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29th August
1st September 2021
MiCo Convention Centre
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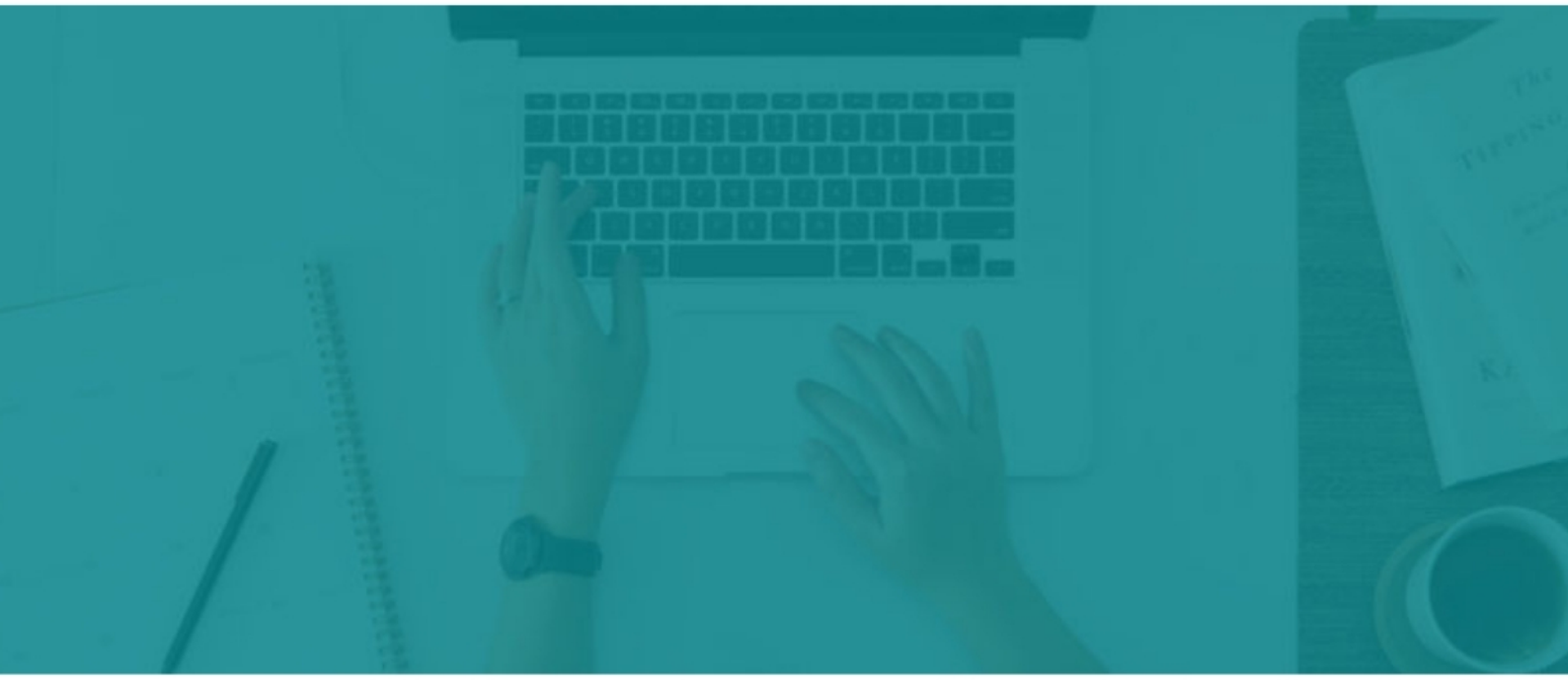

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Transplant International ISSN 0934-0874

CASE REPORT

Sirolimus as the main immunosuppressant in the early postoperative period following liver transplantation: a report of six cases and review of the literature

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Keywords
immunosuppression, liver transplantation.

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Received: 29 May 2006
Revision requested: 14 June 2006
Accepted: 20 July 2006

doi:10.1111/j.1432-2277.2006.00381.x

Summary

The use of sirolimus as the main immunosuppressant in a calcineurin inhibitor-free regimen in the early postoperative period of liver transplantation (LT), when the incidence of rejection is the highest, has seldom been reported. We report six patients who received sirolimus in association with steroids only, at a median time of 10 days after LT (range 3–23). Tacrolimus, initially given as the standard immunosuppressant, was discontinued because of nephrotoxicity in three of these patients and neurotoxicity in the other three. Resolution of the neurological symptoms was observed in all cases and a marked improvement of the renal function in two of three patients. Two patients died, one of sepsis and the other of recurrent hepatitis C virus hepatitis, after 47 and 143 days respectively. Three patients developed acute rejection which responded to intravenous steroids. In this cohort of patients, the use of sirolimus appeared safe and provided an adequate prophylaxis against rejection, even though the drug was administered in the immediate postoperative period after LT.

Introduction

Sirolimus is an immunosuppressant drug at present licensed for use in association with cyclosporine to prevent acute rejection following renal transplantation. In liver transplantation (LT), the use of sirolimus is mainly limited to those patients who develop serious side-effects, first of all nephrotoxicity, related to treatment with calcineurin inhibitors (CIs), cyclosporine or tacrolimus, or whose renal function or neurological status is already severely compromised at the time of transplantation and can be worsened by the administration of CIs [1–3]. Another emerging indication for the use of sirolimus is the avoidance of tumor recurrence in patients transplanted for hepatocellular carcinoma (HCC) [4]. After LT, sirolimus is usually administered in association with CIs to reduce their dosage [5].

In the few reports on the use of sirolimus as the main immunosuppressant after LT, CIs were usually withdrawn after the first postoperative month, the period when the incidence of acute rejection is the highest [6]. Very little is known about the possibility of employing sirolimus as the main immunosuppressant starting from the early postoperative period.

We describe a single-center experience with the use of sirolimus as the main immunosuppressant in the early postoperative period of LT.

Patients and methods

From 1986 to 2005, 1018 LTs were performed at the Transplantation Centre of the University of Bologna where standard immunosuppression is based on tacrolimus and steroids.

Since May 2004, tacrolimus has been withdrawn and replaced by sirolimus (Rapamune) as the main immunosuppressant in six patients; tacrolimus was discontinued because of nephrotoxicity in three patients and neurotoxicity in the other three.

There were five male and one female patients, whose average age was 57 years (range 49–65). Indications for LT were HCC on HBV-related cirrhosis in two patients,

Table 1. Patient details.

Patient no.	Sex/age (years)	Primary disease	Reason for TAC withdrawal	Effect of sirolimus on TAC toxicity	Time from LT to TAC withdrawal (days)	Time from LT to steroids withdrawal (days)	Median SRL blood level (ng/ml)	Follow-up (days)	Outcome
1	M/58	HCC/HBV cirrhosis	Neurotoxicity	Improved	7	121	6	577	Alive and well
2	M/49	HCC/HCV cirrhosis	Nephrotoxicity	Unchanged	3	33	6	485	Alive and well
3	M/55	HCC/HBV cirrhosis	Neurotoxicity	Improved	14	204	7	250	Alive and well
4	M/64	HCV cirrhosis	Neurotoxicity	Improved	15	113	7.7	143	Died of recurrent HCV hepatitis
5	M/54	HCC/ALD	Nephrotoxicity	Improved*	7	11	2.7	67	Alive and well
6	F/65	HCV cirrhosis	Nephrotoxicity	Improved†	7	Not withdrawn	9.8	47	Died of sepsis

LT: liver transplantation, TAC: tacrolimus, SRL: sirolimus, HCC: hepatocellular carcinoma, HBV: hepatitis B virus, HCV: hepatitis C virus, ALD: alcoholic liver disease.

*Creatinine dropped from 2.7 to 1.3 mg/100 ml within 10 days of sirolimus treatment.

†Creatinine dropped from 2.9 to 0.9 mg/100 ml within 10 days of sirolimus treatment.

HCC on HCV-related cirrhosis in one patient, HCC on alcoholic cirrhosis in one patient and HCV-related cirrhosis in the remaining two patients (Table 1). One of these patients (no. 6, Table 1) received sirolimus following retransplantation because of primary graft non-function (PGNF).

Neurotoxicity consisted of a severe speech disorder in one case and encephalopathy in the other two; in all these cases, graft function was satisfactory; there was no electrolyte imbalance and in particular no hypomagnesemia, and the blood level of tacrolimus never exceeded the value of 10 ng/ml.

Nephrotoxixcity consisted of oliguria and a severe impairment of renal function tests not secondary to graft dysfunction; two of these patients required hemodialysis.

Sirolimus was given as the main immunosuppressant, in association with steroids only, at a median time of 10 days after LT (range 3–23). The median period of sirolimus-based immunosuppression was 261 (47–577) days. After a loading dose of 5 mg, the dosage was adjusted according to the liver function tests; mean serum levels in the six patients ranged between 2.8 and 9.8 ng/ml (Table 1). Regular screening was performed with Doppler ultrasonography for vascular complications.

Results

Two patients died, one after 47 days, the other after 143 days of sirolimus-based immunosuppression, of sepsis and recurrent HCV hepatitis respectively.

The patient who died of sepsis was the one retransplanted for PGNF; this patient required long-term mechanical ventilation and developed bacterial sepsis because of *Pseudomonas* that had already been isolated when sirolimus was started.

No severe side-effect directly related to sirolimus was recorded.

Three acute rejection episodes (two mild and one moderate at histology) were observed in three patients and successfully treated with one intravenous bolus of methylprednisolone (1 g).

Steroids were withdrawn in five of the six patients after a median time of 113 days (range: 11–204).

Resolution of the neurological symptoms was observed in the three patients who suffered from CI-associated neurotoxicity. Of the three patients with renal function impairment, two showed a substantial improvement and came off dialysis, while the other patient, whose renal dysfunction was initially milder (not requiring dialysis), maintained altered serum creatinine levels once he was switched to sirolimus.

No patient who underwent LT because of HCC experienced tumor recurrence.

Discussion

Although CIs represent the milestone of immunosuppression in LT, some of their side-effects are now well known: in particular, nephrotoxicity, neurotoxicity and increased risk of malignancy justify the attempt to develop new strategies of immunosuppression for some categories of patients, aiming at minimizing the dosage or avoiding the use of CIs [5].

Sirolimus is a newer immunosuppressant that blocks postreceptor signal transduction and interleukin-2-dependent proliferation; nephrotoxicity and neurotoxicity are not reported among its possible side-effects while there is evidence of an antineoplastic action of the drug [1,5]. An increased incidence of hepatic artery thrombosis in patients treated with sirolimus was observed in early

studies but has not been confirmed by subsequent reports [5,7]. Because of its inhibition of fibrogenesis, sirolimus can cause a delay in surgical wound repair. Other possible side-effects include anemia, thrombocytopenia, peripheral swelling, hypercholesterolemia and gastrointestinal disturbances [1,5,8]. None of the above-mentioned side-effects were observed in our series. A higher incidence of infections under sirolimus treatment was recently reported by Fisher; however, in that study, patients who were administered sirolimus had a more compromised clinical status at the time of LT in comparison with controls [9]. In our series, one patient died of sepsis; when sirolimus was started, this patient was in the intensive care unit following retransplantation for PGNF and her clinical condition was critical.

There are no data regarding the influence of sirolimus on recurrent HCV disease apart from a report of two cases where the HCV was cleared under treatment with sirolimus [10]; it is impossible to establish whether there was a relationship between the severity of the recurrent HCV hepatitis observed in one of our patients and the use of sirolimus. In the overall experience of our center, early recurrence of HCV hepatitis is not an exceptional finding in patients treated with CIs and it carries a poor prognosis [11].

While few reports are available in the literature where sirolimus was administered in association with CIs to reduce their dosage after LT, the use of sirolimus as the main immunosuppressant in a CI-free regimen has to our knowledge only been investigated in three studies.

Kneteman *et al.* [4] evaluated 40 patients transplanted for HCC who were administered sirolimus in association with CIs and steroids for the first 3–6 postoperative months and then left on sirolimus monotherapy. The study showed a good efficacy in preventing rejection and a relatively low number of side-effects, although the target blood level of sirolimus in these patients was remarkably high (15 ng/ml in the first 24 months); however, CIs were administered in the immediate postoperative period when the incidence of rejection is the highest [6].

Watson *et al.* [12] described 15 patients who received sirolimus starting from the day of transplantation; in 11 of these patients sirolimus was associated with cyclosporine and steroids or cyclosporine alone. Of the four patients treated with sirolimus only, one experienced steroid-resistant rejection and was given cyclosporine.

Chang *et al.* [2] reported 14 patients with a renal insufficiency or acute mental status impairment treated with sirolimus associated with high dosages of mycophenolate mofetil (up to 3 g daily) and steroids. Improvement of the renal function and resolution of the neurological symptoms were observed with a good rejection control and low incidence of sirolimus-related side-effects. However, once the renal function or the mental status had improved, the CIs were introduced or resumed in 10 of these 14 patients within the first postoperative month.

In the present series, six patients received sirolimus as the main immunosuppressant in a CI-free regimen starting from the early postoperative period; sirolimus was associated with low-dose steroids only; in two patients steroids were withdrawn early after LT (11 and 33 days). Adequate rejection prophylaxis, resolution of neurological disorders and improvement of the renal dysfunction were achieved. Both in terms of patient numbers and the length of follow-up, the present series is the largest reported so far on the use of sirolimus as the main immunosuppressant in LT starting from the early postoperative period. In fact, the longest follow-up period reported by Watson *et al.* was 118 days, while the length of follow-up is not specified by Chang *et al.*

Although the small number of patients reported herein does not allow definitive conclusions to be drawn, our experience seems to indicate that sirolimus can be safely employed as the main immunosuppressant starting from the immediate LT postoperative period to provide adequate rejection control. Sirolimus might therefore represent an important tool for treating those LT patients who have serious contraindications for therapy with CIs. Larger studies are, however, needed to confirm our observation.

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