Indian J Med Res 135, January 2012, pp 84-91

A pilot study on area under curve of mycophenolic acid as a guide for its optimal use in renal transplant recipients

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Received August 4, 2009

***Background & objectives*: The immunosuppressants administered to renal transplant subjects are usually monitored therapeutically to prevent graft rejection and drug toxicity. Mycophenolic acid (MPA) is an immunosuppressant. The present prospective study was undertaken to establish the utility of plasma level monitoring of MPA and to correlate it with clinical outcomes in renal transplant receipients.**

***Methods*: MPA plasma level at 2, 4 and 9 h and the area under concentration-time curve (AUC) were estimated using high performance liquid chromatography in 24 renal transplant recipients receiving immunosuppressant MPA plus tacrolimus and steroid.**

***Results*: There was wide inter-individual variation in MPA plasma level and the AUC. The incidences of gastrointestinal adverse drug events (diarrhoea and acidity) were significantly more in the high MPA AUC patients. Though biopsy proven acute rejection was not found, of the six subjects with lower MPA AUC (<30 mg.h/l), three were clinically diagnosed to develop tacrolimus nephrotoxicity. The Gastrointestinal Symptom Rating Scale (GSRS) and Gastrointestinal Quality of Life Index (GIQLI) scores represented better health related quality of life in lower MPA AUC than in the higher MPA AUC (>60 mg.h/l).**

***Interpretation & conclusions*: The present findings suggest the MPA AUC of 30 - 60 mg.h/l in the maintenance stage of renal transplant patients to have optimum clinical benefit and relegated adverse events profile indicating the usefulness of AUC of MPA with limited sampling strategy in optimizing its use.**

Key words Adverse drug events - area under the curve (AUC) - health related quality of life - mycophenolic acid (MPA) - renal transplant

The requirement of renal transplantation is increasing globally due to rise in the incidence of end stage kidney disease[1]. For optimal graft function, renal transplant recipients are usually maintained on immunosuppressants like cyclosporine or tacrolimus, steroid, and mycophenolic acid (MPA), *etc*. Renal toxicity is a frequently observed side effect with calcineurin inhibitors[2]. Thus, minimizing the use of calcineurin inhibitors and substituting with non-nephrotoxic MPA is being increasingly evaluated[2-5]. Mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS), the prodrugs of MPA are generally used in fixed doses (MMF 500 or 1000 mg twice daily, EC-MPS 360 or 720 mg twice daily) as these contain equivalent amount of MPA[6]. Several factors affecting the blood concentration of MPA and its metabolites have been highlighted[7]. A limited sampling strategy using C_2, C_4 and C_9 (*i.e*. sampling at 2, 4 and 9 h after MMF dosing) has been shown to provide a reliable, accurate, less cumbersome

and patient compliant method of estimation of MPA area under curve (AUC). This limited sampling strategy had a significant correlation ($r^2 = 0.877$)[8] with 0-12 h AUC. To optimize MMF therapy in transplantation, the optimum MPA AUC has been recommended to be in the range of 30-60 mg.h/l[9]. However, the exact correlation of MPA concentration and AUC with efficacy and toxicity is still debated[8,10]. Various studies have demonstrated the value of monitoring of plasma level of MPA in optimizing its therapeutic use; however, there is a lack of consensus on the usefulness of plasma level monitoring of MPA[8]. The present study thus aimed to explore the clinical utility of MPA AUC with limited sampling strategy in optimizing its use and reducing the side effect profile in renal transplant receipients.

Material & Methods

Study population: This was a single centre non-randomized longitudinal prospective open-label study. Consecutive patients between 20-60 yr of either sex coming for follow up at Nephrology Outpatient Department, All India Institute of Medical Sciences (AIIMS), New Delhi, between October 2008 and July 2009, who had renal transplantation at least 3 wk before, and receiving MMF or EC-MPS for a minimum period of 7 days along with tacrolimus and steroid were included in the study. Patients not agreeing to give written informed consent, using any other immunosuppressants, with multi-organ transplant, evidence of graft rejection or treatment of acute rejection within two months prior to screening and unwilling to return for follow up were excluded. After obtaining written informed consent, blood was collected for estimation of plasma MPA AUC. The patients were followed up for a minimum period of three months. As per the existing practice in the hospital, all the enrolled patients were on fixed dose of either MMF (500 mg) or EC-MPS (360 mg) twice daily. The study protocol was approved by the Institutional Ethics Committee.

Study objectives: The primary endpoint was to correlate MPA AUC with episodes of adverse drug events (ADEs). Additional analyses were done on the correlation of MPA AUC with renal function status, patient reported outcomes, and concomitant tacrolimus dosing. All study personnel and participants were blinded to the plasma levels of MPA until completion of patient recruitment and data collection during the follow up.

Categorization of patients: After estimation of MPA AUC, the patients were categorized into three groups: Lower range (LR) group: MPA AUC <30 mg.h/l, Optimal range (OR) group: MPA AUC between 30-60 mg.h/l and Higher range (HR) group: MPA AUC >60 mg.h/l.

Estimation of plasma MPA level: At 2, 4 and 9 h after MPA morning dose, 2 ml of blood was collected from antecubetal vein in an EDTA vial. Plasma was stored at -20ºC until analysis by high performance liquid chromatography (HPLC) within the next 2 days. Levels of drug in plasma were quantified by reverse phase HPLC (Agilent Technologies, 1200 series with Chemstation software, 76337 Waldbronn, Germany) using a kit (ClinRep® kit for Mycophenolic Acid, M/S Recipe, GmbH, Germany). The kit contained the mobile phase (acetonitrile), calibrator (lyophilized plasma of human origin), precipitation reagent (methanol), controls (lyophilized plasma of human origin, spiked with mycophenolic acid of three different concentrations) and the analytical column. The pump flow rate of mobile phase was 1.2 ml/min, column temperature was set at 30°C, the back pressure of the column did not exceed 200 bars, wavelength of UV detector was set at 215 nm, injection volume was 50 µl, and injection interval was 9 min per sample. Sample preparation and running of samples were done according to kit procedure. MPA plasma levels were estimated for every patient at 2, 4 and 9 h by the calculation procedure of the kit. The coefficient of variation (CV) of the MPA assay was 3.3 per cent.

MPA AUC calculation: By limited sampling strategy using MPA concentration C_2, C_4 and C_9 (*i.e.* 2, 4 and 9 h after MPA dosing) MPA AUC was estimated by the following formula[8]:

$$\text{MPA AUC (mg.h/l)} = 1.77 \times C_2 + 2.34 \times C_4 + 4.76 \times C_9 + 15.94$$

Renal function test: Serum creatinine (SCr), estimated glomerular filtration rate (eGFR) and blood urea level were estimated for assessment of renal function[11]. Estimated GFR was calculated by the four variables Modification of Diet in Renal Disease (MDRD) study equation[12]. SCr >0.3 mg/dl than nadir value[11,13] and eGFR <60 ml/min/ 1.73 m^2 during the study period[14] were considered as indicators of poor renal function. Wherever feasible, biopsy of the graft was done to confirm graft dysfunction.

Estimation of plasma tacrolimus trough level: Tacrolimus trough level was estimated by chemiluminescent microparticle immunoassay (CMIA) technology using Abbott Architect® Tacrolimus assay kit (Abbott Laboratories, Abbott Park, Illinois, USA).

Assessment of adverse drug events (ADEs): ADEs assessment was done clinically and by investigations during follow up. Haematologic side effects were defined according to the following criteria: total leucocyte count (TLC) <4 x 10^3/mm^3 for leucopenia, haemoglobin (Hb) <12 g/dl for anaemia, and platelet count <50 x 10^3/μl^3 for thrombocytopenia.

Patient reported assessments: Patients were given a 15-item questionnaire to report their perception regarding the GI symptom burden using the self-assessed Gastrointestinal Symptom Rating Scale (GSRS)[15,16]. The GSRS having five subscales was scored using a 4-graded Likert scale[17]. A higher score indicated worsening of GI symptoms[15].

Patient's health related quality of life focused upon GI complications was assessed by Gastrointestinal Quality of Life Index (GIQLI), a 36-item questionnaire[18,19]. GIQLI scale also had five subscales, scored using a 5-graded Likert scale. A higher score represented improved health related quality of life[18].

Statistical analysis: A modified intention-to-treat analysis was done. Patients who did not take even a single dose of MMF or EC-MPS were not included in the study. Analysis of data was done with the help of Stata™ (version 9.0) (Stata Corporation, Texas, USA). Continuous variables were expressed as mean ± SE and categorical variables were expressed as median (range) or frequency (percentage). MPA plasma levels and AUC were expressed as median (range) along with 95 per cent confidence interval (CI). Patient reported outcomes were expressed as mean ± SE with 95 per cent CI. Comparison of distribution of sex, age, MPA formulations, and ADEs among patients having different MPA AUC was done by Fisher's exact test. Kruskal-Wallis test was used for comparison of dose of drugs, laboratory data, MPA plasma levels and patient reported outcomes. $P<0.05$ was considered as statistically significant. Two-sample Wilcoxon rank-sum (Mann-Whitney) test with Bonferroni-correction was used for post hoc analysis. After Bonferroni's correction for three comparisons, $P<0.017$ was considered significant between two individual groups.

Results

Patient characteristics: Of the 25 patients enrolled 24 completed the modified intention-to-treat analyses (Fig. 1). There was no significant difference in the demographic profile and doses of immunosuppressive therapy among the three groups of MPA AUC (LR, OR and HR). All subjects had live donor renal transplantation. One patient had a re-transplantation due to first graft loss (Table I).

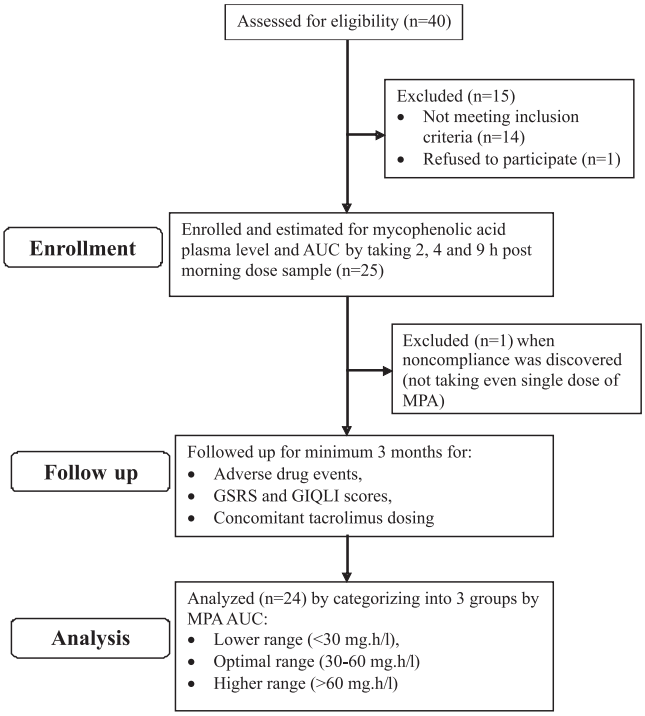

Fig. 1. Overview of screening, enrollment, and follow-up of the patients. GSRS, Gastrointestinal Symptom Rating Scale; GIQLI, Gastrointestinal Quality of Life Index.

MPA plasma concentration and AUC: There was considerable inter-patient variability in pharmacokinetic profile of MPA. The C_2, C_4 and C_9 values showed linear increase with rise in MPA AUC among LR, OR and HR groups (Table II). Majority of patients (15, 62.5%) were in OR group, whereas six (25%) patients were in LR group and three (12.5%) in HR group. The maximum MPA concentration among the three time points *i.e.* 2, 4 and 9 h in MMF treated patients was seen at 2 h (median: 4.0 mg/l), whereas in EC-MPS treated patients, the maximum concentration was seen at 4 h (median: 4.9 mg/l). The MPA AUC for these two formulations were also comparable with median value of AUC 32.81 mg.h/l (range: 27.43 - 43.24 mg.h/l) in MMF treated patients and 42.74 mg.h/l (range: 27.18 - 103.53 mg.h/l) in EC-MPS treated patients.

Laboratory parameters: Laboratory data at the time of enrollment and at the end of follow up (3 months) were compared among LR, OR and HR groups. Though there was no significant difference at the time of enrollment, the blood urea values in OR and LR groups were significantly higher as compared to HR group at the time of follow up (41.83 ± 3.03 and 50 ±

Table I. Characteristics of enrolled patients

Variables	All patients (n=24)	LR group (n=6)	OR group (n=15)	HR group (n=3)
Sex				
Male	18	5	10	3
Female	6	1	5	No patient
Patients in age group (yr)				
20-40	18	4	12	2
41-60	6	2	3	1
Weight* (kg)	58.1 ± 1.8	61.7 ± 3.1	56.5 ± 2.3	59 ± 7.8
Donor age* (yr)	46.9 ± 2.1	46. 7 ± 6.1	48 ± 2.4	42 ± 4.0
First degree relative donor	19	6	11	2
Time since recent transplantation in days (Median)	172	130	180	195
Cause of end stage renal disease				
Hypertension	13	4	7	2
Primary renal disease	5	1	3	1
Stone in urinary tract	2	1	1	No patient
Others**	4	No patient	4	No patient
Duration of drug administration (days)*				
Mycophenolic acid	180 ± 21	207 ± 66	171 ± 21	180 ± 30
Tacrolimus	195 ± 30	207 ± 66	195 ± 42	180 ± 30
Steroid	195 ± 30	207 ± 66	195 ± 42	180 ± 30
MPA formulation				
MMF	13	4	9	No patient
EC-MPS	11	2	6	3
*Concomitant other immunosuppressant**				
Tacrolimus (mg/day)	6.75 ± 0.52	7.00 ± 0.93	6.80 ± 0.74	6.00 ± 1.00
Steroid (mg/day)	9.90 ± 0.63	9.58 ± 1.19	10.17 ± 0.90	9.17 ± 0.83

Values given as *Mean ± SE; **Other causes of end stage renal disease were vesico-ureteric reflux, primary graft failure, calcineurin inhibitor induced nephrotoxicity. LR, lower range; OR, optimal range; HR, higher range; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium

4.20 vs. 32.21 ± 6.90 mg/dl, respectively, $P<0.05$). The overall renal function as assessed by SCr and eGFR was apparently better in HR group as compared to OR and LR groups; however, the difference was not statistically significant.

During the study period, biopsy proven acute rejection was not observed in any patient. However, in six patients, poor renal graft function (SCr >0.3 mg/dl than nadir value and eGFR <60 ml/min/ 1.73 m^2) was observed. Among these patients, one was clinically diagnosed as chronic allograft nephropathy and in the remaining five, biopsy was performed. In one patient, histopathology revealed chronic allograft nephropathy with polyoma (BK) virus infection whereas normal features were observed in the remaining four. Among these four cases, one had recurrent urinary tract infection, which settled down in the course of the study and in three cases tacrolimus-induced nephrotoxicity was diagnosed clinically. These three patients of tacrolimus toxicity had tacrolimus trough level 9.4, 9 and 18.4 ng/ml, which was further reduced (7.6, 7.6 and 13.2 ng/ml, respectively) with a decrease in tacrolimus dosing. The MPA AUCs (29.75, 27.18 and 27.84 mg.h/l) of these three patients were in the LR group. Tacrolimus trough level was less in the HR and OR groups as compared to LR group, but was not statistically significant. Haematological parameters (Hb, TLC, platelet count) were not significantly different among the three groups.

Incidence of adverse drug events (ADEs): During the study, seven patients were hospitalized for 10 adverse events related to MPA: diarrhoea with dehydration (2 patients), septicaemia (3 patients), lower respiratory tract infection (2 patients), urinary tract infection (1 patient), leucopenia (1 patient) and thrombocytopenia (1 patient). Though not statistically significant, lower

Table II. MPA AUC and plasma concentrations at 2, 4 and 9 h (C2, C4 and C9) among LR, OR and HR MPA AUC groups

Variables		MPA AUC in mg.h/l	MPA plasma concentrations in mg/l		
			C2	C4	C9
All patients (n=24)	Med (R)	36.5 (27.2–103.5)	3.4 (0.5-35.4)	1.9 (1.04-15.2)	1.5 (0.3-5.0)
	95% CI	34.0-47.9	1.8-7.5	2.2-5.2	1.3-2.2
LR group (n=6) AUC (<30)	Med (R)	27.7 (27.2-29.7)	2.9 (0.9-4.9)	1.17 (1.0-1.5)	0.7 (0.3-1.6)
	95% CI	27.2-28.8	1.4-4.0	1.1-1.4	0.5-1.3
OR group (n=15) AUC (30-60)	Med (R)	37.8 (31.1-51.5)	3.6 (0.5-6.9)	2.3 (1.2-11.2)	1.6 (0.3-3.4)
	95% CI	35.5-42.3	2.3-4.4	2.0-5.3	1.3-2.2
HR group (n=3) AUC (>60)	Med (R)	65.7 (62.5-103.5)	8.1 (1.7-35.4)	6.5 (4.9-15.2)	2.0 (1.7-5.0)
	95% CI	50. 9-103.6	-5.6-35.7	2.5-15.3	0.8-5.0

Med (R), Median (Range), 95% CI (confidence interval). C2, C4 and C9 represent concentration after 2, 4 and 9 h after morning dose. LR, lower range; OR, optimal range; HR, higher range

respiratory tract infection and urinary tract infection were more with a rise in MPA AUC. The other infections observed were cytomegalovirus infection, tuberculosis, chicken pox, sepsis and hepatitis B virus infection in two patients each. Chronic suppurative otitis media, giardiasis, polyoma (BK) viral nephropathy, wound infection and cellulitis were observed in one patient each. Patients in HR group had significantly higher incidence of diarrhoea and acidity (P<0.05) as compared to LR group (Table III).

Two patients discontinued MPA during follow up due to ADEs. EC-MPS was discontinued in one patient following leucopenia and thrombocytopenia and was re-administered after one and half month duration. In another patient, MMF was completely stopped after one month of study due to development of persistent leucopenia.

Table III. Distribution of adverse drug events among patients having different MPA AUC

Variables	All patients (n=24)	LR group (n=6)	OR group (n=15)	HR group (n=3)
Diarrhoea	14 (58.3)	1	10	3*
Vomiting	3 (12.5)	0	2	1
Acidity	9 (37.5)	0	6	3*
Fever	15 (62.5)	3	9	3
Lower respiratory tract infection	11 (45.8)	2	6	3
Urinary tract infection	11 (45.8)	2	7	2
Other infections	11 (45.8)	2	7	2
Diabetes uncontrolled	2 (8.3)	0	2	0
Leucopenia	2 (8.3)	0	2	0
Thrombocytopenia	1 (4.2)	0	1	0
Anaemia	14 (58.3)	3	10	1

Variables expression: Frequency (percentage)
*P<0.05 compared to LR group

Patient reported outcomes: The overall GSRS score was significantly (P<0.05) higher in HR group [0.87 ± 0.14 (95% CI 0.59-1.15)] as compared to OR [0.51 ± 0.10 (95% CI 0.32-0.70)] and LR [0.32 ± 0.09 (95% CI 0.14-0.50)] groups. Diarrhoea and reflux disease

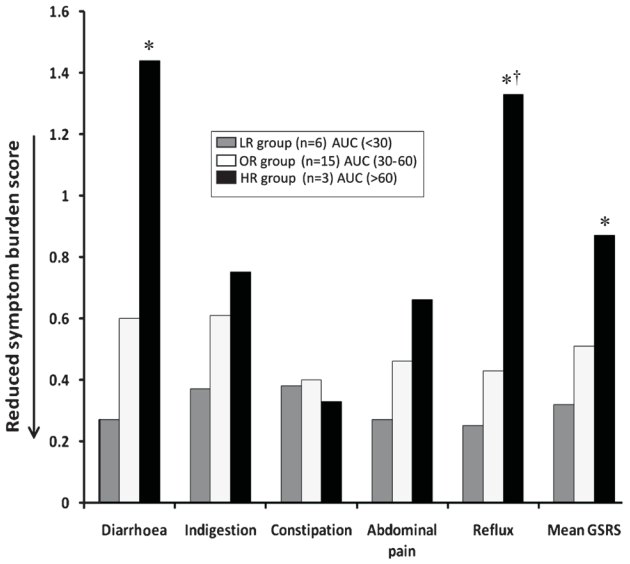

Fig. 2. Gastrointestinal Symptom Rating Scale (GSRS) subscales scores among patients having different MPA AUC. Data presented as mean score. Significant difference was seen in Diarrhoea subscale, Reflux subscale and Mean GSRS score. P*<0.05 compared to LR, †<0.05 compared to OR group.

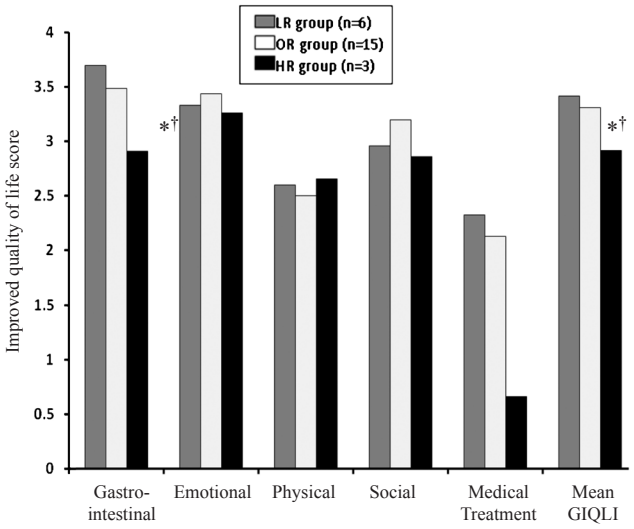

Fig. 3. Gastrointestinal Quality of Life Index (GIQLI) subscales scores among patients having different MPA AUC. Data presented as mean score. Significant difference was seen in Gastrointestinal subscale (P=0.004) and Mean GIQLI score (P=0.010). P*<0.05 compared to LR; †<0.01 compared to OR.

subscale scores were higher in HR group (P<0.05) as compared to OR and LR groups (Fig. 2).

In HR group, the health related quality of life was poor with significantly low overall GIQLI score [2.92 ± 0.26 (95% CI 2.41-3.43)] as compared to OR [3.31 ± 0.14 (95% CI 3.03-3.59)] and LR [3.42 ± 0.22 (95% CI 2.99-3.85)] groups (P=0.010). GI symptoms subscale of GIQLI revealed significant deterioration in HR group [2.91 ± 0.07 (95% CI 2.77-3.05)] as compared to OR [3.49 ± 0.06 (95% CI 3.38-3.60)] and LR [3.7 ± 0.05 (95% CI 3.60-3.80)] groups (P=0.004) (Fig. 3).

Discussion

Renal transplant patients are treated with both the formulations *i.e*. MMF and EC-MPS for immunosuppression, and the active metabolite in both these is MPA. Therefore, patients treated with both the formulations were included in the study for assessment of clinical outcomes. However, these are generally used as fixed dose regimen. The role of plasma level monitoring of MPA is still equivocal because of inconclusive evidence to suggest that blood concentration or AUC measurement will guide for better efficacy and least toxicity of MPA. The conventional multipoint (0-12 h) AUC estimation poses a problem of high cost and poor compliance. Therefore, the present exploratory study was conducted to study the usefulness of MPA AUC monitoring using limited sampling strategy.

It has been reported that the MPA is not different in terms of MPA AUC when EC-MPS 720 mg twice daily and MMF 1000 mg twice daily were administered[6,20]. The patients of present study were on similar proportion of doses *i.e.* 360 mg of EC-MPS or 500 mg of MMF twice daily. Therefore, the observed difference in MPA AUC among different subjects with above doses cannot be attributed to the two different formulations. The probable reason for such difference could be due to inter-individual variation in the pharmacokinetic profile, for which optimization of dosing based on monitoring of MPA AUC is proposed.

In the present study, for EC-MPS patients, three sampling time points *i.e*. 2, 4 and 9 h were used for MPA AUC calculation on basis of recent reports[21-24]. Treatments of equivalent doses of MMF and EC-MPS have shown bioequivalence and have comparable MPA AUC[20,21]. This was also evident in the present study as both the formulations (EC-MPS and MMF) showed equivalent MPA AUC. In this pilot study the mathematical equation for MPA AUC calculation validated for MMF[8] was used for EC-MPS also. This is as per consideration of little chance for gross difference in the shape of AUC of these two formulations having comparable AUC. Our results are in agreement with the results of previous studies[8,20,25] which have shown delayed peak concentration of approximately 0.5 h with EC-MPS as compared to MMF due to delayed absorption of EC-MPS.

Patients with lower MPA AUC (LR group) had higher tacrolimus trough levels and 3 cases of calcineurin inhibitors induced nephrotoxicity were noted in this group. As a fixed-dose strategy is used for MPA, to maintain good immunosuppression, patients are usually given higher doses of tacrolimus and other immunosuppressants. But considering the impact of calcineurin inhibitors induced nephrotoxicity, the long-term maintenance with lower trough level of tacrolimus along with optimal MPA AUC may be a better option to minimize the role of calcineurin inhibitors induced nephrotoxicity. This is in line with the proposed lower long-term doses of tacrolimus with optimal doses of MMF and EC-MPS[11]. There was no biopsy proven acute rejection in the study patients. However, it was difficult to conclude a definite correlation with the MPA plasma levels due to the small sample size of this study.

In the randomized concentration controlled trial on the safety and efficacy of MMF, van Gelder

et al[26] demonstrated that MPA AUC correlates with incidence of acute rejection but not with the toxicity. In the present study, there were more incidences of diarrhoea and acidity in the higher MPA AUC groups compared to lower MPA AUC. This is in contrast to the findings of an earlier study[27] wherein the GI side effects and infections had no correlation with AUC, though haematological side effects increased with higher MPA AUC. Our findings were in accordance with the observations of a previous study[28], wherein GI side effects were observed in 42 per cent cases during 3-month study period.

Though patient reported outcomes *i.e*. GSRS and GIQLI scales were validated in post-renal transplant patients[16,19,29], we incorporated evaluation of patient reported outcomes in various ranges of MPA AUC. The mean GSRS score on a 4-graded Likert scale ranged from 0.4 to 0.61 and the mean GIQLI scores ranged from 2.13 to 3.49 in the optimal MPA AUC group (30-60 mg.h/l) and were comparable to those of previous studies[16,19,29]. The GSRS and GIQLI scores were in parallel with clinically reported ADEs. There was significant deterioration of GI symptoms and poor health related quality of life in higher MPA AUC group (HR group) as compared to OR and LR groups. In the three month follow up period there was no change in the treatment pattern which would have led to a change in quality of life. So the difference in patient reported outcomes may be due to inter-individual variability in the quality of life among the subjects in this study.

In conclusion, the results of this exploratory study suggest the potential of plasma level monitoring guided dosage regimen by estimation of MPA AUC with limited sampling strategy in optimizing its use and thus relegating side effect profile of MMF or EC-MPS. However, there is a need of prospective randomized trials with long-term follow up using a larger sample size to demonstrate the ultimate benefit of MPA therapeutic drug monitoring with respect to patient outcome and graft survival.

Acknowledgment

The authors thank the patients and their healthcare providers for participation in this clinical trial. The authors also thank Dr Amber Khaira for his valuable assistance in this trial and Shri Bhupendar for assisting in statistical analysis. The work was funded by Institute Research Grant from All India Institute of Medical Sciences, New Delhi.

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