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Correlation between Limited Sampling Strategy for the Estimation of Mycophenolic Acid Area Under the Time Concentration Curve with Incidence of Rejection and Opportunistic Infections in Post Renal Transplant Patients

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Abstract

Mycophenolate mofetil (MMF) has become the single most used immunosuppressant in solid-organ transplantation. Hence this study was done to assess Mycophenolate Mofetil dosing and MPA levels with incidence of acute rejection and opportunistic infections in early post renal transplant period .Forty four consecutive early post transplant patients were randomized 1: 1 to receive concentration controlled (CC) {n=22} or fixed dose (FD){n=22}of mycophenolate mofetil. In CC group 13 patients (60%) were below therapeutic range. 9(40%) were in the therapeutic range and no patients were above the therapeutic range. In FD group 7(30%) patients were below the therapeutic range and 14 (64%) patients were in the therapeutic range. Acute rejection in first 6 months post transplant in CC group was 18% and in FD group was 14% ($p = 0.5$). All rejections were seen within first 3 months post transplant. The overall cumulative incidence of infection in CC group was 24% compared to 7.5% in FD group which reached statistical significance ($p<0.01$) in particular at 3 months post transplant. This study has demonstrates that MMF dose individualization with therapeutic drug monitoring is not an effective method in renal transplant patients to prevent the complications in the post-transplant period such as rejection and infection.

Keywords: MPA Levels; Post Transplant; Infection; Rejection.

Introduction

The success of solid organ transplantation lies in the appropriate utilization of immunosuppressive medications [1]. In simplest terms one would like to administer an adequate dosage of an agent (a dose that adequately suppresses the alloimmune response) while at the same time avoiding toxicity related to excessive immunosuppression or concentration-related secondary toxicities.

Mycophenolate mofetil (MMF) has become the single most used immunosuppressant in solid-organ transplantation. Despite a well-documented relationship and efficacy (in terms of acute rejection prophylaxis) and exposure to mycophenolic acids (MPA) as measured by area under the curve (AUC), excellent results have been achieved using a fixed-dosage regimen.A number of pharmacokinetic studies have shown an increased risk for acute rejection in patients with lower MPA exposure, suggesting that efficacy may improve by adjusting the dose on the basis of plasma concentrations. On the basis of these studies, a target window has been adopted for MPA exposure (area-under-the curve [AUC] values between 30 and 60 mg/L). Accumulating evidence suggests that this target is not reached in every patient with the standard MMF dose, with some studies reporting a 10-fold between-patient variability of MPA exposure, changes of

exposure over time with a fixed MMF dose, and influence of co-medication. Consequently, individualization of the MMF dose may be necessary to achieve adequate MPA exposure in every patient. The risk of post transplant infection is associated with overall degree of immunosuppression, & MPA exposure may have a significant influence on this.

Hence, this study is aimed at studying Correlation between Limited sampling strategy for the estimation mycophenolic acid area under the time concentration curve with incidence of rejection and opportunistic infections in post renal transplant patients.

Subjects and Methods

It was a prospective, exploratory, observational study conducted between June / 2013 to March / 15 in the department of Nephrology, St. Johns Medical College and Hospital, Bangalore.

A total of 44 patients, aged 18 to 62 years, who had received a first or second live related kidney transplant were eligible for inclusion in to the study. Important exclusion criteria were previous graft loss within 12 months after transplantation, multi organ recipient, cardiac death donor, ABO-incompatible transplant, current panel-reactive antibody level >20%. The aim of the study was emphasized on short term outcome of graft (i.e 6 months period) and long term outcome of graft has not been included. Also there were number of drop outs in the initial period and the approval from ethical board and hospital (for waving off the expenses) was limited to sample size 40. The sample size for this pharmacokinetic study was chosen with respect to the exploratory nature of this study and was not based on statistical power considerations.

Immunosuppressive Protocol

Patients were randomized 1: 1 to receive concentration controlled (CC) {n = 22} or fixed dose (FD){n=22}of mycophenolate mofetil, along with 0.1mg / kg / day in 2 divided doses of tacrolimus and 1gram iv od of injection methylprednislone for 3 days, followed by 20mg / day of oral prednisolone. Tacrolimus trough levels were done on day 4 and day 30 of post transplant period and the dose was adjusted to achieve a target trough level of 9-12ng / ml for the first 3 months and 5-7 ng / ml thereafter in both the groups .In both the groups MMF was started as standard dose of 1000mg / d for < 70 kg and 1500mg / d for >70 kg patients in 2 divided doses. In CC group, MMF dose adjustments were made based on five – point limited sampling strategy, namely samplings at 0,0.5, 1.0, 1.5 and 3 hours post dose at day 30 post transplant. In CC group, MMF dose adjustments were done so as to reach MPA AUC closer to 30 – 60 mg / h / L but no dose adjustments were made in FD group even after five – point limited sampling.

Indications for dose reduction or cessation were leucopenia (total white cell count below 4.0 —ÿ 109 / L), persistent anemia (hemoglobin less than 10 g / dL), sepsis requiring hospitalization or persistent diarrhea (greater than 2 weeks duration) in the absence of a defined alternative etiology .Patients were treated with either basiliximab (20 mg on days 0 and 4 after transplantation) or ATG (1 mg / kg on alternate days for 5-7 doses) depending upon the discretion of the treating nephrologists (few nephrologists favor basiliximab over ATG and others vice versa). Also ATG was favoured over basiliximab in patients with historic positive PRA's and second transplant. In CC group ,2 patients received ATG and 6 patients received basiliximab. In FC group, 3 patients received ATG and 5 received basiliximab.

The study was approved by the institutional ethical committee. All patients gave written informed consent. Some of the commonly prescribed comedications included antihypertensives, antivirals, hypolipidemic drugs, proton pump inhibitors, anticoagulants, and vitamins.

It was mandatory that all patients had at least 2 full days of the same MMF dose given twice a day before pharmacokinetic investigation. Patients in CC and FD group had fastened from the previous night and arrived at the Renal unit at 8:00 AM on the day of the test. As per standard protocol, food was allowed only 2 hours after the MMF dosing. Water was allowed as and when required. After a cannula was inserted, blood samples were collected into K2 ethylenediamine tetra acetic acid containing tubes before MMF was administered and at 0, 0.5, 1.0, 1.5 and 3 hours post dose. Altogether, 240 plasma samples were analyzed for 5 point MPA trough levels.

Measurement of Total and Free MPA and MPAG

Plasma concentrations of MPA and MPAG were determined by reverse-phase HPLC, using a Symmetry-C18 column. Briefly, 200 microlit of ethylenediaminetetra-acetic acid plasma was mixed with 100 microlit of acetonitrile containing the carboxy butoxy ether of MPA (15 mg / L) as internal standard. This was followed by sequential addition of 20 microlit of perchloric acid (150 g / L) and 20 pA of sodium tungstate solution (250 g / L).

After mixing and centrifugation, 50 microlit of supernatant was applied to the C-18 column. The mobile phase for elution of the column consisted of solution A (250 ml of acetonitrile and 750 ml of 20 mM phosphate buffer, pH 3.0). and solution B (700 ml of acetonitrile and 300 ml of 20 mM phosphate buffer, pH 6.5), which formed the following

Gradient: 0 to 4.5 mm 3% B; 5 to 12 mm 30% B; 12.5 to 14.5 mm 100% B. Compounds were quantified in parallel by absorbance at 254 and 215 nm. For calibration of MPA and MPAG, drug-free plasma was spiked with either of the two compounds at concentrations of 3 and 200 mg/L, respectively. Using drug-free plasma spiked with MPA or MPAG, the method was found to be linear up to 50 mg/L for MPA and 500 mg/L for MPAG.

The detection limit (signal-to-noise ratio of 3) at 215 nm for plasma samples was 0.01mg/L for total MPA and 0.03 mg/L for MPAG. Between-run imprecision ranged from 3.3 to 9.2% for MPA and 4.1to 6.1% for MPAG. The Centrifree Micropartition System was used to obtain an ultrafiltrate for free MPA determination. For the ultrafiltration procedure, 300 microlit of plasma was added to the sample reservoir and the tube was centrifuged at 2000 x *g* (20 degree C) for 40 min, yielding approximately 150 microlit of ultrafiltrate. This was mixed with internal standard (2.5 mg/L) at a ratio of 10: 1 (vol / vol), and 100 ýd was then injected directly into the C-18 column. A solution of 9 g/L NaC1 adjusted to pH 7.4 with phosphate buffer (67 mmol/L) and spiked with 0.05 mg/L MPA was used for calibration of free MPA determination. The detection limit for free MPA at 215 nm was 0.005 mg/L. Because of an imprecision of >20% at *0.005* mg/L, the limit of quantification for free MPA was set at 0.01 mg/L. The within-day imprecision ranged from 6.5 to 1 1.8% and the between-day imprecision from 7.2 to 15.8%. Before starting this investigation, it was confirmed that freezing and thawing of samples did not influence the protein binding of MPA.

Pharmacokinetic Analysis

The following pharmacokinetic data for MPA, free MPA, and MPAG were determined: time to maximum concentration *(Tmax***),** maximum concentration *(Cmax* mg/L), area under the curve (AUC) from 0 to 2 h (mg X h/L) using the linear trapezoidal rule, and minimum concentration (C*min* ,mg/L). *C min* was defined by the formula: *Cmin* =(C*time* 0 +*Ctjme* 2) / 2. The pharmacokinetic analysis was performed using the computer program BiAS .

Acute Rejection Episodes and Infection Episodes

The primary outcome criterion for the determination of the PK relationship for MPA was the occurrence of acute rejection episodes and infection rates over the 6-mo study period after transplantation. Seven of 44 patients experienced at least one acute rejection episode during the 6-mo study period, none of them had two rejection episodes.

Acute rejection episodes were diagnosed based on graft biopsy, histological examination and classification of a core biopsy was done according to the Banff criteria . If a biopsy was logistically impossible or clinically contraindicated, the diagnosis of "presumed rejection" was based on clinical judgment (supported by one or more of the following clinical findings: increased body temperature, graft swelling, graft tenderness, rise in serum creatinine level of more than 20% from the baseline level, or oliguria).

Acute rejection episodes were treated initially with high-dose intravenous corticosteroids (1 g/day of inj methylprednisolone, for 3 consecutive days). If the rejection episode failed to respond to this therapy, treatment with antithymocyte globulin was started, but none of the patients required ATG for reversal of rejection. Bacterial infection was defined as fever with positive identification of an organism on culture, or fever with accompanying clinical features of bacterial infection including neutrophilia and an elevation in C-reactive protein, rapidly improving with antibiotics; Viral infection was defined as Clinical features of viral infection, with either (a) viral identification on histology, polymerase chain reaction, culture or electron microscopy or (b) leucopenia or raised alanine transaminase, with symptoms resolving following anti-viral therapy.

Other Clinical Variables in the Multivariate Analysis

Other donor and recipient variables with a potential impact on clinical endpoints were analyzed: donor and recipient demographics (age, ethnicity, gender, primary disease, time on dialysis, donor source and, CMV serology, HLAmismatch and panel reactive antibody sensitization, repeat transplantation);total daily MMF dose (individual MMF dose multiplied by dosing frequency); delayed graft function (dialysis requirement in the first week post transplantation).

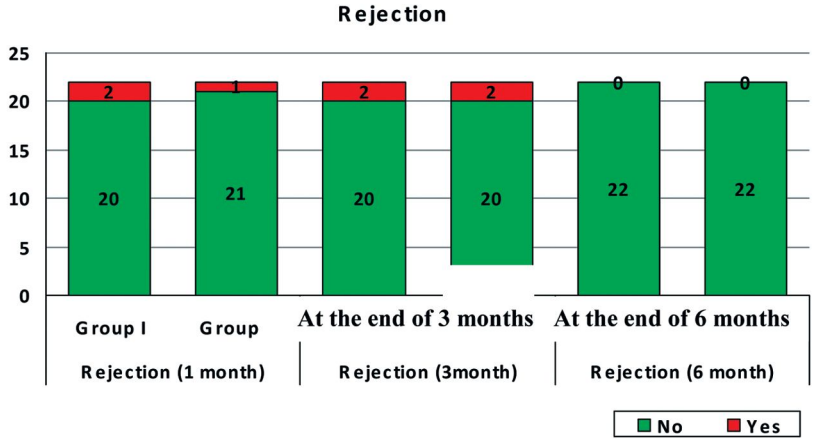
Statistical Analysis

The data was analysed using Statistical Package for the Social Sciences (SPSS17 for Windows (SPSS

Inc., Chicago, IL). The comparison of outcome amongst the two study groups was done by Chi-square test and paired student t test. For comparisons of continuous parameters between groups and within a group over time, repeated measures ANOVA was used. The association of MPA levels and other clinical variables with continuously distributed data was analyzed by population averaged linear regression, using robust standard errors. Data showing a skewed distribution underwent logarithmic transformation. A p value of <0.05 was considered significant.

Results

This was a prospective, exploratory, observational study conducted between June 2013 and March 2015, in the department of Nephrology, St. Johns Medical College and Hospital, Bangalore.



The characteristics of study population is shown in figure 1, a total of 44 patients who underwent renal transplantation were included in the study. There were a total of 22 (50%) patients who received concentration controlled mycophenolate triple immunosuppressive therapy (CC group) and 22 (50%) patients who received fixed dose mycophenolate triple immunosuppressive therapy (FD group).

Most of the patients (47.5%) were in the age group 40 – 50 years. In the population studied 13 patients were females and 31 patients were males.

Table 1: Charlsons index (n = 44)

	Charlsons index		Total	p value	Significance
	0	1			
CC Group	20	2	22	1	Not Significant
FD Group	19	3	22		
Total	39	5	44		

Table 2: Induction regimen (n = 44)

	Induction Regimen		Total	p Value	Significance
	Nil	Yes			
CC Group	14	8	22	0.517	Not Significant
FD Group	16	6	22		
Total	30	14	44		

Table 3: Difference in blood urea during follow up (n = 44)

	Group	n	Mean	SD	p value	Significance
Blood Urea (1month)	CC Group	22	29.82	12.06	0.054	Not Significant
	FD Group	22	36.68	10.82		
Blood Urea (3month)	CC Group	22	31.55	10.65	0.155	Not Significant
	FD Group	22	36.14	10.39		
Blood Urea (6month)	CC Group	22	34.77	12.47	0.858	Not Significant
	FD Group	22	35.41	10.97		

Table 1 shows that the difference in Charlsons index between CC group and FD group is not statistically significant, hence both groups are comparable.

Table 2 shows that the difference in usage of induction regimen between CC group and FD group is not statistically significant, hence both groups were comparable.

Table 3 shows the mean difference in blood urea between CC group and FD group at 1, 3 and 6 months. Even though the mean blood urea was higher in FD group at 1, 3 and 6 months, the difference was not statistically significant.

The mean creatinine of FD group was comparatively higher at 1, 3 and 6 months when compared to CC group . But the difference between the groups was not statistically significant (Table 4).

The serum albumin at 1, 3 and 6 months was almost similar in both the groups (Table 5).

Table 4: Difference in creatinine during follow up (n = 44)

	Group	n	Mean	SD	p value	Significance
Creatinine (1month)	CC Group	22	1.064	0.228	0.064	Not Significant
	FD Group	22	1.223	0.319		
Creatinine (3month)	CC Group	22	1.11	0.25	0.181	Not Significant
	FD Group	22	1.24	0.36		
Creatinine (6month)	CC Group	22	1.173	0.278	0.402	Not Significant
	FD Group	22	1.255	0.358		

Table 5: Difference in serum albumin during follow up (n = 44)

	Group	n	Mean	SD	p value	Significance
Albumin (1month)	CC Group	22	3.936	0.376	0.764	Not Significant
	FD Group	22	3.905	0.32		
Albumin (3month)	CC Group	22	3.986	0.381	0.713	Not Significant
	FD Group	22	3.95	0.26		
Albumin (6month)	CC Group	22	3.973	0.299	0.91	Not Significant
	FD Group	22	3.964	0.228		

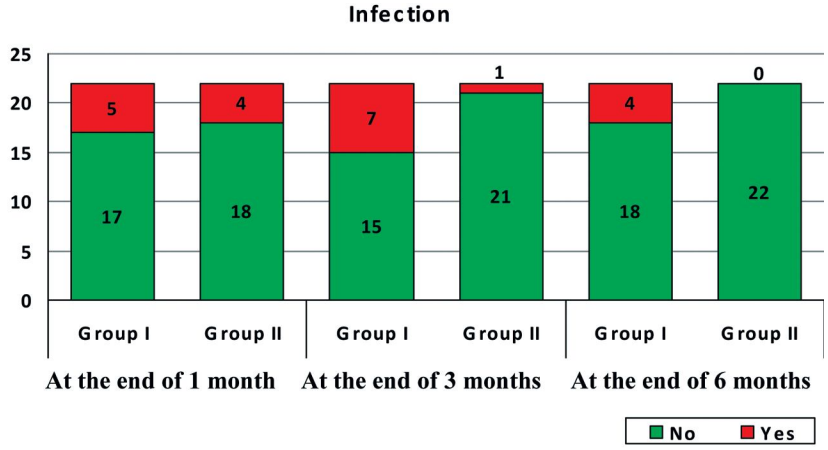


Fig. 2: Incidence of rejection during follow up (n=44)

Table 6: Incidence of rejection during follow up

	Rejection (1month)		Rejection (3month)		Rejection (6 month)	
	No	Yes	No	Yes	No	Yes
CC Group	20	2	20	2	22	0
FD Group	21	1	20	2	22	0
p value	0.5		0.697		Not applicable	
Result	Not Significant		Not Significant			

Acute rejection in first 3 months post transplant in CC group was 18% (4/22) and in FD group was 14% (3/22), and did not reach statistical significance (p=0.5) (Figure 2 and Table 6). All rejections were seen within predominantly first 3 months post transplant period.

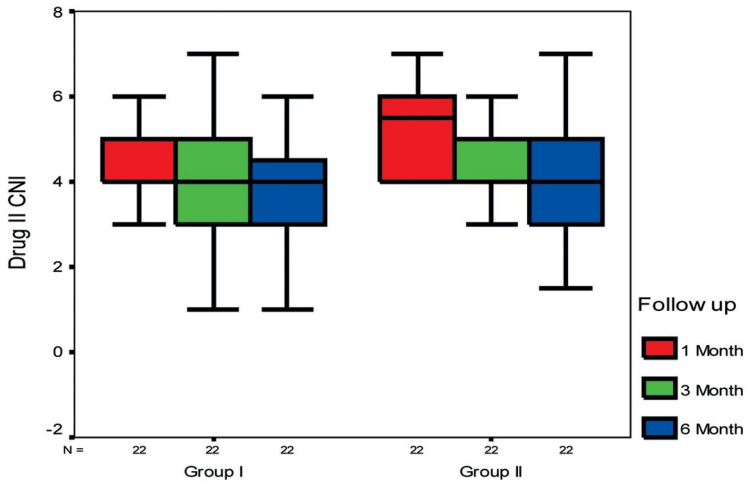


Fig. 3: Incidence of infection during follow up (n=44)

Table 7: Incidence of infection during follow up

	Infection (1month)					Total	p value	Result
	UTI	**Nil**	**Pneumonia**	**Pyelonephritis**	**Sepsis**			
CC Group	3	17	1	1		22	0.5	Not Significant
FD Group	2	18			2	22		
	4	35	1	1	2	44		
			Infection (3month)			Total	p value	Result
	UTI	Nil	CMV	TB	Sepsis			
CC Group	3	15	2	1	1	22	0.023	Significant
FD Group		21	1			22		
	3	36	3	1	1	44		
			Infection (6month)			Total	p value	Result
	UTI	Nil	CMV	TB	Pneumonia			
CC Group	1	18	1	1	1	22	0.054	Not Significant
FD Group		22				22		
	1	40	1	1	1	44		

Infections which were seen during follow up are urinary tract infection, pyelonephritis , pneumonia, tuberculosis, cytomegalovirus infection and sepsis.

5 patients in CC group and 4 patients in FD group had developed infection by the end of first month of follow up. 7 patients in CC group and 1 patient in FD group had developed infection by the end of third month of follow up. 4 patients in CC group and no patients in FD group had developed infection by the end of sixth month of follow up. Overall incidence of infection was much higher in CC group compared to FD group, but this difference was statistically significant at 3 months. The overall cumulative incidence of infection in CC group was 24% compared to 7.5% in FD group which reached statistical significance ($p<0.05$). In CC group, almost all patients who developed infection had MMF trough levels within the therapeutic range i.e., 30-60 mg/h/L, except for 3 patients who developed infection below the therapeutic range which included 2 patients with UTI and 1 patient with CMV infection. Similarly, in FD group 3 patients developed infections within therapeutic range, 1 patient above and below therapeutic range.

The difference in tacrolimus dose between CC group and FD group was not statistically significant (Figure 4).

The mean MMF dose was 1.368 in CC group and 1.182 in FD group, this difference is not statistically significant. However the difference in MMF dosing at 3 months and 6 months, between CC group and FD group were statistically significant.

The mean steroid dosing in CC group was 20.23, 17.73 and 17.05 at 1, 3 and 6 months respectively. The mean steroid dosing in FD group was 19.77, 17.5 and 16.82 at 1, 3 and 6 months respectively. This difference is not statistically significant.

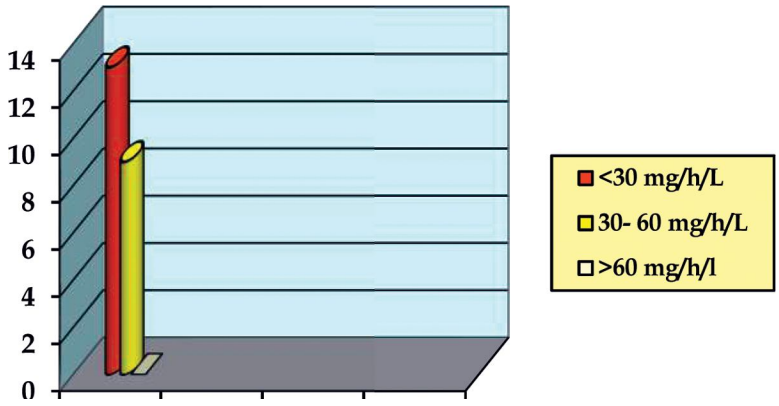


Fig. 4: Tacrolimus dose (n=44)

Table 8: Difference in MMF dosing (n = 44)

	Group	n	Mean(gms/d)	SD	p value	Significance
MMF (1month)	CC Group	22	1.068	0.234	0.124	Not Significant
	FD Group	22	1.182	0.246		
MMF (3month)	CC Group	22	1.386	0.435	0.021	Significant
	FD Group	22	1.136	0.228		
MMF (6month)	CC Group	22	1.295	0.295	0.025	Significant
	FD Group	22	1.136	0.228		

Table 9: Difference in steroid dosing (n = 44)

	Group	n	Mean(g/d)	SD	p value	Significance
Steroid (1month)	CC Group	22	20.23	3.93	0.703	Not Significant
	FD Group	22	19.77	3.93		
Steroid (3month)	CC Group	22	17.73	4.56	0.866	Not Significant
	FD Group	22	17.5	4.3		
Steroid (6month)	CC Group	22	17.05	4.98	0.878	Not Significant
	FD Group	22	16.82	4.77		

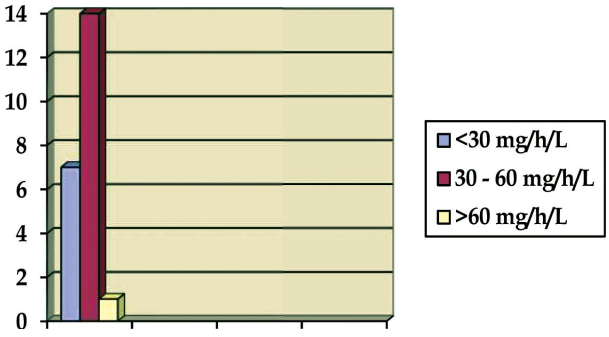


Fig. 5: MMF trough level (n=22) at 1 month post transplant period

As shown in Figure 5, MMF trough level of < 30 mg/h/L was observed in 13 patients, therapeutic range of 30 – 60 mg/h/L was observed in 9 patients and no patients had MMF trough level above 60 mg/h/l in CC group at 1 month post transplant period. Accordingly , only 10 patients needed an increase in the dose of MMF, as other 3 patients could not tolerate(GI symptoms) the hiked dose and 9 patients in therapeutic range were continued on same dose of immunosuppression in CC group.

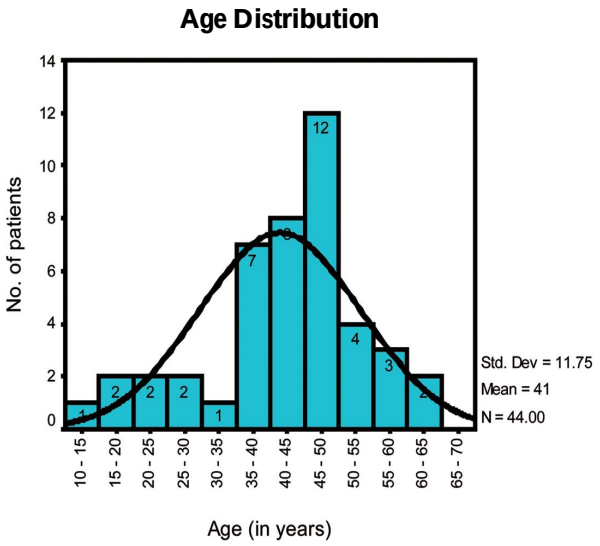


Fig. 6: MMF trough level (n=22) at 1 month post transplant period

Figure 6 shows, in FD group, 14 patients were within the therapeutic range (30-60 mg/h/l) and 7 patients were below therapeutic range. However, no dose adjustments were made in this group.

Discussion

In this study , maximum number of transplants were in the age group of 35-55 years and included 70% male recipients . In terms of induction regimen, 2 patients in CC group and 3 patients in FD group received ATG which did not reach statistical significance, and similarly for basiliximab in both the groups (p=0.8). Only 5 patients (3 in FD & 2 in CC group) underwent second transplant. Native kidney disease in both groups included predominantly chronic glomerulonephritis, diabetic nephropathy and chronic interstitial nephritis on multivariate analysis.The degree of HLA mismatch did not reach statistical significance (p=0.5). The dosing of Tacrolimus (p value=0.9) and steroids (p value=0.8) in both the groups also did not reach statistical significance(in both the groups). The mean MMF dose was 1.368g/d in CC group and 1.182g/d in FD group, but the difference in MMF dosing at 3 months and 6 months, between CC group and FD group was statistically significant., CC group receiving more dose than FD group. All patients were followed for a minimum of 6months; median of 7 months (range : 7-9 months).

There were no deaths or graft loss occurred during this period. Blood urea, serum creatinine and albumin were almost similar in both groups. None of the patients had delayed graft functions.

In CC group 13 patients (60 %) were below therapeutic range .Only 10 patients in CC group needed an increase in dose (as 3 could not tolerate the hiked dose due to GI intolerance and hence were continued on same dose). None of the patients were above the therapeutic range. In FD group only 7 patients (30%) were below the therapeutic range and 14 patients (64 %) were within the therapeutic range. Acute rejection in first 6 months post transplant in CC group was 18% and in FD group was 14% (p=0.5). All rejections were seen within first 3 months post transplant. The overall cumulative incidence of infection in CC group was 24% compared to 7.5% in FD group which reached statistical significance (p<0.01) in particular at 3 months post transplant.

The majority of patients in the CC group regimen did not reach MPA therapeutic levels day 30 after transplantation .An intensified dosing regimen may also have potential drawbacks .It increases the risk for overexposure and toxicity if the starting dosage is either too high or given for too long.

CC group regimen was generally well tolerated during the higher dosage phases, and the majority of patients stayed on the intensified dosing scheme. Previous studies that used higher MMF dosages in combination with CsA [2-6] or standard dosages in combination with tacrolimus [7,8] reported similar MPA exposure (<30 mg/h per L).

Mean MPA-AUC in this study was 29.4 mg/h per L on day 30 in CC group and 26.7 mg/h per L on day 30 in FD group.

Mean MPA-AUC was only 33.7 mg/h per L on day 14 in the Apomygre study, and levels <40 mg/h per L were not achieved until month 1 using a concentration-controlled approach [9]. Similarly, mean MPA-AUC of CsA treated patients on day 10 was 34.4 mg/h per L in the Fixed-Dose Concentration-Controlled (FDCC) Study [10] .

There was a large interindividual variation of PK data, despite the fact that all patients were receiving the same per kg body weight –adjusted MMF dosage.

Both the group were comparable either in terms of native kidney disease, induction regime ,HLA matching ,immunosuppressive protocol. There were no difference in cumulative incidence for rejection in both the groups, however there was increased incidence of infection noted in the CC group. In FD group, majority of the patients were in the therapeutic range, compared to CC group. Hence, it can be concluded that there are no added benefits of monitoring MPA levels in post transplant period Our data has demonstrated that therapeutic drug monitoring of MMF doses has no role in improving clinical outcomes in post transplant period.

Like the FDCC (FD vs. CC) MMF trial [11], which showed no improvements in outcomes with CC MMF dosing, our study also showed similar results.

Recommended therapeutic window for MPA AUC has been derived from the original study done by Binu S et. al.[12], in renal patients who were on triple therapy with MMF, prednisolone and tacrolimus.

The variability in MPA exposure following the administration of MMF observed in this study and previously reported by other investigators is a result of its complex pharmacokinetics. In the early posttransplant period, MPA AUC in renal allograft recipients is positively predicted by levels of serum creatinine and serum albumin [13], reflecting the impact of renal function and protein binding on MPA clearance.

In the current study, patients in the CC group received almost similar doses of MMF as the FD group at 1 month,but at 3 month the CC group had received increased dose with an increased occurrence of infections. A possible explanation may be that there were insufficient numbers of patients to identify

significant differences between groups in adverse events. Other studies attempting to correlate MPA exposure with adverse events have also yielded inconsistent findings; however, one study reported a correlation between adverse events and MPA AUC and C30 (30-min post-dose) MPA levels [14] , while others found a relationship between free MPA levels and hematological toxicity [15,16]. The lack of consistent correlations between MPA levels and adverse events may reflect the nature of the events, which have multiple causes, and may be further complicated by the fact that small numbers of patients were evaluated in many of these studies as well.

MPA monitoring is not yet widely accepted due to the complexities of MPA pharmacokinetics, lack of accurate measurement tools and MPA AUC calculations.

The concentration–effect relationship for mycophenolic acid (MPA), and the high variability in MPA concentrations in patients on standard dose mycophenolate mofetil (MMF) therapy, for some centers has provided enough evidence to implement therapeutic drug monitoring (TDM) for MMF in daily practice. Two randomized trials, Adaption de Posologie du MMF en Greffe Renale (APOMYGRE) [18] and fixed-dose versus concentration controlled (FDCC) [17] investigated the added benefit of TDM for MMF in renal transplant recipients.

The APOMYGRE study showed a significant reduction in the incidence of acute rejection in concentration controlled patients, while the FDCC study had a negative outcome, despite a similar study design. In Opticept, concentration-controlled MMF combined with reduced level calcineurin inhibitor was found to be noninferior to concentration-controlled MMF combined with standard level calcineurin inhibitor and noninferior to fixed-dose MMF combined with standard level calcineurin inhibitor.

There are few limitations in the study 1) Sample size need to be larger to power the study. 2) 5-point MPA trough levels were estimated once only (30 days post transplant) in both the groups, even after dose adjusting in CC group. Many studies have looked at sampling at various intervals, which was not feasible in our study due to financial constraints and patients co -operation for drawing multiple blood samples

References

1. Kaplan B. Introduction: pharmacokinetics and pharmacodynamics of immunosuppressive agents. Graft. 1999; 2: 175.
2. Sollinger HW: Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. US Renal Transplant Mycophenolate Mofetil Study Group. Transplantation. 1995; 60: 225–232.
3. Bullingham R, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. Clin Pharmacokinet. 1998; 34: 429– 455.
4. Bernard O, Guillemette C. The main role of UGT1A9 in the hepatic metabolism of mycophenolic acid and the effects of naturally occurring variants. Drug Metab Dispos. 2004; 32: 775–778.
5. Guillemette C. Pharmacogenomics of human UDPglucuronosyltransferase enzymes. Pharmacogenomics J. 2003; 3: 136–158
6. Shipkova M, Strassburg CP, Braun F et al. Glucuronide and glucoside conjugation of mycophenolic acid by human liver, kidney and intestinal microsomes. Br J Pharmacol. 2001; 132: 1027–1034.
7. Hesselink DA, Van Hest RM, Mathot RA, Bonthuis F, Weimar W, de Bruin RW, van Gelder T: Cyclosporine interacts with mycophenolic acid by inhibiting the multidrug resistance-associated protein 2. Am J Transplant. 2005; 5: 987–994.
8. Atkinson AJ. Drug absorption and bioavailability. In: Atkinson AJ, Daniels CE, Dedrick RL, Grudzinskas CV, Markey SP, eds.Principles of Clinical Pharmacology. San Diego: Academic Press. 2001; 31–41.
9. Wilkinson GR, Shand DG. Commentary: a physiological approach to hepatic drug clearance. Clin Pharmacol Ther. 1975; 18: 377–390.
10. Koch-Weser J. Bioavailability of drugs (first of two parts). N Engl J Med. 1974; 291: 233–237.
11. van Gelder T, Tedesco-Silva H, de Fijter H et al. An open, prospective, randomized, controlled, multicenter study comparing fixed dose vs. concentration controlled mycophenolate mofetil regimens for de novo patients following renal transplantation (the FDCC trial)[abstract]. Am J Transplant .2006: 6(Suppl 12): 343.
12. Cattaneo D, Gaspari F, Ferrari S, Stucchi N, Del Priore L, Perico N, Gotti E, Remuzzi G: Pharmacokinetics help optimizing mycophenolate mofetil dosing in kidney transplant patients. Clin Transplant. 2001; 15: 402–409.
13. de Fijter JW, Mourer JS, den Hartigh J, Mallat MJ, Berger SP. Concentration-controlled systemic exposure provides improved safety after CNI or MMF withdrawal [abstract]. Am J Transplant. 2007; 7(Suppl 2): 208.
14. Mourad M, Malaise J, Chaib Eddour D et al. Correlation of mycophenolic acid pharmacokinetic parameters with side effects in kidney transplant

patients treated with mycophenolate mofetil. Clin Chem. 2001; 47: 88–94.

15. Weber LT, Shipkova M, Armstrong VW, Wagner N, Schu¨ tz E, Mehls O, Zimmerhackl LB, Oellerich M, Tonshoff B: The pharmacokinetic-pharmacodynamic relationship for total and free mycophenolic acid in pediatric renal transplant recipients: A report of the German study group on mycophenolate mofetil therapy. J Am Soc Nephrol. 2002; 13: 759–768.
16. Heller T, Armstrong VW, Brandhorst G, Streit F, van Gelder T, Oellerich M. Relationship between free mycophenolic acid and hematologic side effects: Interim results from the FDCC study [abstract]. Transplantation. 2006; 15: 82(1 Suppl 2): 344.
17. van Gelder T, Silva HT, de Fijter JW et al. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: The fixed-dose concentration-controlled trial. Transplantation. 2008; 86: 1043–1051.
18. Le Meur Y, B¨ uchler M, Thierry A et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant. 2007; 7: 2496–2503.