Conversion to sirolimus-based immunosuppression in maintenance liver transplantation patients

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Abstract

Sirolimus (SRL) has been proposed to replace calcineurin inhibitors (CNI) in case of CNI-induced toxicity. The aim of this study was to evaluate the efficacy and safety of conversion from CNI to SRL in maintenance liver transplantation (LT) patients. Between 2002 and 2006, conversion was performed in 48 patients (17 female, 31 male; mean age 57 +/- 10 yr) after a median delay of 19.4 months (range 0.2-173 months) after LT. Indication for conversion was renal impairment (RI) (78%), CNI neurotoxicity (13%), or post-LT cancer (9%). Median follow-up was 22.6 +/- 11 months. Median SRL dosage and trough levels were 2.4 +/- 1.3 mg and 8.1 +/- 2.7 microg/L. Immunosuppression consisted of SRL alone (33%), or SRL + mycophenolate mofetil (MMF) (39%), SRL + prednisone (15%), SRL + CNI (4%), or SRL + MMF + prednisone (8%). Mean glomerular filtration rate (GFR) improved from 33 to 48 mL/minute in patients with severe RI (P = 0.022) and from 56 to 74 mL/minute in patients with moderate RI (P = 0.0001). After conversion, main complications were albuminuria (36%), hyperlipidemia (49%), dermatitis (14%), edema (14%), oral ulcers (12%), [...]
Conversion to Sirolimus-Based Immunosuppression in Maintenance Liver Transplantation Patients

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Sirolimus (SRL) (Rapamycin; Wyeth-Ayerst, Zug, Switzerland) is a new immunosuppressive drug that has been proposed to replace calcineurin inhibitors (CNI) in case of CNI-induced toxicity. It is approved for renal transplantation. Randomized, controlled trials comparing SRL with conventional immunosuppressive drugs have not been yet completed in liver transplantation (LT) but several publications have documented the efficacy and safety of SRL in terms of graft and patient survival.1 Conversion from CNI to SRL or addition of SRL to achieve lower CNI target levels improved renal function in pediatric2-4 as well as in adult LT recipients.5-12 CNI-related neurotoxicity also decreased or resolved after conversion to SRL.7,13-15 In addition, in vitro, SRL is able to inhibit the growth of different human carcinoma cells.16 Therefore, it has been proposed as an immunosuppressive drug in LT for hepatocellular carcinoma.17,18 However, SRL is associated with frequent side effects such as anemia, thrombocytopenia, edema, dyslipidemia, joint pain, pulmonary disease, oral ulcers, and dermatitis.4,7,8,11,13,19-21 These adverse effects often significantly affect the patient’s quality of life, requiring SRL discontinuation in about 25% of cases (15-37%).2,7,8,10,11,13,19

The aim of this study was to assess the feasibility, efficacy, and safety of conversion from CNI to SRL as a maintenance immunosuppressive drug after LT and to determine whether conversion is associated with reversal of CNI toxicity.

PATIENTS AND METHODS

Indications for Conversion from CNI to SRL

Between 1985 and March 2006, 312 adult LTs were performed in our center and 231 patients (74%) were

Abbreviations: SRL, sirolimus; CNI, calcineurin inhibitors; LT, liver transplantation; RI, renal impairment; MMF, mycophenolate mofetil; AR, acute rejection; GFR, glomerular filtration rate; cGFR, GFR, glomerular filtration rate evaluated by the Cockroft formula.

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alive on March 1, 2006. Since March 1, 2002, patients with renal function impairment, CNI neurotoxicity, or post-LT cancer were converted from CNI to SRL. Renal impairment (RI) was defined as mild (glomerular filtration rate [GFR] evaluated by the Cockroft formula \( cGFR^22 \times H110^70 \text{mL/minute} \), moderate (GFR 40-70 mL/minute), or severe (GFR 20-40 mL/minute). Patients with mild RI were converted from CNI to SRL in cases with recent and significant decrease in their renal function (>10 mL/minute over 1 yr) despite reduction of CNI doses, or in case of CNI neurotoxicity or post-LT cancer (recurrent hepatocellular carcinoma or posttransplantation lymphoproliferative disease).

Conversion Protocol
CNI were discontinued at day 0; and 12 hours after the last administration of CNI, SRL was given at an initial loading dose of 6 mg (day 1) followed by 2 mg once a day during the first week (day 2-7). SRL trough level was measured after 5 days and the SRL dose was adjusted to maintain trough levels between 5 and 10 \( g/L \). Other immunosuppressive drugs such as mycophenolate mofetil (MMF), azathioprine, and/or corticosteroids were maintained.

Follow-Up
Clinical and laboratory data related to the clinical course of the patients were prospectively recorded to investigate the safety and efficacy of conversion. The data collected after conversion included SRL dosage, SRL serum trough level at steady state, occurrence of acute rejection, presence of hypercholesterolemia (defined by the ratio of total cholesterol/high-density lipoproteins >5 or by the presence of therapy), diabetes or hypertension, and clinical outcome. Laboratory data were recorded through the last follow-up available and included blood cell count, liver function tests, cGFR,22 and albuminuria. Liver biopsies were obtained as clinically needed for assessment of graft dysfunction and, systematically, once per year after LT. Diagnosis of rejection was always proven by biopsy. Histological changes were graded according to the Banff classification.23

Statistical Analysis
Differences between groups were tested with nonparametric tests, Mann-Whitney or Wilcoxon. The statistical software used was SPSS 10.0 for Windows (SPSS Switzerland; Zürich, Switzerland).

RESULTS
Characteristics of the Patient Population
Between March 2 and March 6, 48 patients (17 females, 31 males; mean age 57 ± 10 yr) were converted from CNI to SRL after a median delay of 19.4 months (range 0.2 to 173 days). Conversion from CNI to SRL was performed in the first 3 months after LT in 6 patients presenting early severe CNI-associated neurotoxicity and nephrotoxicity. Median follow-up after conversion was 22.6 ± 11 months. Indications for LT and demographic data of the patients are detailed in Table 1.

The immunosuppressive regimen at the time of conversion consisted of CNI alone in 19% of patients, CNI with MMF or azathioprine in 53%, and CNI with MMF or azathioprine and corticosteroids in 28%. Tacrolimus was used in 51% of patients with mean trough levels of 7 ± 4 \( \mu g/L \) and cyclosporine in 47% with mean trough levels of 96 ± 57 \( \mu g/L \).

### Table 1. Demographic Data

| Total (n) | 48 |
| Female (n) | 17 |
| Age at conversion (yr) | 57 ± 10 |
| Time from LT to conversion (months) (median, range) | 42.9 (0.2-173 months) |
| Comorbidities: |  |
| Diabetes mellitus (%) | 32 |
| Hypertension (%) | 68 |
| Hypercholesterolemia (%) | 32 |
| Cause of liver disease |  |
| Alcohol (%) | 38 |
| HCV (%) | 34 |
| HBV (%) | 11 |
| Cholestatic diseases (%) | 9 |
| Other (%) | 8 |
| Immunosuppression at time of conversion |  |
| CNI in monotherapy (%) | 19 |
| CNI in association with MMF/AZA (%) | 53 |
| CNI in association with MMF/AZA and CS (%) | 28 |
| Tacrolimus (mean trough level) | 51% (7 ± 4 \( \mu g/L \)) |
| Cyclosporine (mean trough level) | 47% (96 ± 57 \( \mu g/L \)) |

**Abbreviations:** HCV, hepatitis C virus; HBV, hepatitis B virus; AZA, azathioprine; CS, corticosteroids.
Indication for conversion from CNI to SRL was renal function impairment (78%), CNI neurotoxicity (13%), or post-LT cancer (9%). Before conversion, 19% of patients presented a severe RI, 45% a moderate RI, and 36% of them had a GFR greater than 70 mL/minute.

Six patients were converted to SRL because of neurological symptoms attributed to or exacerbated by CNI. One patient presented severe headache and a second one invalidating tremor. A third patient suffered of chronic partial epilepsy with frequent crisis despite antiepileptic treatment. Generalized tonic-clonic crisis occurred in the first weeks after transplantation in 3 patients who had severe encephalopathy and pontic myelolysis before LT.

Cancer occurred as: 1 biliary posttransplantation lymphoproliferative disease 8 yr after LT (patient 1); hepatocellular carcinoma recurrence with metastases (patients 2 and 3) 5 and 20 months after LT; and esophageus adenocarcinoma with pulmonary metastases (patient 4) discovered 1 yr after LT. These patients were converted to SRL just after the diagnosis of malignancy was made: 3,193 days (patient 1), 155 days (patient 2), 625 days (patient 3), and 371 days (patient 4) after LT.

Mean SRL daily dosage and trough levels at steady state were 2.4 g/11006 1.3 mg and 8.1 g/11006 2.7 mg/L, respectively. Immunosuppressive drugs consisted of SRL alone (40%), SRL in association with MMF (35%), SRL in association with prednisone (15%), SRL in association with CNI (2%), or SRL in association with both MMF and prednisone (8%).

GFR Evolution After Conversion From CNI to SRL

GFR values increased > 10 mL/minute in 44% of patients, specially in the subgroups of patients with severe (56%) and moderate (50%) RI before conversion. Decrease in GFR value >10 mL/minute occurred in 5% of the patients with moderate RI and in 47% with cGFR >70 mL/minute but in no patients with severe RI. No patient needed dialysis or kidney transplantation during the study period (Table 2). Mean cGFR improved from 33 ± 3.8 to 48 ± 17.7 mL/minute in patients with severe RI before conversion (P = 0.022) and from 56 ± 6.23 to 74 ± 27.2 mL/minute in patients with moderate RI before conversion (P = 0.001). Patients with a cGFR >70 mL/minute did not benefit from the conversion to SRL therapy (mean cGFR 93 ± 21.8 mL/minute before and 94 ± 26.1 after the conversion) (Fig. 1). In the subgroups of patients converted to SRL for neurotoxicity (n = 6) and for tumors (n = 4), mean cGFR evolved from 84.6 to 103.2 mL/minute and from 102 to 98 mL/minute, respectively.

Neurotoxicity and Cancer

Neurological symptoms attributed or exacerbated by CNI improved after conversion to SRL in all patients. Headache and tremor completely disappeared after the switch. Chronic partial epileptic crisis did not relapse after CNI withdrawal and SRL initiation. After conversion to SRL and initial treatment with antiepileptic drugs and thyrotropin releasing hormone, the 3 patients with severe encephalopathy and generalized epilepsy did not experience relapse of crisis and their cognitive function significantly improved.

Four patients were converted to SRL because of cancer: 1 of them with biliary posttransplantation lymphoproliferative disease is alive 30 months after treatment with anti-CD20 and conversion to SRL. Three patients died 20, 15, and 12 months after conversion to SRL from metastatic evolution of esophageal adenocarcinoma (n = 1) or recurrent hepatocellular carcinoma (n = 2).

Safety and Tolerance of Conversion

Incidence of diabetes and arterial hypertension did not significantly vary with SRL (30% vs. 32% and 74% vs. 70%, after and before conversion, respectively). Before conversion, 37.5% of the patients were treated by 1, 19% by 2, 2% by 3, and 2% by 4 antihypertensive drugs. After conversion, 37.5% of the patients were treated by

### Table 2. Renal Function Evolution After Conversion to SRL Therapy

<table>
<thead>
<tr>
<th>Initial renal function</th>
<th>cGFR &lt;40 mL/minute</th>
<th>cGFR &gt;40 and &lt;70 mL/minute</th>
<th>cGFR &gt;70 mL/minute</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 9) (%)</td>
<td>(n = 22) (%)</td>
<td>(n = 17) (%)</td>
</tr>
<tr>
<td>Increasing of cGFR &gt;10 mL/minute</td>
<td>5 (56)</td>
<td>11 (50)</td>
<td>4 (23)</td>
</tr>
<tr>
<td>No cGFR modification</td>
<td>4 (44)</td>
<td>10 (45)</td>
<td>5 (30)</td>
</tr>
<tr>
<td>Decreasing of cGFR &gt;10 mL/minute</td>
<td>0</td>
<td>1 (5)</td>
<td>8 (47)</td>
</tr>
</tbody>
</table>

Figure 1. GFR modification after conversion to SRL therapy.
Albuminuria before and after conversion to SRL (available in 28 patients).

DISCUSSION

With the use of CNI and the increasing success of LT, therapeutic challenges associated with the use of immunosuppressive agents has shifted from short-term survival toward minimizing drug toxicity and long-term morbidity and mortality of transplant recipients. High trough CNI level early after LT and high cumulative CNI dosage after LT are significant risk factors for late severe renal dysfunction. CNI nephrotoxicity may be due to vasoconstriction, which is reversible, and to the production of transforming growth factor \( \beta \) leading to interstitial fibrosis, which is often progressive and irreversible. Therefore, it may be an important goal to prevent further deterioration of renal function as soon as patients develop a moderate RI.

Various strategies are used to prevent or slow down the progression of renal dysfunction in LT recipients. CNI reduction may be insufficient to prevent progression to end-stage renal failure. Conversion from CNI to MMF monotherapy has been attempted in several small studies but all of them except 1 reported an unacceptable rate of severe irreversible AR or chronic rejection. We confirm here that conversion from CNI to SRL alone or in association with MMF seems to be a safe and efficient strategy.

CNI were discontinued in all our patients except 1 because of early conversion post-LT. The great majority of patients presenting upon SRL initiation presented with a normal or reduced RI and experienced a slow improvement of RI. The RI was reversible in all cases presenting a normal RI at the end of follow-up.

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One of the most relevant findings of our study is the occurrence of significant albuminuria in patients who underwent liver and not renal transplantation and were treated without CNI. SRL-associated glomerulonephritis has previously been described after renal transplantation,35-39 as well as in patients with chronic glomerulonephritis.40 SRL may potentiate CNI nephrotoxicity35,37,41 and may also display direct tubular or, to a lesser degree, glomerular toxicity. Our results show that initial albuminuria >20 mg/L, and the use of 2 or more antihypertensive drugs before conversion are predictive of development of significant albuminuria after conversion. SRL could worsen preexisting glomerular renal lesions, due to its negative effects on cell regeneration and survival.37 In addition, SRL may potentiate tubular toxicity of proteinuria per se.39,40 We observed that albuminuria >500 mg/L after conversion to SRL was associated with renal function improvement in 2 patients and impairment in 2 others. The significance and prognostic value of albuminuria in patients treated with SRL need further evaluation. We recommend screening patients before converting them to SRL, and avoiding this therapy in cases of severe arterial hypertension and/or of significant albuminuria.

In our study, adverse events required SRL discontinuation in 17% of patients. This rate is similar to those previously reported.2,7,8,10,11,13,19,20,42 Preconversion albuminuria >30 g/L and SRL trough levels >9.5 μg/L (vs. 7.7 μg/L) were significantly associated with treatment withdrawal (P < 0.05).

In our study, 17% of patients experienced AR after conversion to SRL. This rate, probably due to low SRL trough level in our series, is higher than reported in the literature: SRL alone or in association with MMF was associated with a rate of rejection varying from 0 to 5%4,7-9,15 and exceptionally to 48%.1 However, in our series, 75% of these episodes occurred during the first year after LT and none evolved toward chronic rejection. The rate of AR in our cohort of patients treated with CNI was treated with SRL alone (40%) or in association with MMF (35%). Other studies documented the safety of SRL without CNI4,5,7-9,15 but to the best of our knowledge our report of 48 cases is one of the largest that has been published.

The present study shows that renal function, assessed by cGFR,22 improved significantly after conversion in patients with severe as well as moderate RI. We choose to switch patients from CNI to SRL before development of severe RI to prevent further deterioration. In a recently published study, only patients with severe renal insufficiency were switched to SRL: median GFR increased from 34 to 43 mL/minute at the last follow-up. In several other publications, significant improvement of renal function was observed only in subjects with shorter time between LT and conversion (60 vs. 112 months6 and 91 vs. 147 months2) or with higher creatinine clearance11 (53 vs. 36 mL/minute) at the time of conversion, suggesting that chronic nephrotoxicity may be ameliorated by early conversion to SRL.

SRL is associated with adverse events that could significantly affect the quality of life. In a large retrospective series of 175 patients, Montalbano et al.20 described bilateral lower extremity edema (57.1%), dermatitis (25.3%), oral ulcers (24.2%), joint pain (23%), pleural effusion (16.5%), increase in abdominal girth (5.5%), general edema (5.5%), pericardial effusion (5.5%), facial edema (2.2%), and upper extremity edema (1.3%). Dyslipidemia was reported in up to 44% of patients.4,8,11,19 In our study, hypercholesterolemia incidence increased from 32% before to 49% after conversion. Interestingly, in our series, neither anemia nor thrombocytopenia were observed even when SRL was associated with MMF or azathioprine. The lower rate of adverse events in our population was probably due to lower SRL trough levels than in other reports and to the use of low dosage of MMF or azathioprine.

One of the most relevant findings of our study is the occurrence of significant albuminuria in patients who underwent liver and not renal transplantation and were treated without CNI. SRL-associated glomerulonephritis has previously been described after renal transplantation,35-39 as well as in patients with chronic glomerulonephritis.40 SRL may potentiate CNI nephrotoxicity35,37,41 and may also display direct tubular or, to a lesser degree, glomerular toxicity. Our results show that initial albuminuria >20 mg/L, and the use of 2 or more antihypertensive drugs before conversion are predictive of development of significant albuminuria after conversion. SRL could worsen preexisting glomerular renal lesions, due to its negative effects on cell regeneration and survival.37 In addition, SRL may potentiate tubular toxicity of proteinuria per se.39,40 We observed that albuminuria >500 mg/L after conversion to SRL was associated with renal function improvement in 2 patients and impairment in 2 others. The significance and prognostic value of albuminuria in patients treated with SRL need further evaluation.

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was 62.5% during the first year after LT and 21.5% after the first year.

In conclusion, our data suggest that conversion from CNI to SRL significantly improves cGFR in patients with severe or moderate RI. SRL is a safe and effective immunosuppressant, usually well tolerated at trough levels <9.5 μg/L. Association with MMF and/or steroids is safe and allows low trough levels to be maintained. However, SRL may worsen nephropathy, especially in patients with severe hypertension and preexisting albuminuria. Randomized, controlled trials of conversion to inhibitors of mammalian target of rapamycin are needed.

REFERENCES


