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**Article** *in* Transplantation Proceedings · June 2007

DOI: 10.1016/j.transproceed.2007.03.006 · Source: PubMed

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# Changing Treatment Protocol From Azathioprine to Mycophenolate Mofetil: Decrease in Renal Dysfunction, Increase in Infections

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ABSTRACT

Introduction. Immunosuppression for renal transplantation has shifted from azathioprine (AZA) regimens to those containing mycophenolate mofetil (MMF). This study investigated the impact of this change on the causes for rehospitalization as well as on graft and patient survival.

Methods. In this retrospective cohort study, we reviewed long-term patient and graft survivals as well as the causes of posttransplant admissions for 893 kidney recipients. Data on survival and readmissions were available for 811 subjects, who were divided to into the AZA cohort ($n$ = 289, transplantation between 1998 and 1999) and the MMF cohort ($n$ = 567, transplantation between 2000 and 2001). Survival, the cause for readmission, time interval between transplantation and readmission, intensive care unit (ICU) admission, mortality, and graft loss were compared between the two cohorts.

Results. Five-year patient and graft survival rates were 85% and 67% for the AZA cohort and 91% and 68% for the MMF cohort ($P$ = .013). There were 202 (71%) and 371 (72%) readmissions registered for the AZA and MMF groups, respectively. In comparison with the AZA cohort, while readmissions secondary to graft rejection showed a significant decrease in the MMF cohort (62% vs 35%, $P$ = .000), readmissions secondary to infections exhibited a significant increase (37% vs 50%, $P$ = .002). A marginally significant increased mortality rate (2% vs 5%, $P$ = .087) and ICU admission rate (3% vs 6%, $P$ = .062) were also observed in the MMF cohort by comparison with the AZA cohort.

Conclusion. The shift in the immunosuppression protocol from AZA to MMF, albeit advantageous in many instances, can sometimes undermine the outcome by giving rise to such complications as high infection rates.

EVER SINCE ITS APPROVAL by the US Food and Drug Administration for use in renal transplantation in June 1995, mycophenolate mofetil (MMF) has rapidly gained acceptance among clinicians as a replacement for azathioprine (AZA) in immunosuppression protocols.[1] There are, however, long-standing questions as regards the efficacy, safety, and cost-effectiveness of MMF. The adverse effects of MMF are believed to vary among different races[2]; indeed, there are researches reporting that the beneficial effects of MMF are particularly dependent upon race.[3] Available data on the efficacy of MMF are contradictory. While a European trial indicated better survival rates with MMF, investigations in the United States suggest otherwise.[4] The existing graft survival data still cannot justify the costs of this new immunosuppression treatment,[5] much less its long-term cost-effectiveness.[6] We designed this study to investigate the impact of this shift in immunosuppression on graft and patient survivals as well as on the causes of rehospitalization.

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This study was fully supported and funded by Baqiyatallah Medical Sciences University.

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0041-1345/07/$–see front matter
doi:10.1016/j.transproceed.2007.03.006

## MATERIALS AND METHODS

In this retrospective cohort study we reviewed long-term patient and graft survivals as well as the causes of posttransplant admissions for kidney recipient. A total of 893 kidney recipients were selected: 326 having undergone transplantation between 1998 and 1999, and 567 between 2000 and 2001. Data on survival and readmissions were available for 811, who were divided into the AZA cohort ($n = 289$, transplantation between 1998 and 1999) and the MMF cohort ($n = 567$, transplantation between 2000 and 2001).

Cyclosporine (CsA), AZA, and prednisone were utilized as the initial maintenance immunosuppression before the year 2000. Thereafter, the initial maintenance immunosuppression consisted of CsA, MMF (CellCept, Roche, Nutley, NJ, USA), and prednisone. All the patients received CsA microemulsion 74 (Neoral, Novartis) concurrently. The initial dose of CsA was 7 mg/kg twice daily. Cyclosporine was controlled by $C_0$, $C_2$, and liver enzymes/clinical status. The dose of MMF was 1 g twice daily. The patients loaded with 2 to 3 mg/kg AZA were maintained on 1 mg/kg/d. All the patients received pulse therapy with 50 mg prednisone before transplantation. Postoperative prednisone was tapered from 2 mg/kg/d on the first postoperative day down to 0.3 mg/kg/d by day 15 and remained at that dose for the first 6 months.

## REHOSPITALIZATION

Rehospitalization was defined as a hospital admission that occurred for any reason after discharge from the initial transplantation hospitalization. We extracted from hospital records patients' ages, sexes, end-stage renal disease (ESRD) etiology, length of hospital stay, time interval between initial transplantation and rehospitalization, hospitalization charges as well as mortality data. The primary diagnoses recorded in the patients' hospital-discharge records were classified to broad categories of infection, infection-induced graft rejection, non-infection-induced graft rejection, ischemic heart disease, cerebrovascular accident, diabetes mellitus, malignancy, and miscellaneous etiologies, such as posttransplantation diabetes mellitus, benign prostatic hyperplasia, posttransplantation hypertension, anemia, intestinal necrosis, transient thrombotic purpura, and cholestasis.

The costs of rehospitalization were considered from a societal perspective. It is noteworthy that the hospitalization costs of the kidney recipients in Iran are fully covered by the government, neither the patient nor insurance companies bearing the costs. The hospitalization cost was defined as the total cost charged by the hospital for rehospitalization, including the costs of accommodation, medication, surgical procedures, laboratory tests, imaging tests, and miscellaneous costs. It should be added that indirect costs, such as those related to productivity loss (ie, days of work lost due to disease), were not taken into account. Since the hospitalization costs were recorded in different years, it was necessary to adjust them for the inflation rates so that comparing the costs across different years would make sense. Considering the year 2006 as our adjustment reference year, the costs recorded across the years 2000 to 2005 were inflated to those of the year 2006, assuming an annual inflation rate of 10%.[7] The final costs were made internationally comparable by converting the costs from Iranian rials to PPP$ (purchase power parity or international dollar). The conversion rate for PPP$ was based on a recently published Iranian study calculating PPP$ to be equal to 2727 Iranian rials according to the information from the Central Bank of Iran and the World Bank database.[8]

### Survival

One-year, 3-year, and 5-year graft and patient survival data were extracted from the outpatient clinic. Survival times were censored when the patients were lost to follow-up, changed immunosuppression, received a second transplant, or died before a failure event.

### Statistical Analysis

Statistical analysis was composed of two distinct parts: rehospitalization and survival. For the analysis of rehospitalization, ranked variables and continuous variables with non-normal distribution were compared using the Mann-Whitney $U$ test. Chi-square test was used to compare the frequencies of the categorical variables. For the analysis of survival, the two cohorts were compared in terms of their patient survival rates using the log-rank test. The Kaplan-Meier method was utilized to estimate graft and patient survival. Survival curves were compared by means of the log-rank test after stratification. Data analysis was conducted with SPSS for Windows version 13. $P$ values less than .05 were considered to be significant.

## RESULTS

### Patients

Of the 811 patients with available data, 29% were women, and 31% were over 50 years of age. Source of kidney was living related donors in 92%, living unrelated donors in 5%, and cadavers in 3%. ESRD was caused by diabetes in 18%, by hypertension in 21%, and by other diseases in 61%. The two cohorts were not different in terms of age $> 50$, sex, and ESRD etiology. The relative frequency of cadaveric kidney as source of kidney was higher in the MMF cohort than it was in the AZA cohort (1.4% vs 3.8%, $P = .05$).

### Survival

One-year, 3-year, and 5-year graft survival rates were 82%, 75%, and 67% for the AZA cohort and 86%, 77%, and 68% for the MMF cohort ($P = .013$). One-year, 3-year, and 5-year patient survival rates were 92%, 88%, and 85% for the AZA cohort and 95%, 94%, and 91% for the MMF cohort ($P = .001$).

### Rehospitalization Pattern

There were 202 (71%) and 371 (72%) readmissions registered for the AZA and MMF groups, respectively ($P > .05$). The MMF cohort, compared with the AZA cohort, showed

a significant decrease in admissions secondary to graft rejection (62%, 35%, $P = .000$), whereas those secondary to infections were significantly increased (37%, 50%, $P = .002$). Admissions due to macrovascular diseases, cancer, and surgical complications were the same in the two groups. A marginally significant increase in the mortality rate of inpatients (2% vs 5%, $P = .087$) and the intensive care unit (ICU) admission rate (3% vs 6%, $P = .062$) was also observed in the MMF cohort compared with the AZA cohort (Table 1).

## DISCUSSION

The results presented herein showed that changing the immunosuppression protocol from AZA to MMF in Iran in the year 2000 may have brought about better general long-term patient and graft survival rates, but for those rehospitalized, not only has inpatient survival deteriorated but also the ICU admission rates have risen. In terms of the type of complications, the shift in the treatment protocol seems to have brought about two noticeable changes: an increased rate of infection and a decreased rate of graft rejection.

In our study, MMF was accompanied with better long-term graft survival. The existing data in this field are, however, controversial. While some authors have suggested that MMF may improve long-term outcome in kidney recipients,[9,10] randomized trials did not show an improvement in patient or graft survival by MMF at 1 year[11] or three years[12] compared with AZA. Studies that do not report a better long-term actual graft survival with MMF suggested that the lower incidence of acute rejection early after transplantation observed with MMF was not synonymous with a long-term benefit, possibly due to the influence of nonimmunological factors, such as hypertension, higher rate of calcineurin inhibitor toxicity, and more frequent cytomegalovirus infections.[4]

In our center, another benefit of replacing AZA with MMF, in conjunction with CsA and corticosteroids, in posttransplant regimens was observed in patient survival rates. In another study, a marginally significant trend toward a higher recipient survival for patients receiving MMF was noted,[13] which was in contrast with the results of other randomized trials, in which it did not improve short-term patient survival.[11,12] The notion that the beneficial effect of MMF on patient survival can be described by a decreased cardiovascular risk factors and death with a functioning graft[14–16] was controversial, in that this impact was only observed after a long follow-up.

In our study, patients under maintenance treatment with MMF reported a lower rate of allograft rejection, which tallies with the results of some other researches.[9,17–20] A similar pattern has also been reported in randomized, double-blind, controlled trials.[11,12]

In our study, infection was seen more often as a complication among patients receiving MMF. Some studies have reported similar overall incidences of infection as well as of bacterial and fungal infections among patients receiving MMF versus AZA-based therapy.[13,21] Most studies in this field have focused only on the effect of MMF on cytomegalovirus disease—some reporting an increase[18–20, 22–24] and others not.[13,25,26] We believe it is reasonable to expect more frequent infectious complications with MMF, which is a more potent immunosuppressive drug. Consequently, in the elderly, who are more prone to the development of infection and less likely to have graft loss, it is advisable that MMF either be used at a low dose or be replaced by less potent alternatives.

The findings of retrospective studies such as ours should be interpreted with caution. Our patients were not randomized into immunosuppression study groups, and one group was treated before the other. Although the groups appeared comparable by the variables examined, the results may have become biased by unidentified factors that changed over time or that could not be accounted for in the analysis.

In summary, despite the above-mentioned limitations, this study supported the findings of other related investigations, which maintained that MMF, in combination with CsA and steroid, improved long-term survival and prevented allograft rejection better than AZA. There are, however, undesirable outcomes, such as higher rates of infection, higher ICU admission rates, and even inpatient deaths.

**Table 1. Comparison Between Demographic, Clinical, and Hospitalization Data and Outcomes in the Study Cohorts**

| Factor | AZA Cohort ($n = 208$) | MMF Cohort ($n = 371$) | $P$ Value |
|---|---|---|---|
| Admission cause | | | |
| Infection | 77 (37%) | 186 (50%) | .002 |
| Renal dysfunction | 129 (62%) | 130 (35%) | .000 |
| Surgical complications | 12 (6%) | 26 (7%) | .564 |
| Macrovascular disorder | 2 (1%) | 11 (3%) | .10 |
| Others | 14 (7%) | 30 (8%) | .555 |
| Length of hospital stay (d) | 11.58 ± 10.7 | 10.1 ± 9.3 | .150 |
| ICU admission | 6 (3%) | 24 (6%) | .062 |
| Hospital mortality | 5 (2%) | 18 (5%) | .087 |

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