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Safety and Efficacy of a Preemptive Mycophenolate Mofetil Dose Reduction Strategy in Kidney Transplant Recipients

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Background. There are no high-quality data to guide long-term mycophenolate mofetil (MMF) dosing in kidney transplant recipients (KTRs) to balance the long-term risks of allograft rejection with that of infections and malignancy. At our center, KTRs are managed with either a "preemptive" dose reduction strategy, where the MMF dose is reduced after the first year before the development of adverse events, or with a "reactive" dosing strategy, where they are maintained on the same MMF dose and only reduced if they develop an adverse event. We hypothesized that a preemptive MMF dosing strategy after the first year of transplantation is associated with decreased infections without increasing alloimmune complications. **Methods.** We conducted a retrospective cohort study of all KTRs receiving MMF from January 1, 2015, to December 31, 2020. The primary outcome was the incidence of infections requiring hospitalization. **Results.** One hundred forty-two KTRs met the inclusion criteria, of whom 44 (31%) were in the preemptive group and 98 (69%) were in the reactive group. The median follow-up was 4 y (interquartile range, 3.8–4.0). Multivariable analysis showed that a preemptive MMF dose reduction strategy was associated with a lower risk of infections requiring hospitalization (adjusted hazard ratio = 0.39; 95% confidence interval, 0.16-0.92). There was no difference in graft loss, rejection, or estimated glomerular filtration rate slope. **Conclusions.** Preemptive MMF dose reduction in KTRs may be an effective strategy to prevent infections without increasing the risk of allograft rejection. Randomized clinical trials are needed to confirm these findings.

(*Transplantation Direct* 2024;10: e1697; doi: 10.1097/TXD.0000000000001697.)

Received 30 April 2024. Revision received 17 June 2024.

Accepted 3 July 2024.

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The study was supported in part by the Harold and Ellen Danser Endowed/Distinguished Chair in Transplantation at Massachusetts General Hospital (Boston, MA).

The authors declare no conflicts of interest.

K.Y., A.A., and L.V.R. conceived and designed the study. K.Y., A.A., C.E., L.M., F.E.H., R.V., and D.S.P. participated in data collection. K.Y., A.A., G.T.R., D.S.P., and L.V.R. analyzed the data. All authors contributed to writing and reviewing the article.

The data underlying this article cannot be shared publicly to protect the privacy of individuals who participated in the study. Deidentified data will be shared on reasonable request to the corresponding author.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001697

Long-term immunosuppression in kidney transplant recipients (KTRs) is associated with risks of infection and malignancy.[1] Using the minimum amount of immunosuppression needed to suppress alloimmune responses in KTRs is an attractive strategy to preserve allograft function and reduce infectious and malignant complications of immunosuppression. The combination of tacrolimus and mycophenolate mofetil (MMF), with or without steroids, is the maintenance immunosuppression regimen used in approximately 90% of adult KTRs.[2] Although studies have evaluated optimal tacrolimus trough targets to prevent alloimmune responses (eg, de novo donor-specific anti-HLA antibody [DSA] formation),[3] limited data exist on optimal MMF dosing and timing of dose reduction after transplantation to reduce posttransplant infectious and malignant complications. MMF dosing strategies remain primarily empiric, with reactive adjustments to address over or under-immunosuppression. Attempts for therapeutic drug monitoring of MMF in solid organ transplantation have been proposed but remain hindered by the pharmacokinetic profile of the drug, which is influenced by enterohepatic circulation, genetics, drug-drug interactions, albumin-bound fraction, and kidney and liver function.[4-6] Studies have proposed weight-based dosing of MMF because of more predictable pharmacodynamics, yet fixed dosing remains the adopted protocol at most transplant centers.[7,8]

This study aims to evaluate the outcomes of KTRs who, after the first year of transplant, had a preemptive decrease in MMF dosing (preemptive strategy), compared with those who

were maintained on their MMF dose and only reduced it if they ever developed complications of MMF (reactive strategy). We hypothesized that a preemptive MMF dosing strategy after the first year of transplantation is associated with decreased infections without increasing alloimmune complications.

MATERIALS AND METHODS

Study Design

This is a retrospective cohort study of all KTRs who received kidney allografts at Massachusetts General Hospital from January 1, 2015, to December 31, 2020, and were on MMF-based immunosuppression. Exclusion criteria included multiorgan transplant, history of previous solid organ or stem cell transplantation, cyclosporine use because of the inhibition of enterohepatic circulation of MMF resulting in reduced levels,[9,10] age less than 18 y at the time of transplantation, MMF dose reduction in the first year to a dose of <1500 mg/d, and being on an MMF-free regimen. KTRs were identified using the list of transplanted patients at the center and then each patient's medical record was reviewed manually to ensure the accuracy of collected data and group assignment. The standard maintenance immunosuppression protocol of our center is described in **Supplemental Methods** (**SDC,** http://links.lww.com/TXD/A695). In our study, patients received either mycophenolic acid or MMF. MMF doses are all expressed in MMF equivalents (ie, 180 mg of mycophenolic acid = 250 mg of MMF). Because there are no high-quality data to guide MMF dosing in KTRs after the first year, at our center, transplant nephrologists use 1 of 2 MMF dose reduction strategies. Some transplant nephrologists use a preemptive MMF dose reduction strategy where the MMF dose is reduced after the first year (typically by 500 mg, eg, from a total daily dose of 1500 mg to 1000 mg) to prevent long-term complications of immunosuppression. We only included MMF reductions with >2-wk duration to minimize the effects of transient dose changes. In contrast, others use a reactive MMF dose reduction where the MMF dose is maintained and only reduced in response to an adverse event (eg, infection, malignancy, leukopenia, others). This study aims to evaluate the association between the 2 MMF dosing strategies with patient and allograft outcomes after the first year of transplantation.

The primary efficacy outcome was infections requiring hospitalization, which was defined as any infection resulting in hospitalization during follow-up. Secondary efficacy outcomes included viral infections (including BKV, cytomegalovirus [CMV], and Epstein-Barr virus infections confirmed via polymerase chain reaction; urinary tract infections (UTIs) confirmed via urine cultures with bacterial or fungal growth exceeding 100 000 colony-forming units; and SARS-CoV-2 infection confirmed via nasopharyngeal polymerase chain reaction or viral antigen testing; and radiographically confirmed pneumonia) and malignancies. Safety outcomes included death, allograft loss, biopsy-proven rejection, de novo DSA development, and estimated glomerular filtration rate slope. Reports of DSA with a mean fluorescence intensity below our center's positive cutoff (≤1000) or in the setting of a high nonspecific background signal deemed to be not clinically significant were considered negative for DSA. The study was approved by the Mass General Brigham institutional review board (protocol No.: 2019P002526). Data are reported in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Statistical Analysis

Differences between continuous variables in the 2 groups were assessed using an unpaired *t* test (normal distribution) or a Wilcoxon rank-sum test (nonnormal distribution). Differences between categorical variables were assessed using a chi-square test or Fisher exact test, as appropriate. The incidence of outcomes was estimated using Kaplan-Meier analysis, and differences were assessed using the log-rank test. Our initial follow-up duration was set to 5 y posttransplantation. However, because of high attrition rates after 4 y of follow-up, individuals were censored either at their last follow-up or at 4 y, whichever occurred earlier. Cox regression was used to assess associations between potential risk factors and outcomes for analyses where the proportional hazards assumption was met. Multivariable Cox regression was then used to adjust for possible confounding variables. The number of categorical variables included in the multivariable model was limited to prevent model overfitting. Induction immunosuppression was not included in the multivariable model as the model then did not meet the proportional hazards assumption. For all survival and Cox regression analyses, events occurring in the MMF reduction group were included whether or not they preceded MMF reduction to (1) reduce the risk of immortal time bias[11] and (2) to not bias our findings as we expected some reduction events in the reactive group to be in response to infections. Prism version 9.5.1 and SPSS version 24 were used for figure creation and statistical analysis, respectively.

RESULTS

Patient Characteristics

We screened all KTRs at our center between January 1, 2015, and December 31, 2020 (n = 821). One hundred forty-two KTRs met the inclusion criteria for the study (Table 1; **Figure S1, SDC,** http://links.lww.com/TXD/A695). The median age was 50.5 y (interquartile range [IQR], 38.3–61.0), 35.2% were women, and glomerular diseases were the most common cause of end-stage kidney disease. Living donor transplants were received by 46.5% of patients, the median number of HLA-ABDR antigen mismatches was 4 (IQR, 3–5), and pretransplant DSAs developed in 4.2% of patients. For induction immunosuppression, 121 (85.2%) received antithymocyte globulin, 18 (12.7%) received only basiliximab, and 3 (2.1%) received no antibody induction. For maintenance immunosuppression, 119 (83.8%) received tacrolimus, 23 (16.2%) received belatacept, and 112 (78.9%) received prednisone. The remaining baseline characteristics of the study cohort are shown in **Table S1** (**SDC,** http://links.lww.com/TXD/A695. Tacrolimus trough level means and coefficients of variation are shown in **Table S2** (**SDC,** http://links.lww.com/TXD/A695. At 1 y posttransplant, 18 (12.7%) were on a total daily dose of 2000 mg of MMF, whereas the remaining 124 (87.3%) were on a total daily dose of 1500 mg of MMF.

The median follow-up after transplantation was 4.0 y (IQR, 3.8–4.0 y). During years 2–4 after transplantation, 33 KTRs (23.2%) developed infections requiring hospitalization (**Figure S2A, SDC,** http://links.lww.com/TXD/A695). With regards to the prespecified viral infections, 5 developed BK viremia, 1

TABLE 1.

Baseline characteristics

Characteristic	Cohort (N = 142)	Reactive strategy cohort (N = 98)	Preemptive strategy cohort (N = 44)	*P*
Age at transplantation, median (IQR)	50.5 (38.3–61.0)	48.5 (34.3–48.5)	57.0 (45.8–64.3)	0.015[a]
Female, n (%)	50 (35.2)	32 (32.7)	18 (40.9)	0.446[b]
Race, n (%)				0.496[b]
White	99 (69.7)	65 (66.3)	34 (77.3)	
Black	20 (14.1)	17 (17.3)	3 (6.8)	
Hispanic or Latino	13 (9.2)	9 (9.2)	4 (9.1)	
Asian	9 (6.3)	6 (6.1)	3 (6.8)	
Other	1 (0.7)	1 (1.0)	–	
Living donor transplant, n (%)	66 (46.5)	44 (44.9)	22 (50.0)	0.703[b]
Pretransplant DSA, n (%)	6 (4.2)	3 (3.1)	3 (6.8)	0.374[c]
PRA, median (range)	0 (0–99)	0 (0–99)	0 (0–95)	0.959[a]
HLA-ABDR mismatches, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.920[a]
Induction immunosuppression, n (%)				0.151[b]
Antithymocyte globulin[d]	121 (85.2)	87 (88.8)	34 (77.3)	
Basiliximab	18 (12.7)	10 (10.2)	8 (18.2)	
None	3 (2.1)	1 (1.0)	2 (4.5)	
Maintenance immunosuppression				
MMF dose, mg, median (IQR)	1500 (1500–1500)	1500 (1500–1500)	1500 (1500–1500)	>0.999[a]
Tacrolimus, n (%)	119 (83.8)	80 (81.6)	39 (88.6)	0.295[b]
Belatacept (de novo), n (%)	7 (4.9)	3 (3.1)	4 (9.1)	0.209[c]
Belatacept (conversion), n (%)	16 (11.3)	15 (15.3)	1 (2.3)	0.023[b]
Prednisone, n (%)	112 (78.9)	75 (76.5)	37 (84.1)	0.307[a]

[a]Statistics by the Mann-Whitney *U* test.
[b]Statistics by the chi-square test.
[c]Statistics by the Fisher exact test
[d]Includes 2 individuals who received antithymocyte globulin then were switched to basiliximab.
DSA, donor-specific antibody; IQR, interquartile range; MMF, mycophenolate mofetil; PRA, panel-reactive antibody.

developed CMV viremia, and 2 developed Epstein-Barr virus viremia (**Table S3, SDC,** http://links.lww.com/TXD/A695). During follow-up, 13 KTRs (9.2%) developed 13 malignancies (**Figure S2B and Table S4, SDC,** http://links.lww.com/TXD/A695). DSAs were checked in 59 KTRs after the first year of transplantation, of whom 6 developed de novo DSAs. Death-censored graft loss developed in 4 KTRs (**Figure S2C and Table S5, SDC,** http://links.lww.com/TXD/A695) and allograft rejection occurred in 8 KTRs (**Figure S2D, SDC,** http://links.lww.com/TXD/A695). One death occurred during follow-up (**Figure S2E, SDC,** http://links.lww.com/TXD/A695).

MMF Dose Reduction

During follow-up, the MMF dose was reduced preemptively in 44 KTRs (31%) with a median time to first MMF dose reduction of 1.7 y (IQR, 1.2–2.9) after transplant. The MMF dose was reduced on average by 33% (±8.9%) from a median of 1500 mg (IQR, 1500–1500) to a median of 1000 mg (IQR, 1000–1250). Among the remaining 98 KTRs (69%) in the reactive dose reduction group, 47 KTRs (33%) were maintained on the same MMF dose until the end of follow-up, whereas the dose was reduced in 51 KTRs (36%) in response to infectious, malignant, or other complications (Table 2). The cumulative exposure to MMF, represented by the average dose during the study, was lower in the preemptive versus reactive dosing group, respectively (952 ± 151 versus 992 ± 219 mg). The median MMF dose at the end of the follow-up was lower in the preemptive dosing strategy group 1000 mg (IQR, 1000–1000), when compared with the reactive dosing group 1500 mg (IQR, 1000–1500). The 2 groups had similar sex distributions, race distributions, HLA-ABDR antigen mismatches, the proportion of individuals with pretransplant DSAs, and induction immunosuppression regimens ($P > 0.05$ for all). The main difference between the groups was the younger age in the reactive strategy group (median age of 48.9 versus 57.5 y, a difference of –8.6; 95% confidence interval [CI], –12.0 to –1.5; $P = 0.015$). With regards to maintenance immunosuppression, there was no difference in the proportion of KTRs on prednisone maintenance ($P = 0.307$) or belatacept versus tacrolimus maintenance ($P = 0.295$). However, a higher proportion of KTRs in the reactive group had belatacept conversion ($P = 0.023$) than de novo belatacept.

TABLE 2.

Reasons for first mycophenolate mofetil dose change in the reactive strategy cohort

Reason for dose change	Reactive strategy cohort (N = 98), n (%)
Other infections (nonviral)	15 (15.3)
SARS-CoV-2 infection	8 (8.2)
GI side effects	6 (6.1)
Cytopenia	4 (4.0)
BK polyomavirus infection	4 (4.0)
Cytomegalovirus infection	3 (3.0)
Other	4 (4.0)
Epstein-Barr virus infection	2 (2.0)
Malignancy	1 (1.0)
Multiple reasons	1 (1.0)

GI, gastrointestinal.

Infectious Complications

To evaluate the association between MMF dosing strategies and infections, we compared the incidence of (1) respiratory infections (ie, pneumonia, SARS-CoV-2), (2) UTIs, and (3) infections requiring hospitalization in KTRs managed with preemptive versus reactive MMF dose reduction strategies.

We found a lower incidence of respiratory infections in KTRs managed with a preemptive compared with a reactive MMF dose reduction strategy (Figure 1A; log-rank $P = 0.006$). Univariable analysis showed that a preemptive MMF reduction strategy (unadjusted hazard ratio [HR] = 0.34; 95% CI, 0.15-0.76; $P = 0.008$) and a higher absolute lymphocyte count (ALC; unadjusted HR = 0.50 per additional 1000 cells/μL; 95% CI, 0.28-0.92; $P = 0.024$) were associated with a lower risk of respiratory infections (Figure 1B). Multivariable analysis showed that a preemptive MMF reduction strategy (adjusted HR = 0.21; 95% CI, 0.09-0.49; $P < 0.001$) and a higher ALC (adjusted HR = 0.49 per additional 1000 cells/μL; 95% CI, 0.25-0.93; $P = 0.028$) were associated with a lower risk of respiratory infections, whereas prednisone maintenance was associated with a higher risk of respiratory infections (adjusted HR = 2.36; 95% CI, 1.01-5.49; $P = 0.046$; Figure 1C).

Next, we evaluated UTIs and found no difference in the incidence of UTIs between KTRs managed with a preemptive compared with a reactive MMF dose reduction strategy (Figure 2A; log-rank $P = 0.986$). Univariable analysis showed that older age at transplantation (unadjusted HR = 1.39 per 10-y increase, 95% CI: 1.09-2.29, $P = 0.016$), a higher MMF dose at 12 mo (unadjusted HR = 1.85 per 250 mg increase; 95% CI, 1.10-3.10; $P = 0.020$), and a higher weight-adjusted MMF dose (unadjusted HR = 1.12 per 1 mg/kg increase; 95% CI, 1.02-1.21; $P = 0.012$) were associated with a higher risk of UTIs (Figure 2B). Multivariable analysis was not performed because of the limited number of events.

When evaluating infections requiring hospitalization, there was no significant difference in their incidence between KTRs who had MMF dose reduction preemptively compared with those who did not (Figure 3A; log-rank $P = 0.344$). Univariable analysis (Figure 3B) showed no association between preemptive MMF dose reduction and the risk of developing infections requiring hospitalization (unadjusted HR = 0.68; 95% CI, 0.30-1.52; $P = 0.347$). Older age at transplantation (unadjusted HR = 1.39 per 10-y increase; 95% CI, 1.06-1.82; $P = 0.016$) and higher MMF doses at 12 mo (unadjusted HR = 1.68 per 250 mg increase; 95% CI, 1.13-2.52; $P = 0.011$) were associated with a higher risk of developing infections requiring hospitalization. To control for potential confounding variables, a multivariable model was created (Figure 3C), which showed that preemptive MMF dose reduction was associated with a lower risk of developing infections requiring hospitalization (adjusted HR = 0.39; 95% CI, 0.16-0.92; $P = 0.032$). Older age at transplantation (adjusted HR = 1.56 per 10-y increase; 95% CI, 1.16-2.14; $P = 0.004$), higher MMF dose at 12 mo (adjusted HR = 2.07 per 250 mg increase; 95% CI, 1.35-3.16; $P = 0.001$), and lower ALC at 12 mo (adjusted HR = 0.52 per 1000 additional cells/μL; 95% CI, 0.27-0.99; $P = 0.049$) were also associated with a higher risk developing infections requiring hospitalization in the multivariable model.

Malignant and Alloimmune Complications

There was no difference in the incidence of malignancies in the preemptive versus reactive MMF reduction strategies (Figure 4A; log-rank $P = 0.678$; **Table S4, SDC,** http://links.

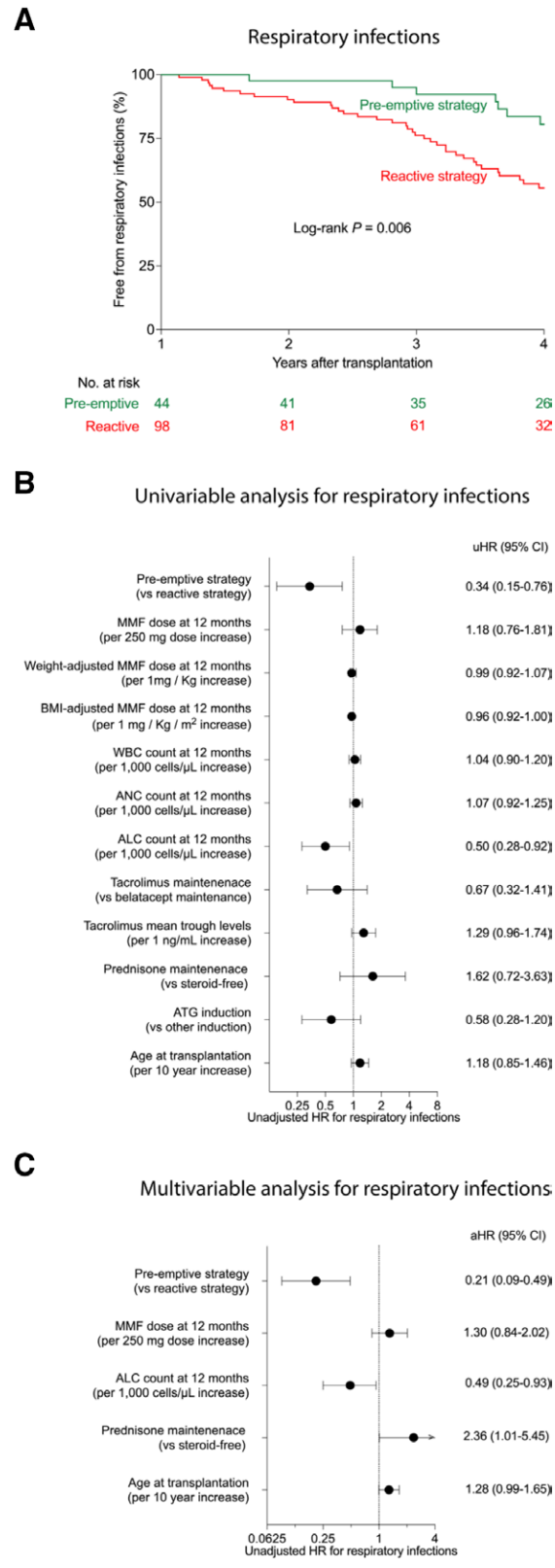

FIGURE 1. Respiratory infections in kidney transplant recipients analyzed by MMF dosing strategy. Kaplan-Meier survival curves (A), univariable Cox regression (B), and multivariable Cox regression (C) of the incidence of respiratory infections in kidney transplant recipients managed by a preemptive or reactive MMF dose reduction strategy (n = 142 for all). Statistics by log-rank test (A), univariable Cox regression (B), and multivariable Cox regression (C). aHR, adjusted hazard ratio; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; ATG, antithymocyte globulin; BMI, body mass index; CI, confidence interval; MMF, mycophenolate mofetil; uHR, unadjusted HR; WBC, white blood cell.

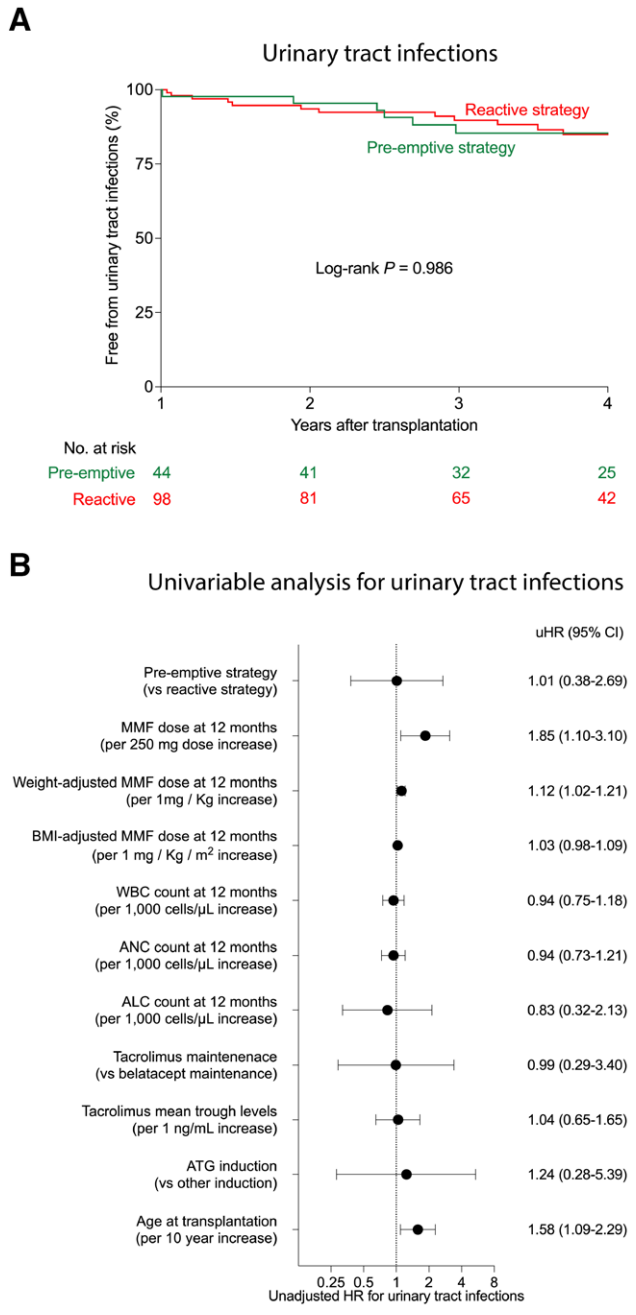

FIGURE 2. Urinary tract infections in kidney transplant recipients analyzed by MMF dosing strategy. Kaplan-Meier survival curves (A) and univariable Cox regression (B) of the incidence of urinary tract infections in kidney transplant recipients managed by a preemptive or reactive MMF dose reduction strategy (n = 142 for all). Statistics by log-rank test (A) and univariable Cox regression (B). ALC, absolute lymphocyte count; ANC, absolute neutrophil count; ATG, antithymocyte globulin; BMI, body mass index; CI, confidence interval; MMF, mycophenolate mofetil; uHR, unadjusted hazard ratio; WBC, white blood cell.

lww.com/TXD/A695). There was no difference in the incidence of death-censored graft loss or rejection between the preemptive versus reactive MMF reduction groups (Figure 4B and C; log-rank $P > 0.05$ for all; **Table S5, SDC,** http://links.lww.com/TXD/A695). There was also no difference in estimated glomerular filtration rate slope during follow-up between the 2 groups ($P = 0.189$; **Figure S3, SDC,** http://links.lww.com/TXD/A695). In the 6 KTRs with pretransplant DSA, none developed allograft rejection or loss during follow-up.

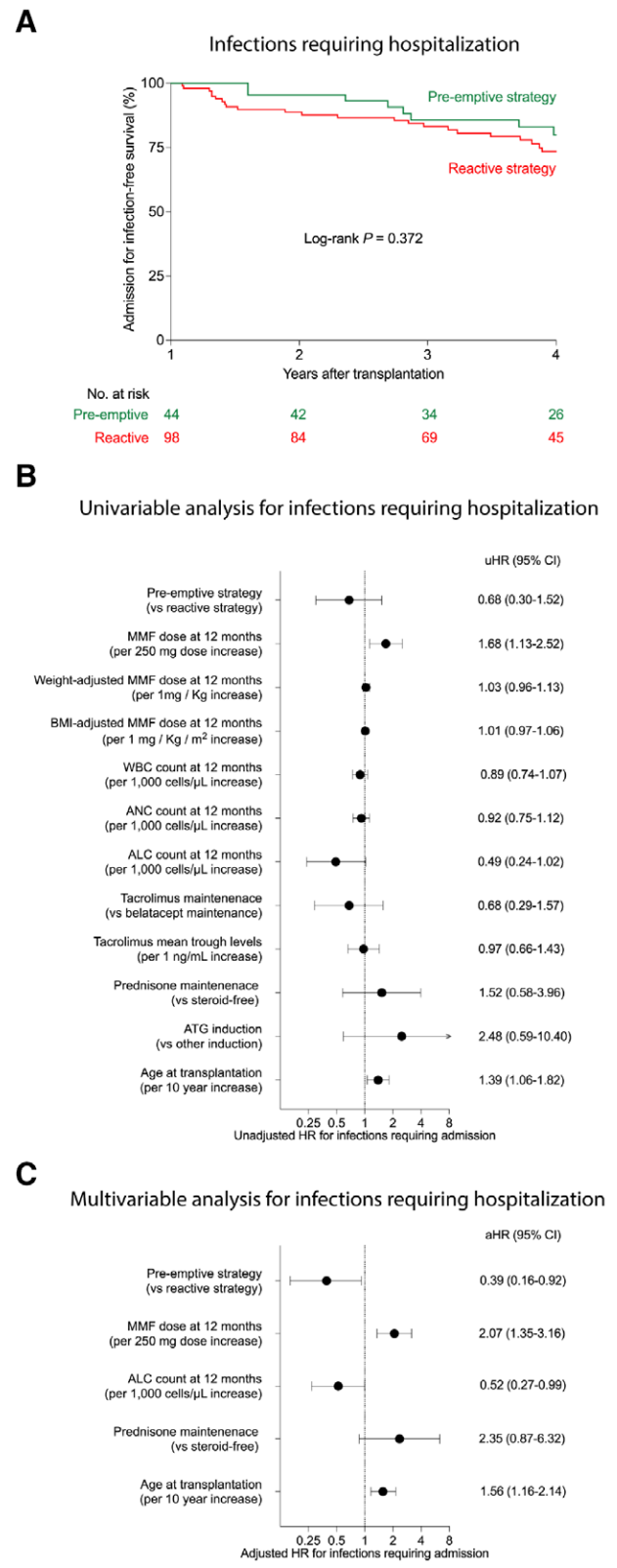

FIGURE 3. Infections requiring hospitalization in kidney transplant recipients analyzed by MMF dosing strategy. Kaplan-Meier survival curves (A), univariable Cox regression (B), and multivariable Cox regression (C) of the incidence of infections requiring hospitalization in kidney transplant recipients managed by a preemptive or reactive MMF dose reduction strategy (n = 142 for all) Statistics by log-rank test (A), univariable Cox regression (B), and multivariable Cox regression (C). aHR, adjusted hazard ratio; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; ATG, antithymocyte globulin; BMI, body mass index; MMF, mycophenolate mofetil; uHR, unadjusted HR; WBC, white blood cell.

FIGURE 4. Malignant and alloimmune outcomes in kidney transplant recipients managed by a preemptive or reactive mycophenolate mofetil dose reduction strategy. Kaplan-Meier survival curves for malignancy (A), death-censored graft survival (B), and allograft rejection (C) in kidney transplant recipients managed by a preemptive or reactive mycophenolate mofetil dose reduction strategy (n = 142 for all). Statistics by the log-rank test.

After the first year of transplantation, 6 KTRs developed de novo DSA (5 KTRs in the reactive versus 1 KTR in the preemptive MMF reduction group).

DISCUSSION

We hypothesized that a preemptive MMF dosing strategy after the first year of kidney transplantation is associated with a decrease in infections and no significant increase in allograft rejection or graft failure. To the best of our knowledge, this is the first study to investigate the safety and efficacy of a preemptive versus reactive MMF dose reduction strategy in KTRs. We found that after the first year after kidney transplantation, a preemptive MMF dose reduction strategy, compared with a reactive dose reduction strategy, was associated with a lower risk of developing both respiratory infections, specifically pneumonia and SARS-CoV-2, and infections requiring hospitalizations. There was no difference in the incidence of malignancy, allograft rejection, or death-censored graft loss. These findings suggest that a preemptive MMF dose reduction strategy in KTRs on contemporary immunosuppressive regimens may be safe from an alloimmune standpoint and beneficial with regard to preventing infectious complications of immunosuppression. These findings require confirmation in a randomized clinical trial.

Most published studies on MMF dosing and infectious outcomes did not investigate either the rationale or timing of MMF dose reduction or solely considered the initial posttransplantation MMF dose. The heterogeneity of these studies has led to conflicting results and makes them difficult to compare to our study. For example, a retrospective study evaluating the first year posttransplantation showed that a lower initial posttransplant dose of MMF (1.5 versus 2 g/d) was associated with similar rates of admissions for infection at 12 mo. However, both cohorts had a similar MMF dose at 12 mo (1.5 g/d), decreasing the exposure time to a higher MMF dose in the higher MMF dose group. With regards to viral infection, the same study found that the initial MMF dose was associated with lower rates of BK viremia but similar rates of BK nephropathy and CMV viremia at 12 mo.[12] In our study, the number of viral infections was too low to evaluate for differences in their incidence by MMF dosing strategy. The differences in findings regarding MMF dosing and the incidence of infectious outcomes between our study and others may be because of differences in (1) MMF dosing protocols, (2) timing of MMF dose reduction, (3) duration of follow-up, and (4) cohort characteristics influencing the risk of infection (eg, age, induction immunosuppression protocols). Similar to our findings, that study showed that the total white blood cell count was not associated with an increased risk of infections. However, we found that a lower ALC at 12 mo was associated with a higher risk of infections requiring hospitalization during years 2–4 posttransplant. Therefore, the ALC may be a better marker of the future risk of infection in KTRs on MMF-based immunosuppression compared with total white blood cell count. In the future, MMF dose reduction could potentially be guided by other biomarkers or patient characteristics. For example, MMF dose reduction might be informed by the degree of HLA mismatching as has been previously described for calcineurin inhibitors.[13] Similarly, older recipients may benefit more from a preemptive dose reduction

strategy relative to younger recipients because of a lower overall risk for rejection likely because of immunosenesence.[14]

In our study, the rates of incident malignancy were similar between the preemptive and reactive MMF dosing strategy groups. Nonmelanoma skin cancers were the most frequently diagnosed, as previously described posttransplantation.[15-17] However, the total number of cancer events was overall low. This is most likely multifactorial. First, we only considered histologically confirmed cancer diagnoses in our electronic health record, leading to possible missed diagnoses, especially if KTRs received care outside our institution. Second, the relatively short duration of follow-up of 4 y was shorter than the time to diagnosis of both posttransplantation skin cancers (median 4.9–6.0 y)[2,16] and non–skin cancers (mean 4.2–15.2 y).[18] Third, our study lacked the statistical power to detect the previously described increased incidence of cancer with higher doses of MMF.[1]

In our study, a preemptive, as opposed to a reactive, MMF dose reduction strategy was associated with a similar risk of rejection and allograft loss. Our findings are consistent with that from another study in which a reduction of <50% in MMF dosing was not associated with an increased risk of allograft rejection.[19] An important caveat is that KTRs in our cohort only had for-indication biopsies and only 42% had anti-HLA antibody testing after the first year of transplantation; therefore, subclinical rejection could have been missed. An important confounder in our study is that 55% of KTRs (54/98) in the reactive MMF dosing group went on to have a reduction in MMF dosing by the end of the study. Consequently, the reduced MMF exposure potentially reduced differences in cumulative MMF exposure[20] and duration of exposure to lower doses of MMF,[21] both of which have been associated with increased allograft rejection. However, because of the small number of events, we were unable to perform subgroup analyses comparing individuals who never reduced their MMF dose to other subgroups.

The limitations of our study include (1) its retrospective observational study design, which only allows for associations between exposure and outcome variables to be made and is susceptible to confounding; (2) the inherent bias in the nonrandomized, physician-driven, MMF dosing strategy where KTRs at high risk of adverse events related to immunosuppression may have been overly represented in the preemptive dose reduction group; (3) the small sample size and moderate duration follow-up, which may have underpowered our study to find differences in certain long-term outcomes such as malignancy and did not allow us to perform certain subgroup and multivariable analyses; (4) anti-HLA antibodies were not checked in all participants and, therefore, de novo DSA development could have been missed in some individuals; and (5) the underrepresentation and exclusion of certain groups, such as KTRs with pretransplant DSA and multiorgan transplant recipients, respectively, to whom our findings cannot be extrapolated. Furthermore, our study excluded KTRs with MMF dose reductions in the first year posttransplantation, limiting the applicability of our findings to all KTRs. However, we hypothesize that KTRs requiring MMF dose reduction, because of adverse events, during the first year posttransplantion when the risk of rejection is the highest represent a distinct, high-risk population that warrants further future investigations.

In summary, we found that a preemptive MMF dose reduction strategy after the first year in KTRs on MMF-based immunosuppression was associated with a lower risk of respiratory infections and infections requiring hospitalization and with similar malignancy and allograft outcomes. A randomized controlled trial is needed to validate these findings and provide insight into long-term outcomes for different MMF dosing strategies. Prospective studies are also needed to find biomarkers to help guide which KTRs are likely to benefit versus not from MMF dose reduction.

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