Conversion of Liver Transplant Recipients on yclosporine With Renal Impairment to ycophenolate Mofetil

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The management of liver transplant recipients with renal function impairment remains controversial because cyclosporine withdrawal from triple immunosuppression regimens may be followed by graft rejection. A nonnephrotoxic and powerful immunosuppressant such as mycophenolate mofetil (MMF) could allow a reduction of cyclosporine dosage or its withdrawal and an improvement in renal function in these patients. Eleven patients with serum creatinine levels greater than 1.5 mg/dL, normal graft function, and a rejection-free period of at least 1 year started MMF at a dose of 2000 mg/d (reduced in case of adverse events) while cyclosporine dosage was slowly reduced. At last follow-up (63 ± 5 weeks), 7 patients remained free of cyclosporine (6 of those patients are also free of steroids), 2 patients reduced their cyclosporine dose, and 2 patients developed mild acute rejection that responded to a switch to tacrolimus therapy. Serum creatinine and urea levels in the 7 patients free of cyclosporine decreased from 2.22 ± 0.13 to 1.90 ± 0.19 mg/dL ($P = .05$) and 0.95 ± 0.10 to 0.60 ± 0.10 g/L ($P < .001$), respectively. Creatinine clearance increased from 38.16 ± 5.60 to 47.01 ± 6.76 mL/min ($P = .005$). Control of arterial hypertension also improved. Tolerance to MMF was good, but 6 patients required dose reductions, mainly because of asymptomatic anemia. In conclusion, in liver transplant recipients with stable graft function, MMF may allow cyclosporine dose reduction or discontinuation, thus improving renal function and the control of arterial hypertension. This change of treatment must be carefully monitored because of the frequent need for MMF dose reduction and the risk for rejection.

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During the 1980s, cyclosporine use allowed a marked improvement in graft and patient survival after orthotopic liver transplantation (OLT).[1] Unfortunately, nephrotoxicity associated with cyclosporine is frequent,[2] and it may cause renal function impairment or contribute to further deterioration of renal function in patients with previous kidney disease. The management ofthese patients with poor renal function is difficult be-cause cyclosporine withdrawal from triple immunosuppression regimens (cyclosporine, azathioprine, and prednisone) in kidney[3] and liver transplant recipients[4] may cause graft rejection, thus making this therapeutic option unacceptable in stable patients. Tacrolimus does not seem to be a good alternative to cyclosporine because both drugs seem to be equally nephrotoxic.[5]

Mycophenolate mofetil (MMF) is a potent inhibitor ofinosine monophosphate dehydrogenase, with a relatively selective effect on lymphocyte activation, which inhibits proliferation of T and B lymphocytes.[6] Its main secondary effects are gastrointestinal and hematologic,[7] thus providing a potential therapeutic alternative in patients developing cyclosporine or tacrolimus neurotoxicity or nephrotoxicity. In four liver transplant recipients with cyclosporine neurotoxicity, the use of MMF allowed the discontinuation or dose reduction of cyclosporine or tacrolimus, with subsequent alleviation of neurological symptoms.[8] In the setting of renal transplantation, the use of MMF instead of azathioprine and the concomitant reduction or discontinuation of cyclosporine dosage resulted in an improvement in renal function in patients with cyclosporine nephrotoxicity.[9]
On this basis, a pilot study of MMF use and cyclosporine dose reduction in liver transplant recipients with impairment of renal function was performed.

PATIENTS AND METHODS PATIENTS

Between April and December 1997, the immunosuppressive treatment of 11 liver transplant recipients with stable graft function and renal function impairment was changed from cyclosporine-based therapy to partial or total cyclosporine withdrawal and the addition of MMF. Patients were selected to be included in this trial if they fulfilled the followingcriteria: (1) follow-up of at least 12 months after OLT; (2) treatment with cyclosporinebased immunosuppression; (3) free of graft rejection for at least 12 months; (4) normal or near-normal graft function (i.e., serum alanine aminotransferase [ALT] levels less than twice the upper normal limit); (5) moderate to severe kidney dysfunction, evidenced by a serum creatinine level greater than 1.5 mg/dL confirmed on at least two occasions; (6) verbal/written informed consent; and (7) ability to attend the outpatient clinic every 2 to 3 weeks. Baseline and demographic characteristics of the patients are listed in Table 1.

Pre-MMF Immunosuppression

All patients were receiving cyclosporine-based immunosuppression. Their mean ± SEM daily cyclosporine dose was 195 ± 17 mg/d (range, 100 to 300 mg/d), with a mean trough blood cyclosporine level of 101 ± 8 ng/mL (range, 67 to 155 ng/mL). Nine patients were also receiving prednisone in doses ranging from 2 to 7.5 mg/d. Seven patients were receiving azathioprine, 25 to 100 mg/d.

Change in Immunosuppressive Therapy and Monitoring

At the baseline visit, MMF was started at a dose of 2000 mg/d and, if applicable, azathioprine was discontinued. Patients underwent evaluation every 2 to 3 weeks thereafter. This evaluation included anamnesis; clinical examination; blood pressure monitoring; complete blood count; serum levels of creatinine, urea, aspartate amino-transferase, ALT, alkaline phosphatase, y-glutamyltransferase, and total bilirubin; and whole-blood cyclosporine level. Creatinine clearance was estimated using the following formula:

Creatinine clearance (milliliters per minute):

$$\frac{(140 - \text{age in years}) \times (\text{weight in kilograms})}{72 \times \text{serum creatine (in milligrams per deciliter)}} \times (0.85 \text{ in female})$$

Once tolerance to MMF was verified, the cyclosporine dose was reduced at every visit by 25 mg/d until its discontinuation or evidence of graft dysfunction (i.e., increase in ALT level to at least twice the upper normal limit). In case of graft dysfunction, cyclosporine dose was increased to the prior dose. If MMF dose needed to be reduced (mainlybecause ofmyelotoxicity), cyclosporine dose was not reduced until a stable MMF dose was reached. Prednisone dose remained unmodified until cyclosporine was completely withdrawn. In patients who tolerated complete withdrawal of cyclosporine, prednisone dose was slowly reduced until discontinuation, providing graft function remained stable.

Diagnosis and Treatment of Rejection

Liver biopsy was performed when graft function remained abnormal despite a cyclosporine dose increase. The diagnosis of cellular rejection was made in the presence of a predominantly mononuclear portal infiltrate plus nonsuppurative ductal cholangitis and/or endotheliitis.[10] Patients with cellular rejection were switched to tacrolimus-based immunosuppression and both cyclosporine and MMF were discontinued.

Follow-Up

To assess the evolution after the modification ofimmunosuppressive therapy, a comparison between the baseline visit (just before MMF was started) and the most recent follow-up before November 1998 was performed. This comparison included blood pressure, liver function test results, lipid profiles, serum levels of creatinine and urea, and estimation of creatinine clearance. Two intermediate analyses were performed: first, when cyclosporine dose was 50%ofbaseline and, second, when cyclosporine was fully withdrawn. The mean follow-up was 63 ± 5 weeks (range, 34 to 82 weeks). To assess the evolution of renal function before the treatment change, blood pressure, serum creatinine, and urea values at baseline were compared with their respective values in a previous period similar to the time elapsed from baseline to the most recent follow-up. Patients who were switched to tacrolimus were not included in this comparison.

Statistical Analysis

Quantitative data are expressed as mean ± SEM and range. The comparison between data in two different situations was performed using Studenát-test for paired data. A difference was considered statistically significant for two-tailed *P* less than .05.

RESULTS

Global Evolution

Despite a reduction of cyclosporine dose to 50% of baseline achieved in 10 of 11 patients (91%), complete withdrawal of cyclosporine was achieved in 7 of 11 patients (64%). In 4 patients, cyclosporine withdrawal was not possible. One patient remained free of cyclosporine for 3 months, but a later reduction of prednisone dose from 5 to 2.5 mg/d was followed by graft dysfunction that did not reverse despite resuming the previous prednisone dose; cyclosporine was started again and liver function test results improved slowly. Because of this, a liver biopsy was performed that showed portal inflammation without cholangitis or endothelütis. One patient with hepatitis C virus infection showed an increase in aspartate aminotransferase and ALT levels when cyclosporine dose was decreased, which remained stable thereafter without further changes in cyclosporine dose. In this patient, a liver biopsy showed chronic active hepatitis. Two patients had mild but progressive worsening of liver function test results when cyclosporine had not been completely withdrawn. In both cases, liver biopsy was consistent with allograft rejection, and both started treatment with tacrolimus, with resolution ofbiochemical alterations.

Evolution of Renal Function

Ten patients achieved a cyclosporine dose reduction of 50%. At that time, serum levels of urea and creatinine decreased, and creatinine clearance increased in 9 of 10 patients (0.87 ± 0.08 *v* 0.69 ± 0.11 g/L, $P < .01$; 2.10 ± 0.12 *v* 1.89 ± 0.14 mg/dL, $P < .01$; and 42.48 ± 4.65 *v* 48.89 ± 6.00 mL/min, $P < .005$, respectively).

At last follow-up, 7 patients remained free of cyclosporine. In these patients, despite a significant increase in serum creatinine level in the period before receiving MMF from 1.74 ± 0.15 to 2.22 ± 0.13 mg/dL ($P = .002$), it decreased to 1.90 ± 0.19 mg/dL ($P = .05$) in the last follow-up. Creatinine level decreased gradually as cyclosporine dose was reduced, reaching its minimum when cyclosporine was withdrawn, and remained stable thereafter. Creatinine clearance increased from 38.16 ± 5.60 to 47.01 ± 6.76 mL/min ($P = .005$). Serum urea levels decreased in all 7 patients. Mean serum urea levels decreased from 0.95 ± 0.10 to 0.60 ± 0.10 g/L ($P < .001$). The evolution of serum levels of creatinine and urea and creatine clearance after treatment with MMF and cyclosporine withdrawal is shown in Figs. 1, 2, and 3.

At last follow-up, two patients were receiving MMF and had reduced their cyclosporine dose. Their renal function improved modestly.

Effect on Blood Pressure

Six of 7 patients who were still receiving treatment with MMF and had withdrawn cyclosporine were hypertensive before the change of therapy. At the baseline visit, mean systolic and diastolic blood pressures were 146 ± 7 and 80 ± 4 mm Hg. At the last follow-up visit, blood pressures (132 ± 6 and 77 ± 3 mm Hg, respectively) tended to be less than at baseline, despite a significant (P = .005) reduction in the number of antihypertensive drugs required by the patients (Fig. 4). At last follow-up, only 2 patients required antihypertensive drugs to remain normotensive.

Comparison of Liver Function Test Results

No significant variation was found when liver function test results at baseline were compared with those at last follow-up. Liver function test results (mean ± SEM) before the change oftherapy and at last follow-up are listed in Table 2.

Comparison of Lipid Profiles

No significant variation was found when cholesterol levels at baseline were compared with those at last follow-up, whereas triglyceride levels significantly decreased (P = .02; Table 3).

Evolution of Immunosuppressive Therapy

As previously mentioned, 2 of 11 patients had to be switched to tacrolimus-based immunosuppression because of graft rejection. Two additional patients were maintained on cyclosporine, but with a 33% and 50% dose reduction compared with baseline doses. Seven patients are free of cyclosporine for a period of 42 ± 4 weeks (range, 24 to 54 weeks). After cyclosporine withdrawal, prednisone was slowly tapered and, at the last visit, 6 of the 7 patients are free of steroids (1 patient was also steroid free at baseline), whereas the other patient receives prednisone, 2.5 mg/d. MMF dose was reduced in all but 3 of 9 patients to a daily dose of 1500 (1 patient), 1250 (1 patient), and 1000 mg (4 patients) because of adverse events.

Adverse Events

Although MMF dosage was reduced in 6 of 11 patients because of adverse events, MMF was well tolerated. and in no case did MMF-related adverse events lead to drug discontinuation. The most frequent adverse event was asymptomatic bone marrow depression, which reversed completely after dose reduction. Remarkably, one of the patients with biopsy-proven mesangial glomerulonephritis and marked proteinuria before OLT, which became quiescent after OLT, developed nephrotic syndrome with proteinuria, hypoalbuminemia, and edema when the cyclosporine dose was reduced. This patient was treated with oral enalapril, 5 mg/d, with marked reduction of proteinuria and resolution of edema. MMF dose was not changed. Currently, the patient remains on enalapril without proteinuria. Adverse events are listed in Table 4.

Baseline Factors Associated With Cyclosporine Withdrawal

None ofthe baseline factors studied (liver function tests, treatment with azathioprine or

prednisone, cyclosporine dosage, cyclosporine levels, age, sex, or past history of acute graft rejection) were associated with a significant probability ofmaintaining stable graft function after complete cyclosporine withdrawal.

DISCUSSION

One ofthe main side effects ofthe use ofcyclosporine as an immunosuppressant for solid organ transplantation is nephrotoxicity.[2] It may lead to progressive renal dysfunction and the development of end-stage nephropathy in up to 6.5% of cardiac transplant recipients surviving for more than 3 years.[11] In the setting of OLT, this secondary effect may add to a variety ofglomerulopathies associated with liver diseases, such as mesangial glomerulonephritis in alcoholic cirrhosis[12] and membranoproliferative glomerulonephritis in hepatitis C virus infection.[13] The pathogenesis ofcyclosporine nephrotoxicity appears related to renal vasoconstriction and further development ofrenal arteriolar hyalinosis and glomerular sclerosis, even in the absence of early increases in serum creatinine level. These histological changes become more severe as the dose and time of cyclosporine treatment increase.[14]

To manage cyclosporine nephrotoxicity, several changes in immunosuppression have been proposed. In patients with stable graft function, cyclosporine dose reduction or withdrawal while maintaining azathioprine and prednisone therapy may be followed by renal function improvement. The safety of this approach is not completely clear because, despite the negligible incidence of rejection in one series,[15] in another series it was followed by a cellular rejection rate of 50%, ductopenic rejection rate of 25%, and mortality rate of 17%.[4]

Another potential approach to the treatment of cyclosporine nephrotoxicity is changing cyclosporine to tacrolimus. Despite the known nephrotoxicity of this drug and the absence of significant differences in renal function in patients treated with either cyclosporine or tacrolimus,[5] changing cyclosporine to tacrolimus was followed by an improvement in renal function in two thirds of the patients.[16]

MMF causes a relatively lymphocyte-selective impairment of de novo purine synthesis.[6] Compared with azathioprine, MMF seems to be a more powerful immunosuppressive drug.[7] It has been used in the setting of kidney,[7] liver,[17] heart,[18] and lung[19] transplantation and in the treatment of autoimmune diseases, such as Wegener's granulomatosis, microscopic polyangütis, immunoglobulin A nephropathy,[20] and other glomerular diseases.[21] In the setting of OLT, the use of MMF seems to allow a reduction in cyclosporine or tacrolimus dose and therefore decreased toxicity.[22]

In this report, the use of MMF allowed us to reduce the dose of cyclosporine, even achieving complete withdrawal in most patients. Cyclosporine withdrawal was followed by a moderate but significant improvement in renal function, with a decrease in serum creatinine and urea levels of 0.35 ± 0.14 mg/dL and 0.35 ± 0.04 g/L, respectively, and an increase in creatinine clearance of 8.86 ± 2.08 mL/min. This effect is noticeable because renal function showed a progressive worsening in these patients before therapy was changed. This improvement was not uniform in all patients, probably because patients with other kidney diseases apart from cyclosporine toxicity were not excluded. Not surprisingly, cyclosporine dose reduction and/or withdrawal also made possible a better control of

arterial hypertension, with a significant reduction in the number of antihypertensive drugs. The improvement in renal function seems to be parallel to the reduction in cyclosporine dose. Therefore, a difficult question is raised in patients treated with MMF in whom renal function partially improved before complete cyclosporine withdrawal. Cyclosporine withdrawal may be followed by a further improvement in renal function, but it poses a risk for rejection. In patients who have achieved acceptable renal function, combined immunosuppressive therapy with MMF and a very low dose of cyclosporine could be a safe alternative.

Conversely, MMF was well tolerated. The episodes of graft dysfunction and/or rejection were controlled with an increase in cyclosporine dose or a switch to tacrolimus, and no episode led to graft failure. Remarkably, none of the patients required high doses of steroids to treat rejection. Two thirds of the patients who are still receiving MMF therapy do not receive other immunosuppressive drugs and maintain stable graft function.

Most of our patients required a reduction of MMF dose because of adverse events (without loss of effectiveness). The reason for this high frequency of dose-related adverse events is not clear, because mycophenolic acid blood levels do not increase in patients with renal failure.[23]

In conclusion, liver transplant recipients with stable graft function and renal function impairment may benefit from treatment with MMF and the reduction of cyclosporine dose or its complete withdrawal, ifpossible. This approach is, in general terms, well tolerated, but a careful follow-up is advisory because of the frequent need for MMF dose adjustment and the potential risk for rejection. This therapeutic approach also allows better control of arterial hypertension and may be used in patients with poorly controlled arterial hypertension in the setting of cyclosporine therapy. The high immunosuppressive power of MMF and its lack of nephrotoxicity add new possibilities to the armamentarium ofimmunosuppressants to be used after OLT.

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Table 1. Baseline and Demographic Characteristics of Patients

Age (yr)	62± 2 (50-74)
Sex (male/female)	8/3
OLT indication	
Alcoholic cirrhosis	5*
α_1-AT deficiency	1
Hemochromatosis	1*
Wilson's disease	1
Primary biliary cirrhosis	1
Hepatitis C virus cirrhosis	1*
Budd-Chiari syndrome	1
Time since OLT (wk)	140 ± 19 (62-252)
Prior liver allograft rejection (yes/no)	4/7
Pre-OLT serum creatinine (mg/dL)	1.35 ± 0.15 (0.8-2.2)
Pre-OLT serum urea (g/L)	0.54 ± 0.11 (0.26-1.34)
Baseline serum creatinine (mg/dL)	2.04 ± 0.12 (1.6-2.7)
Baseline urea (g/L)	0.88 ± 0.07 (0.67-1.45)
Baseline systolic blood pressure (mm Hg)†	140 ± 5 (120-170)
Baseline diastolic blood pressure (mm Hg)†	79 ± 2 (70-90)
Baseline arterial hypertension (yes/no)	10/1
No. of antihypertensive drugs	1.73 ± 0.33 (0-4)

Abbreviation: a1-AT, alpha1-antitrypsin.
*One patient with alcoholic cirrhosis, 1 with hemochromatosis, and 1 with hepatitis C virus cirrhosis had hepatocellular carcinoma.
†Receiving antihypertensive therapy.

Table 2. Evolution of Liver Function Test Results in 7 Patients Treated With MMF and Cyclosporine Withdrawal

	Before MMF	Last Follow-Up
AST (IU/L)	12 ± 2	13 ± 1
ALT (IU/L)	17 ± 3	21 ± 4
Alkaline phosphatase (IU/L)	158 ± 30	159 ± 14
GGT (IU/L)	20 ± 3	23 ± 4
Total bilirubin (mg/dL)	0.80 ± 0.15	0.62 ± 0.16

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; MMF, mycophenolate mofetil.

Table 3. Evolution of Lipid Profiles in 7 Patients Treated With MMF and Complete Cyclosporine Withdrawal.

	Before MMF	Last Follow-Up	P
Total cholesterol (mg/dL)	202 6 8	187 6 12	NS
HDL-cholesterol (mg/dL)	40 68	41 65	NS
LDL-cholesterol (mg/dL)	119 6 3	124 6 10	NS
Triglycerides (mg/dL)	217 6 49	157 6 32	.02

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MMF, mycophenolate mofetil; NS, not significant.

Table 4. Non–Graft-Related Adverse Events in 11 Patients Treated With MMF and Cyclosporine Withdrawal

Anemia	4*
Mild GI complaints	2*
Asthenia	1*
Neutropenia	1*
Vertigo	1*
Pruritus	1†
Nephrotic syndrome	1‡
Renal colic	1

Abbreviations:MMF, mycophenolate mofetil; GI, gastrointestinal.
*Reversed with dose reduction.
†Reversed with cyclosporine dose increase.
‡Exacerbation of previously diagnosed nephrotic syndrome; reversed with enalapril.

Figure 1. Evolution of serum creatinine levels in patients (n = 7) on MMF therapy and without cyclosporine at last follow-up. *P < .05 compared with baseline.

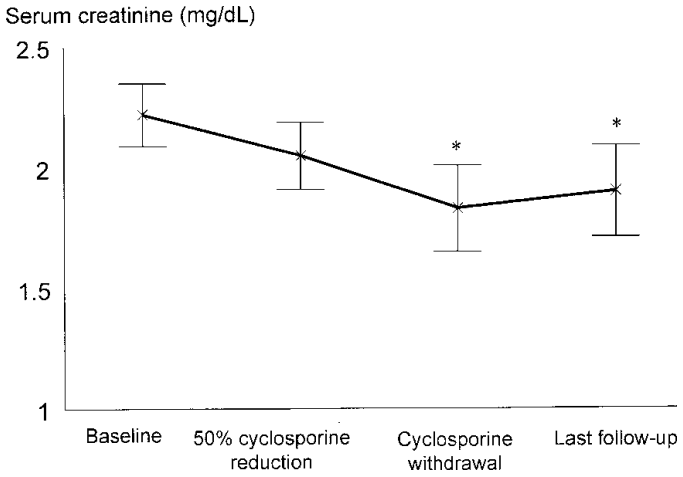

Figure 2. Evolution of serum urea levels in patients (n = 7) on MMF therapy and without cyclosporine at last follow-up. *P < .05 compared with baseline.

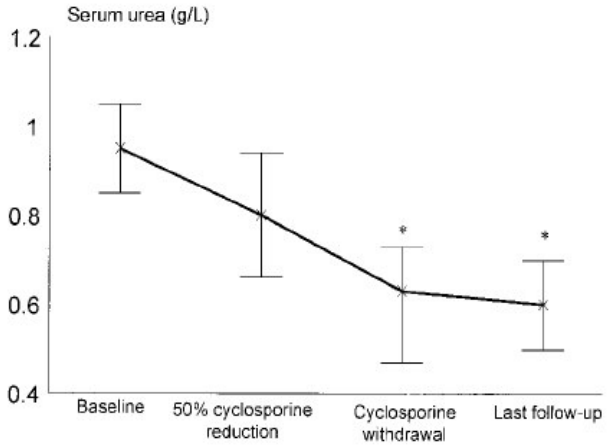

Figure 3. Evolution of creatinine clearance in patients (n = 7) on MMF therapy and without cyclosporine at last follow-up. *P < .05 compared with baseline.

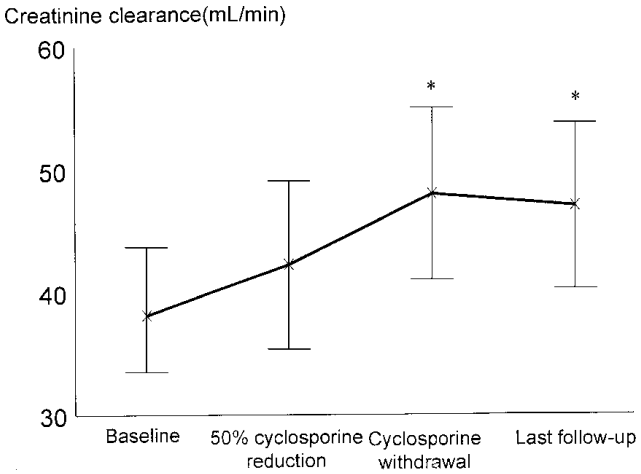

Figure 4. Need for antihypertensive drugs before change in immunosuppressive therapy and at last follow-up in patients receiving treatment with MMF and without cyclosporine (n = 7).