

Conversion From Calcineurin Inhibitors to Mycophenolate Mofetil in Liver Transplant Recipients With Diabetes Mellitus

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ABSTRACT

Diabetes mellitus, a frequent metabolic complication in liver transplant recipients, may be produced by the diabetogenic effect of calcineurin inhibitors cyclosporine and tacrolimus. The aim of this study was to investigate the safety and metabolic effects of a gradual switch from cyclosporine or tacrolimus to mycophenolate mofetil among 12 diabetic liver transplant recipients. One patient was withdrawn from the study due to gastrointestinal side effects. Of the 11 remaining patients, cyclosporine or tacrolimus was completely withdrawn in five patients. Two patients developed suspected acute rejection episodes that were controlled by increasing the tacrolimus dosage. Glycosylated hemoglobin A1C and C-peptide levels were significantly lower at 3 and 6 months after the initiation of mycophenolate mofetil ($P < .03$ in all cases). Furthermore, urea and uric acid levels were significantly reduced after the change of treatment. In conclusion, a switch from cyclosporine/tacrolimus to mycophenolate mofetil may produce beneficial metabolic effects in diabetic liver transplant recipients, but poses a risk of graft rejection.

DIABETES MELLITUS (DM) is a frequent metabolic complication in liver transplant (LT) recipients. Despite the lack of universal agreement, some studies have observed worsened short- and mid-term survival among diabetic LT recipients.¹⁻⁷ Furthermore, DM is a wellknown risk factor for cardiovascular disease, which is one of the leading causes of death of LT recipients in the long term.⁸ Calcineurin inhibitors (CI) also predispose to DM through islet cell toxicity, diminished insulin synthesis or release, as well as decreased peripheral insulin sensitivity.⁹ Mycophenolate mofetil (MMF) has proven to be useful as a CI-sparing agent. The use of MMF has allowed physicians to reduce cyclosporine exposure in LT recipients with renal functional impairment.¹⁰ Some patients have been maintained on MMF monotherapy, but this strategy poses the risk of graft rejection.¹¹ The aim of the present study was to examine whether conversion to MMF for stable LT recipients with DM allows the reduction/withdrawal of CI and results in improve metabolic control.

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PATIENTS AND METHODS

We performed a progressive switch from CI to MMF in stable LT recipients with DM who fulfilled the following inclusion criteria: (1) follow-up longer than 12 months after LT; (2) DM diagnosed by fasting serum glucose level above 126 mg/dL on 2 separate days and/or the need for antidiabetic therapy to achieve good glycemic control; (3) stable anti-diabetic therapy during the previous 3 months; and (4) the possibility of monthly follow-up. Exclusion criteria were: (1) graft rejection during the last 6 months; (2) steroid therapy in the last 3 months; (3) previous MMF therapy; (4) hemoglobin level < 10 g/dL; (5) white blood cell count (WBC) < 2500/mm³; (6) platelet count < 60,000/mm³; (7) peptic ulcer disease or significant gastroesophageal reflux disease.

MMF Therapy

At the first visit, azathioprine was discontinued (in three patients that were receiving this drug) and MMF was started at a daily dose of 1500 mg. MMF dose was reduced to 1000 mg/d in cases of hematologic toxicity (hemoglobin level < 10 g/dL, WBC count < 2500/mm³, or platelet count < 60,000/mm³). The MMF dose was increased to 2000 mg/d if the baseline mycophenolic acid (MPA) levels were below 1.0 µg/mL after 30 days of MMF therapy with the initial dose.

Adjustment of CI Therapy

One month after initiation of MMF, the baseline dose of CI was reduced each month by 25% to 35%. If serum aspartate aminotransferase (AST) levels increased >25%, the CI dose was not further reduced. In case of a greater increase in AST, the CI dose was increased until there was normalization of the AST.

The following variables were recorded at baseline as well as 3 and 6 months after initiation of MMF: mean arterial pressure, complete blood count (CBC), liver function tests, urea, creatinine, fasting glucose, glycosylated hemoglobin A1C (HbA1C), C-peptide, fasting lipid profile, and dose of CI and MMF, as well as MPA levels. Monthly visits included recording of CBC and liver function tests. Drug therapy for DM, arterial hypertension, and dyslipidemia were maintained unchanged during the 6-month follow-up.

Statistical Analysis

Quantitative data are expressed as median values (interquartile range). Baseline data were compared with 3- and 6-month data using Wilcoxon test for paired data. A difference was considered statistically significant if the *P* value was less than .05. All statistical analyses were performed using SPSS for Windows, version 9.0 (SPSS Inc, Chicago, Ill, USA).

RESULTS

Of the 18 patients selected for the trial, six failed to give consent. One of the 12 patients discontinued MMF due to gastrointestinal side effects. Thus, 11 patients completed the 6-month study. Ten had been transplanted for alcoholic cirrhosis and one for Budd-Chiari

syndrome. All but one were men. Their median age was 62 (53–66) years. They had been transplanted 52 (33–76) months before the change in therapy. Seven were on tacrolimus monotherapy; two received tacrolimus and azathioprine; one, cyclosporine, and one, cyclosporine and azathioprine. Three patients were not receiving antidiabetic drugs, four were on oral hypoglycemic agents, one was on insulin, and three were on insulin as well as oral hypoglycemic agents.

Change in Immunosuppressive Therapy

At the end of 6-month follow-up, the daily dose of MMF was 1500 mg in six patients and 2000 mg in five. Their mycophenolic acid levels were 2.4 (1.4–2.7) $\mu\text{g/mL}$; five patients were on MMF monotherapy. Overall the doses of CI were 20% (0%–40%) of baseline.

Effect on Glucose Metabolism

The effect of the altered immunosuppression on glucose metabolism is shown in Table 1. Mild and insignificant decreases in fasting glucose levels were observed at 3 and 6 months after change of therapy. HbA1C levels were significantly lower at 3 months but not at 6 months. C-peptide levels were significantly lower at 6 months after MMF initiation. After the end of the 6-month period of follow-up, one patient who was free of CI had good glycemic control without antidiabetic drugs despite a previous requirement of insulin (10 units/d) and acarbose.

Effect on Renal Function, Uric Acid Levels, and Lipid Profile

As shown in Table 2 serum urea and uric acid levels significantly decreased at 3 and 6 months. Creatinine, cholesterol, and triglyceride levels did not change significantly. No changes in mean arterial pressure were observed.

Side Effects

As previously mentioned, one patient discontinued MMF within the first month due to gastrointestinal side effects. Four patients who had mild increases of AST (~50% over the upper limit of normal range) were maintained on reduced doses of CI. Two patients developed suspected graft rejection after reducing tacrolimus dose to 25% of baseline (from 4 and 2 to 1 and 0.5 mg/d, respectively). Liver function tests improved after tacrolimus dose increases to 3 and 1 mg/d, respectively. The evolution of liver function tests is shown in Table 2. There was no case of hematological toxicity requiring MMF dose reduction. MMF therapy did not significantly change hemoglobin levels or WBC or platelet counts.

DISCUSSION

In this trial, we attempted to utilize MMF to reduce or withdraw CI, and thereby improve DM among a series of LT recipients. The effect of CI reduction on glucose metabolism was modest. We have

observed a significant reduction in HbA1C at 3 months after the initiation of the change in therapy, but it did not maintain statistical significance at 6 months. Despite this small apparent benefit, it was sufficient to allow one patient to discontinue insulin and oral hypoglycemic agents while maintaining good glycemic control. The finding of a reduced C-peptide level following the change of immunosuppression suggests improved insulin resistance following CI dose reduction.

This strategy to change immunosuppression posed a risk of graft rejection. Previous experiences in LT recipients with renal functional impairment reported controversial results. In our experience, episodes of graft rejection were well controlled with an increase in CI,¹⁰ but others have observed a poor responses.¹² In the present paper, two patients (18%) developed a rejection episode, both of which responded to increases in CI. No patient required steroid therapy. On the other hand, five patients (45%) are currently on MMF monotherapy with good graft function.

Other potential metabolic benefits of a change in therapy relate to the renal toxicity of CI. Despite the fact that most of our patients displayed good renal function initially, conversion of immunosuppression resulted in significant decreases in urea and uric acid. The decreased uric acid levels may benefit LT recipients with hyperuricemia and gout.

The modest effect of the change in immunosuppression on glucose metabolism described herein may be explained in part by the initially low doses of CI. Five of nine patients receiving tacrolimus were on baseline daily doses less than or equal to 2 mg/d. All of these nine patients displayed tacrolimus trough levels below 6 ng/mL. On the other hand, institution of MMF monotherapy at an earlier time may have posed a greater risk of rejection. A better strategy for patients who are in the early posttransplant period may be to combine low doses of CI with MMF, instead of attempting early MMF monotherapy.

In conclusion, the switch from CI to MMF among diabetic LT recipients may help to improve metabolic control, but it is followed by a low risk of graft rejection. Careful follow-up and a gradual decrease in CI are more advisable strategies.

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Table 1. Changes in Fasting Serum Glucose, HbA1C, and CPeptide Levels 3 and 6 Months After Initiation of MMF Therapy

	Baseline	3 months	6 months
Glucose (mg/dL)	144(115–151)	125(100–148)	132(121–142)
HbA ₁ C (%)	6.7(5.8–7.3)	6.2(5.6–7.1)*	6.4(5.8–7.3)
C-peptide (ng/mL)	3.0(1.8–5.1)	3.4(1.9–5.7)	1.8(1.2–4.6)**

* $P = .025$ compared with baseline. ** $P = .029$ compared with baseline.

Table 2. Evolution of Urea, Creatinine, and Uric Acid Levels and Liver Function Tests 3 and 6 Months After Initiation of MMF Therapy

	Baseline	3 months	6 months
Urea (g/L)	0.46(0.39–0.57)	0.42(0.32–0.46) ^a	0.41(0.32–0.50) ^b
Creatinine (mg/dL)	1.0(1.0–1.3)	1.1(0.9–1.2)	1.0(0.9–1.2)
Uric acid (mg/dL)	6.4(4.8–7.4)	5.2(4.5–5.7) ^c	5.3(4.8–6.3) ^d
ALT (IU/L)	15(13–20)	17(14–36)	20(14–25) ^e
AST (IU/L)	19(14–28)	25(17–30)	25(16–38)
AP (IU/L)	108(99–137)	116(104–196)	116(96–194)
GGTP (IU/L)	19(15–37)	33(15–103)	27(19–51)
Bilirubin (mg/dL)	0.77(0.66–1.17)	0.82(0.69–1.08)	0.96(0.81–1.18)

^a $P = .01$ compared with baseline; ^b $P = .028$ compared with baseline; ^c $P = .016$ compared to baseline; ^d $P = .04$ compared with baseline; ^e $P = .021$ as compared with baseline.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; AP: alkaline phosphatase; GGTP: gamma-glutamyl transpeptidase.

