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RESEARCH ARTICLE

Tolerability of mycophenolate sodium in renal transplant recipients

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Abstract

Background Kidney transplant recipients (KTR) receive fixed daily doses of mycophenolate sodium as part of the immunosuppressive regimen. Dose reductions occur primarily due to adverse events and may be associated with an increased risk of acute rejection and graft loss. *Objectives* To evaluate the tolerability of mycophenolate in kidney transplant recipients receiving tacrolimus and prednisone. *Setting* The study was performed at Hospital do Rim, Federal University of São Paulo in Brazil. *Method* This was a retrospective cohort study including 506 patients. Tolerability of mycophenolate sodium was classified into the following groups: Temporary reduction (TR), definitive reduction (DR), temporary interruption (TI), permanent discontinuation (PD) and without modification (WM). *Main outcome measure* The cause of mycophenolate dose change and its influence on rejection-free survival during the first 3 years after transplantation. *Results* The cumulative incidence of dose change was 51.2% (11%TR, 44%DR, 24%TI, and 21%PD). Gastrointestinal (45.3%), infection (31.9%) and hematological (14.9%) systems accounted for most of the dose changes. The adverse events with higher incidence were diarrhea, cytomegalovirus (CMV) infection and leukopenia. Changes in dose of mycophenole were associated with reduced acute rejection-free survival compared with patients WM group (71.4%TR, 58.9%DR, 56.7%TI, 53.7%PD vs. 74.2%WM, $p=0.020$). Only patients with PD showed inferior patient (59.3% vs. 94.4%, $p=0.001$) and death-censored graft (83.3% vs. 92.5%, $p=0.074$) survivals compared to patients WM. *Conclusion* In this cohort, changes in the dose of mycophenolate were associated with increased risk of acute rejection and permanent discontinuation was associated with inferior patient and graft survival.

Keywords Adverse drug reaction · Graft survival · Immunosuppression · Kidney Transplant · Mycophenolate sodium · Tolerability

Abbreviations

AUC-MPA	Area under the curve of mycophenolic acid
BPAR	Biopsy-proven acute rejection
CMV	Cytomegalovirus
CTCAE	Common terminology criteria for adverse events
DGF	Delayed graft function
DNA	Deoxyribonucleic acid
DR	Definitive reduction
IMPDH	Inosine monophosphate dehydrogenase
MMF	Mycophenolate mofetil
MPA	Mycophenolate acid
MPS	Mycophenolate sodium
PD	Permanent discontinuation
PRED	Prednisone
r-ATG	Rabbit anti-thymocyte globulin
RNA	Ribonucleic acid
TAC	Tacrolimus
TI	Temporary interruption
TR	Temporary reduction
WM	Without modification

Impact on practice

- Temporary or permanent discontinuation of mycophenole treatment after kidney transplant increase the chances of allograft rejection on the longer term.
- Poor tolerability to mycophenolate due to emergence of adverse events in practice may require dose reduction, temporary interruption or permanent discontinuation.

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- Patients should promptly report any mycophenolate-associated adverse reaction and health care professionals should provide close monitoring to decide on drug dose reduction or substitution to mitigate the increased risk of rejection.

Introduction

Mycophenolic acid (MPA) is a non-competitive reversible inhibitor of the inosine monophosphate dehydrogenase (IMPDH), a key rate-limiting enzyme in the de novo purine synthesis pathway. [1]. Mycophenolate mofetil (MMF; *CellCept*, Roche Pharmaceuticals, Basel, Switzerland) is a prodrug of morpholinoethyl ester that is completely converted to its MPA, the active pharmacological form, in the stomach after oral absorption [2]. Despite its high efficacy for the prevention of acute rejection, the use of MMF has been associated with an array of adverse events, mostly in gastrointestinal and hematological systems, along with higher incidence of infections [3–5]. Gastrointestinal intolerance may occur in up to 45% of patients, leading to dose reduction/interruption that has been associated with increased incidence of acute rejection and reduced graft and patient survivals [6]. Enteric-coated mycophenolate sodium (ECMPS, Myfortic®, Novartis Pharma AG; East Hanover, NJ) is a delayed-release formulation that delivers MPA in the small intestine. This sodium salt formulation was developed to mitigate the upper gastrointestinal adverse events associated with the use of MMF. In de novo kidney transplant recipients receiving cyclosporine and steroids, MPS (720 mg BID) has been shown to be therapeutically equivalent to MMF (1000 mg BID) [7–9].

Several studies have suggested that the incidence of gastrointestinal adverse events and the consequent dose reduction is lower among patients receiving MPS compared to those receiving MMF [10, 11]. While several open-label studies have reported improved gastrointestinal tolerability of MPS, evidence from blinded trials has not yet confirmed these observations, suggesting that other demographic factors may account for the conflicting results [12]. One key variable is the type of calcineurin inhibitor used in combination with MPA. Most studies have compared MMF and MPS in kidney transplant recipients treated with cyclosporine. However, it is well known that tacrolimus (TAC) is associated with a higher incidence of gastrointestinal adverse events compared to cyclosporine [13]. Furthermore, patients receiving cyclosporine show lower MPA plasma concentrations than those receiving tacrolimus due to the inhibition of the enterohepatic recirculation [14]. In a well design crossover study, MPA trough concentrations are approximately 20% higher in patients receiving tacrolimus compared to cyclosporine microemulsion [15]. Another variable is diarrhea, the most frequent gastrointestinal adverse event in patients receiving MPA [16–18]. The incidence of infectious diarrhea, the most frequent differential diagnosis, is influenced by environmental factors in endemic regions [19].

A recent large international multicenter trial determined that the use of full doses of MPA (2 g of MMF or 1.44 g of MPS) in combination with reduced doses of tacrolimus is the standard care therapy for most kidney transplant recipients [20]. Yet, this regimen was associated with the highest incidence of gastrointestinal adverse events (41%). Given this scenario, this retrospective analysis aimed to evaluate MPS tolerability in kidney transplant recipients receiving tacrolimus and the influence of dose changes on transplant outcomes.

Ethics approval

The study design was reviewed and approved by the local Ethics Committee (CEP- UNIFESP) at number 22347313.4.0000.5505.

Methods

Study design

This was a single center retrospective study that aimed to evaluate the tolerability of MPS in kidney transplant recipients receiving tacrolimus and prednisone. The study design was reviewed and approved by the local Ethics Committee.

Population

This analysis primarily included all first kidney transplant recipients between January 1st, 2007 and December 31st, 2011, who received tacrolimus, MPS, and prednisone. We excluded (1) recipients of combined pancreas or liver transplants; (2) pediatric kidney transplant recipients; (3) patients with re-transplants; (4) patients receiving antithymocyte globulin as induction therapy; (5) patients receiving azathioprine, cyclosporine, sirolimus or everolimus; (6) patients who underwent a planned conversion from MPS to another drug during the follow up period. Demographics, MPS dose changes and clinical outcomes were obtained by retrospective and adjudicated review of patient's chart during a follow up of 3 years after the transplant.

Immunosuppression

All patients received a 1 g dose of methylprednisolone before graft reperfusion. Patients also received basiliximab induction (20 mg on days 0 and 4), depending on the perceived immunological risk. Recipients of kidneys recovered from living donors or standard deceased donors received an initial 0.1 mg/kg tacrolimus dose twice daily. This dose was adjusted to maintain trough whole blood concentrations between 3 and 8 ng/mL. Recipients of kidneys recovered from expanded-criteria deceased donors received an initial 0.05 mg/kg tacrolimus dose twice daily, adjusted to maintain trough whole blood concentrations between 3 and 5 ng/mL. All patients received fixed 720-mg doses of MPS twice daily that were reduced only due to the emergence of an adverse event. All patients also received 0.5 mg/kg of prednisone (maximum of 30 mg) tapered to 5 mg/day by day 45. All drugs were administered within 24 h of graft revascularization.

Prophylaxis

All patients received albendazole as prophylaxis against parasitic infections and sulfamethoxazole-trimethoprim for prophylaxis against urinary tract infection and *Pneumocystis jiroveci* pneumonia for at least 6 months. No pharmacological prophylaxis against cytomegalovirus infection was administered. Instead, pre-emptive therapy was used to monitor viral replication using pp65 antigenemia test.

Endpoints

The primary endpoint of this analysis was MPS tolerability. Secondary endpoints included the incidence of acute rejection episodes, patient and death-censored graft survivals.

Definitions of MPS tolerability

All MPS dose changes associated with adverse events during the follow up period were recorded. As multiple MPS dose changes may occur after transplantation, we defined 5 mutually exclusive categories based on the dose change observed over the period of observation: (1) temporary reduction (TR), defined as temporary reduction of the initial dose, regardless of its duration but without interruption until return to full initial dose; (2) definitive reduction (DR), defined as a definitive reduction of the initial dose without any interruption; (3) temporary interruption (TI), defined as a temporary interruption of the initial dose, regardless of its duration or previous dose reduction, until return to full initial dose; (4) permanent discontinuation (PD), defined as

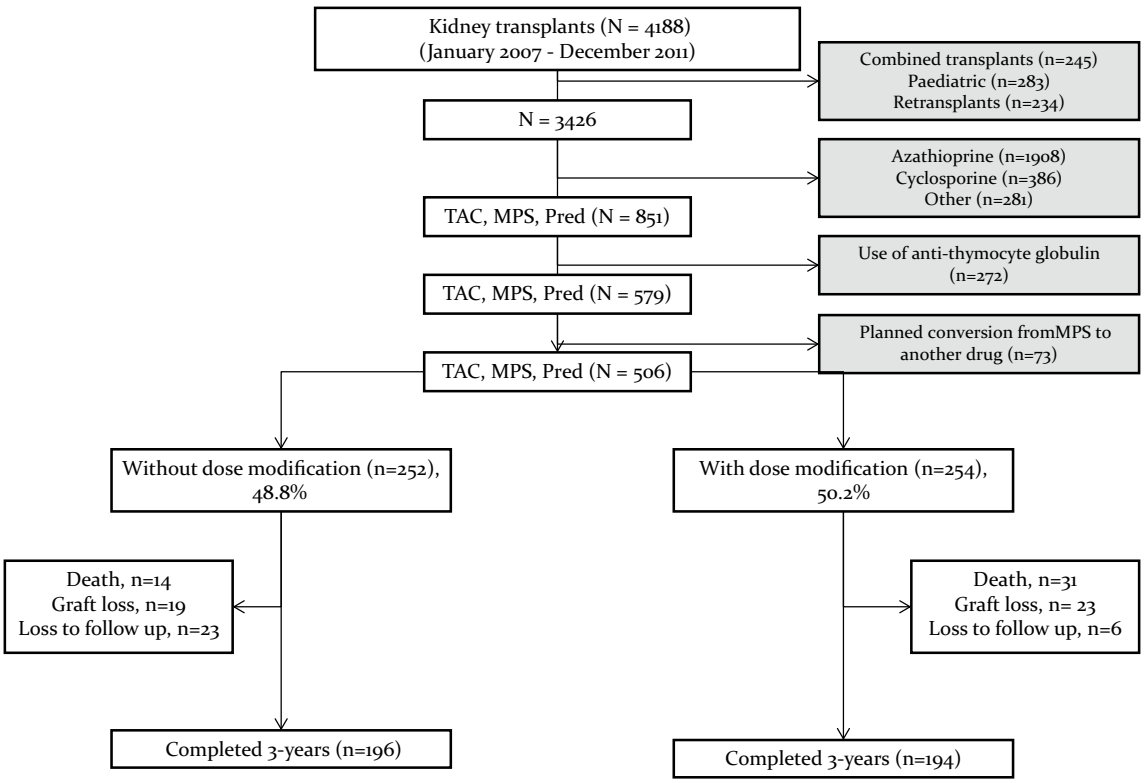

Fig. 1 Patient disposition. *TAC* tacrolimus, *Pred* prednisone, *MPS* mycophenolate sodium

permanent drug withdrawal, regardless of duration of previous dose reduction, with or without replacement by another immunosuppressive drug; (5) without modification (WM), defined as no changes in the initial dose up to 36 months after transplantation.

Treatment discontinuation has been defined as the permanent discontinuation of any immunosuppressive drug that was originally proposed or its replacement with another drug. All adverse events leading to MPS dose changes were categorized and classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [21].

Clinical outcomes

All episodes of graft dysfunction, defined by a 20–30% increase in serum creatinine, were thoroughly investigated. After ruling out infections, obstruction, and renal flow impairment, all patients underwent a core needle biopsy, unless clinically contraindicated. All biopsy proven acute rejection episodes (BPAR) were classified according to the Banff 2007 scheme and treated accordingly based on the severity scores with corticosteroids of polyclonal antibodies. Clinical acute rejection was defined as an episode of graft dysfunction, with a biopsy showing no signs of rejection or without a biopsy, successfully treated with corticosteroids. All causes and timing of death and graft loss were recorded

Table 1 Demographic characteristics of the transplant recipients

Variables	With modification (n = 254)	Without modification (n = 252)	
Recipient age, years (mean ± SD)	48.5 ± 12.1	45.8 ± 12.8	$p = 0.188$
Recipient sex, male, N(%)	156 (61.4)	155 (61.5)	$p = 0.983$
Recipient ethnicity, N(%)			$p = 0.574$
White	128 (50.4)	140 (55.5)	
Black	36 (14.2)	33 (13.1)	
Mixed	79 (31.1)	66 (26.2)	
Others	11 (4.3)	13 (5.2)	
Recipient weight, kg (mean ± SD)	65.1 ± 14.6	69.6 ± 14.3	$p = 0.747$
Chronic kidney disease, N(%)			$p < 0.0001$
Undetermined	88 (34.7)	99 (39.3)	
Diabetes Mellitus	58 (22.8)	34 (13.5)	
Glomerulonephritis	34 (13.4)	36 (14.3)	
Hypertension	12 (4.7)	0 (0)	
Other	62 (24.4)	83 (32.9)	
Time on dialysis, months (mean ± SD)	53.0 ± 45.4	39.7 ± 35.0	$p = 0.002$
Type of treatment, N(%)			$p = 0.289$
Hemodialysis	227 (89.4)	213 (84.6)	
Peritoneal	18 (7.1)	21 (8.3)	
Conservative	9 (3.5)	18 (7.1)	
PRA Class I ≤ 50%, N(%)	244 (96.1)	246 (97.6)	$p = 0.317$
PRA Class II ≤ 50%, N(%)	242 (95.3)	247 (98.0)	$p = 0.087$
HLA mismatches (mean ± SD)	2.65 ± 1.3	2.6 ± 1.4	$p = 0.114$
Recipient CMV IgG positive, N(%)	240 (94.5)	241 (95.6)	$p = 0.552$
Donor age, years (mean ± SD)	49.6 ± 12.5	47.7 ± 12.8	$p = 0.402$
Donor gender, male, N(%)	120 (47.2)	128 (50.8)	$p = 0.425$
Donor type, N(%)			$p < 0.0001$
Living	47 (18.5)	102 (40.5)	
Deceased standard criteria, N(%)	108 (42.5)	80 (31.7)	
Deceased expanded criteria, N(%)	99 (39.0)	70 (27.8)	$p = 0.829$
Cold ischemia time, hours (mean ± SD)	25.3 ± 6.3	25.5 ± 6.0	$p = 0.634$
Basiliximab induction, N(%)	173 (68.1)	124 (49.2)	$p < 0.0001$
Delayed deceased graft function, N(%)	135 (65.2)	73 (48.6)	$p = 0.002$

CMV cytomegalovirus, *PRA* panel reactive antibodies, *HLA* human leukocyte antigens, *SD* standard deviation

and cumulative patient and death-censored graft survival analyzed according to MPS tolerability group.

Statistical analysis

Continuous variables are presented as mean and standard deviations. The difference between MPS dose modification groups was identified using the independent student *t* test between two groups and analysis of variance (ANOVA) for more than two groups. Categorical variables were expressed as frequencies and percentages, while the differences between them were identified using the Chi square test. Survival curves were obtained using the Kaplan–Meier method and the log-rank test was used to identify statistical differences between groups. Statistical analysis was performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Logistic regression analysis was performed using the absolute value of continuous variables. The statistical difference was defined as $p < 0.05$.

Results

Population

Of 4188 kidney transplants performed between January 1st, 2007 and December 31st, 2011, 506 patients were included in this retrospective analysis (Fig. 1). The overall prevalence of MPS dose reduction/interruption was 50.2%. Patients requiring MPS dose reduction/interruption due to adverse events had a higher prevalence of chronic kidney disease

Table 2 System organ classes according to CTCAE associated with MPS dose modification

System organ class	Temporary reduction n = 28 (11%)	Definitive reduction n = 112 (44%)†	Temporary interruption n = 60 (24%)	Permanent discontinuation n = 54 (21%)	Total (n = 254)
Gastrointestinal	14 (50.0)	53 (47.3)	28 (46.8)	20 (37.0)	115 (45.3)
Infection and infestations	9 (32.1)	24 (21.5)	26 (43.4)	22 (40.9)	81 (31.9)
Hematological	3 (10.7)	24 (21.4)	5 (8.3)	6 (11.1)	38 (14.9)
Investigation	2 (7.1)	10 (8.9)	0 (0)	3 (5.5)	15 (5.9)
Metabolism and nutrition	0 (0)	1 (0.9)	1 (1.7)	0 (0)	2 (0.8)
Neoplasm	0 (0)	0 (0)	0 (0)	2 (3.7)	2 (0.8)
Nervous system	0 (0)	0 (0)	0 (0)	1 (1.9)	1 (0.4)

CTCAE common terminology criteria for adverse events, *MPS* mycophenolate sodium

† Chi square test, $p = 0.003$

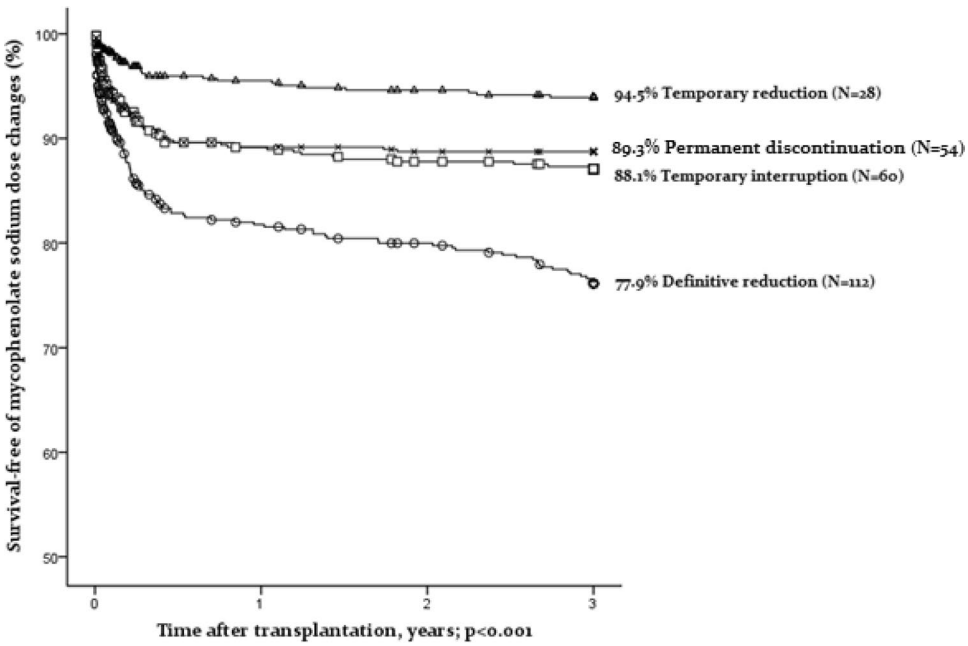

Fig. 2 Survival-free of mycophenolate sodium dose changes during the first 3 years after kidney transplantation

due to diabetes mellitus, a longer time on dialysis, a higher prevalence of transplants with deceased donor kidneys, were more likely to receive basiliximab induction, and showed a higher incidence of delayed graft function (Table 1).

MPS Tolerability

Among patients with MPS dose changes, 11% were TR (n = 28), 44% were DR (n = 112), 24% were TI (n = 60), and 21% were PD (n = 54) (Table 2). The cumulative survival free of MPS dose changes by category is shown in Fig. 2. Overall, 79% of MPS dose modifications occurred within 6 months post-transplant, but patients in the DR group continued to required dose changes up to 3 years of follow up. The median time for TR was 73 days (ranging from 4 to 947) and for TI was 10 days (ranging from 2 to 409). Importantly, only 40% of the patients requiring TI resumed full dose of MPS.

The classes of organ systems and associated adverse events requiring MPS dose changes are shown in Table 2. Over 90% of the adverse events involved gastrointestinal (45.3%), infection/infestation (31.9%), and hematological (14.9%) systems. The adverse events within each organ system class and the corresponding MPS dose changes in each group are described in Fig. 3. In the gastrointestinal system, diarrhea was the most prevalent adverse event (TR = 46.4%, DR = 47.3%, TI = 41.7%, and PD = 37.0%). In the infection/infestation system, cytomegalovirus infection was the most frequent (TR = 14.3%, DR = 10.7%, TI = 31.7%,

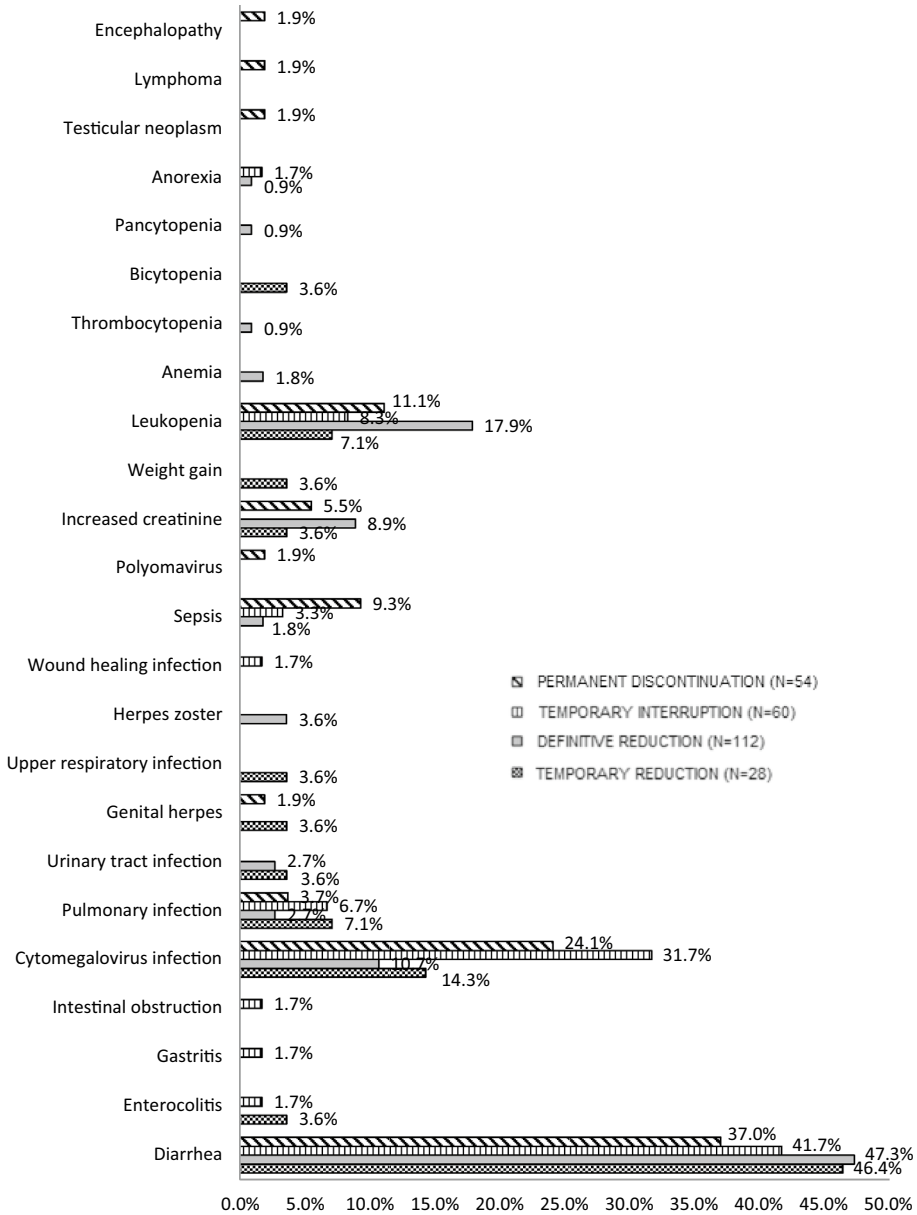

Fig. 3 Incidence and type of adverse events associated with mycophenolate sodium dose changes, according to mycophenolate sodium dose change groups

Table 3 Acute rejection, death, and graft loss

Variable	Temporary reduction (n = 28)	Definitive reduction (n = 112)	Temporary interruption (n = 60)	Permanent discontinuation (n = 54)	Without modification (n = 252)	Total (n = 506)	
All treated rejections, n (%)	10 (35.7)	48 (42.9)	28 (46.7)	28 (51.9)	65 (25.8)	179 (35.4)	$p < 0.05$
Biopsy proven acute rejection	4	27	13	20	39	103	
Clinical acute rejection	6	21	15	8	26	76	
Before MPS dose modification	5 (50.0)	28 (58.3)	16 (57.1)	14 (50.0)	NA	63 (35.2)	
After MPS dose modification	5 (50.0)	20 (41.7)	12 (42.9)	14 (50.0)	NA	51 (28.5)	
Death (%)	1 (3.6)	7 (6.3)	1 (1.7)	22 (40.8)	14 (5.5)	45 (8.9)	$p = 0.07$
Cardiovascular	1 (100)	0	0	2 (10)	5 (36)	8 (18)	
Infection	0	4 (57)	1 (100)	18 (82)	6 (43)	29 (64)	
Neoplasm	0	0	0	1 (4)	0	1 (2)	
Others	0	3 (43)	0	1 (4)	3 (21)	7 (16)	
Creatinine, mg/dl	1.1	2.07 ± 0.83	3.18	3.47 ± 2.07	3.38 ± 2.42		
Graft loss (%)	0 (0)	11 (9.9)	3 (5.0)	9 (16.7)	19 (7.6)	42 (8.8)	$p = 0.07$
Immunological IF/TA	0 (0)	2 (18.2)	0 (0)	4 (44.5)	4 (21.2)	10 (2.0)	
Non-immunological IF/TA	0 (0)	6 (54.5)	1 (33.3)	2 (22.2)	1 (5.3)	10 (2.0)	
Rejection	0 (0)	1 (9.1)	2 (66.7)	0 (0)	2 (10.6)	5 (1.0)	
Non-adherence	0 (0)	1 (9.1)	0 (0)	1 (11.1)	1 (5.3)	3 (0.6)	
Technical failure	0 (0)	0 (0)	0 (0)	0 (0)	10 (52.3)	10 (2.0)	
Others	0 (0)	1 (9.1)	0 (0)	2 (22.2)	1 (5.3)	4 (0.8)	

IF/TA interstitial fibrosis/tubular atrophy, *MPS* mycophenolate sodium, *NA* not applicable

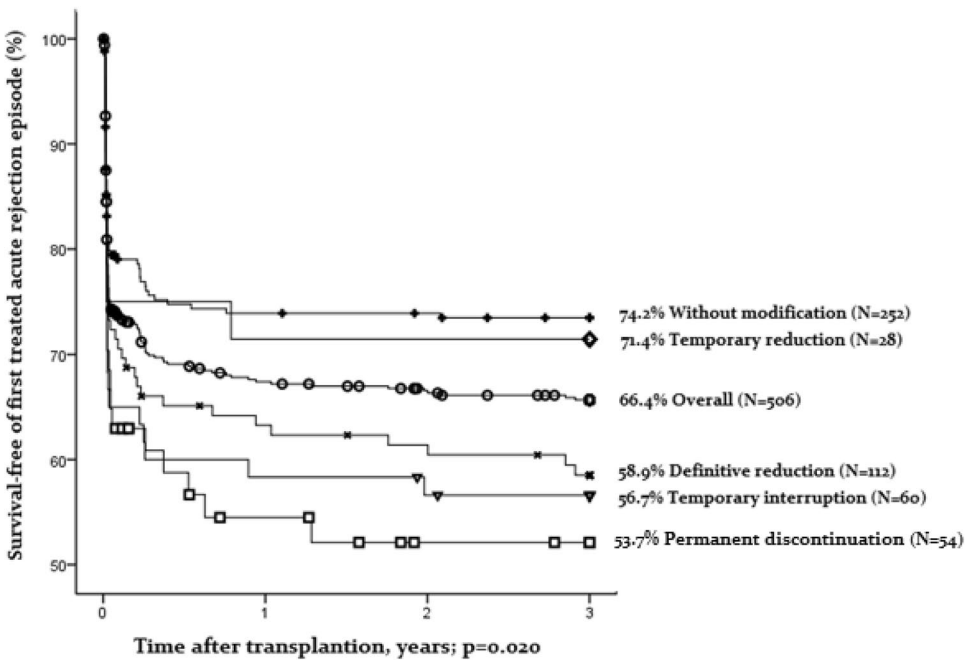

Fig. 4 Survival-free of first treated acute rejection episode according to mycophenolate sodium dose change groups, during the first 3 years after kidney transplantation

and PD = 24.1%). The adverse event, leukopenia, was the most frequently occurring in the hematological system (TR = 7.1%, DR = 17.9%, TI = 8.3%, and PD = 11.1%).

Acute rejection, death, and graft loss

Higher incidences of treated acute rejections episodes were observed among all MPS dose changes groups, apart from the TR group. Among patients with MPS dose changes,

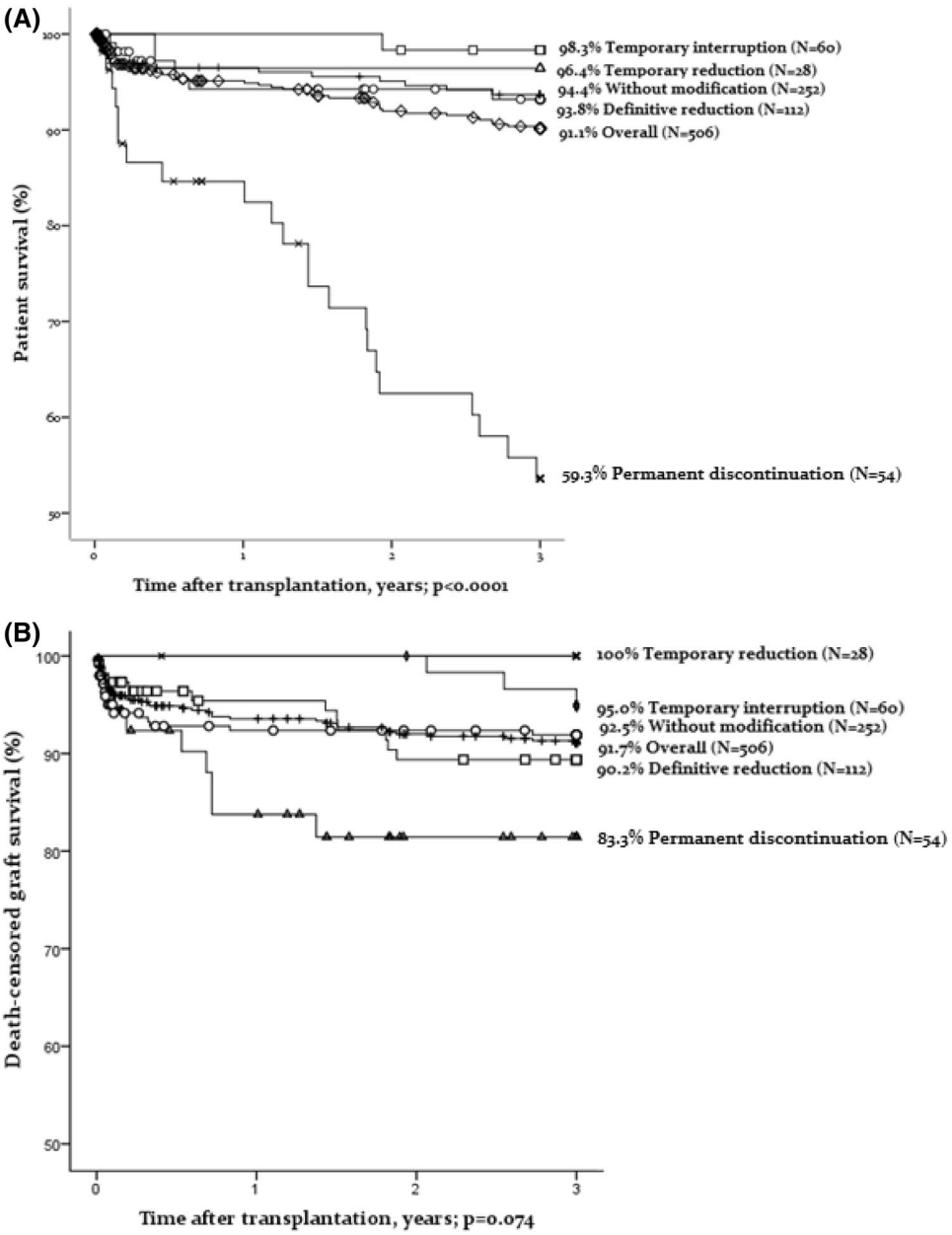

Fig. 5 Patient survival **a** and death-censored graft survival, **b** according to mycophenolate sodium dose change comparison groups, during the first 3 years after kidney transplantation

44.7% were treated for an acute rejection episode after MPS dose changes (Table 3). The overall 3-years cumulative survival-free of first episode of treated acute rejection was 66.4%. Compared to WM, only patients in the TR group showed comparable cumulative survival-free of first episode of treated acute rejection (Fig. 4).

The overall 3-year patient and death-censored graft survivals were 91.1 and 91.7%, respectively. Only patients in the PD group showed inferior patient (Fig. 5a) and death-censored (Fig. 5b) graft survivals compared to the WM group. While the most frequent cause of death was an infection in all groups, immunological and non-immunological interstitial fibrosis and tubular atrophy were the main causes of graft loss (Table 3). Significant graft dysfunction (defined by increased serum creatinine) was observed at the time of death in all groups, except for one patient in the temporary dose reduction group.

The time frame association between MPS dose changes and acute rejection, death, or graft loss is shown in Table 4. The mean time between MPS dose change and acute rejection was 3 months, except for the temporary interruption group. Similar findings were observed in case of death. Finally, the mean time between MPS dose change and graft loss was shorter in the PD group (Table 4). A logistic regression was performed to identify risk factors associated with MPA dose modification. Recipient weight (OR

Table 4 Relationship between MPS dose changes and acute rejection, death, or graft loss

	Temporary reduction (n = 28)	Definitive reduction (n = 112)	Temporary interruption (n = 60)	Permanent discontinuation (n = 54)	*p*
Acute rejection episodes after MPS dose change, n	5	20	12	14	0.664
Time between MPS dose change and first acute rejection episode days, median [range]	229 [38–398]	57.5 [1–1091]	24 [5–516]	28 [4–303]	
Acute rejection episodes before MPS dose change, n	5	28	16	14	0.831
Time between first acute rejection episode and MPS dose change, days, median [range]	2 [1–4]	71 [3–1032]	36 [1–749]	52 [1–961]	
Death, n	1	7	1	22	0.397
Time between MPS dose change and death, days, median [range]	61	23 [2–171]	244	16 [2–544]	
Graft loss, n	0	11	3	9	< 0.001
Time between MPS dose change and graft loss, days, median [range]	0	178 [5–616]	679 [332–802]	32 [4–195]	< 0.001

MPS mycophenolate sodium

Table 5 Risk factors for MPA dose modification

	Odds ratio	IC 95%	*p*
Receptor age	1.01	0.99–1.02	0.180
Weight	0.97	0.96–0.99	0.000
Time on dialysis	1.00	0.99–1.00	0.281
Diabetes Mellitus	1.89	1.11–3.23	0.018
Living donor vs. deceased donor	0.52	0.21–1.32	0.174
Cold ischemia time	0.99	0.96–1.02	0.694
Induction with basiliximab	1.23	0.74–2.04	0.425
Acute rejection	1.82	1.20–2.78	0.005
Delayed graft function	1.68	1.06–2.67	0.028

0.97, 95%CI 0.96–0.99, $p = 0.000$), diabetes mellitus (OR 1.89, 95%CI 1.11–3.23, $p = 0.018$), treated acute rejection (OR 1.82, 95%CI 1.20–2.78, $p = 0.005$), and delayed graft function (OR 1.68, 95%CI 1.06–2.67, $p = 0.028$) were independent risk factors associated with MPA dose modification (Table 5).

Discussion

This retrospective analysis showed that 50.2% of patients receiving fixed daily dose of MPS required dose changes due to an adverse event during the first 3 years after kidney transplantation. The majority of MPS dose changes occurred within the first 6 months and 65% of them were definitive, either reduction or interruption. Over 92% of MPS dose changes were due to gastrointestinal, infectious, and hematological adverse events. These changes were associated with subsequent higher incidences of acute rejection, graft loss, or death, and were more evident in the PD group.

Changes in MPS dose occurred mostly in older diabetic patients, who had spent a longer time on dialysis and had predominantly received kidneys recovered from deceased donors. Unsurprisingly, higher incidence of delayed graft function (DGF) was observed in this group of patients. It is well-known that the tolerability of MPS is lower in patients with diabetes mellitus [22] and also during the DGF period after the transplant surgery [23]. The DGF period may also have contributed to a higher incidence of adverse events among patients receiving MPS. Patients with DGF have been reported to have significantly lower corrected dose AUC-MPA in the first month after renal transplantation, presumably as a result of increased MPA clearance, which is attributable to the high amounts of free MPA [23]. In addition, elevated uremia reduces the binding of MPA to albumin, increasing the concentration of free MPA, which leads to the higher toxicity observed during this period [24].

Typically, MPS is administered in identical fixed doses to all kidney transplant recipients, and there is no consensus on whether monitoring MPA plasma concentration is associated with improved efficacy for the prevention of acute rejection or with reduction in the incidence of adverse events [25, 26]. Therefore, most centers still advise on dose adjustments based on the emergence of adverse events. A few centers promote programmed dose reduction early after transplantation without evidence of lower efficacy [27]. Given the fact that tacrolimus has shown superior efficacy for the prevention of acute rejection compared to cyclosporine [20] and that patients receiving tacrolimus show a 20% higher exposure to MPA [14, 25], it is possible that some of these patients may require lower doses of MPS, which could be associated with a better safety profile and lower prevalence of dose changes due to adverse events.

Three main organ system classes of CTCAE, gastrointestinal, infections, infestations, and hematological, accounted for the majority of MPS dose modifications. There was no clear pattern of the MPS dose changes advised to patients due to specific adverse events. In another cohort of 702 renal transplant patients, gastrointestinal and infectious adverse events were reported in 57.5 and 69% of patients, respectively [7, 28]. The most frequent adverse events leading to MPS dose modification were diarrhea, cytomegalovirus infection, and leukopenia [29, 30].

The incidence of acute rejection was higher in patients requiring MPS dose changes than those who had received full-dose throughout the study period. Furthermore, approximately 40% of all acute rejection episodes occurred after MPS dose changes. Studies have shown that MPS dose reductions and discontinuations, as a consequence of adverse gastrointestinal events, have previously been reported as a risk factor of acute rejection and graft loss, in addition to a higher cost associated with short-term treatment [31]. Treatment for acute rejection with either methylprednisolone or r-ATG has been associated with higher incidence of infectious complications [32].The overall 3-year patient and death-censored graft survival rates were 91.1 and 91.7%, respectively, which matches the results previously published by our center [33]. Inferior patient (59.3%) and death-censored graft (83.3%) survivals were observed in the PD group. Yet, in this group of patients MPS dose interruption had to be implemented due to the anticipated poor prognosis.

This analysis has several limitations, including its single-center and retrospective design, limited and recent enrollment period, relative small sample size, and unintended selection bias associated with the demographic characteristics of the transplant population. The analysis also excluded patients receiving anti-thymocyte globulin as induction therapy immunosuppressive regimen. Despite the fact that these data suggest an association between MPS dose changes and inferior kidney transplant outcomes, it is not possible to establish direct causality as many other ongoing competing events may be involved. The interaction between demographic characteristics, clinical events, and MPS dose changes certainly influenced the observed outcomes. As therapeutic drug monitoring is not routinely used or might not be useful after kidney transplantation, it is difficult to determine the correct individual dose and dose adjustments over time for each patient as is conventionally implemented with calcineurin inhibitors [25]. Finally, because follow up was restricted to 3 years after transplant, the influence of tolerability to mycophenolate on long-term outcomes could be analyzed.

Conclusion

In summary, in this cohort of kidney transplant recipients receiving tacrolimus and prednisone, the tolerability of MPS was low and up to 50% of the patients required dose reductions during the period of follow up. Overall, clinical outcomes were inferior in patients who had their MPS dose modified compared to those without any dose changes, primarily in patients in whom MPS had been permanently discontinued. Patients requiring dose changes due to adverse events need to be followed-up closely, although currently, it is not possible to determine the ideal therapeutic strategy. More research is necessary to determine whether prompt attempts to resume full MPS dosage or the switch to an alternative drug with better tolerability are the best options for the prevention of acute rejection, graft loss, or death in the long-term.

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