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A Retrospective Review of Sirolimus (Rapamune) Therapy in Orthotopic Liver Transplant Recipients Diagnosed with Chronic Rejection

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Treatment options are limited for orthotopic liver transplant (OLT) recipients suffering from chronic rejection (CR). We performed a retrospective review of OLT recipients diagnosed with CR and treated with sirolimus. The medical records of all OLT recipients treated with sirolimus between October, 1998 and October, 2000 were retrospectively reviewed. The diagnosis of CR was made by both clinical and histologic criteria: bile duct to hepatic artery ratio less than 0.7, histologic activity index, hepatic arterial wall thickening, and chronic elevation of liver chemistries. Two groups were defined in regard to sirolimus response: sirolimus responders (SR) and sirolimus nonresponders (SNR). Response to treatment was granted only when patients were found to have resolution of abnormal liver transaminases and an improvement in hepatic artery to bile duct ratio. Serum collections for liver chemistries were collected on days 1, 30, 60, and 90. Liver biopsies were reviewed in blinded fashion from day 1 and at least 180 days on therapy by double-blinded pathologists. Sirolimus-related complications were recorded and include drug toxicity, anemia with and without treatment, hospitalizations, infections, immunosuppression complications, lipid profile disorders, edema, muscle aches, and gastrointestinal complaints. Twenty-one patients were diagnosed with CR. The SR group included 13 of 21, and 8 of 21were in the SNR group. Anemia was diagnosed in 12 of 21 patients: SR, 7 of 13; SNR, 5 of 8; with 5 patients requiring red blood cell transfusions (2 SR, 3 SNR). Recombinant erythropoietin was started in 5 of 21 patients. Sirolimus serum levels were found to be greater than 20 ng/dL in 12 patients. Sirolimus was discontinued in 9 patients, (7 SR, 2 SNR primarily because of drug intolerance. The results show that sirolimus may help OLT recipients suffering from CR; however, a large number of patients experienced drug related side effects and were unable to tolerate therapy. (*Liver Transpl 2003;9: 477-483.*)

Therapeutic regimens for orthotopic liver transplant (OLT) recipients suffering from chronic rejection (CR) are sparse. To date, tacrolimus-based regimens for CR have been used and tend to offer only minimal help. Mycophenolate mofetil (MMF) combined with tacrolimus recently was reported as a remedy for CR in patients with low serum bilirubin levels.[1,2] Therapeutic agents for CR are currently under investigation. The safety and benefit of sirolimus for CR is currently unknown. We intend to report our results using sirolimus therapy for OLT recipients suffering from CR.

Sirolimus is a macrocyclic triene antibiotic that initially was found to have antifungal properties but also may act as a primary immune suppressant or antitumor agent. Calcineurin inhibitors, tacrolimus and cyclosporine, are structurally similar to sirolimus but have different side-effect profiles and modes of action. Calcineurin inhibitors block interleukin-2 gene transcription, whereas sirolimus inhibits postreceptor signal transduction and interleukin-2–dependent proliferation.[3,4] Sirolimus appears to modify the sirolimus effector protein, culminating in cell-cycle arrest at the G1 to S phase.[5,6]

Introducing sirolimus into immune suppression regimens was intended to test its potential as a rescue agent and decrease calcineurin inhibitor side-effect frequency. Nephrotoxicity, neurotoxicity, and diabetogenesis are not commonly seen with sirolimus. However, leukopenia, thrombocytopenia, hyperlipidemia, edema, and joint aches are reported as common complications.[7,8]

Anecdotal experiences and case reports of successful sirolimus therapy in CR are limited. We report a retrospective review that includes sirolimus outcomes and safety in OLT recipients suffering from CR.

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Methods

Under Institutional Review Board approval, a retrospective review was completed of adult OLT recipients suffering from CR who were treated with sirolimus between October, 1998 and October, 2000. Data collected included gender, age, time to diagnosis from OLT, immune suppression, and pre-OLT diagnosis for end-stage liver disease.

Liver function tests were collected from day 1, 7, and 14 and then monthly. Liver biopsies were evaluated from day 1 and at least 6 months out from treatment and reviewed by two different pathologists in blinded fashion. Control data was collected retrospectively from 5 patients diagnosed with CR and not treated with sirolimus.

The patients were divided into two groups: sirolimus responders (SR) and sirolimus nonresponders (SNR) based on the following criteria:

Initial histologic criterion for CR:
Bile duct to hepatic artery ratio < 0.7
Arterial wall thickening
Histologic activity index (HAI)
Clinical correlation of CR

Initial clinical criteria for CR were chronic elevation of liver chemistry tests by at least 1.5 times normal (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, and alkaline phosphatase).

Response to therapy was defined as resolution of liver chemistry elevation and improvement in bile duct to hepatic artery ratio to greater than 0.7.

Nonresponse to therapy were defined as persistent liver chemistry elevation, lack of complete improvement in hepatic artery to bile duct ratio, or both.

Standard immunosuppression therapy data was collected. Tacrolimus, the standard calcineurin inhibitor at our institution, was maintained in both groups at serum levels of 8 to 10 ng/dL. Sirolimus was given in bolus doses with 0.5 mg/kg and then maintained at daily doses of 0.07 mg/kg and 0.08 mg/kg in SR and SNR, respectively (Table 3). Maintenance sirolimus whole blood levels required continual adjustments to keep levels between 10 and 15 ng/mg. When patients received both tacrolimus and sirolimus, the combination sirolimus and tacrolimus drug levels were maintained at 10 to 15. All liver transplant recipients are treated with thrice-weekly lifelong sulfamethoxazole trimethoprim. Complications were recorded and included: anemia with and without treatment, hospitalizations, incidence and type of infections, over immunosuppression, lipid profile disorders, and gastrointestinal complaints. Statistics to evaluate our data included receiver operating characteristic curve, sensitivity and specificity, and predictive values. All patients received sirolimus for at least 6 months and were greater than 18 years of age.

Results

Twenty-one patients met criteria for CR and had the following pretransplant diseases: chronic hepatitis C virus (10), cryptogenic cirrhosis (2), autoimmune (1), Budd-Chiari (1), fulminant hepatic failure (2), Wilson's Disease (1), primary sclerosing cholangitis (2), biliary atresia (1), and hepatoblastoma (1) (see Table 1). Thirteen patients met both biochemical and histologic diagnosis for SR and 8 with SNR criteria. Demographics in both groups were: female/male, 6/7 (SR) and 5/3 (SNR); age range (years), 19 to 65 (SR) and 22 to 48.5 (SNR); and median age (years), 43.5 (SR) and 41.5 (SNR) (see Tables 1 and 2).

Each patient's posttransplant immune suppression regimen included tacrolimus and tapering doses of methyl prednisolone. The median duration of sirolimus therapy was 7 months. The average duration of time for laboratory return of sirolimus levels was 9 days. Sirolimus levels varied without dose adjustments in all patients, with levels greater than 20 ng/mL found in 12 of 21 patients. High levels of sirolimus, greater than 20 ng/mL, were seen in both patient groups, those with solo sirolimus therapy and those with combined sirolimus/tacrolimus therapy.

The histologic review showed that the hepatic artery to bile duct ratio and histologic activity index improved in all recipients (Figs 1, 2). However, the hepatic artery to bile duct ratio in SNR patients did not reach above 0.7. The serum bilirubin improved in both groups and continued toward baseline through the study period of 180 days (Figs 3).

Hyperlipidemia occurred in 8 of 21 patients and resolved in 3 patients, but 5 required antilipid therapy. SRs tended toward higher initial serum triglyceride levels, but soon returned to normal levels (Fig 4). On the other hand, nonresponders experienced an increase in serum triglycerides that often required treatment with lipid lowering agents or close observation. Serum cholesterol in the SR group peaked and returned to normal levels within 180 days (Fig 5). Most SNR patients started with high serum cholesterol levels that further escalated once sirolimus therapy was commenced.

The liver chemistries, namely AST and ALT, resolved in the SR group, whereas the alkaline phosphatase did not improve in either group (Figs 6-8). Serum

Table 1. Patient Demographics and Graft Survival

Patient	Gender	Age (yr)	Etiology	Time from OLT (mo)	Graft Survival (mo)	Patient Survival	Rapa Toxic (>20)	Rapa Level (Range)	Complications
1	Male	44	HCV	27	20	Yes	Yes	3.7-28.0	None
2	Female	51	HCV	35	19	Yes	Yes	2.0-21.0	Wound
3	Male	45	HCV	18	20	Yes	Yes	6.4-28.1	None
4	Male	61	HCV	48	16	Yes	Yes	5.4-44.0	OU
5	Male	44	HCV	47	12	Yes	No	7.0-11.2	None
6	Female	26	HCV	115	14	Yes	Yes	7.0-35.6	Wound
7	Male	49	HCV	24	15	Yes	Yes	5.0-23.1	OU
8	Female	46	HCV	26	18	Yes	No	1.2-18.8	OU
9	Male	51	HCV	7	17	Yes	No	3.8-10.1	OU
10	Male	41	PSC	79	24	Yes	Yes	4.2-59	Legionella
11	Male	34	FHF	55	18	Yes	Yes	1.7-31.7	PTLD
12	Female	47	HCV	36	30	Yes	Yes	2.3-42.9	None
13	Female	32	BCS	30	10	Yes	Yes	2.5-21	None
14	Female	50	PSC	66	14	Yes	Yes	3.6-68.5	OU
15	Female	37	Crypto	29	27	Yes	Yes	2.7-29.6	Wound
16	Female	35	FHF	84	18	No	Yes	7.5-40.0	Pneumonia/sepsis
17	Male	66	Crypto	54	17	Yes	No	2.1-11	None
18	Female	20	AIH	11	15	Yes	No	4.5-14	None
19	Female	23	Biliary atresia	12	24	Yes	Yes	5.2-25	None
20	Male	17	Hepatoblastoma	24	32	No	No	5.0-15.5	None
21	Male	55	Laennec's	24	18	Yes	Yes	4.8-23	OU

Abbreviations: OU, oral ulcers; wound, wound breakdown or infection; AIH, autoimmune hepatitis.

bilirubin levels tended to improve in both groups within the first 60 days of treatment, but trended higher in the SNR group between 60 and 180 days. Multiple values (Table 3) were investigated for statistical significance and included: mean sirolimus dose, AST, ALT, fibrosis score, Histologic Activity Index score, bilirubin, alkaline phosphatase, cholesterol and bile duct to hepatic artery ratio. Univariate analysis revealed age, total bilirubin, alkaline phosphatase, cholesterol, and bile duct to hepatic artery ratio to be significant (P value $< .05$). However, only total bilirubin via multivariate analysis was significant ($P = .03$). Analysis of the

Table 2. Patient Demographics and Sirolimus Therapy

Responders demographics
- 13 patients, 6 females, 7 males
  - Median age: 43.5 years, range 19-65
  - Median duration of sirolimus treatment: 7 months (2-16)
  - Median total sirolimus dose: 1100 mg (111-4000)
  - Median daily dose: 0.07 mg/kg (0.01-0.13)

Non-responders demographics
- 8 patients, 5 females, 3 males
  - Median age: 41.5 years, range 22-48.5
  - Median duration of sirolimus treatment: 7 months (2-16)
  - Median total sirolimus dose: 1100 mg (111-4000)
  - Median daily dose: 0.08 mg/kg (0.02-0.24)

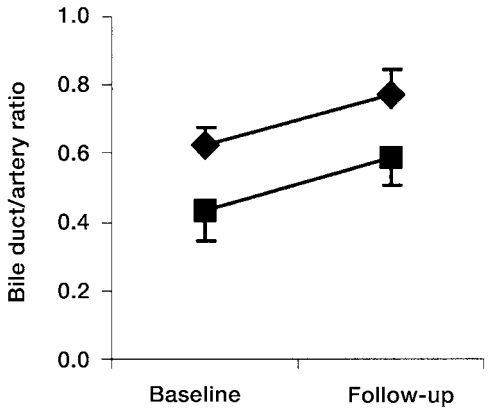

Figure 1. Bile duct-to-artery ratio in baseline and follow-up biopsies in all transplanr recipients with chronic rejection treated with sirolimus. Responders (diamonds) and nonresponders (squares) are shown. T0 is the day of initiation of sirolimus treatment. $P < .05$ vs nonresponders (Student's t-test), $P < .05$ vs baseline (paired Student's *t*-test).

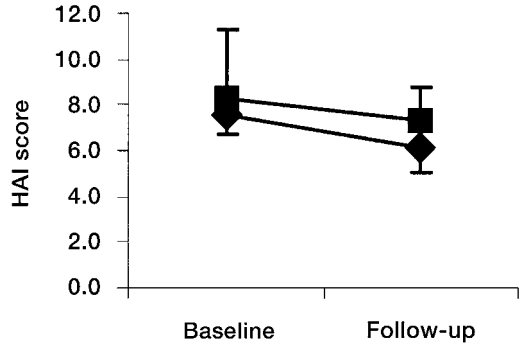

Figure 2. HAI score of baseline and follow-up biopsies in all liver transplant recipients with chronic rejection treated with sirolimus. Responders (diamonds) and non-responders (squares) are shown. T0 is the day of initiation of sirolimus treatment.

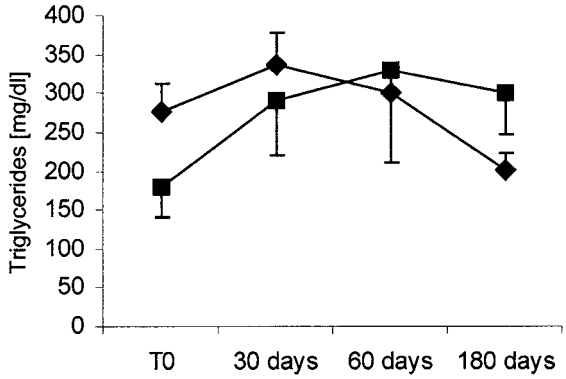

Figure 4. Time curve of triglycerides serum levels in all liver transplant recipients with chronic rejection treated with sirolimus. Responders (diamonds) and non-responders (squares) are shown. T0 is the day of initiation of sirolimus treatment. $P < .05$ vs nonresponders (Student's *t*-test).

sirolimus therapeutic response, found that hepatic artery to bile duct ratio and initial bilirubin level did not reach statistical significance (Table 4, Fig 9).

Anemia (hemoglobin <10 g) developed in 12 of 21 patients: SNR 5 of 8, SR 7 of 13 resulting in 5 patients requiring red blood cell transfusions (2 SR, 3 SNR) and 5 patients needing recombinant erythropoietin (Table 3).

Four patients with elevated immunosuppression (sirolimus levels greater than 20 ng/mL) resulted in infections, including: 2 fungal, 1 wound, 1 pneumonia. Lower extremity swelling was seen in 11 of 21 and did not tend to resolve unless sirolimus was discontinued. Apthous ulcers developed in 5 of 21 and persisted until drug withdrawal. Overall, 9 patients were intolerant of sirolimus and required treatment cessation, 2 SNR and 7 SR.

A historical control group of 5 patients suffering CR during the same time period, but not treated with sirolimus, was compared with both SR and SNR groups (4 male patients, 1 female patient, age range [years], median age [years]). Immune suppression consisted of tacrolimus therapy maintained at a level of 8 to 10 ng/dL. The hepatic artery to bile duct ratio and liver chemistries did not improve in any patient.

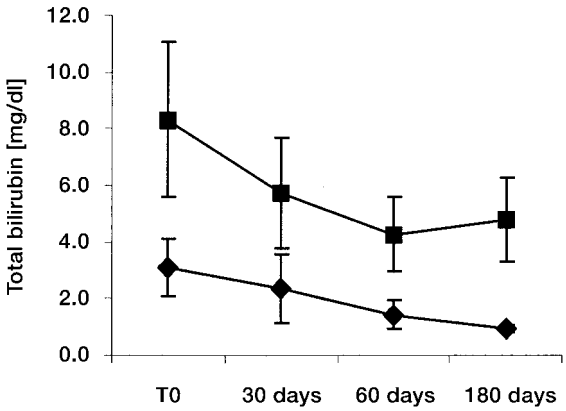

Figure 3. Time curve of bilirubin serum levels in all liver transplant recipients with chronic rejection treated with sirolimus. Responders (diamonds) and nonresponders (squares) are shown. T0 is the day of initiation of sirolimus treatment. $P < .05$ vs T0 (paired Student's *t*-test).

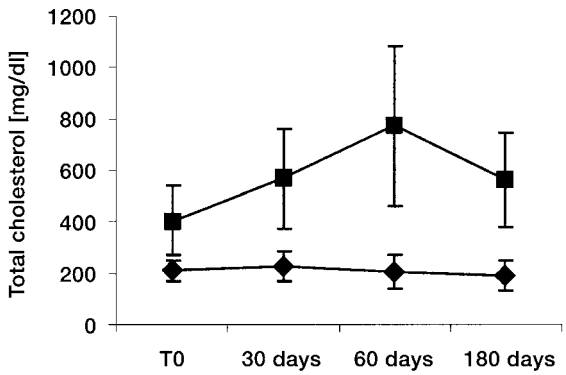

Figure 5. Time curve of total cholesterol serum levels in all liver transplant recipients with chronic rejection treated with sirolimus. Responders (diamonds) and non-responders (squares) are shown. T0 is the day of initiation of sirolimus treatment. $P < .05$ vs non-responders (Student's *t*-test), $P < .01$ vs non-responders (Student's *t*-test).

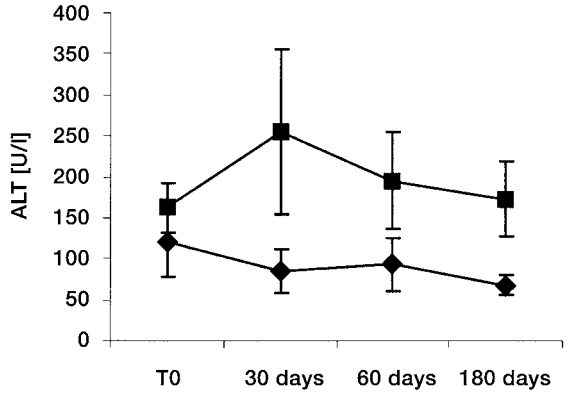

Figure 6. Time curve of alanine amino-transferase serum levels in all liver transplant recipients with chronic rejection treated with sirolimus. Responders (diamonds) and non-responders (squares) are shown. T0 is the day of initiation of sirolimus treatment. $P < .05$ vs T0 (paired Student's *t*-test).

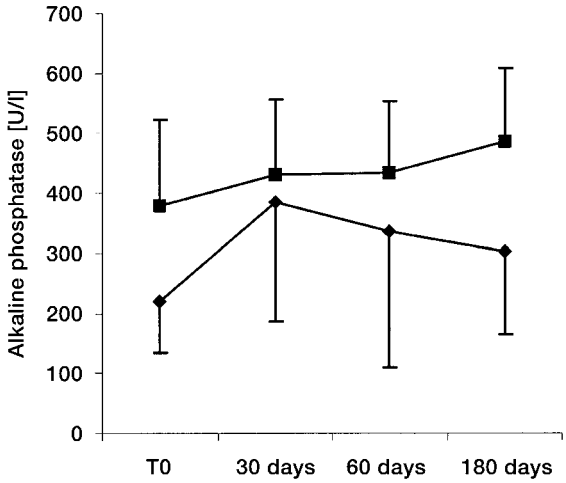

Figure 8. Time curve of alkaline phosphatase serum levels in all liver transplant recipients with chronic rejection treated with sirolimus. Responders (diamonds) and non-responders (squares) are shown. T0 is the day of initiation of sirolimus treatment.

Discussion

The prevalence of CR in liver transplant recipients is approximately 5% and continues to decline as a result of advances in immune suppression regimens and posttransplant care. The pathogenesis of CR is poorly understood. Treatment strategies are specifically aimed at suppressing the immune system attack in hopes of decreasing the damage to hepatocytes and allograft bile duct epithelium while maintaining bile duct function. However, immune suppression therapies for CR are most often ineffective, especially when graft function is damaged beyond repair and synthetic function is compromised.[9]

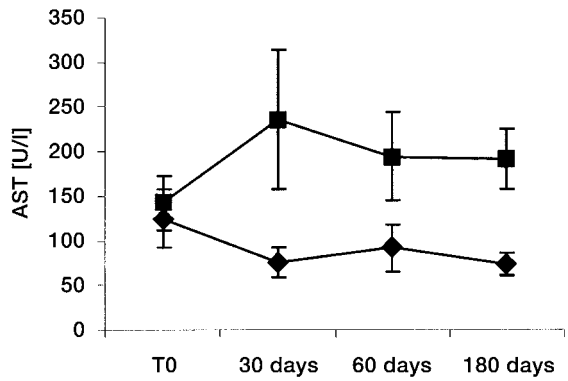

Figure 7. Time curve of aspartate amino-transferase serum levels in all liver transplant recipients with chronic rejection treated with rapamycine. Responders (diamonds) and nonresponders (squares) are shown. T0 is the day of initiation of rapamycine treatment. $P < .05$ vs T0 (paired Student's *t*-test).

Current strategies for CR treatment in the hepatic arena come from experience with renal transplants and remains one of the major challenges facing transplant teams.[9] However, immunosuppressive therapies most often are found to be ineffective, and when graft function is damaged beyond repair, synthetic function is compromised. Adjustment of calcineurin inhibitors to a therapeutic level theoretically may stabilize bile duct damage and prevent further progression of fibrosis. Thus, further immunosuppressant adjustment will not alter the course of graft failure.

There is evidence that low-dose cyclosporine with MMF in renal dysfunction may halt the progressive graft function loss. This particular combination of immunosuppression in 28 renal transplant patients with renal compromise, and without evidence of acute rejection on biopsy, resulted in a significant decrease in the loss rate of renal function ($P = .003$). Further follow-up showed that renal function improved in 21 of 28 patients (75%), whereas only 1 patient continued with renal function deterioration.[10] This success in renal transplant patients with MMF lead to its use in CR for liver transplant recipients. In fact, MMF has been reported in abstract form to assist CR with low bilirubins.[1]

Similarly, the patients in our review that responded to sirolimus therapy tended to start with a lower bilirubin level. This may suggest that patients with better hepatic synthetic function appear to respond to CR treatment

Table 3. Side-effects and Treatment Complications

Patient	Gender	R/NR	Anemia*			Infection	Lipid Abnl†	GI Complaints
			Yes/No	Epogen	PRBCs			
1	Male	R	No	No	No	No	Yes	Denied
2	Female	R	No	No	No	Yes/wound	No	Diarrhea
3	Male	R	No	No	No	No	No	Diarrhea
4	Male	R	Yes	No	No	Yes/oral	No	Diarrhea
5	Male	R	Yes	No	Yes	No	Yes	Denied
6	Female	NR	Yes	No	No	Yes/wound	No	Denied
7	Male	NR	Yes	Yes	Yes	Yes/oral	No	Denied
8	Female	R	No	No	No	Yes/oral	Yes	Denied
9	Male	R	Yes	No	No	Yes/oral	No	Denied
10	Male	NR	No	No	No	Yes/pneumonia	No	Denied
11	Male	NR	No	No	No	No	Yes	Denied
12	Female	NR	Yes	No	No	No	Yes	Denied
13	Female	NR	No	No	No	No	No	Denied
14	Female	NR	Yes	Yes	Yes	Yes/oral	No	Denied
15	Female	NR	Yes	Yes	Yes	Yes/pneumonia	Yes	Denied
16	Female	R	Yes	Yes	Yes	Yes/sepsis	No	Denied
17	Male	R	Yes	Yes	Yes	No	No	Denied
18	Female	R	No	No	No	No	No	Denied
19	Male	R	Yes	No	No	No	Yes	Denied
20	Female	R	No	No	No	No	No	Denied
21	Female	R	Yes	No	No	Yes/OU	Yes	Denied

Abbreviations: R, responder to sirolimus therapy; SNR, nonresponder to sirolimus therapy.
*Anemia defined as hemoglobin less than 10 g.
†Lipid abnormality defined as cholesterol elevated to greater than 300 while on treatment.

strategies. However, because both groups showed an improvement in serum bilirubin, we were unable to find the bilirubin level that provided therapeutic statistical significance or projected sirolimus treatment failure.

Table 4. Determinants for Response to Rapamycin

Univariate analysis	
Age	$P = .04$
Total bilirubin	$P = .02$
Alkaline phosphatase	$P = .05$
Total cholesterol	$P = .03$
Bile duct/artery ratio	$P = .05$
Multivariate analysis	
Total bilirubin	$P = .03$
Other factors assessed	
Mean sirolimus dose/kg/day, AST, ALT, fibrosis score, HAI score	
Significant differences	
Cholesterol 211 vs 399	$P < .05$
Trend	
Total bilirubin 3.9 vs 7.2	$P = .11$

NOTE. Increase in cholesterol and/or high bilirubin is a risk factor for absence of response to sirolimus.

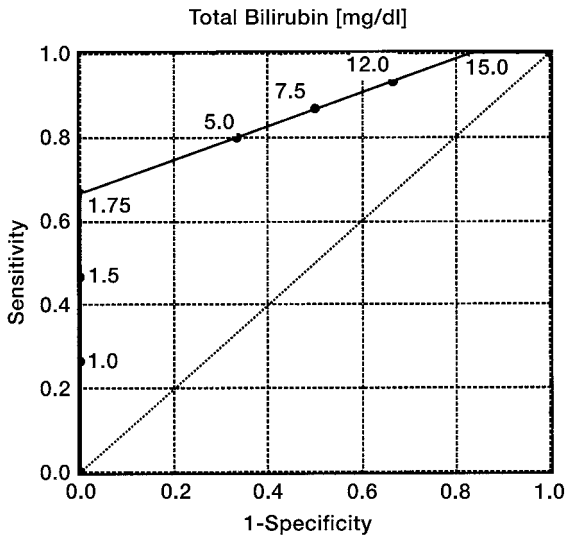

Figure 9. ROC curve plotting the true positive rate (sensitivity: proportion of responders that test positive) vs the true negative rate (1-specificity: proportion of non-responders that test negative) for various cutoff values of serum bilirubin. Cutoff values are indicated on the graph next to the corresponding point on the curve.

The side effects as listed in Table 2 show a common problem with sirolimus, edema, and anemia. In fact, 12 of our patients had a significant drop in their hemoglobin to less than 10 g. The reduction in sirolimus whole blood levels to 10 to 15 ng/mL appeared to result in a decreased incidence of anemia, but not complete resolution. It is important to note that both groups experienced complications with elevated sirolimus levels despite stable serum tacrolimus levels. The question still remains, as to what sirolimus serum level is required to maintain allograft preservation, while preventing anemia, edema and infections.

Sirolimus maintenance levels and dosing adjustments are handicapped by a delay in real-time testing and a prolonged time period of 3 to 5 days for the drug to reach steady state. This 3- to 5-day period, together with another 2 to 5 days awaiting laboratory results, means proper observation and adjustment to sirolimus dosing is difficult, as seen in 15 of our patients with consequential anemia and sirolimus levels greater than 20 ng/dL. Lower sirolimus starting doses and an increased prudence with conversion may help answer this problem.

Hyperlipidemia was quite frequent amongst our patients, but often resolved in the SR group. Figs 3 and 4 demonstrate an early elevation of lipids while most patients trended back towards normal levels after 30-60 days. However, the SNR group required further observation, with some requiring medical management.

The current standard of care at our institution for treating liver transplant–related CR is adjustment of tacrolimus to serum levels of 8 to 10 ng/dL. If therapeutic tacrolimus levels have been maintained throughout the postoperative phase, we will attempt to add sirolimus to the immune suppression regimen or convert to monotherapy with sirolimus over an extended period of 3 to 6 months. If sirolimus is started, we follow the patient closely for several months to provide both drug level control and early detection of sirolimus-related complications.

In conclusion, sirolimus may be useful in liver transplant recipients suffering from CR. Furthermore, the high likelihood of adverse events suggests that careful attention should be directed toward establishing safe concentration mixtures of sirolimus based combinations to extend the benefits of this drug to more patients with CR.

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