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Mycophenolate Monotherapy in HLA-Matched Kidney Transplant Recipients: A Case Series of 20 Patients

Anthony J. Hennes, PharmD, BCPS,[1] Kimberly E. Holdener, PharmD, BCPS,[1] William J. Burlingham, PhD,[2] Didier A. Mandelbrot, MD,[3] Sandesh Parajuli, MD,[3] Maha A. Mohamed, MD,[3] Neetika Garg, MD,[3] Fahad Aziz, MD,[3] Brad C. Astor, PhD, MPH,[3,4] and Arjang Djamali, MD, MS[3]

Background. The ideal minimizing strategy for maintenance immunosuppression in HLA-matched kidney transplant recipients (KTR) is unknown. We hypothesized that mycophenolate (MPA) monotherapy is a safe and effective approach for maintenance therapy in this group of KTR. **Methods.** Data were abstracted for 6-antigen HLA-matched KTR between 1994 and 2013. Twenty recipients receiving MPA monotherapy secondary to infection, cancer, calcineurin inhibitor (CNI) side effects, or immunosuppression minimization strategies were evaluated in this case series. **Results.** MPA monotherapy had a low incidence of death-censored graft failure (3.19/100 person-y), rejection (0/100 person-y), hospitalization (1.62/100 person-y), malignancy (3.61/100 person-y), and infection (1.75/100 person-y). Further, 12-month mean or median serum creatinine (1.29 mg/dL), estimated glomerular filtration rate (64.3 mL/min/1.73 m2), urine protein creatinine ratio (143.2 mg/g), hemoglobin (13.9 g/dL), platelets (237.8 K/uL), and white blood cell count (9.04 K/uL) were favorable. There was a successful conversion rate of 90% (18 of 20) with 2 patients converting back to CNI-based regimens secondary to recurrence of membranous nephropathy and post-transplant lymphoproliferative disorder. **Conclusions.** Our findings indicate that MPA monotherapy may be a promising immunosuppression minimization strategy for HLA-matched KTR.

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It is known that HLA-matched kidney grafts have significantly better graft and patient survival when compared with HLA-mismatched grafts.[1–5] This lower immunogenic risk also manifests through a reduced immunosuppressive requirement of these patients.[6,7] The need for some level of immunosuppression in transplant patients is almost universal, but it does not come without cost to the patient. There is a significant risk of infection and adverse effects in patients taking immunosuppressive medications. Ensuring that patients receive the most appropriate amount of immunosuppression is important to prevent complications and maximize benefits.

Literature is sparse describing immunosuppressive minimization in low-risk patients such as HLA-matched recipients. A 1999 study by Bartucci et al[8] described azathioprine monotherapy in 12 HLA-matched live donor kidney transplant recipients (KTR) who showed improvements in metabolic outcomes such as systolic blood pressure and cholesterol without sacrificing graft outcomes.[8] A 10-year follow-up study by Thierry et al[9] reviewing the use of calcineurin inhibitors (CNI) in KTR concluded that minimization of maintenance immunosuppression in selected low-risk patients was safe and maintained good graft and patient outcomes. Finally, Hurault de Ligny et al[10] described a retrospective analysis of healthy, well-matched Caucasian KTR and found that KTR with low immunologic risk and stable graft function may benefit from transition to a CNI-based monotherapy regimen.

Overall, there are little data describing immunosuppressive monotherapy in HLA-matched KTR, and the ideal minimizing strategy for maintenance immunosuppression is unknown.

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[1] Department of Pharmacy, UW Health, Madison, WI.

[2] Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI.

[3] Division of Nephrology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI.

[4] Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI.

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Correspondence: Anthony J. Hennes, PharmD, BCPS, Department of Pharmacy, UW Health, 715-630-9455 600 Highland Ave, Madison, WI. 53729. (ahennes@uwhealth.org).

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It is important to explore these data to better understand the immunosuppressive needs of these patients. We hypothesized that mycophenolate (MPA) monotherapy is a safe and effective approach for maintenance therapy in HLA-matched KTR.

MATERIALS AND METHODS

Study Population and Design

The Wisconsin Allograft Recipient Database was initiated in 1984 to collect information on all solid organ transplants performed at the University of Wisconsin. All patients who received a primary kidney transplant at the University of Wisconsin between January 1, 1994, and June 30, 2013, and were at least 18 years of age at the time of transplantation were eligible for inclusion in this study. Patients had follow-up through 2014. This study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin.

A total of 278 HLA-matched transplants were performed from 1994 to 2013. Of these, 25 recipients received MPA monotherapy at any point during their post-transplant follow-up. The decision for MPA monotherapy was based on clinical variables: infection, cancer, CNI side effects, or immunosuppression minimization strategies. For patients with infections, malignancy, or CNI toxicity, CNI therapy was discontinued immediately and never resumed. For patients undergoing immunosuppression minimization strategies, CNI dose was reduced by 50% for 1 month and then discontinued altogether.

All 25 patients received a kidney from a living donor. Of these, 21 received no induction immunosuppression and 20 had sufficient follow-up to be included in the analyses. All HLA-matched recipients received organs from siblings.

Patient monitoring occurred based on institutional protocols. Before 2009, patients were monitored with monthly serum creatinine measurements and kidney biopsies as needed. After 2009, an institutional protocol was created for low-, moderate-, and high-risk patients which includes donor-specific antibody (DSA) monitoring for low-risk patients at 6 months, 12 months, and annually thereafter.

Data collection included demographics, cause of end-stage renal disease, serum creatinine, estimated glomerular filtration rate at 12 months post-transplant, and immunosuppressive regimens before conversion. We were unable to determine pretransplant DSA in a large cohort of patients transplanted before 2003 (when we implemented routine DSA measurements at our organization). The primary outcomes of this study were incidence of graft failure, rejection, death, readmission, infection, and malignancy.

RESULTS

Baseline Characteristics

A total of 20 HLA-matched recipients receiving MPA monotherapy were included in the analyses. The baseline characteristics of the patient population are described in Table 1. Patients were exclusively Caucasian and there was a nearly even mix of male (55%, 11 of 20) and female (45%, 9 of 20) patients. There was no incidence of delayed graft function and half of the patients (50%, 10 of 20) underwent a pre-emptive transplant. Median time to MPA monotherapy from transplant was 7.9 years (range: 1.1–20.7 y). Two patients returned to CNI-based regimens secondary to recurrence of membranous nephropathy and post-transplant lymphoproliferative disorder, yielding a successful monotherapy conversion rate of 90%. MPA monotherapy dosing regimens included 500 mg BID (10%, 2 of 20), 750 mg BID (10%, 2 of 20), 720 mg BID (55%, 11 of 20), and 1000 mg BID (25%, 5 of 20).

TABLE 1.
Patient characteristics

	MPA monotherapy (n = 20)
Mean age at time of transplant (y)	44.1 (9.2)
Nonwhite (%)	0
Female (%)	9 (45.0)
Expanded criteria donor (%)	0
Etiology of end-stage renal disease (%)	
Hypertension	1 (5.0)
Polycystic kidney disease	3 (15.0)
Glomerular nephropathy	10 (50.0)
Other	6 (30.0)
Body mass index (kg/m^2)	26.2 (2.7)
Living donor (%)	20
Pre-emptive transplant (%)	10 (50.0)
Delayed graft function (%)	0
Peak panel reactive antibody (%)	1.7 (4.1)
Duration of hemodialysis pretransplant (mo)	6.8 (12)
Time to mycophenolate monotherapy (y)	7.9 (3.8)
Maintenance immunosuppression before conversion (%)	
Cyclosporine, mycophenolate	11 (55.0)
Tacrolimus, mycophenolate	5 (25.0)
Prednisone, mycophenolate	1 (5.0)
Sirolimus, mycophenolate	1 (5.0)
Cyclosporine	1 (5.0)
Tacrolimus	1 (5.0)
Mycophenolate dosing after conversion (%)	
Mycophenolate mofetil 500 mg BID	2 (10.0)
Mycophenolate mofetil 750 mg BID	2 (10.0)
Mycophenolate mofetil 1000 mg BID	5 (25.0)
Mycophenolate sodium 720 mg BID	11 (55.0)

MPA, mycophenolate.

Graft Failure, Rejection, Death, Hospitalization, Infection, and Malignancy

MPA monotherapy was associated with a low incidence of death-censored graft failure (3.19/100 person-y; Figure 1), death (3.19/100 person-y), hospitalization (1.62/100 person-y; Figure 1), malignancy (3.61/100 person-y; Figure 1), or infection (1.75/100 person-y; Figure 1). The single infection event was a bacterial urinary tract infection and the 2 malignancies were of the lung and skin. Concerning graft loss 1 was related to malignancy and 1 was due to unknown causes. Of the 2 total deaths, 1 was related to malignancy and 1 was due to unknown causes. No MPA monotherapy patients experienced rejection (Table 2).

Kidney Function and Marrow Suppression

MPA monotherapy was associated with favorable kidney function at 12 months: serum creatinine of 1.29 ± 0.34 mg/dL, estimated glomerular filtration rate of 64.3 ± 22.2 mL/min/1.73 m^2, and urinary protein to creatinine ratio of 143.2 ± 53.6 mg/g. There were also encouraging findings concerning hemoglobin 13.9 g/dL ± 1.1 g/dL, platelet count 237.8 K/uL ±

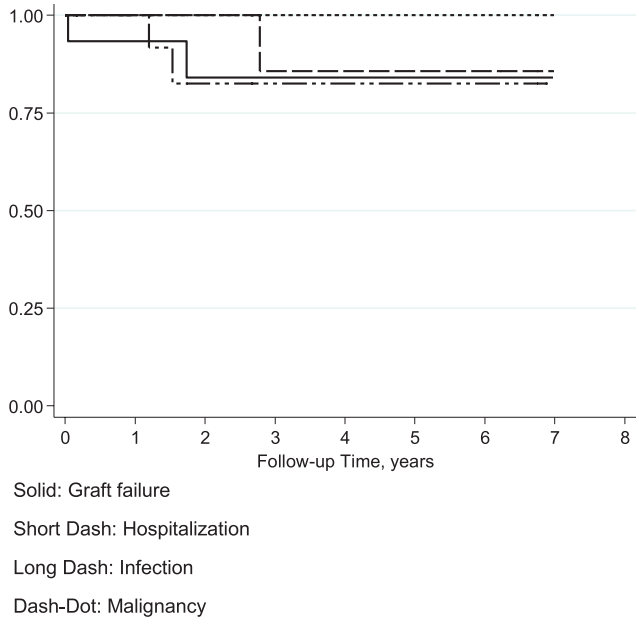

FIGURE 1. Kaplan-Meier survival curve for primary outcomes. MPA monotherapy was associated with a low incidence of death-censored graft failure (3.19 per 100 person-y), hospitalization (1.62 per 100 person-y), malignancy (3.61 per 100 person-y), and infection (1.75 per 100 person-y). Solid: graft failure; short dash: hospitalization; long dash: infection; dash-dot: malignancy. MPA, mycophenolate.

70.6 K/uL, and white blood cell count 9.04 K/uL ± 4.74 K/uL in MPA monotherapy patients (Table 3).

DISCUSSION

The results of our study echo those of the limited literature that describes MPA monotherapy. GascÓ et al[11] described 6 HLA-matched KTR who transitioned to MPA monotherapy with 100% graft and patient survival at last follow-up up to 121 months. This study showed similar long-term patient and graft outcomes for MPA monotherapy. Similarly, a prospective pilot study evaluated 46 stable KTR who were gradually converted to MPA monotherapy, much like our patient population.[12] The authors described successful conversion to MPA monotherapy at a rate of 83% (38 of 46) which was similar to our rate of 90% (18 of 20). The authors also reported 3 graft failures (1.28/100 person-y) in the MPA monotherapy group which was comparable to our 2 graft failures (3.19/100 person-y) reported. Finally, a 1999 prospective pilot study by Zanker et al[13] described late conversion from a CNI-based regimen to a MPA monotherapy regimen in KTR. Again, a conversion rate of 93% was seen in the MPA monotherapy group. The authors concluded that MPA-based immunosuppression can be used safely in these patients and can help spare renal toxicity associated with CNIs.

Before MPA monotherapy, patients were characteristically on 1 or 2 drug immunosuppressive regimens based on institutional protocols. Drug regimens before enrollment were comprised of a mixture of corticosteroids, CNIs, mammalian target of rapamycin inhibitors, and antimetabolites. Patients were converted to MPA monotherapy because of CNI toxicity (10%, 2 of 20), infection (5%, 1 of 20), malignancy (10%, 2 of 20), or immunosuppression minimization strategies (75%, 15 of 20) (Table 4). One patient experienced a urinary tract infection (2.8 y before conversion) and 1 experienced recurrence of glomerular nephropathy (6 d before conversion). Two monotherapy patients received 2 kidney biopsies each before monotherapy conversion (range: 6–2839 d before conversion).

Another important consideration with MPA monotherapy is its potential impact on cost and medication adherence. It is important to note that this study does not formally evaluate these suspected benefits. For patients with financial hardships or who lack consistent insurance coverage, immunosuppressive medications can become unaffordable. An article published by James and Mannon[14] estimated that maintenance immunosuppression therapies can cost patients upwards of $2500 per month with the average annual cost of medications

TABLE 2.
Incidence of outcomes following initiation of MPA monotherapy

	MPA monotherapy (n = 20)
Total graft loss	
No. of events	2
Incidence rate (per 100 person-y)	3.19
Rejection	
No. of events	0
Incidence rate (per 100 person-y)	0
Death	
No. of events	2
Incidence rate (per 100 person-y)	3.19
Hospitalization	
No. of events	1
Incidence rate (per 100 person-y)	1.62
Malignancy	
No. of events	2
Incidence rate (per 100 person-y)	3.61
Infection	
No. of events	1
Incidence rate (per 100 person-y)	1.75

MPA, mycophenolate.

TABLE 3.
Laboratory measurements at 12 mo from date of monotherapy

	MPA monotherapy
Serum creatinine, mg/dL (n = 39)	1.29 ± 0.34
Estimated glomerular filtration rate, mL/min/1.73 m^2 (n = 39)	64.3 ± 22.2
Urinary protein:creatinine, mg/g (n = 39)	143.2 ± 53.6
Hemoglobin, g/dL (n = 117)	13.9 ± 1.1
White blood cell, K/uL (n = 113)	9.04 ± 4.74
Platelets, K/uL (n = 113)	237.8 ± 70.6

MPA, mycophenolate.

TABLE 4.
Reasons for MPA monotherapy conversion

	Minimization strategy	Infection	Malignancy	CNI toxicity
Number of patients converted	15 (75%)	1 (5%)	2 (10%)	2 (10%)

CNI, calcineurin inhibitor; MPA, mycophenolate.

being $10 000–$140 000 per patient per year.[14] MPA monotherapy would significantly reduce medication costs for patients and health systems alike making a sustainable model more attainable. It is also clear that medication nonadherence in solid organ transplantation leads to poor patient outcomes and increased cost.[15–17] One of the recommended strategies for improving medication adherence is simplifying immunosuppressive regimens.[17] A decrease in the number of medications taken, reduction of adverse effects, and simpler administration instructions are potential benefits of a more simplified medication regimen.

A final consideration is concerning the laboratory measurements 12 months after starting MPA monotherapy. Patients maintained stable kidney function and hematologic laboratory values 12 months after MPA monotherapy conversion. This is especially important to consider in a patient population which frequently suffers from hematologic toxicity due to medications and infectious complications.[18] Further, the decision for MPA monotherapy compared with an alternative monotherapy strategy such as CNI monotherapy was directly related to the known and accepted risks of these medications. CNI therapy, on average, is associated with more cardiovascular adverse effects compared with MPA therapy.[19] These findings further support the safety of MPA monotherapy in these low-risk patients.

Our study has several limitations. The small sample size and retrospective nature of this work limit the conclusions that can be made and applied across a broader patient population. Further, our study population received organs exclusively from living donors and received no induction therapies, which is not typical in solid organ transplantation. It is well established that living donor transplants have improved outcomes compared with deceased donor transplants.[20,21] Limiting our patient population to very low immunologic risk patients limits the conclusions that can be made for a wider patient population. The MPA monotherapy patients were chosen specifically by the treating nephrologist and therefore a component of selection bias must be considered. It is also unclear exactly how and why these patients were chosen for MPA monotherapy and what protocols, if any, were used to manage patients after conversion. Finally, the median time to MPA monotherapy was 7.9 years out from transplant, which limits the utility of MPA monotherapy conversion in patients who are closer to date of transplant.

MPA monotherapy may be a safe and effective immunosuppression regimen for 6-antigen HLA-matched KTR. However, further studies exploring this minimization strategy in low-risk patients may clarify the best maintenance regimen options for the HLA-matched patient population. Any effort to better understand how to safely minimize immunosuppression while optimizing patient and graft outcomes is critical to advancing the field of solid organ transplantation.

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