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Original Article

Effect of conversion from azathioprine to mycophenolate mofetil on renal function in stable kidney transplant recipients

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Abstract

Introduction. This study investigated the effect of mycophenolate mofetil (MPA) treatment instead of azathioprine (AZA) on renal function after kidney transplantation.
Methods. Thirteen of all recipients were taking a cyclosporine-based regimen and serum creatinine levels were above 1.5 mg/dL. In 13 patients, MPA treatment was started instead of AZA. Renal functions were evaluated for 12 months after MPA treatment.
Results. Serum creatinine levels increased from 2.11±0.48 mg/dL to 2.16±0.72 mg/dL at 12th months. This increase was not statistically significant. Serum creatinine levels decreased in 5 of 13 patients.
Conclusions. In selected patients, conversion from AZA to MPA may slow down the rate of deterioration in graft functions.

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Keywords: Azathioprine, mycophenolate mofetil, kidney transplant recipients.

Introduction

Recipients receive immunosuppressive therapy in order to prevent acute rejection after kidney transplantation. Current maintenance immunosuppression may include glucocorticoids, calcineurin inhibitors (CNIs; tacrolimus: TAC or cyclosporine: CsA), antimetabolic agents (mycophenolate mofetil: MMF, enteric-coated mycophenolate sodium,: EC-MPS or azathioprine: AZA), mammalian target of rapamycin (mTOR) inhibitors (sirolimus or everolimus) or costimulatory blockade agents (belatacept).[1] Antimetabolic agents interfere with the synthesis of nucleic acids and inhibit the proliferation of both T and B lymphocytes.[2] The 2009 KDIGO clinical practice guidelines suggest mycophenolate as the first-line antimetabolic agent rather than AZA.[3] Because mycophenolate is superior in preventing acute rejection and has a better side-effect profile.[4] MMF is an ester pro-drug which is metabolized to the active compound mycophenolic acid (MPA) in the body. MPA is a noncompetitive inhibitor of a rate-limiting purine biosynthetic enzyme, inosine-5'-monophosphate dehydrogenase (IMPDH). IMPDH is involved in de novo synthesis of

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purines, and lymphocytes rely exclusively on this de novo pathway for nucleotide synthesis. Therefore, MMF selectively targets lymphocyte proliferation.[5,6] The Symphony study showed that a combination of low-dose TAC and MMF was the best of various combined immunosuppressive therapies investigated.[7] In A retrospective analysis of 51,303 patients undergoing deceased-donor kidney transplantation, MPA treatment was associated with a lower risk of acute rejection and a higher risk of hospitalization because of infection when compared to AZA.[8] Renal allograft failure is one of the most common causes of end-stage renal disease and accounts for 25 to 30% of patients awaiting kidney transplantation. MMF may positively affect the long-term graft survival in the long term as well as reduce the occurrence of acute rejection. This study aimed to evaluate changes of graft function in kidney transplant recipients who received MMF treatment instead of AZA.

Methods

For this retrospective study, patients who underwent transplant surgery in our center were evaluated. Thirteen (11 male, 2 female, live donor) recipients with CsA-based regimen and serum creatinine levels above 1.5 mg/dL were included in the study. These patients with chronic allograft dysfunction without biopsy were treated with 2 g/day MMF instead of AZA. Serum creatinine levels were measured at 1th, 3rd, 6th and 12th after MMF treatment.

The data was analyzed using SPSS Software package of version 20. Numerical variables were given as mean±standard deviation (SD). The Wilcoxon signed-rank test was used for intragroup comparisons. P values less than 0.05 were considered to be significant.

Results

The mean age of the patients was 35±5.4 (range: 26-41) years. Serum creatinine levels before MMF were 2.11±0.48 mg/dL. The mean serum creatinine levels after MMF were 2.28±0.75, 2.19±0.73, 2.16±0.67 and 2.16±0.72 mg/dL at the 1st, 3rd, 6th and 12th months, respectively. The difference between mean creatinine levels before and after MMF treatment was not statistically significant ($p>0.05$). Serum creatinine levels decreased in 5 patients, increased in 4 patients and remained unchanged in 4 patients during the MMF follow-up period. In two patients, symptoms of diarrhea alleviated by reducing the MMF dose (1.5 g/day). No other MMF-related side effects observed. None of the patients had cytomegalovirus (CMV) infection.

Discussion

In our study, we observed that at least some transplant patients with chronic allograft dysfunction preserved renal function by conversion from AZA to MMF over a one-year period. Despite improving immunosuppressive protocols in kidney transplantation, chronic allograft nephropathy (CAN) is one of major causes of graft failure after the first year. This clinical condition is expressed in various terms: chronic rejection, CAN, chronic allograft dysfunction, transplant nephropathy, transplant glomerulopathy or chronic allograft injury. This clinicopathological entity is incompletely understood. A retrospective single-center study on 214 recipients with chronic allograft dysfunction among 1,534 kidney transplant recipients revealed that type of immunosuppression (MMF vs AZA), age of donor, proteinuria, pre-transplant hypertension, pre-transplant diabetes, delayed graft function and stage of allograft dysfunction at the start of chronic allograft dysfunction are the major risk factors for late renal allograft dysfunction.[9] Additionally, using MMF versus AZA reduced death-censored graft loss.[9]

The optimal immunosuppressive regimen for a patient with CAN is unknown. CNI withdrawal is safe and conversion to MMF or mTOR inhibitors may be beneficial.[10] In a systematic review of 23 trials involving 3,301 kidney transplant recipients, MMF reduced the risk of death-censored graft loss, acute rejection and CAN when compared with AZA.[4] Numerous large trial and meta-analysis results support lower acute rejection rates and better graft survival with MMF compared with AZA.[4,11-19] Renal function

can be better preserved in patients using MMF instead of AZA.[11,20] After conversion from AZA to MMF with concomitant CsA withdrawal in 31 patients with chronic allograft dysfunction, proteinuria decreased with improved graft survival and renal function.[21] In 49,666 transplant recipients, continuous use of MMF versus AZA was associated with a protective effect against declining renal function beyond 1 year after transplantation.[22]

MMF may also be useful in patients with CAN or chronic progressive allograft dysfunction.[23-28] In the Creeping Creatinine study, addition of MMF followed by withdrawal of CsA in 122 patients with progressively deteriorating renal function secondary to CAN resulted in a significant improvement in graft function without the risk of acute rejection.[27] In an another study, renal function after introduction of MMF in patients with biopsy-proven chronic allograft nephropathy remained stable with a significant change in the slope of the glomerular filtration rate.[28] Three years after conversion to MMF in patients with progressive CAN, patient and graft survival were reported to be 95% and 79%, respectively.[29] In a large cohort, MMF reduced the relative risk for CAN development by 27%.[30] In a study evaluating the effect of immunosuppression conversion on CAN progression, MMF or low dose CsA was superior to TAC-for-CsA and standard dose CsA in patients with CAN, at least in the short term.[31]

In our study, no serious side effects were observed in patients after the transition from AZA to MMF. Leukopenia is the most serious side effect of AZA. Mycophenolate treatment combined with prednisolone and CsA in fifty-nine transplant patients shifted to an AZA-based regimen for 720 days. Absolute leukocyte counts statistically significant decreased 12 months after starting AZA.[32] While thrombocytopenia and elevated liver enzymes were more frequent with AZA, gastrointestinal symptoms such as diarrhea and risk of tissue-invasive CMV disease were higher with MMF.[4,9-17]

The important limitations of our study were the relatively low number of patients, the lack of graft biopsy and the short follow-up period. In conclusion, conversion from AZA to MMF in patients with chronic allograft dysfunction can be a safe strategy for improvement of graft survival. However, the transplant physician should evaluate the potential benefits (graft survival) and harms (infections, malignancies and possible side effects) of the two drugs in the individual patient.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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