological safety. Before Sir was available, we tried to convert patients with CNI nephrotoxicity to MMF and steroids in a clinical trial. While in some patients the regimen proved to be sufficient, others revealed new onset of acute rejections and of GVD [20]. This was not seen in the current study. Not a single acute rejection occurred, graft function remained stable and there was no detectable onset of GVD in patients under MMF and Sir treatment, indicating an excellent efficacy of this combination.

Despite the safety profile and reversal of CNI side effects, MMF and Sir immunosuppressive therapy was also associated with adverse effects.

A high number of cases of specific reversible (Sir-) acne occurred during the first 3–6 weeks, although they declined without further treatment. Aphtulcers were seen in two patients with elevated trough levels. These wound healing problems could be explained by the antiproliferative action of Sir, well documented in other de novo transplant studies [19,21]. Severe hyperlipidemia is known to be associated with Sir use [19,21,22]. Although in this study serum cholesterol and triglyceride levels increased significantly, hyperlipidemia was not as pronounced as in other studies [19,21,22]. This could be explained by the routine statin treatment to reduce the risk for GVD and by lower Sir target trough levels, which were possible because of the combined use with MMF.

Side effects, which are known for both drugs (MMF and Sir) such as leukopenia and gastrointestinal dysfunction [21]...
were seen in several cases in this study, but were generally mild. Leukopenia might be an alarming and difficult adverse event, since both drugs could be the causative agent, which has to be identified, while immunosuppressive safety has to be maintained. Overall, no patient was removed from the study because of side effects.

Thus the beneficial effects of the MMF and Sir combination with respect to side effects seem to outweigh in patients suffering from serious side effects of a CNI-based immunosuppressive combination.

One important factor for the long-term or de novo use of a new combination, is its impact on the development of GVD. In the historical control group an annual incidence of GVD of 9% was seen, which is consistent with the reported incidence of GVD of 5–10% per year independent of GVD of 9% was seen, which is consistent with the annual incidence of GVD. In the historical control group an annual incidence of GVD.

As in other studies the antiproliferative action of Sir and MMF seemed to have a positive impact in the prevention of vascular intimal hyperplasia [23–25]. This effect is, however, not helpful, when GVD is already present. It is unclear if the antiproliferative properties can offset the Sir-induced hypercholesteremia and reduce chronic rejection.

Since the number of patients was limited and the study was not a randomized trial, our results might be preliminary. Nevertheless, this study suggests that conversion to MMF and Sir is the most successful strategy for HTx-patients with severe renal impairment to date, which may reverse renal failure and reduce other CNI-induced side effects after HTx. However, a longer follow-up is needed to ensure long-term safety and efficacy.

5. Conclusions

After conversion to MMF and Sir in HTx-recipients with chronic renal failure, kidney function improved significantly in the absence of acute rejection episodes and severe side effects.

Due to the fact that this was a prospective, but non-randomized study, efficacy and safety of the completely CNI-free immunosuppression has to be confirmed in a prospective randomized trial. Furthermore, the impact of long-term effects of this new regimen on other commonly occurring complications after HTx (e.g. hypercholesterolemia, GVD, gastro-intestinal disorders) has to be evaluated.

References


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**Appendix A. Conference discussion**

*Dr A. Liebold (Regensburg, Germany):* Did you perform renal biopsies before you switched the patients to ensure that they have really a CNI-induced nephrotoxicity. I mean, there are other reasons for nephropathy after transplantation, for instance, diabetes. And you had, as far as I remember, you had also 4 non-responders.

*Dr Groetzner:* We planned to do that, but our nephrologist declined renal biopsies, especially in these severely ill patients, and so we didn’t perform any myocardial biopsies. We excluded other renal diseases non-invasively. On the other hand, we can say that the fact that most of the patients responded to the treatment is also a hint that most of the patients suffered indeed from calcineurin-inhibitor-associated side effects.

*Dr Liebold:* Would you advocate to switch such patients without performing renal biopsy?

*Dr Groetzner:* We did that and our approach was successful. Therefore I would recommend conversion without renal biopsy.

*Dr S. Aziz (Washington, DC, USA):* Did you see any change in lipid profile in these patients before, when you changed?

And secondly, when you did your echocardiography did you see any improvement in any diastolic relaxation parameters?

*Dr Groetzner:* We did see other lipid profiles during the follow-up. Hypercholesteremia and hypertriglycerideremia occurred. The mean cholesterol levels increased significantly, but we didn’t see any changes in the diastolic function.