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Original Article

Mycophenolate mofetil in liver transplant patients with calcineurin-inhibitor-induced renal impairment

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Abstract

Background: **Calcineurin inhibitors (CNIs) provide effective immunosuppression after orthotopic liver transplantation (OLTx), but the associated nephrotoxicity can cause substantial morbidity and mortality among transplant patients. In this study, we retrospectively investigated the efficacy and safety of mycophenolate mofetil (MMF) in OLTx patients with CNI-induced renal impairment.** ***Patients & Methods:*** **A chart review was undertaken of all liver transplant recipients followed at the Vancouver General Hospital. Twenty-one (12 male) patients were converted to either MMF monotherapy (n = 18) or MMF with corticosteroids (n = 3) for CNI-induced renal dysfunction. Six were excluded because of other factors contributing to renal dysfunction. Mean time from OLTx to conversion was 11.3 years and mean age was 60. Non-parametric Wilcoxon's signed rank testing was used to determine whether there was a difference between the serum creatinine (SCr) before conversion, and 3 or 6 months after conversion.** ***Results:*** **Median follow-up was 294 days, ranging from 35 to1103 days. The median SCr was significantly reduced from 144 µmol/L before conversion to 129 µmol/L and 139 µmol/L at 3 and 6 months follow-up (p = 0.001 and 0.008, respectively). MMF was well tolerated. Only one patient (6.7%) had elevated liver enzymes and required addition of sirolimus while two (13.4%) experienced gastrointestinal intolerance.** ***Conclusions:*** **MMF appears to be safe for stable OLTx recipients with CNI-induced nephrotoxicity. Serious side effects were uncommon as only one patient required discontinuation of the medication. However, longer follow-up and larger study populations are needed in the future to better determine its efficacy and safety.**

Key words: Calcineurin-inhibitors, mycophenolate mofetil, nephrotoxicity, liver transplantation.

Introduction

Over the past few decades, liver transplantation has allowed organ replacement for end-stage cirrhosis, with an excellent long-term survival benefit. Calcineurin inhibitors (CNI), i.e. tacrolimus or cyclosporine, are considered the cornerstone immunosuppressant medications in liver transplantation. With these CNI-based regimens, patient and graft survival rate is about 85% at 1 year, and 77% at 3 years.[1] However, CNI are associated with a considerable side effect profile: nephrotoxicity, neurotoxicity, arterial hypertension, hyperglycemia, and increased risk of secondary malignancy. All of these can lead to substantial long-term morbidity and mortality among transplant patients.[2,3]

Nephrotoxicity is the most important complication for transplant recipients' long-term survival and quality of life. Several retrospective studies have suggested that approximately 20% of patients on CNI will develop chronic renal failure (CRF) anywhere from 3 to 13 years post-transplant with an associated increased mortality risk.[2,4-6] Management of this complication is difficult because CNI dose reduction generally does not improve renal function and CNI withdrawal can be associated with graft rejection.[7,8] Recent studies suggest that mycophenolate mofetil (MMF) might be an alternative immunosuppressant and conversion from CNI to MMF might improve renal function in liver transplant recipients. MMF, an ester prodrug of mycophenolic acid, is a reversible inhibitor of inosine monophosphate dehydrogenase, a vital enzyme implicated in *de novo* purine biosynthesis.[9] This pathway is necessary for T- and B-lymphocyte proliferation in acute

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rejection. MMF has immunosuppressive potency similar to CNI but lacks nephrotoxicity, neurotoxicity, and other side effects associated with CNI. Furthermore, an antiproliferative and antiviral effect similar to that of ribavirin has been attributed to MMF.[10,11] The most common adverse effects attributed to MMF are gastrointestinal (e.g. nausea, vomiting, and diarrhea) and hematologic cytopenias.

The purpose of this study was to evaluate the efficacy and safety of mycophenolate mofetil (MMF) in stable liver transplant patients with CNI-induced renal impairment. The primary goal was to determine whether conversion from CNI to MMF would lead to stabilization and possible improvement of a patient's renal function. The second aim was to determine the incidence of adverse events, including graft rejection rates, when patients were on MMF.

Patients and methods

Study setting

We reviewed the medical records of all patients who underwent liver transplant and were followed by the Solid Organ Transplant Clinic at the Vancouver General Hospital, Vancouver, British Columbia (BC), from 1989 to 2006. The Solid Organ Transplant Clinic follows all liver transplant recipients in British Columbia. The first liver transplant in BC was performed in 1989 and since then, over 500 British Columbians have received a liver transplant.

Patients population

All stable liver transplant patients converted to either MMF monotherapy or MMF with corticosteroids for CNI-induced renal impairment were included in the study. CNI-induced renal impairment was considered to be serum creatinine (SCr) levels greater than 110 μmol/L for at least 3 months. To be included in this study, the patients had to be followed up for at least 1 year after the last liver transplant with no evidence of graft rejection in the preceding 12 months. Exclusion criteria included: patients who were on dialysis before conversion and continued to be dialyzed post conversion, those who had chronic renal disease not related to CNI, and those who were switched back to CNIs.

Treatment

Conversion to MMF was done by introducing MMF at an initial dose of 500 mg twice daily, and then reaching a dose of 1g twice daily by two weeks if tolerated. At the same time, CNI was progressively reduced until discontinuation. The MMF dose was adjusted according to clinical tolerance.

Measurement & follow-up

The type of immunosuppression pre- and post-conversion, mean time between transplant and conversion, side effects of MMF, and mean follow-up after conversion were all reviewed. All patients had regular monthly bloodwork and were followed by the transplant team every three months. Serum creatinine was measured pre-transplant, before conversion to MMF, as well as 3 months and 6 months after conversion. Liver enzymes were measured at the same intervals, and liver biopsy was performed if indicated to rule out rejection. Lastly, adverse events were documented in the chart by the transplant team at each visit.

Statistical analysis

Data were collected and analyzed using the SPSS 13.0 computer software package (SPSS Inc, Chicago IL). Non-parametric Wilcoxon's signed rank testing was used to determine whether the difference between the serum creatinine (SCr) before conversion, and 3 or 6 months after conversion was significant. The level of statistical significance for a two-tailed test was < 0.05 (i.e. p value < 0.05).

Results

Serum creatinine before and after switching from calcineurin inhibitor (CNI) to MMF

Twenty-one (12 male, 9 female) patients were converted to either MMF monotherapy, 1g twice daily (n = 18) or MMF with corticosteroids, ≤ 10mg prednisone (n = 3), for CNI-induced (15 cyclosporine, 6 tacrolimus) renal dysfunction. Six patients were excluded from the study: one patient had sepsis contributing to renal dysfunction; two were started on dialysis before conversion; and three were switched back to CNIs because of anemia, profound diarrhea and atrial fibrillation. The demographic characteristics of the patients are presented in *Table I*.

Sixty percent were male. The mean age was 58.9 ± 10.9 years. The indications for liver transplant were hepatitis C cirrhosis (3), primary biliary cirrhosis (3), primary sclerosing cholangitis (3), alcoholic cirrhosis (1), autoimmune hepatitis (2), and other diseases (3). The median time since transplantation was 10 years (range 3.4 to19.6 years). The median duration the transplant recipients were on calcineurin inhibitors was 9.4 years (range 2.0 to 14.14 years) and the mean time from transplant to MMF conversion was 11.3 years.

Median follow-up on MMF was 294 days (range 35 to 1103 days). All fifteen patients had no other underlying renal diseases except CNI nephrotoxicity and their serum creatinine was within the normal range before liver transplantation (median serum creatinine, 99 μmol/L). At the

Table I. Demographic characteristics of the patient population.

Number of patients	15
% Male	60
Age, Mean ± SD, years	58.9 ± 10.9
Indications for liver transplant:	
• Hepatitis C related end-stage liver disease	3 (20.0%)
• Primary biliary cirrhosis	3 (20.0%)
• Primary sclerosing cholangitis	2 (13.3%)
• Autoimmune hepatitis	2 (13.3%)
• Alcoholic cirrhosis	1 (6.7%)
• Others*	4 (26.7%)
Pre-transplant co-morbidities:	
• None	5 (33.3%)
• Gastrointestinal	
Inflammatory bowel diseases	3 (20.0%)
Peptic ulcer disease	1 (6.7%)
Cardiovascular (e.g. HTN, CAD)	1 (6.7%)
• Hematological (e.g. anemia)	2 (13.4%)
• Endocrinological (e.g. hypothyroidism)	1 (6.7%)
• Gynecological (e.g. endometriosis)	1 (6.7%)
• Musculoskeletal (e.g. degenerative disc disease)	1 (6.7%)
CNIs	
• Cyclosporine	9 (60%)
• Tacrolimus	6 (40%)
Median time since transplant, years	10 (3.4-19.6)
Median duration transplant recipients on CNIs, years	9.4 (2.0-14.14)
Median follow-up time post conversion to MMF, days	294

* Others include: chronic hepatitis B; hepatocellular carcinoma; Wilson's disease; non-alcoholic steatohepatitis

time of the study, thirteen patients had switched to MMF for more than 3 months while nine had been on MMF for more than 6 months. As illustrated in *Table II*, all patients had a decrease in serum creatinine levels post MMF conversion.

The median serum creatinine before MMF conversion was 144 μmol/L (n = 15). After conversion, the median serum Cr at 3 and 6 months was 129 μmol/L (n = 13) and 139 μmol/L (n = 9), respectively. The differences between pre-MMF conversion and post-MMF conversion were statistically different, with a p value of 0.001 and 0.008 respectively when signed rank testing was applied *(Figure 1)*. However, the difference between the median serum creatinine levels at 3 and 6 months was not statistically significant.

Adverse events

MMF was generally well tolerated with minimal side effects. Only three patients experienced gastrointestinal intolerance: one (6.7%) reported having stomach upset while two (13.4%) experienced diarrhea. The side effects improved with dose reduction; however, one patient continued to have profound diarrhea and required discontinuation of the medication. In addition, two other patients required discontinuation of MMF because of anemia and atrial fibrillation. Although the transplant physician did not believe MMF was the cause of atrial fibrillation, the medication was discontinued.

Table II. Serum Creatinine (Cr) before and after switching from calcineurin inhibitor to mycophenolate mofetil (MMF).

Patients	Serum creatinine (Cr) before switch (μmol/L)	Serum Cr 3 mo post switch to MMF (μmol/L)	Serum Cr 6 mo post switch to MMF (μmol/L)
1	113	110	88
2	152	150	136
3	236	156	145
4	144	129	131
5	167	158	161
6	277	268	244
7	174	144	139
8	142	119	n/a
9	112	92	n/a
10	131	127	n/a
11	122	95	n/a
12	156	n/a	n/a
13	134	n/a	n/a
14	235	199	180
15	132	124	104

Graft rejection

After conversion to MMF, only one patient had elevated liver transaminases. Unfortunately, liver biopsy was not performed and the patient was treated with the addition of another immunosuppressant, sirolimus. Subsequently, the transaminases improved.

Discussion

Although calcineurin-inhibitors (CNI) have markedly improved the results of solid organ transplantation, they induce a number of undesirable side effects that can dramatically influence the transplant recipient's mortality, morbidity and quality of life. Nephrotoxicty and subsequent renal insufficiency remain the main problem of long-term CNI-based immunosuppression. This discrepancy between excellent graft survival and serious side effects has prompted efforts to develop and use alternative immunosuppressive agents. One of these agents is mycophenolate mofetil (MMF). In recent years, MMF has been suggested for liver transplant patients with CNI-induced renal insufficiency.

In their study, Schlitt *et al.*[11] detected significant improvement of renal function, represented by serum creatinine values, blood pressure and serum uric acid values among MMF monotherapy patients compared with CNI-treated controls. Similarly, in their studies, Herrero *et al.*[12] and Jain *et al.*[13] found that partial or total conversion of cyclosporine to MMF, or the addition of MMF and re-

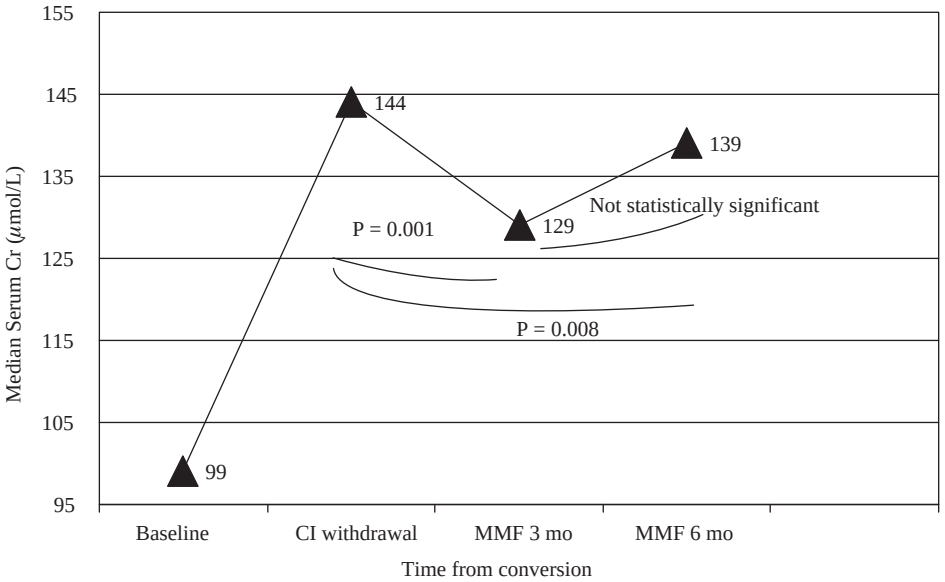

Figure 1. Evolution of serum creatinine levels in patients on MMF therapy.

duction of tacrolimus dose appear to improve renal dysfunction related to CNI.

In our study, renal function also appeared to improve after conversion to MMF. However, the difference between the median serum creatinine levels at 3 and 6 months post MMF conversion was not statistically significant. One possible explanation is that there were only nine patients who were converted to MMF for more than six months. This small sample size limits the ability to detect any statistical significance. The explanation for a lack of further improvement beyond 3 months could be that irreversible renal damage remains and cannot be resolved even in the absence of CNI.[11,14-17] Therefore, nephrotoxic drugs should be discontinued early and ideally before any severe and irreversible damage to the kidneys. Consequently, for conversion to MMF to be effective, sustained and progressive, it has to be undertaken before the renal damage has become irreversible. One study[18] had suggested that MMF conversion should be performed within one year of CNI-induced renal impairment in order to gain a better level of renal function improvement; however, larger prospective studies remain to be conducted to elucidate the ideal time frame for MMF conversion.

In previous published MMF monotherapy trials, there have been wide variations of rejection rates. Some studies have shown severe rejections and graft loss after MMF conversion.[11,19,20] In the Newcastle study[19], 60% (3 out of 5) of patients on MMF monotherapy demonstrated rejection and in the German study[11] 50%, but all showed renal function improvement. On the other hand, in the study by Raimondo *et al.*, acute rejection was seen in only 6% (1/16) of the patients receiving MMF monotherapy.[21] In this study, the rejection rate was relatively low after MMF conversion. Only one patient (6.7%) developed transaminitis and required the addition of sirolimus. However, all patients included in this study had been transplanted for several years before switching to MMF (mean time after transplant 9.4 yr), suggesting a less immunogenic patient profile that could potentially contributing to the low rejection rate observed in this study. Since currently there are no means to predict rejection with MMF, this patient population should be monitored closely for an indefinite period.

Consistent with previous studies, our study showed that MMF was generally well-tolerated, with few undesirable side effects. Gastrointestinal intolerance (e.g. diarrhea) was the most common side effect, followed by hematological cytopenias (e.g. anemia).

This study has several limitations. The study was retrospective and was conducted at a single Canadian transplant centre. Thus, the results might not be applicable to other patient populations. Furthermore, the sample size was small. At the end, we only had nine patients who were converted to MMF for 6 months. A larger prospective study is needed in the future to better determine the efficacy and safety of MMF monotherapy in liver transplant patients. Thirdly, we had used serum creatinine as a surrogate marker for a patient's renal function. Ideally, the best way to define a patient's renal function is calculation of their creatinine clearance; however, our reasoning for use of serum creatinine was because a number of previous studies had also used serum creatinine levels as surrogate markers of renal function. Comparisons to the results from these studies would be easier if the same parameters were being measured.

Conclusion

Calcineurin inhibitor free regimens with MMF treatment appear to be a safe alternative for stable liver transplant recipients with CNI-induced nephrotoxicity. Side

effects are uncommon. However, longer follow-up and larger prospective randomized trials are needed in the future to better determine the efficacy and safety of MMF in liver transplant patients.

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