



## CHAPTER IV

### RESULT

#### 1. Demographic data, the standard curve for determining MPA plasma concentrations, and MPA plasma concentrations data

##### 1.1 Demographic data

There were 25 patients participated in this study, however 2 patients were dropped-out, one was due to non-compliance while another was died. Therefore, only 23 patients data were included for further analysis.

As shown in table 4.1 a, the numbers of male and female patients included in this study were nearly equal, 12 patients (52.17%) were female. The mean  $\pm$  SD of age was  $43.70 \pm 10.02$  years, (range = 20.00 – 58.00 years), the mean  $\pm$  SD of weight was  $58.42 \pm 9.73$  kg, (range = 41.00 – 88.70 kg), the mean  $\pm$  SD of height was  $161.70 \pm 6.35$  cm, (range = 150.00 – 171.00 cm), while the mean  $\pm$  SD of body surface area (BSA) was  $1.6153 \pm 0.1444$  m<sup>2</sup> (range = 1.3157 – 2.0040 m<sup>2</sup>). The ideal body weight (IBW) was  $58.24 \pm 7.62$  kg (range = 45.50 – 69.02 kg) which was very closed to the actual body weight. Mean  $\pm$  SD of body mass index (BMI) was  $22.4963 \pm 3.4094$  kg/m<sup>2</sup> (range = 17.4191 – 33.3848 kg/m<sup>2</sup>). The occupation of most patients was commercial (7 patients = 30.43 %) and the second was government officer (6 patients = 26.09 %).

As shown in table 4.1 b, the mean  $\pm$  SD of duration of hemodialysis before renal transplantation (HD time) was  $35.37 \pm 36.09$  months. The data of 3 patients were missing. There were high variation of HD times. Majority of the donors were cadaveric (78.26 %), 4 were living-donor and 1 was spouse donor. Mean  $\pm$  SD of duration after renal transplantation (KT time) to the time of study was  $21.31 \pm 14.51$

months. Mean  $\pm$  SD of duration which patients received MMF administration (MMF time) was  $20.56 \pm 13.66$  months. It should be noticed that KT time was nearly equal to MMF time, which meant that most of the patients received MMF right after transplantation.

Kidney function of patients was demonstrated by blood urea nitrogen (BUN), serum creatinine (Scr) and creatinine clearance (CrCl). Mean  $\pm$  SD of BUN was  $21.78 \pm 8.42$  mg/dL while mean  $\pm$  SD of Scr was  $1.44 \pm 0.48$  mg/dL and mean  $\pm$  SD of CrCL was  $52.9395 \pm 17.0150$  mL/min, (range = 24.1719 – 83.0231 mL/min). There were 3 patients who have both BUN and Scr higher than mean  $\pm$  SD which were patients number 8 (BUN = 42 mg/dL, Scr = 2.4 mg/dL), number 10 (BUN = 33 mg/dL, Scr = 2.7 mg/dL) and number 22 (BUN = 43 mg/dL, Scr = 2.3 mg/dL).

There were 2 patients who showed abnormality of SGOT and SGPT values but no abnormality of clinical sign was recorded. The data of 3 patients were missing.

None of the patients had smoking or drinking habits. 95.65 % (22 patients) had hypertension as concomitant disease while 56.52 % (13 patients) had hyperlipidemia. Other less common concomitant diseases were demonstrated in table 4.1 c.

Table 4.1 d showed concomitant medications of patients. All patients received triple immunosuppressive regimen which composed of CSA, prednisolone and MMF. Mean  $\pm$  SD of CSA dose was  $141.30 \pm 56.21$  mg daily while CSA level was  $161.13 \pm 60.04$  ng/mL. 11 patients (47.83 %) took MMF 1000 mg daily as base line while 8 patients (34.78 %) took MMF 1500 mg daily and 4 patients (17.39 %) took MMF 2000 mg daily. Mode of prednisolone dose per day was 5 mg daily (12 patients = 52.17 %) while the second common dose was 10 mg daily (30.43 %). The most common CSA sparing agent used was diltiazem (90 % = 18 patients) while the other were diflucan (5 %) and verapamil (5 %). Only 3 patients did not receive any CSA sparing agent. 13 patients (65 %) took single antihypertensive agents while 6 patients (30 %) received combined antihypertensive agents. The most common antihypertensive agents used was the calcium channel blocker especially amlodipine. The most common antihyperlipidemic agent used was atorvastatin (10 patients = 79.62 %). The other concomitant medications were presented in table 4.1 d.

None of the patients received any drugs which could cause either pharmacokinetic or pharmacodynamic drug interactions with MMF, such as antacid, aspirin or cholestyramine.

## 1.2 The standard curve for determining MPA concentrations in plasma samples

After several steps of sample preparation according to the modified method of Na-Bangchang K, et al.<sup>23</sup> and Hosotsubo H, et al.<sup>24</sup> as mentioned in detail in chapter III, the samples were injected into HPLC. The retention time of MPA in the pooled blank plasma was about 9.95 minutes while that of the internal standard was about 7.66 minutes. The chromatogram of MPA and IS in standard solution and the pooled blank plasma were demonstrated in figure 3 and 4, respectively.

### 1. Linearity

The standard curve was created from the plot between MPA concentrations versus peak area ratios of MPA and internal standard. The calibration curve of peak area ratio of MPA to IS versus plasma MPA was linear cover all concentration tested with the coefficient of determination of 0.9987. The standard curve of MPA was plotted as a line of best fit (figure 6). The concentration of MPA in each plasma sample was calculated from this standard curve by using the following equation:

Linear regression equations of MPA concentrations in plasma samples:

$$\text{Peak area ratio} = 0.0695 (\text{Concentration}) - 0.0631$$

### 2. Accuracy

The accuracy in term of percent absolute recovery for all concentration was between 92.69 % to 102.48 %. The results implied that the method gave sufficient accuracy.



### 3. Precision

The within run expressed as percent coefficient of variations were 1.07-9.66 % (the % CV at concentrations of 2, 20, 40, 80 mcg/mL were 9.66, 4.78, 4.67 and 1.07, respectively) while the between run expressed as percent coefficient of variations were 1.07-9.66 % and 0.79 – 9.72 % (the %CV at concentrations of 2, 20, 40, 80 mcg/mL were 9.72, 4.22, 3.35 and 0.79, respectively).

### 4. Specificity and selectivity

Six different blank plasma showed no interfering endogenous substances eluting at the retention time of MPA (figure 5A). Potentially coadministered immunosuppressive drug (CSA and steroids) were not detected with the described analytical method. Chromatogram of MPA and IS from patients plasma were shown in figure 5B.

## 1.3 MPA plasma concentrations data

Forty five pharmacokinetic profiles were collected and analyzed. It was found that majority of patients reached the maximum concentration ( $T_{max}$ ) within 0.5 (46.51 %) and 1.0 (51.16 %) hours after MMF dosing. MMF dose, MPA plasma levels and 12-hours MPA AUC from actual collected data and from actual collected plus predicted data were shown in table 4.1 e and 4.1 f, respectively. Example of individual plasma MPA concentrations-time profiles was shown in figure 7. Mean plasma MPA concentrations-time profiles after consuming different MMF doses (1,000, 1,500 and 2,000 mg per day) were demonstrated in figure 8.



Table 4.1a Demographic data of the patients

Patient number	Gender	Age (years)	Weight (kg)	Height (cm)	BSA (m <sup>2</sup> )	IBW (kg)	BMI (kg/m <sup>2</sup> )	Occupation	Status	Region	Allergy
1.PROJ	M	38.00	48.00	166.00	1.4877	64.4882	17.4191	E	M	C	(-)
2.TP	M	55.00	70.10	171.00	1.8248	69.0157	23.9732	G	M	C	(-)
3.AN	M	37.00	54.00	169.00	1.5922	67.2047	18.9069	G	M	C	(-)
4.SW	F	56.00	50.00	150.00	1.4434	45.5000	22.2222	U	M	O	(-)
5.PIRAT	M	51.00	56.50	170.00	1.6334	68.1102	19.5502	U	M	C	(-)
6.SPN	F	49.00	52.00	160.00	1.5202	54.5551	20.3125	U	M	C	(-)
7.JVD	F	44.00	54.00	158.00	1.5395	52.7441	21.6311	G	S	O	(-)
8.NVR	F	34.00	41.00	152.00	1.3157	47.3110	21.1111	C	M	C	(-)
9.AR	F	40.00	63.00	159.00	1.6681	53.6496	24.9199	G	M	C	(-)
10.VN	M	52.00	65.00	165.00	1.7260	63.5827	23.8751	G	M	O	(-)
11.JR	M	37.00	49.90	167.00	1.5214	65.3937	17.8924	G	S	C	(-)
12.VB	M	45.00	59.50	165.00	1.6514	63.5827	21.8549	E	S	C	(-)
13.JP	M	44.00	57.70	154.00	1.5711	53.6220	24.3296	C	M	C	(-)
14.PCN	F	58.00	63.10	154.00	1.6429	49.1220	26.6065	C	M	O	(-)
15.BM	M	49.00	55.70	167.00	1.6074	65.3937	19.9720	C	M	O	(-)
16.CHAN	F	50.00	60.30	160.00	1.6371	54.5551	23.5547	G	M	C	(-)
17.NP	F	20.00	49.50	158.00	1.4739	52.7441	19.8286	S	S	C	amoxicillin

Table 4.1a Demographic data of the patients (continue)

Patient number	Gender	Age (years)	Weight (kg)	Height (cm)	BSA (m <sup>2</sup> )	IBW (kg)	BMI (kg/m <sup>2</sup> )	Occupation	Status	Region	Allergy
18.DK	F	21.00	88.70	163.00	2.0040	57.2717	33.3848	S	S	C	vancomycin
19.PCR	F	43.00	52.60	157.00	1.5146	51.8386	21.3396	U	M	O	amoxicillin, vancomycin
20.ANS	M	47.00	62.50	168.00	1.7078	66.2992	22.1443	C	M	O	nifedipine, amlodipine
21.PP	F	35.00	61.00	154.00	1.6154	49.1220	25.7210	C	M	O	(-)
22.SK	F	54.00	58.70	162.00	1.6253	56.3661	22.3670	G	M	C	(-)
23.NRL	M	46.00	70.80	170.00	1.8285	68.1102	24.4983	C	M	C	(-)
Mean	F=12(52.17%)	43.70	58.42	161.70	1.6153	22.4963	22.4963	E=4(17.39%)	S=5(21.74%)	C=15(65.22%)	
SD	M=11(47.38%)	10.02	9.73	6.35	0.1444	3.4094	3.4094	U=4(17.39%)	M=18(78.26%)	O=8(34.78%)	
SE		2.09	2.03	1.32	0.0301	0.7109	0.7109	G=6(26.09%)			
Min		20.00	41.00	150.00	1.3157	17.4191	17.4191	C=7(30.43%)			
Max		58.00	88.70	171.00	2.0040	33.3848	33.3848	S=2(8.70%)			

Abbreviations ; BSA = Body surface area =  $\{(Weight[kg]*Height[cm])/3600\}^{1/2}$  Type = Type of donors ; L = Living related donor ,

C = cadaveric donor ; BMI = Body mass index =  $Weight [kg] / Height(2) [inch]$

IBW = Ideal body weight =  $50 + (2.3 * (Height over 5 foot [inch]) for a man; 45.5 + 2.3 * (Height [inch] over 5 feet) for a woman$

Occupation; U = unemployed, E = employee, C = commercial, A = agriculturist, G = government officer, S = student

Status = Marital status; M = married, S = single



**Table 4.1 b Duration of hemodialysis, kidney transplantation and MMF administration including kidney function and liver function of the patients**

Patient number	HD time (mo)	Type (C,L)	KT time (mo)	MMF time (mo)	BUN (mg/dL)	Scr (mg/dL)	CrCL (mL/min)	TB/DB	SGOT (IU/L)	SGPT (IU/L)
1.PROJ	132.00	L	1.43	1.43	24.00	1.30	70.2776	1.63/1.2	33.00	86.00
2.TP	(-)	C	15.53	15.53	20.00	1.60	50.923	0.49/0.22	17.00	11.00
3.AN	(-)	C	15.00	15.00	18.00	1.40	68.6667	0.78/0.25	18.00	18.00
4.SW	36.00	C	32.33	32.33	20.00	1.50	30.0806	0.56/0.24	27.00	18.00
5.PIRAT	34.00	C	26.60	26.60	20.00	1.30	64.7646	0.83/0.39	21.00	7.00
6.SPN	(-)	L	7.90	7.90	17.00	1.00	58.6088	0.8/0.44	52.00	77.00
7.JVD	14.00	C	9.20	9.20	10.00	0.80	74.7208	0.79/0.24	17.00	13.00
8.NVR	#	L	19.37	19.37	42.00	2.40	24.1719	0.28/0.12	8.00	9.00
9.AR	48.00	C	28.20	27.97	19.00	1.30	48.5568	0.85/0.25	17.00	18.00
10.VN	11.00	C	33.93	29.73	33.00	2.70	28.7811	(-)	(-)	(-)
11.JR	7.00	L	42.87	42.87	17.00	1.30	71.961	1.75/0.48	18.00	20.00
12.VB	42.00	C	16.60	16.60	19.00	1.60	52.4314	0.29/0.23	18.00	14.00
13.JP	120.00	C	22.47	22.47	24.00	1.10	64.9964	0.87/0.29	49.00	49.00
14.PCN	4.00	C	44.13	31.13	14.00	1.00	47.5528	0.48/0.20	13.00	13.00
15.BM	8.00	C	32.50	32.50	26.00	1.50	55.1002	0.37/0.11	19.00	23.00
16.CHAN	43.00	C	11.80	11.80	13.00	1.10	52.6953	0.84/0.33	20.00	21.00



**Table 4.1 b Duration of hemodialysis, kidney transplantation and MMF administration including kidney function and liver function of the patients (continue)**

Patient number	HD time (mo)	Type (C,L)	KT time (mo)	MMF time (mo)	BUN (mg/dL)	Scr (mg/dL)	CrCL (mL/min)	TB/DB	SGOT (IU/L)	SGPT (IU/L)
17.NP	60.00	C	5.50	5.50	13.00	0.90	83.0231	0.37/0.14	17.00	26.00
18.DK	24.00	C	33.47	33.47	17.00	1.10	64.6467	0.44/0.14	16.00	21.00
19.PCR	12.00	L	6.13	6.13	30.00	1.40	42.4017	0.54/0.25	19.00	25.00
20.ANS	5.00	C	41.03	41.03	18.00	1.30	65.8742	0.92/0.80	15.00	7.00
21.PP	6.00	C	41.90	41.90	21.00	1.80	33.8282	0.37/0.11	12.00	8.00
22.SK	36.00	C	1.23	1.23	43.00	2.30	24.8831	(-)	(-)	(-)
23. NRL	30.00	C	1.10	1.10	23.00	1.40	38.6615	(-)	(-)	(-)
Mean	35.37	L=5(21.74%) C=18(78.26%)	21.31	20.56	21.78	1.44	52.9395	0.71/0.32	21.30	24.20
SD	36.09		14.51	13.66	8.42	0.48	17.0150	0.39/0.26	11.23	21.76
SE	7.53		3.03	2.85	1.75	0.10	3.5479	0.08/0.05	2.34	4.54
Min	4.00		1.10	1.10	10.00	0.80	24.1719	0.28/0.11	8.00	7.00
Max	132.00		44.13	42.87	43.00	2.70	83.0231	1.75/1.20	52.00	86.00

Abbreviations ; HD time = Duration of hemodialysis before kidney transplantation ; KT time = Duration time after kidney transplantation

MMF time= Duration time after MMF administration ; BUN = blood urea nitrogen ; Scr = serum creatinine ; CrCL = creatinine clearance ;

TB/DB = total bilirubin/directed bilirubin ; # = CAPD ; SGOT = serum glutamic-oxaloacetic transaminases

Type = Type of donors; L = living donor, C =cadaveric donor ; SGPT = serum glutamic-pyruvic transaminases (-) = missing data

**Table 4.1c Social habit and concomitant diseases of the patients**

Patient number	Smoking habit	Drinking habit	Concomitant diseases			
			HTN	HLP	HGLY	Convulsion
1.PROJ	-	-	HTN	HLP	-	-
2.TP	-	-	HTN	HLP	-	Convulsion
3.AN	-	-	HTN	HLP	-	-
4.SW	-	-	HTN	-	-	-
5.PIRAT	-	-	HTN	HLP	-	-
6.SPN	-	-	HTN	-	-	-
7.JVD	-	-	HTN	HLP	-	-
8.NVR	-	-	HTN	HLP	-	-
9.AR	-	-	HTN	HLP	-	-
10.VN	-	-	HTN	HLP	-	-
11.JR	-	-	HTN	-	-	-
12.VB	-	-	-	HLP	-	-
13.JP	-	-	HTN	-	-	-
14.PCN	-	-	HTN	-	-	-
15.BM	-	-	HTN	-	-	-
16.CHAN	-	-	HTN	HLP	-	-
17.NP	-	-	HTN	HLP	-	-
18.DK	-	-	HTN	HLP	-	-
19.PCR	-	-	HTN	HLP	HGLY	-
20.ANS	-	-	HTN	-	-	-
21.PP	-	-	HTN	-	-	-
22.SK	-	-	HTN	-	-	-
23.NRL	-	-	HTN	-	-	-
<b>%</b>	<b>0</b>	<b>0</b>	<b>95.65</b>	<b>56.52</b>	<b>4.35</b>	

Abbreviations: HTN=Hypertension; HLP = Hyperlipidemia ; HGLY = Hyperglycemia

Table 4.1 d Concomitant medication of the patients

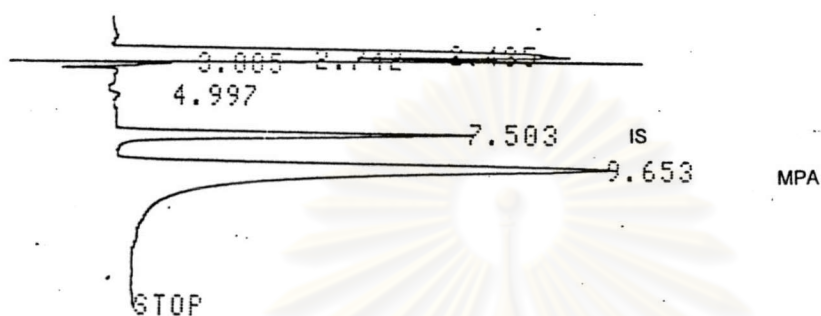
Name	Immunosuppressive agents				CSA- sparing agents	Antihypertensive agents	Antihyperlipidemic agents	Other		
	CSA (mg/day)	CSA level (ng/mL)	MMF (mg/day)	Pred (mg/day)				bactrim	senokot	senokot
1.PROJ	75	321.00	1000	10	(-)	(-)	simvastatin	bactrim	senokot	(-)
2.TP	200	191.00	2000	10	diltiazem	manidipine	atorvastatin	senokot	arbamazepin	phenobarb
3.AN	100	249.00	2000	10	diltiazem	atenolol	simvastatin	(-)	(-)	(-)
4.SW	150	79.00	1000	10	(-)	enalapril	(-)	(-)	(-)	(-)
5.PIRAT	125	172.00	2000	5	diltiazem	amlodipine, ramipril	atorvastatin	(-)	(-)	(-)
6.SPN	125	194.00	1500	10	diltiazem	doxazosin	(-)	(-)	(-)	(-)
7.JVD	175	183.00	1000	5	diltiazem	amlodipine	atorvastatin	Bco	(-)	(-)
8.NVR	175	96.00	1500	5	diltiazem	amlodipine	atorvastatin	omeprazole	folic acid	sodamint
9.AR	125	166.00	1500	5	diltiazem	amlodipine	atorvastatin	(-)	(-)	(-)
10.VN	100	118.00	2000	5	diltiazem	blopress	atorvastatin	(-)	(-)	(-)
11.JR	100	121.00	1000	5	diltiazem	felodipine, minoxidil		ranitidine	(-)	(-)
12.VB	175	134.00	1500	5	(-)	(-)	atorvastatin	acyclovir	(-)	(-)
13.JP	175	163.00	1000	20	diltiazem	felodipine, doxazosin	(-)	(-)	(-)	(-)
14.PCN	100	116.00	1000	5	diltiazem	felodipine	(-)	(-)	(-)	(-)
15.BM	100	117.00	1000	5	diltiazem	doxazosin	(-)	ranitidine	(-)	(-)
16.CHAN	100	159.00	1500	2.5	diltiazem	(-)	atorvastatin	bactrim	(-)	(-)



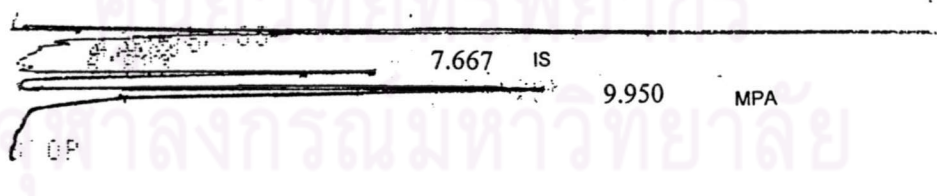
Table 4.1 d Concomitant medication of the patients (continue)

Name	Immunosuppressive agents			CSA- sparing agents	Antihypertensive agents	Antihyperlipidemic agents	Other			
	CSA (mg/day)	CSA level (ng/mL)	MMF (mg/day)				Pred (mg/day)			
17.NP	125	166.00	1000	10	diltiazem	amlodipine,atenolo!	simvastatin	(-)	(-)	(-)
18.DK	150	131.00	1000	5	diltiazem	mlodipine,doxazosi	atorvastatin	(-)	(-)	(-)
19.PCR	125	274.00	1500	10	diltiazem	doxazosin	atorvastatin	bactrim	mycostatin	(-)
20.ANS	150	121.00	1000	5	verapamil	elodipine,propranolo	(-)	(-)	(-)	(-)
21.PP	100	92.00	1000	5	diltiazem	(-)	(-)	folic acid	(-)	(-)
22.SK	350	127.00	1500	20	diltiazem	nifedipine	(-)	famciclovir	swift	folic acid
23.NRL	150	216.00	1500	20	diflucan	nifedipine	(-)	bactrim	swift,senokot	sodamint
Mean	141.30	161.13	1347.83	8.37						
SD	56.21	60.04	382.42	5.20						
SE	11.72	12.52	79.74	1.08						
Min	75.00	79.00	1000.00	2.50						
Max	350.00	321.00	2000.00	20.00						

Abbreviations ; CSA = cyclosporin ; MMF = mycophenolate mofetil ; pred = prednisolone



**Figure 3 : Chromatogram of MPA ( 30 mcg/mL) and IS (4 mcg/mL)  
from standard solution**



**Figure 4 : Chromatogram of MPA ( 30 mcg/mL) and IS (4 mcg/mL)  
from pooled blank plasma**

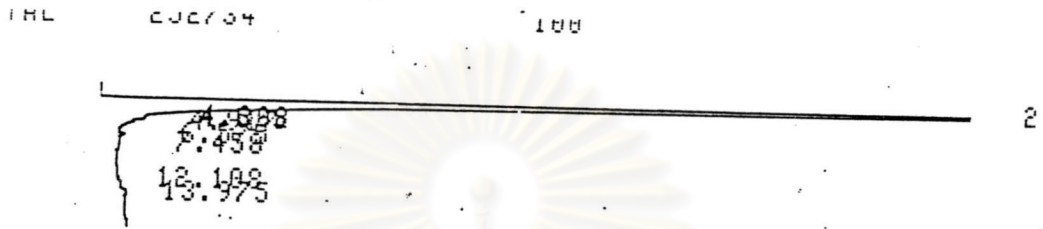


Figure 5 A : Chromatogram of pooled blank plasma

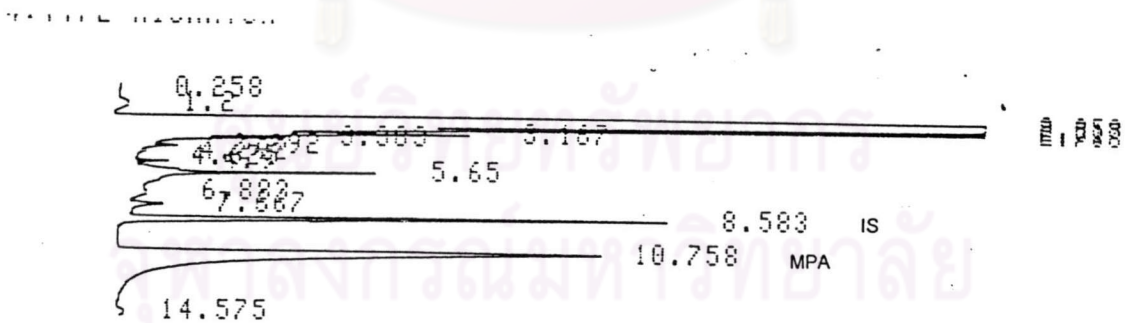


Figure 5 B : Chromatogram of MPA and IS from patients plasma  
( Concentration equaled to 22.80 mcg/mL)



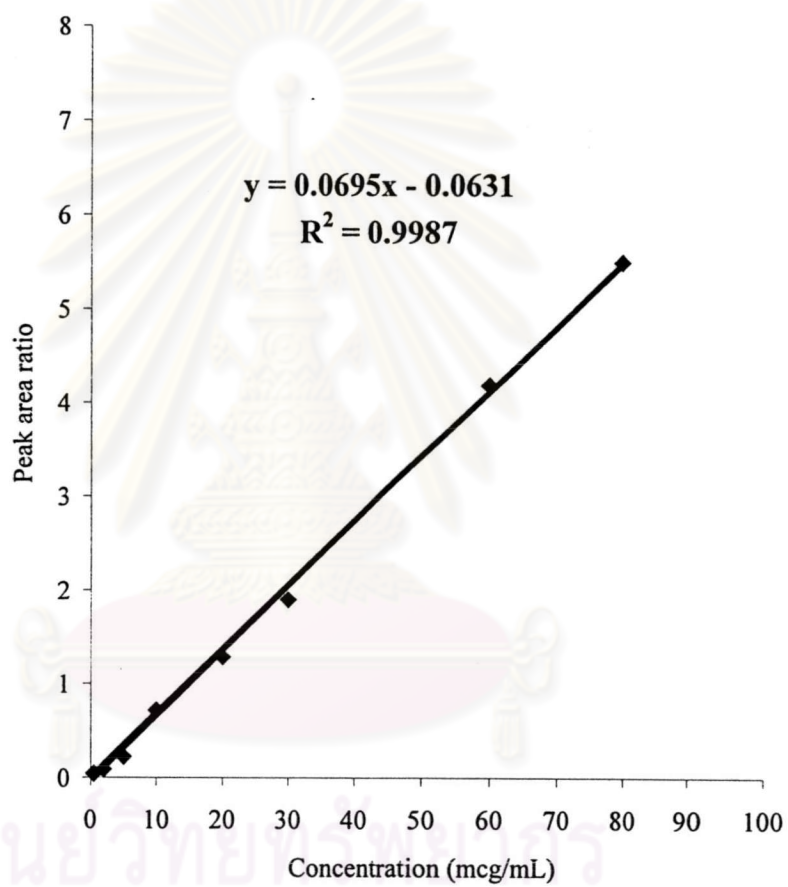


Figure 6: The standard curve of MPA in plasma

Table 4.1e MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected data

Name	MMF dos mg/day	C0 mcg/mL	C0.25 mcg/mL	C0.5 mcg/mL	C1 mcg/mL	C2 mcg/mL	C3 mcg/mL	C4 mcg/mL	C6 mcg/mL	C12 mcg/mL	MPA AUC mcg*hr/mL
1. PROJ*	1000	1.1774	0.8200	0.7250	10.9497	6.1190	2.0182	0.5416	1.4272	nd	23.4947
	1500	nd	-	-	3.6611	-	8.8002	-	3.8552	-	47.2958
	2000	2.3947	-	-	10.5750	-	9.4239	-	2.0431	-	56.9977
2. TP	1500	1.9932	-	27.2109	26.3015	-	3.0973	1.9009	2.2759	-	69.5611
	2000	3.7895	14.2912	48.2767	22.1750	5.5230	4.0811	3.7492	7.2070	3.5225	93.4048
3. AN	1500	3.2647	-	8.6511	39.6006	-	6.5806	4.2973	3.9461	-	74.9054
	2000	5.8795	17.3063	36.6196	34.8207	9.2397	4.0882	4.1818	3.3182	2.8434	86.3130
4. SW	1000	2.3881	3.3190	7.4335	19.9816	7.4622	3.7149	3.0634	1.9387	2.4458	49.7664
	1500	3.2045	-	21.9335	27.2740	-	5.3456	3.0897	3.0123	-	79.0461
5. PIRAT	2000	5.1890	26.2948	54.2648	29.4250	11.5063	4.5551	2.2514	5.3673	4.5412	104.1716
6. SPN	1500	0.8324	7.2053	65.9166	10.4715	2.3890	1.2327	1.1871	1.9827	0.5955	49.5951
	2000	1.1858	-	80.4166	31.4701	-	2.8833	4.0397	0.6888	-	61.6633
7. JVD	1000	2.3402	38.4896	69.0033	27.9927	6.4593	2.7973	2.8333	2.0396	1.2496	82.7237
	1500	3.2085	-	-	36.8756	-	1.6624	-	1.7105	-	78.3962
	2000	3.0683	-	-	44.8917	-	9.4903	-	4.5110	-	122.1017
8. NVR**	1500	6.8704	41.5925	46.4746	41.8508	4.0743	1.0520	1.6723	nd	8.0564	104.9503

Abbreviation ; - = missing data

nd = not detectable

Table 4.1e MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected data (continue)

Name	MMF dos mg/day	C0 mcg/mL	C0.25 mcg/mL	C0.5 mcg/mL	C1 mcg/mL	C2 mcg/mL	C3 mcg/mL	C4 mcg/mL	C6 mcg/mL	C12 mcg/mL	MPA AUC mcg*hr/mL
9. AR	1500	3.5255	6.4862	25.3862	23.3081	16.3684	6.8280	5.7920	4.2238	2.2475	84.5851
	2000	3.7060	-	39.8862	28.3910	-	7.9589	4.0397	4.6333	-	96.2267
10. VN**	1500	2.4023	-	11.7385	10.0480	-	2.7882	2.9152	2.5918	-	45.1587
	2000	5.7212	19.9520	46.3292	40.4296	8.9068	5.4809	4.6125	3.5779	4.6270	102.8979
11. JR*	1000	2.6806	2.5036	11.6975	22.3548	14.5810	6.4643	5.5386	1.9629	4.0029	71.3272
	1500	3.2045	-	26.1975	27.2740	-	5.3456	3.0897	3.0123	-	79.0461
	2000	3.0618	-	40.6975	52.0498	-	12.8018	4.0397	4.0564	-	139.0493
12. VB**	1000	2.4688	-	26.6483	21.6492	-	2.6317	2.0064	1.7714	-	62.4519
	1500	4.5948	4.8982	2.7919	37.9542	13.7443	4.3800	3.0317	2.6795	3.5882	75.4664
13. JP*	1000	3.1179	3.1451	3.6038	30.3249	9.8796	3.9330	3.4512	3.8879	1.9113	65.5461
	1500	3.7562	-	56.1285	33.0133	-	3.0835	3.7130	2.3198	-	99.6862
	2000	4.2631	-	45.0298	37.2893	-	6.2048	4.4287	6.9283	-	126.6462
14. PCN	1000	1.6442	1.6592	2.5304	25.9100	12.0688	4.9422	2.4837	1.1890	2.4699	53.9078
	1500	3.6394	-	15.7231	19.3167	-	5.3661	4.3166	5.1117	-	78.1307
	2000	4.2412	-	11.3270	14.0243	-	10.7590	4.7054	3.3907	-	73.7355

Abbreviation; - = missing data



Table 4.1e MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected data (continue)

Name	MMF dos mg/day	C0 mcg/mL	C0.25 mcg/mL	C0.5 mcg/mL	C1 mcg/mL	C2 mcg/mL	C3 mcg/mL	C4 mcg/mL	C6 mcg/mL	C12 mcg/mL	MPA AUC mcg*hr/mL
15. BM	1000	0.8637	18.0503	22.8037	20.4894	3.9169	1.4792	2.8140	2.4973	0.8637	50.5501
	1500	0.8684	-	27.7167	33.3493	-	3.1278	4.3922	4.3718	-	87.1344
	2000	2.7510	-	43.6228	31.9478	-	2.1685	1.9513	4.0636	-	93.1208
16. CHAN	1000	1.1035	-	53.4576	23.0484	-	1.0404	0.8314	0.8314	-	65.2595
	1500	1.6696	19.0487	64.3390	67.4017	12.6307	4.5963	4.8362	1.7191	-	114.9413
17. NP	1000	1.0103	5.7146	14.3869	37.4995	3.5499	1.2111	1.1358	1.5935	0.8662	50.5119
	1500	1.1288	-	46.6517	27.1913	-	1.4535	1.1983	1.4078	-	70.5923
18. DK	1000	1.0583	1.3918	11.4534	19.1658	4.6904	1.8875	1.3299	1.2560	0.9280	35.5306
	1500	1.5647	-	7.1983	28.1439	-	4.1926	2.9460	1.2641	-	59.6287
19. PCR**	1500	3.5310	40.1578	66.5028	32.3837	6.1365	2.5511	1.1494	1.7112	3.8914	88.6376
20. ANS	1000	2.8626	4.5032	11.2137	30.4081	6.1423	2.5364	1.1765	0.9281	1.0384	45.7661
21. PP	1000	6.4591	25.2012	33.9696	16.3518	6.0420	5.0325	3.1891	1.7876	6.6366	72.8737
22. SK	1500	4.0525	17.8849	27.5664	17.4673	13.7414	2.5686	2.9189	3.0631	4.8003	75.7574
23. NRL	1500	2.1837	2.2834	3.6025	7.6672	5.6835	2.5577	2.5343	2.3698	2.2986	36.3629

Abbreviation ; - = missing data

Table 4.1f MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected plus predicted data

Patient No.	MMF dose (mg/day)	C0 (mcg/mL)	C0.25 (mcg/mL)	C0.5 (mcg/mL)	C1 (mcg/mL)	C2 (mcg/mL)	C3 (mcg/mL)	C4 (mcg/mL)	C6 (mcg/mL)	C12 (mcg/mL)	MPA AUC (mcg*hr/mL)
1.PROJ*	1000	1.1774	0.8200	0.7250	10.9497	6.1190	2.0182	0.5416	1.4272	nd	23.4947
	1500*	nd	1.2000	1.0500	3.6611	9.1200	8.8002	0.7500	3.8552	0.0000	45.2592
	2000	2.3947	1.6000	1.4000	10.575	12.2000	9.4239	1.0000	2.0431	0.0000	56.9977
	Equation,= [R square]	0.0038294*D [1]	0.003404*D [1]	0.003927*D [1]	0.009076*D [1]	0.01006*D [1]	0.004179*D [1]	0.002770*D [1]	0.001789*D [1]	0.001767*D [1]	0.04046*D [1]
2.TP	1000	1.6694	7.1000	21.3103	14.0824	2.8000	2.0054	1.5599	2.6185	1.8000	46.5242
	1500	1.9932	10.6500	27.1746	26.2666	4.2000	3.0958	1.9011	2.2755	2.7000	69.5611
	2000	3.7895	14.2912	48.2767	22.1750	5.5230	4.0811	3.7492	7.2070	3.5225	93.4048
	Equation,= [R square]	0.0018*D-0.1306 [0.9383]	0.0071*D [1]	0.0227*D-1.3897 [0.9571]	0.0126*D+1.4824 [0.8570]	0.0028*D [1]	0.002*D+0.0054 [0.9999]	0.0017*D-0.1401 [0.9274]	0.0031*D-0.4815 [0.7779]	0.0018*D [1]	0.0466*D-0.0758 [1]
3.AN	1000	2.6239	8.7000	12.5056	21.5746	4.6000	3.1407	2.4786	2.1242	1.4000	46.2647
	1500	3.2647	13.0500	8.6511	39.6006	6.9000	6.5806	4.2973	3.9461	2.1000	74.9054
	2000	5.8795	17.3063	36.6196	34.8207	9.2397	4.0882	4.1818	3.3182	2.8434	86.3130
	Equation,= [R square]	0.0028*D-0.1761 [0.9535]	0.0087*D [1]	0.0154*D-2.8944 [0.7027]	0.0195*D+2.0746 [0.8803]	0.0046*D [1]	0.0026*D+0.5407 [0.6557]	0.0023*D+0.1786 [0.9308]	0.0019*D+0.2242 [0.8546]	0.0014*D [1]	0.0447*D+1.5647 [0.9855]

Abbreviations: \*\* = serious GAE

\* = mild GAE

= predicted data

D = MMF dose

nd = not detectable



**Table 4.1f MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected plus predicted data (continue)**

Patient No.	MMF dose (mg/day)	C0 (mcg/mL)	C0.25 (mcg/mL)	C0.5 (mcg/mL)	C1 (mcg/mL)	C2 (mcg/mL)	C3 (mcg/mL)	C4 (mcg/mL)	C6 (mcg/mL)	C12 (mcg/mL)	MPA AUC (mcg*hr/mL)
4.SW	1000	2.3881	3.3190	7.4335	19.9816	7.4622	3.7149	3.0634	1.9387	2.4458	49.7664
	1500	3.2045	4.9500	11.1000	27.2740	11.2500	5.3456	4.6500	3.0123	3.6000	79.0461
	2000	4.4540	6.6000	14.8000	37.1855	15.0000	7.2324	6.2000	3.9851	4.8000	103.9719
	Equation,= [R square]	0.0022*D+0.054 [0.9927]	0.0033*D [1]	0.0074*D [1]	0.0184*D+0.3855 [0.9948]	0.0075*D [1]	0.0036*D+0.0324 [0.9990]	0.0031*D [1]	0.002*D-0.0149 [0.9993]	0.0024*D [1]	0.0523*D-0.6281 [0.9983]
5.PIRAT	1000	2.6000	13.1000	27.1000	14.7000	5.8000	2.3000	1.1000	2.7000	2.3000	52.1
	1500	3.9000	19.6500	40.6500	22.0500	8.7000	3.4500	1.6500	4.0500	3.4500	78.15
	2000	5.1890	26.2948	54.2648	29.4250	11.5063	4.5551	2.2514	5.3673	4.5412	104.1716
	Equation,= [R square]	0.0026*D [1]	0.0131*D [1]	0.0271*D [1]	0.0147*D [1]	0.0058*D [1]	0.0023*D [1]	0.0011*D [1]	0.0027*D [1]	0.0023*D [1]	0.0521*D [1]
6.SPN	1000	0.5912	4.8000	43.9000	11.6798	1.6000	1.1570	0.8000	0.8256	0.0000	30.8075
	1500	0.8324	7.2053	65.9166	10.4715	2.3890	1.2327	1.1871	1.9827	0.5955	49.5951
	2000	1.1858	9.6000	87.8000	31.4701	3.2000	2.8833	1.6000	0.6888	0.8000	56.0396
	Equation,= [R square]	0.0006*D-0.0088 [0.9973]	0.0048*D [1]	0.0439*D [1]	0.0137*D-2.0202 [0.7934]	0.0016*D [1]	0.0013*D-0.1430 [0.8729]	0.0008*D [1]	0.0006*D+0.2256 [0.3473]	0.0004*D [1]	0.0287*D+2.1075 [0.9813]

Abbreviations: \*\* = serious GAE      \* = mild GAE      = predicted data      D = MMF dose



Table 4.1f MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected plus predicted data (continue)

Patient No.	MMF dose (mg/day)	C0 (mcg/mL)	C0.25 (mcg/mL)	C0.5 (mcg/mL)	C1 (mcg/mL)	C2 (mcg/mL)	C3 (mcg/mL)	C4 (mcg/mL)	C6 (mcg/mL)	C12 (mcg/mL)	MPA AUC (mcg*hr/mL)
7.JVD	1000	2.3402	38.4896	69.0053	27.9927	6.4593	2.7973	2.8333	2.0396	1.2496	82.7237
	1500	3.2085	57.7500	103.5000	36.8756	9.7500	1.6624	4.2000	1.7105	1.8000	78.3962
	2000	3.0683	77.0000	138.0000	44.8917	13.0000	9.4903	5.6000	4.5110	2.4000	122.1017
	Equation;= R square	0.0016*D+0.3052 [0.8924]	0.0385*D [1]	0.069*D [1]	0.0227*D+1.9265 [0.9810]	0.0065*D [1]	0.0039*D-0.9239 [0.6468]	0.0028*D [1]	0.0024*D-0.1634 [0.8276]	0.0012*D [1]	0.0576*D+6.0583 [0.9237]
8.NVR**	1000	4.6000	27.7000	31.0000	27.9000	2.7000	0.7000	1.1000	0.0000	5.4000	70.0000
	1500**	6.8704	41.5925	46.4746	41.8508	4.0743	1.0520	1.6723	nd	8.0564	104.9503
	2000	9.2000	55.4000	62.0000	55.8000	5.4000	1.4000	2.2000	0.6600	10.8000	140.0000
	Equation;= R square	0.0046*D [1]	0.0277*D [1]	0.031*D [1]	0.0279*D [1]	0.0027*D [1]	0.0007*D [1]	0.0011*D [1]	0.00033*D [1]	0.0054*D [1]	0.07*D [1]
9.AR	1000	2.1148	4.3000	16.9000	14.8100	10.9000	4.2321	3.9000	2.5152	1.5000	51.9100
	1500	3.5255	6.4862	25.3862	23.3081	16.3684	6.8280	5.7920	4.2238	2.2475	84.5851
	2000	3.7060	8.6000	33.8000	28.3910	21.8000	7.9589	7.8000	4.6333	3.0000	96.2267
	Equation;= R square	0.002*D+0.1148 [0.9608]	0.0043*D [1]	0.0169*D [1]	0.0145*D+0.3100 [0.9945]	0.0109*D [1]	0.0041*D+0.1321 [0.9878]	0.0039*D [1]	0.0024*D+0.1152 [0.9738]	0.0015*D [1]	0.05*D+1.91 [0.9828]

Abbreviations: \*\* = serious GAE

\* = mild GAE

= predicted data

D = MMF dose

nd=not detectable

Table 4.1f MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected plus predicted data (continue)

Patient No.	MMF dose (mg/day)	C0 (mcg/mL)	C0.25 (mcg/mL)	C0.5 (mcg/mL)	C1 (mcg/mL)	C2 (mcg/mL)	C3 (mcg/mL)	C4 (mcg/mL)	C6 (mcg/mL)	C12 (mcg/mL)	MPA AUC (mcg*hr/mL)
10.VN**	1000	2.3094	10.0000	16.0602	13.9809	4.5000	2.2965	2.1163	1.7859	2.3000	41.5947
	1500	2.4023	15.0000	11.7385	10.0480	6.7500	2.7882	2.9152	2.5918	3.4500	45.1587
	2000**	5.7212	19.9520	46.3292	40.4296	8.9068	5.4809	4.6125	3.5779	4.6270	102.8979
	Equation,= [R square]	0.0026*D-0.2906 [0.8670]	0.01*D [1]	0.0196*D-3.5398 [0.7192]	0.0171*D-3.1191 [0.7146]	0.0045*D [1]	0.0025*D-0.2035 [0.9284]	0.0022*D-0.0837 [0.9833]	0.0018*D-0.0141 [0.9992]	0.0023*D [1]	0.0465*D-4.9253 [0.8814]
11.JR*	1000	2.6806	2.5036	11.6975	22.3548	14.5810	6.4643	5.5386	1.9629	4.0029	71.3272
	1500*	3.2890	3.7500	17.5500	28.0024	21.9000	9.2246	8.2500	2.6018	6.0000	70.6124
	2000	3.0618	5.0000	23.4000	52.0498	29.2000	12.8018	11.0000	4.0564	8.0000	117.6947
	Equation,= [R square]	.0016*D+0.418 [0.8374]	0.0025*D [1]	0.0117*D [1]	0.0243*D-1.7840 [0.9453]	0.0146*D [1]	0.0063*D-0.0016 [0.9987]	0.0055*D [1]	0.002*D-0.0457 [0.9855]	0.004*D [1]	0.0551*D+2.9132 [0.9392]
12.VB**	1000	2.4682	3.3000	26.6128	21.6210	9.2000	2.6308	2.0064	1.7717	2.4000	49.6772
	1500	4.5948	4.8982	2.7919	37.9542	13.7443	4.3800	3.0317	2.6795	3.5832	75.4664
	2000**	5.8725	6.6000	16.1039	48.8110	18.4000	5.7380	3.9968	3.5969	4.8000	100.2642
	Equation,= [R square]	0.003*D-0.1275 [0.9785]	0.0033*D [1]	0.0054*D+5.3039 [0.0794]	0.0248*D-0.7890 [0.9880]	0.0092*D [1]	0.0029*D-0.0620 [0.9945]	0.002*D-0.0032 [1]	0.0018*D-0.0031 [1]	0.0024*D [1]	0.0502*D-0.1358 [0.9999]

Abbreviations; \*\* = serious GAE

\* = mild GAE

= predicted data

D = MMF dose



Table 4.1f MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected plus predicted data (continue)

Patient No.	MMF dose (mg/day)	C0 (mcg/mL)	C0.25 (mcg/mL)	C0.5 (mcg/mL)	C1 (mcg/mL)	C2 (mcg/mL)	C3 (mcg/mL)	C4 (mcg/mL)	C6 (mcg/mL)	C12 (mcg/mL)	MPA AUC (mcg*hr/mL)
13.JP*	1000	3.1179	3.1451	3.6038	30.3249	9.8796	3.9330	3.4512	3.8879	1.9113	65.5461
	1500	3.7562	4.6500	56.1285	33.0133	14.8500	3.0835	3.7130	2.3198	2.8500	99.6862
	2000*	4.2631	6.2000	45.0298	37.2893	19.8000	6.2048	4.4287	6.9283	3.8000	126.6462
	Equation;= [R square]	0.0022*D+0.3419 [0.9377]	0.0031*D [1]	0.0274*D-4.666 [0.6724]	0.0188*D+3.9593 [0.8942]	0.0099*D [1]	0.0028*D+0.1713 [0.8585]	0.0022*D+0.4111 [0.9129]	0.0029*D-0.0312 [0.7491]	0.0019*D [1]	0.064*D+0.9673 [0.9984]
14.PCN	1000	1.6442	1.6592	2.5304	25.9100	12.0688	4.9422	2.4837	1.1890	2.4699	53.9078
	1500	3.6394	2.5500	15.7231	19.3167	18.1500	5.3661	4.3166	5.1117	3.7500	78.1307
	2000	4.2412	3.4000	11.3270	14.0243	24.2000	10.7590	4.7054	3.3907	5.0000	78.0335
	Equation;= [R square]	0.0022*D-0.1235 [0.9633]	0.0017*D [1]	0.0071*D-0.5717 [0.6723]	0.0074*D+6.4421 [0.3332]	0.0121*D [1]	0.0049*D-0.2919 [0.9205]	0.0025*D+0.0862 [0.9718]	0.0022*D-0.0124 [0.6588]	0.0025*D [1]	0.0415*D+5.8004 [0.9275]
15.BM	1000	0.8637	18.0503	22.8037	20.4894	3.9169	1.4792	2.8140	2.4973	0.8637	50.5501
	1500	0.8684	27.1500	27.7167	33.3493	5.8500	3.1278	4.3922	4.3718	1.3500	80.5559
	2000	2.7510	36.2000	43.6228	31.9478	7.8000	2.1685	1.9513	4.0636	1.8000	81.2574
	Equation;= [R square]	0.0012*D-0.2291 [0.7789]	0.0181*D [1]	0.0209*D+0.0261 [0.9793]	0.0173*D+1.9556 [0.9211]	0.0039*D [1]	0.0013*D+0.2099 [0.7324]	0.0014*D+0.7451 [0.4100]	0.0022*D+0.222 [0.9097]	0.0009*D [1]	0.0434*D+4.2389 [0.9433]

Abbreviations: \*\* = serious GAE

\* = mild GAE

= predicted data

D = MMF dose



**Table 4.1f MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected plus predicted data (continue)**

Patient No.	MMF dose (mg/day)	C0 (mcg/mL)	C0.25 (mcg/mL)	C0.5 (mcg/mL)	C1 (mcg/mL)	C2 (mcg/mL)	C3 (mcg/mL)	C4 (mcg/mL)	C6 (mcg/mL)	C12 (mcg/mL)	MPA AUC (mcg*hr/mL)
16.CHAN	1000	1.1035	12.7000	53.4576	23.0484	8.4000	1.0404	0.8314	0.8314	0.9000	65.2595
	1500	1.6696	19.0487	64.3390	67.4017	12.6307	4.5963	4.8362	1.7191	1.3115	114.9413
	2000	2.1979	25.4000	91.0369	78.9101	16.8000	5.1663	5.2893	2.1326	1.8000	147.5640
	Equation,= [R square]	0.0011*D-0.0021 [1]	0.0127*D [1]	0.0444*D+2.2639 [0.9697]	0.0418*D-4.6899 [0.8688]	0.0084*D [1]	0.0028*D-0.4337 [0.7734]	0.0011*D-0.06 [0.7248]	0.0009*D [1]	0.0011*D+0.1402 [0.8188]	0.0009*D [1]
17.NP	1000	1.0103	5.7146	14.3869	37.4995	3.5499	1.2111	1.1358	1.5935	0.8662	50.5119
	1500	1.1300	8.5500	46.5874	27.1551	5.2500	1.4543	1.1994	1.4086	1.3500	62.9093
	2000	1.6551	11.4000	53.4103	45.9563	7.0000	2.0518	1.6720	2.1402	1.8000	88.2369
	Equation,= R square	0.0008*D+0.0551 R2=0.9449	0.0057*D [1]	0.0281*D-2.7897 [0.8430]	0.0209*D+4.1563 [0.6776]	0.0035*D [1]	0.001*D+0.0518 [0.9691]	0.0008*D+0.072 [0.9202]	0.001*D+0.1402 [0.8188]	0.0009*D [1]	0.0432*D+1.8369 [0.9787]
18.DK	1000	1.0583	1.3918	11.4534	19.1658	4.6904	1.8875	1.3299	1.2560	0.9280	35.5306
	1500	1.5647	2.1000	7.1983	28.1439	7.0500	4.1926	2.9460	1.2641	1.3500	59.6287
	2000	2.0033	2.8000	12.8260	37.6864	9.4000	5.2055	3.6641	1.8886	1.8000	77.2953
	Equation,= [R square]	0.001*D+0.0033 [0.9999]	0.0014*D [1]	0.0057*D+1.4260 R2=0.5753	0.0188*D+0.0864 R2=0.9997	0.0047*D [1]	0.0027*D-0.1945 R2=0.9400	0.0019*D-0.1359 R2=0.9406	0.0009*D+0.0886 R2=0.8963	0.0009*D [1]	0.0391*D-0.9047 R2=0.9936

Abbreviations: \*\* = serious GAE      \* = mild GAE      = predicted data      D = MMF dose



Table 4.1f MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected plus predicted data (continue)

Patient No.	MMF dose (mg/day)	C0 (mcg/mL)	C0.25 (mcg/mL)	C0.5 (mcg/mL)	C1 (mcg/mL)	C2 (mcg/mL)	C3 (mcg/mL)	C4 (mcg/mL)	C6 (mcg/mL)	C12 (mcg/mL)	MPA AUC (mcg*hr/mL)
19.PCR**	1000	2.4000	26.7000	44.3000	21.6000	4.1000	1.7000	0.8000	1.1000	2.6000	59.1000
	1500	3.5288	40.1029	66.4100	32.3400	6.1305	2.5503	1.1506	1.7116	3.8886	88.6376
	2000**	4.8000	53.4000	88.6000	43.2000	8.2000	3.4000	1.6000	2.2000	5.2000	118.2000
	Equation,= R square	0.0024*D [1]	0.0267*D [1]	0.0443*D R2=1	0.0216*D [1]	0.0041*D [1]	0.0017*D [1]	0.0008*D [1]	0.0011*D [1]	0.0011*D [1]	0.0026*D [1]
20.ANS	1000	2.8626	4.5032	11.2137	30.4081	6.1423	2.5364	1.1765	0.9281	1.0384	45.7661
	1500	4.3500	6.7500	16.8000	45.6000	9.1500	3.7500	1.8000	1.3500	1.5000	68.7000
	2000	5.8000	9.0000	22.4000	60.8000	12.2000	5.0000	2.4000	1.8000	2.0000	91.6000
	Equation,= R square	0.0029*D [1]	0.0045*D [1]	0.0112*D [1]	0.0304*D [1]	0.0061*D [1]	0.0025*D [1]	0.0012*D [1]	0.0009*D [1]	0.0011*D [1]	0.0011*D [1]
21.PP	1000	6.4591	25.2012	33.9696	16.3518	6.0420	5.0250	3.1891	1.7876	6.6366	72.8737
	1500	9.7500	37.8000	51.0000	24.6000	9.0000	7.5000	4.8000	2.7000	9.9000	109.3500
	2000	13.0000	50.4000	68.0000	32.8000	12.0000	10.0000	6.4000	3.6000	13.2000	145.8000
	Equation,= R square	0.0065*D [1]	0.0252*D [1]	0.034*D [1]	0.0164*D [1]	0.006*D [1]	0.005*D [1]	0.0032*D [1]	0.0018*D [1]	0.0018*D [1]	0.0066*D [1]

Abbreviations:

\*\* = serious GAE

\* = mild GAE

= predicted data

D = MMF dose

Table 4.1f MMF dose, MPA plasma levels, 12-hours MPA AUC from actual collected plus predicted data (continue)

Patient No.	MMF dose (mg/day)	C0 (mcg/mL)	C0.25 (mcg/mL)	C0.5 (mcg/mL)	C1 (mcg/mL)	C2 (mcg/mL)	C3 (mcg/mL)	C4 (mcg/mL)	C6 (mcg/mL)	C12 (mcg/mL)	MPA AUC (mcg*hr/mL)
22.SK	1000	2.7000	11.9000	18.4000	11.6000	9.2000	1.7000	1.9000	2.0000	3.2000	50.5000
	1500	4.0525	17.8849	27.5664	17.4673	13.7414	2.5686	2.9189	3.0631	4.8003	75.7574
	2000	5.4000	23.8000	36.8000	23.2000	18.4000	3.4000	3.8000	4.0000	6.4000	101.0000
	Equation,= R square	0.0027*D [1]	0.0119*D [1]	0.0184*D [1]	0.0116*D [1]	0.0092*D [1]	0.0017*D [1]	0.0019*D [1]	0.002*D [1]	0.0032*D [1]	0.0505*D [1]
23.NRL	1000	1.5000	1.5000	2.4000	5.1000	3.8000	1.7000	1.7000	1.6000	1.5000	24.2000
	1500	2.1837	2.2834	3.6025	7.6672	5.6835	2.5577	2.5343	2.3698	2.2986	36.3629
	2000	3.0000	3.0000	4.8000	10.2000	7.6000	3.4000	3.4000	3.2000	3.0000	48.4000
	Equation,= R square	0.0015*D [1]	0.0015*D [1]	0.0024*D [1]	0.0051*D [1]	0.0038*D [1]	0.0017*D [1]	0.0017*D [1]	0.0016*D [1]	0.0015*D [1]	0.0242*D [1]

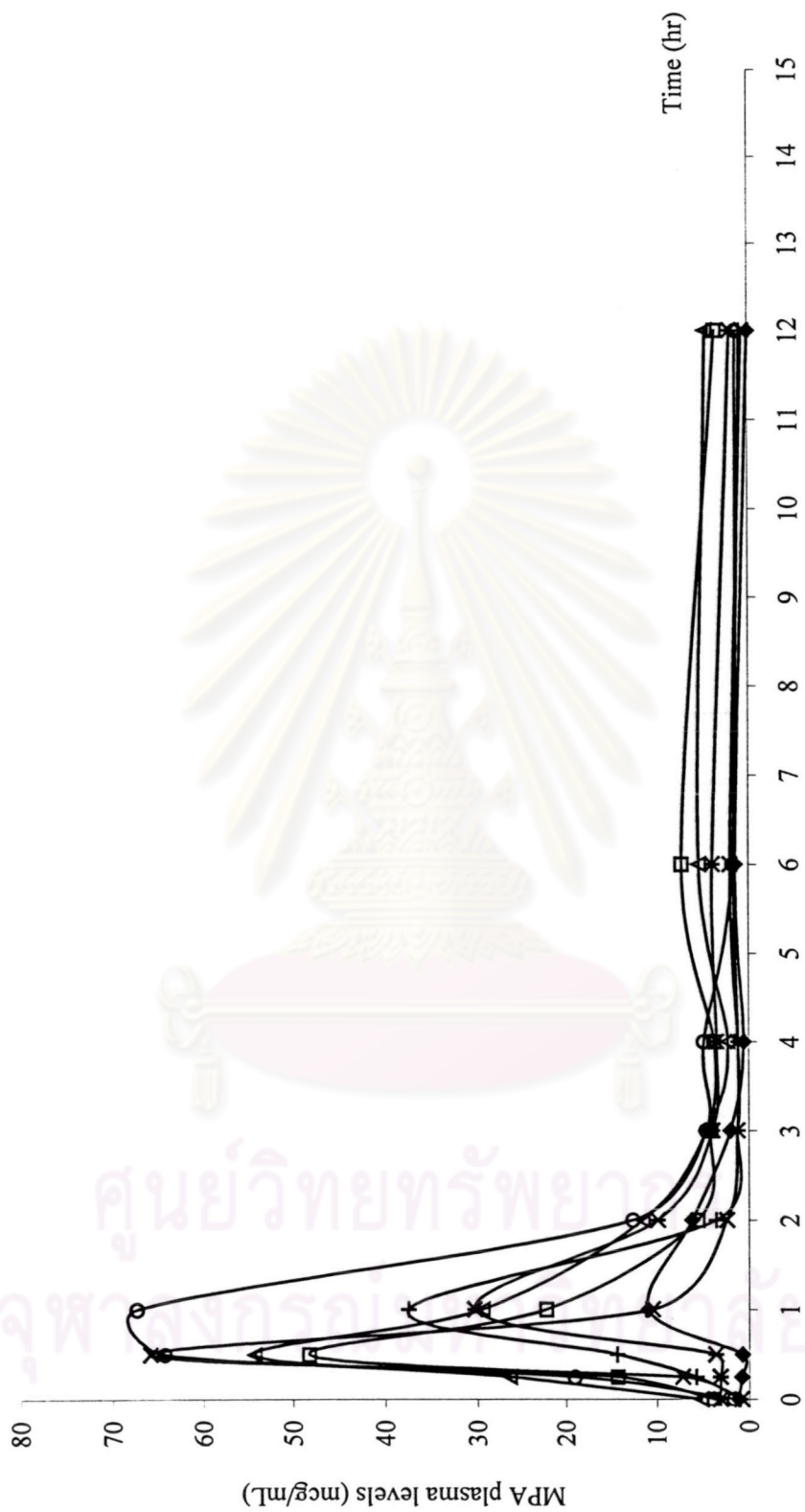
Abbreviations; \*\* = serious GAE

\* = mild GAE

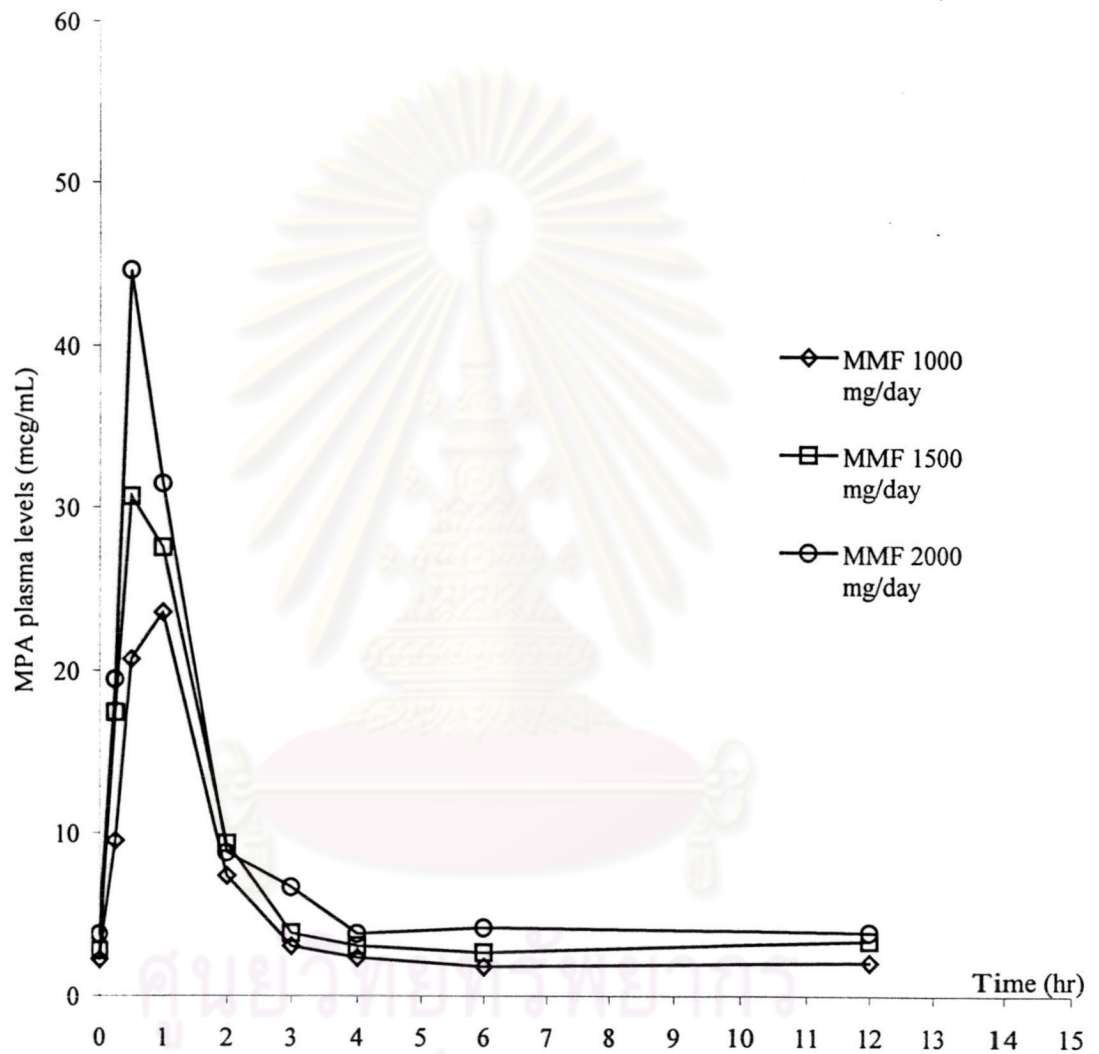
= predicted data

D = MMF dose





**Figure 7 : Example of individual plasma MPA concentration-time profiles**



**Figure 8 : Mean plasma MPA concentration-time profiles after administering different MMF doses**

## 2. Relationship between 12- hours MPA AUC, MPA plasma levels and gastrointestinal adverse event (GAE)

From the total 23 patients participated in this study, there were small number of patients who experienced GAE, 4 patients experienced serious GAE (intractable diarrhea and / or severe abdominal pain) and 3 patients experienced mild GAE (dyspepsia, irritate GI tract, nausea and /or constipation). Our study showed that among all the plasma concentrations obtained at different times, C trough (C0, C12), C peak (C0.25, C0.5, C1) including MPA AUC were best related to the incidence of GAE.

Table 4.2 a showed statistically comparison of MPA plasma levels between groups of patients who had incidence of GAE and who had no incidence of GAE using the total of 45 plasma profiles obtained from actual blood samples collection. The results were as follow: -

C trough was the plasma samples collected at time just before the next dose (C0) or at the end of dosing interval i.e., at time 12 hours after the dose had been given (C12) since MMF was dosing at every 12 hours interval. Both C0 and C12 showed statistically significant difference ( $P < 0.05$ ) between the group of patients who experienced GAE and the group with no incidence of GAE (either considered only serious GAE or considered both mild and serious GAE). The mean  $\pm$  SE of C0 was  $6.2958 \pm 0.5746$  mcg/mL for the patients who experienced serious GAE while it was  $2.7572 \pm 0.2104$  mcg/mL for patients without incidence of GAE. The mean  $\pm$  SE of C12 was  $6.3417 \pm 1.7147$  mcg/mL for the patients who experienced serious GAE while it was  $2.4787 \pm 0.3663$  mcg/mL for patients without incidence of GAE. The mean  $\pm$  SD of C trough (C0) when mild GAE were combined was  $4.2576 \pm 0.9811$  mcg/mL while  $2.7465 \pm 0.2194$  mcg/mL was the mean  $\pm$  SD of the group without mild and serious GAE groups. The mean  $\pm$  SD of C trough (C12) was  $6.3147 \pm 1.7147$  mcg/mL for the group with mild and serious GAE while for the group without mild and serious GAE the C trough (C12) was  $2.4787 \pm 0.3663$  mcg/mL. These results indicated that there were high correlation between high plasma levels at C trough and the incidence of GAE.



C peak was either occurred at time 0.25, 0.5 or 1 hours after the dose had been given and was denoted as C0.25, C0.5 or C1 respectively. Only C0.5 showed statistically significant difference ( $P < 0.05$ ) between the groups with and without incidence of serious GAE while C0.25 and C1 showed no different ( $P > 0.05$ ) based on actual collected data (4.2 a), whereas based on actual collected plus predicted data (4.2 b) only C0.25 and C1 showed statistically significant difference ( $P < 0.05$ ) between the groups with and without incidence of serious GAE while C0.5 showed no different ( $P > 0.05$ ). Neither C0.25, C0.5 or C1 showed statistically significant difference between the groups with and without incidence of GAE when both mild and serious GAE were combined ( $P > 0.05$ ). These results indicated that even though C peak could provide some useful information about serious GAE, it was not a very good parameter to use for mild GAE prediction beside the fact that peak times among patients were varied.

Blood samples were also collected at various other times, i.e., 2, 3, 4 and 6 hours after the dose had been given which were denoted as C2, C3, C4 and C6 respectively. The plasma concentrations obtained at these times showed no statistically significant difference ( $P > 0.05$ ) between the groups with and without incidence of GAE either when considered only serious GAE or when considered together both mild and serious GAE. Mean of MPA plasma concentration between the GAE groups and the none GAE groups were presented in figure 9, 11, 13 and 15.

MPA AUC was mostly calculated from several plasma levels using trapezoidal rule. Mean of MPA AUC between the GAE groups and the none GAE groups were showed in figure 10, 12, 14 and 16. Even though MPA AUC was higher in the group of patients who experienced GAE than the group who did not but these differences in MPA AUC showed no statistically significant difference ( $P > 0.05$ ) between the two groups when based on actual collected data. However, when based on actual collected plus predicted data (4.2 b), MPA AUC were statistically significantly different ( $P < 0.05$ ) between the groups with and without GAE (either considered only serious GAE or considered both mild and serious GAE). The mean  $\pm$  SE of MPA AUC was  $113.2625 \pm 7.3646$  mcg\*hr/mL in the group who experienced serious GAE while the mean  $\pm$  SE was equal to  $72.4706 \pm 3.4269$  mcg\*hr/mL in the group without incidence of serious GAE. When both mild and serious GAE were considered, the mean  $\pm$  SE was  $98.3523 \pm 9.8147$  mcg\*hr/mL in the GAE group and was  $71.5408 \pm 3.4755$  mcg\*hr/mL in the no GAE

group. Although MPA AUC showed statistically significant difference between the group with GAE and the group without GAE when based on actual collected plus predicted data, MPA AUC required several blood samples to achieve, which was not convenient and also quite expensive. C trough required only one blood sample therefore it was more appropriate to use either C0 or C12 for GAE prediction. However, in routine clinical practice, C0 is more convenient to sampling than C12. Therefore, C0 was considered as the best parameter for GAE prediction.

In general, MMF dose was slowly increased to the maximum dose which the patients could tolerate or until the maximum MMF dose (MMF dose 2000 mg) for the prevention of renal rejection was reached. Clearly, probability for the incidence of GAE was increasing with increasing dose of MMF. In this study, high variations were found among inter-individual MPA plasma levels consumed the same dose. Thereby MPA monitoring is necessary for dosage adjustment to avoid inadequate immunosuppression and / or serious toxicity. From our study, we recommend the application of C trough (C0) for routine clinical monitoring.



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**Table 4.2a Comparison of MPA Plasma Levels (Mean  $\pm$  SE) between Patients with Incidence of GAE and without Incidence of GAE (actual collected data)**

	Serious GAE		P value (2-tailed)	Mild and serious GAE		P value (2-tailed)
	with GAE	without GAE		with GAE	without GAE	
C0 (mcg/mL)	Mean $\pm$ SE (95 %CI) 6.2958 $\pm$ 0.5746 (5.2696-7.4220)	(N=2) 2.7572 $\pm$ 0.2104 (2.3448 - 3.1696) (N=43)	0.001	with GAE 4.2576 $\pm$ 0.9811 (2.3346 - 6.1806) (N=5)	without GAE 2.7465 $\pm$ 0.2194 (2.3165 - 3.1765) (N=40)	0.037
C0.25 (mcg/mL)	Mean $\pm$ SE (95 %CI) 30.7723 $\pm$ 10.8203 (9.5645- 51.9801)	(N=2) 12.4121 $\pm$ 2.6305 (7.2543 - 17.5659) (N=21)	0.055	with GAE 30.7723 $\pm$ 10.8203 (9.5645 - 51.9801) (N=5)	without GAE 12.4121 $\pm$ 2.6305 (7.2563 - 17.5679) (N=21)	0.055
C0.5 (mcg/mL)	Mean $\pm$ SE (95 %CI) 46.4019 $\pm$ 0.0727 (46.2594-46.5444)	(N=2) 29.6540 $\pm$ 3.8137 (22.1792 - 37.1289) (N=36)	< 0.001	with GAE 45.9445 $\pm$ 0.4593 (45.0443- 46.8447) (N=3)	without GAE 29.2147 $\pm$ 3.8981 (21.5744 - 36.8550) (N=35)	< 0.001
C1 (mcg/mL)	Mean $\pm$ SE (95 %CI) 41.1402 $\pm$ 0.7106 (39.7474 - 42.5330)	(N=2) 26.7881 $\pm$ 1.8393 (23.1831 - 30.3931) (N=43)	0.103	with GAE 30.1010 $\pm$ 7.0833 (16.2177 - 43.9843) (N=5)	without GAE 27.0916 $\pm$ 1.8710 (23.4242 - 30.7590) (N=40)	0.608
C2 (mcg/mL)	Mean $\pm$ SE (95 %CI) 6.4906 $\pm$ 2.4163 (1.7547-11.2266)	(N=2) 8.4702 $\pm$ 0.8963 (6.7135 - 10.2270) (N=21)	0.519	with GAE 6.4906 $\pm$ 2.4163 (1.7547 - 11.2265) (N=2)	without GAE 8.4702 $\pm$ 0.8963 (6.7135 - 10.2269) (N=40)	0.519
C3 (mcg/mL)	Mean $\pm$ SE (95 %CI) 3.2665 $\pm$ 2.2145 (-1.0739- 7.6069)	(N=2) 4.4107 $\pm$ 0.4204 (3.5867 - 5.2347) (N=43)	0.570	with GAE 5.3767 $\pm$ 1.2474 (2.9318 - 7.8216) (N=5)	without GAE 4.2328 $\pm$ 0.4346 (3.3810 - 5.0846) (N=40)	0.386
C4 (mcg/mL)	Mean $\pm$ SE (95 %CI) 3.1424 $\pm$ 1.4701 (0.2610- 6.0238)	(N=2) 2.9202 $\pm$ 0.2350 (2.4596 - 3.3808) (N=35)	0.830	with GAE 3.5712 $\pm$ 0.9509 (1.7074 - 5.4350) (N=3)	without GAE 2.8759 $\pm$ 0.2376 (2.4102 - 3.3416) (N=34)	0.416
C6 (mcg/mL)	Mean $\pm$ SE (95 %CI) 1.7890 $\pm$ 1.789 (0.0000 - 5.2954)	(N=2) 2.8360 $\pm$ 0.2363 (2.3729- 3.2991) (N=43)	0.365	with GAE 3.4747 $\pm$ 1.1039 (1.3111 - 5.6383) (N=5)	without GAE 2.7038 $\pm$ 0.2298 (2.2534 - 3.1542) (N=40)	0.308
C12 (mcg/mL)	Mean $\pm$ SE (95 %CI) 6.3417 $\pm$ 1.7147 (2.9809- 9.7025)	(N=2) 2.4787 $\pm$ 0.3663 (1.7608 - 3.1966) (N=21)	0.006	with GAE 6.3417 $\pm$ 1.7147 (2.9809 - 9.7025) (N=2)	without GAE 2.4787 $\pm$ 0.3663 (1.7608 - 3.1966) (N=21)	0.006
MPA AUC (mcg*hr/mL)	Mean $\pm$ SE (95 %CI) 103.9241 $\pm$ 1.0262 (101.9127 - 105.9355)	(N=2) 73.8379 $\pm$ 3.8072 (66.3758 - 81.3000) (N=43)	0.099	with GAE 91.7599 $\pm$ 13.8547 (64.6047 - 118.9151) (N=5)	without GAE 73.1020 $\pm$ 3.7997 (65.6546 - 80.5494) (N=40)	0.119

Abbreviations: 95 % CI = 95 % confidence interval; CI = mean  $\pm$  (10.025 \* SE) ; t 0.025 = 1.96 ; P value (2-tailed) = significant levels for two sides

= statistically significant at p value less than 0.05

with GAE= with incidence of gastrointestinal adverse event without GAE= without incidence of gastrointestinal adverse event



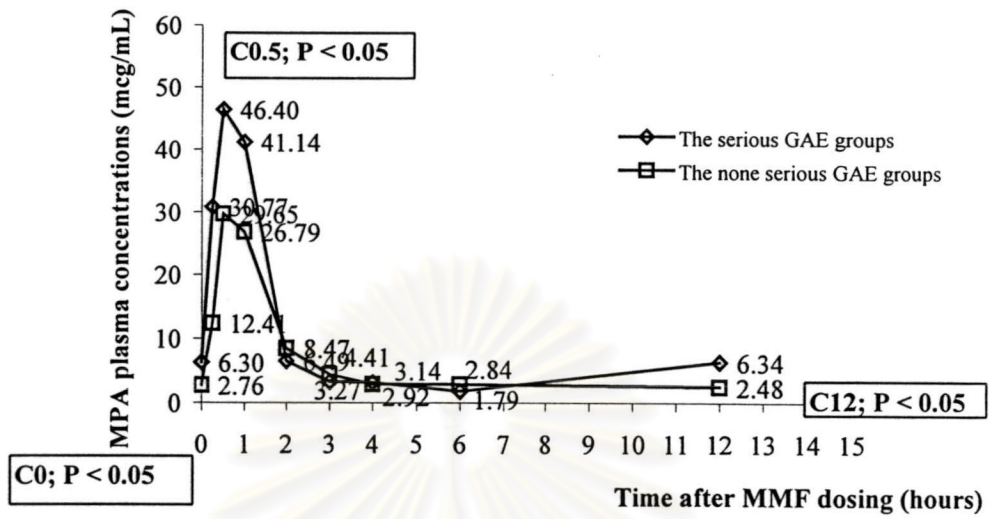


Figure 9: Mean of MPA plasma concentrations between the serious GAE groups and the none serious GAE groups (based on actual collected data)

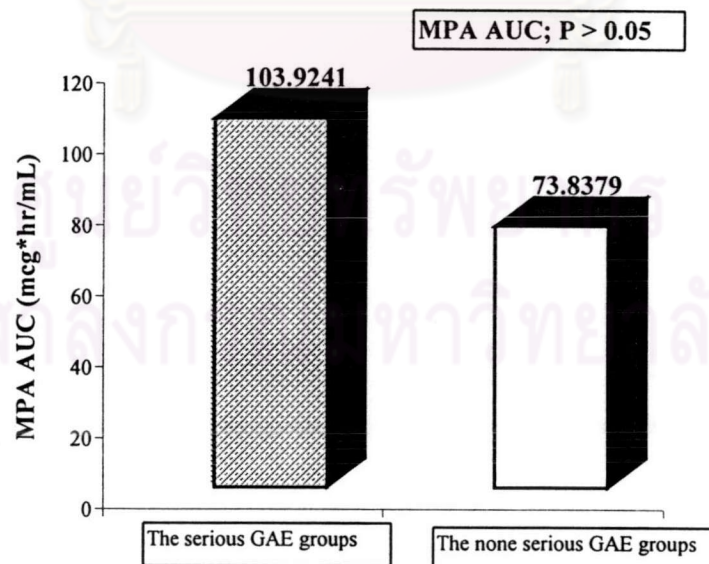
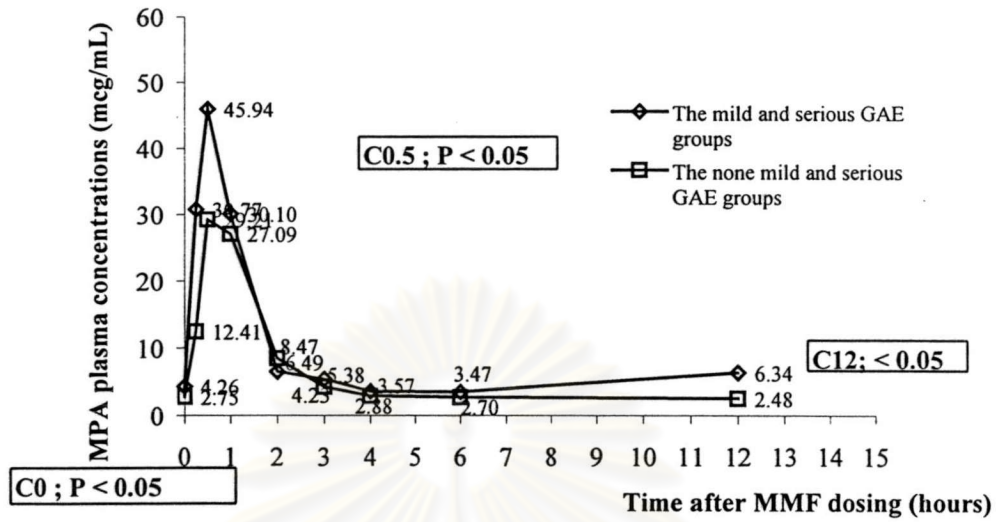
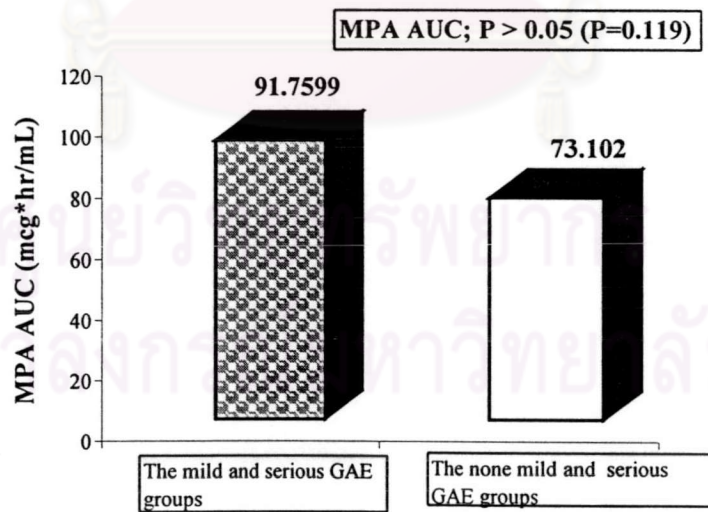


Figure 10: Mean of MPA AUC between the serious GAE groups and the none serious GAE groups (based on actual collected data)



**Figure 11:** Mean of MPA plasma concentrations between the mild and serious GAE groups and the none mild and serious GAE groups (based on actual collected data)



**Figure 12:** Mean of MPA AUC between the mild and serious GAE groups and the none mild and serious GAE groups (based on actual collected data)

**Table 4.2b Comparison of MPA Plasma Levels (Mean  $\pm$  SE) between Patients with Incidence of GAE and without Incidence of GAE (actual collected plus predicted data)**

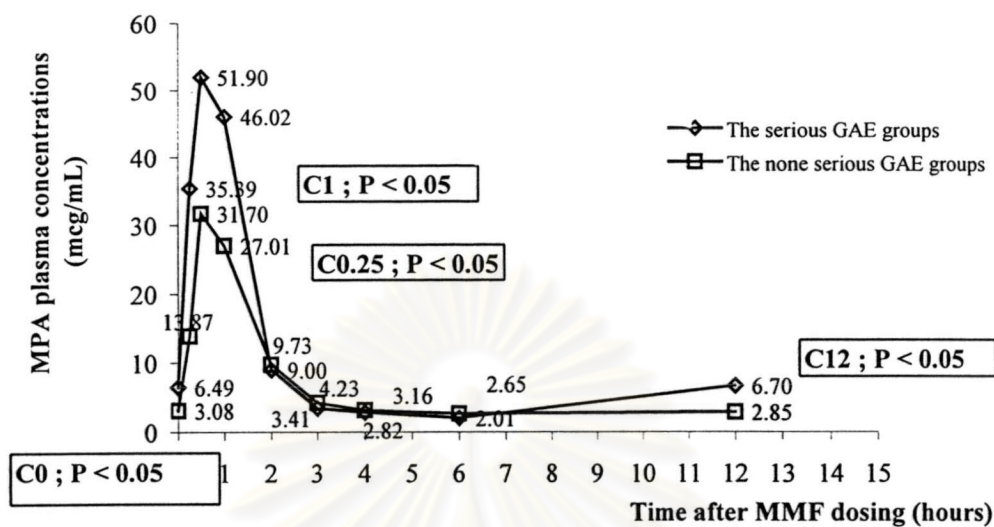
	Serious GAE				P value (2-tailed)	Mild and serious GAE				P value (2-tailed)
	with GAE		without GAE			with GAE		without GAE		
	Mean $\pm$ SE (95 %CI)	(N)	Mean $\pm$ SE (95 %CI)	(N)		Mean $\pm$ SE (95 %CI)	(N)	Mean $\pm$ SE (95 %CI)	(N)	
C0 (mcg/mL)	6.4928 $\pm$ 0.7522 (5.0185-7.9671)	(N=5)	3.0822 $\pm$ 0.2558 (2.5808 - 3.5836)	(N=64)	0.001	4.6702 $\pm$ 0.7424 (3.2151-6.1253)	(N=10)	3.1021 $\pm$ 0.2748 (2.5635-3.6407)	(N=59)	0.036
C0.25 (mcg/mL)	35.3889 $\pm$ 9.5667 (16.6382 - 54.1396)	(N=5)	13.8742 $\pm$ 1.8731 (10.2029 - 17.5455)	(N=64)	0.004	19.4695 $\pm$ 6.9787 (5.7912-33.1478)	(N=10)	14.7491 $\pm$ 1.9899 (10.8489-18.6493)	(N=59)	0.529
C0.5 (mcg/mL)	51.9015 $\pm$ 11.8126 (28.7488-75.0542)	(N=5)	31.7026 $\pm$ 3.4476 (24.9453-38.4599)	(N=64)	0.119	34.7938 $\pm$ 8.8442 (17.4592-52.1284)	(N=10)	32.8904 $\pm$ 3.6479 (25.7411-40.0397)	(N=59)	0.843
C1 (mcg/mL)	46.0183 $\pm$ 2.8287 (40.4741-51.5626)	(N=5)	27.0077 $\pm$ 1.7874 (23.5044-30.5110)	(N=64)	0.005	36.1669 $\pm$ 5.4539 (25.4773-46.8565)	(N=10)	27.0663 $\pm$ 1.8197 (23.4997-30.6329)	(N=59)	0.070
C2 (mcg/mL)	8.9962 $\pm$ 2.5123 (4.0721-13.9203)	(N=5)	9.7334 $\pm$ 0.7197 (8.3228 - 11.1440)	(N=64)	0.783	13.7201 $\pm$ 2.5923 (8.6392-18.8010)	(N=10)	8.9952 $\pm$ 0.6446 (7.7320-10.2584)	(N=59)	0.107
C3 (mcg/mL)	3.4142 $\pm$ 0.9826 (1.4883-5.3401)	(N=5)	4.2284 $\pm$ 0.3383 (3.5653-4.8915)	(N=64)	0.515	6.3526 $\pm$ 1.1915 (4.0173-8.6879)	(N=10)	3.7994 $\pm$ 0.2962 (3.2188-4.3800)	(N=59)	0.064
C4 (mcg/mL)	2.8163 $\pm$ 0.6240 (1.5933-4.0393)	(N=5)	3.1590 $\pm$ 0.2544 (2.6604-3.6576)	(N=64)	0.714	3.9510 $\pm$ 1.0624 (1.8687-6.0333)	(N=10)	2.9957 $\pm$ 0.2161 (2.5721-3.4193)	(N=59)	0.399
C6 (mcg/mL)	2.0070 $\pm$ 0.7374 (0.5617-3.4523)	(N=5)	2.6508 $\pm$ 0.1781 (2.3017-2.9999)	(N=64)	0.339	2.9520 $\pm$ 0.6159 (1.7448-4.1592)	(N=10)	2.5422 $\pm$ 0.1752 (2.2018-2.8886)	(N=59)	0.412
C12 (mcg/mL)	6.6967 $\pm$ 1.2001 (4.3445 - 9.0489)	(N=5)	2.8453 $\pm$ 0.2899 (2.2771-3.4135)	(N=64)	0.001	5.1283 $\pm$ 1.0774 (3.0166-7.2400)	(N=10)	2.7847 $\pm$ 0.2886 (2.2190-3.3504)	(N=59)	0.006
MPA AUC (mcg*hr/mL)	113.2625 $\pm$ 7.3646 (98.8279-127.6971)	(N=5)	72.4706 $\pm$ 3.4269 (65.7539-79.1873)	(N=64)	0.002	98.3523 $\pm$ 9.8147 (79.1155-117.5891)	(N=10)	71.5408 $\pm$ 3.4755 (64.7288-78.3528)	(N=59)	0.005

Abbreviations: 95 % CI = 95 % confidence interval 5 % CI = mean  $\pm$  (10.025 \* SE) ; t 0.025 = 1.96 ; P value (2-tailed) = significant levels for two sides

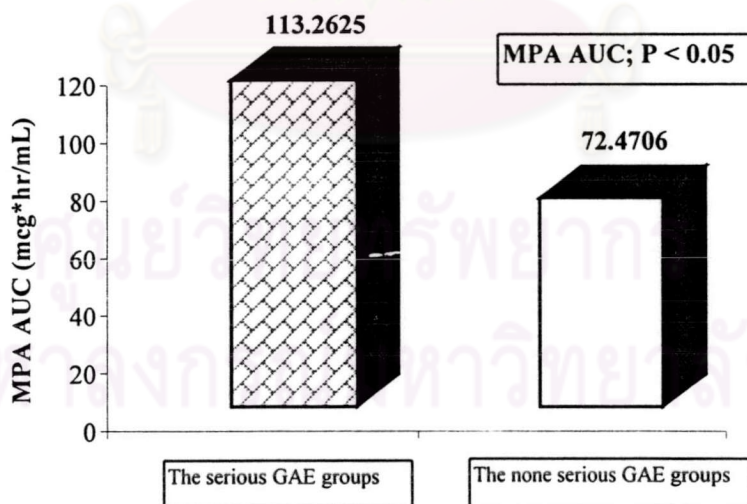
statistically significant at p value less than 0.05

with GAE= with incidence of gastrointestinal adverse event ; without GAE= without incidence of gastrointestinal adverse event

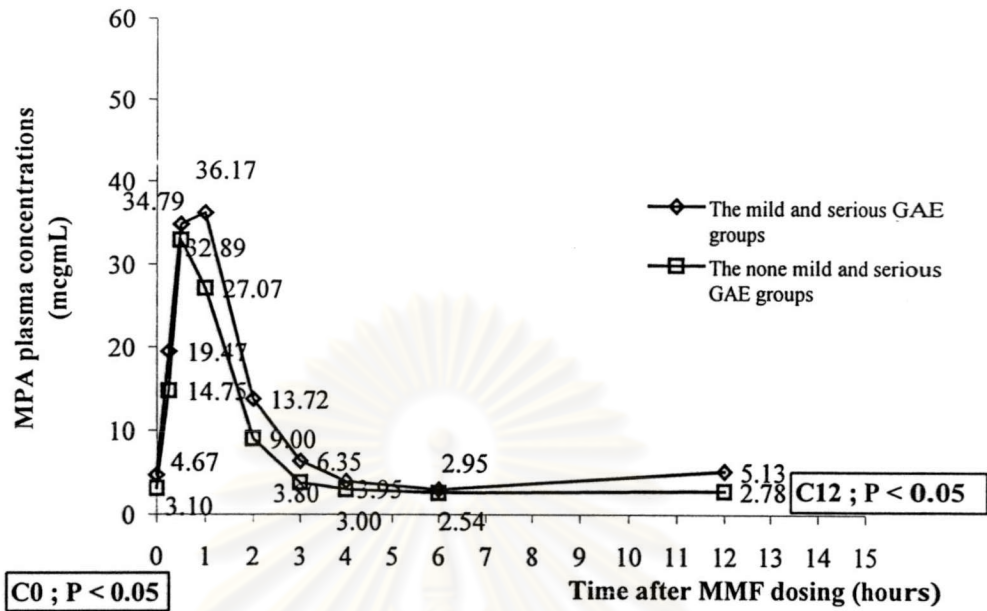




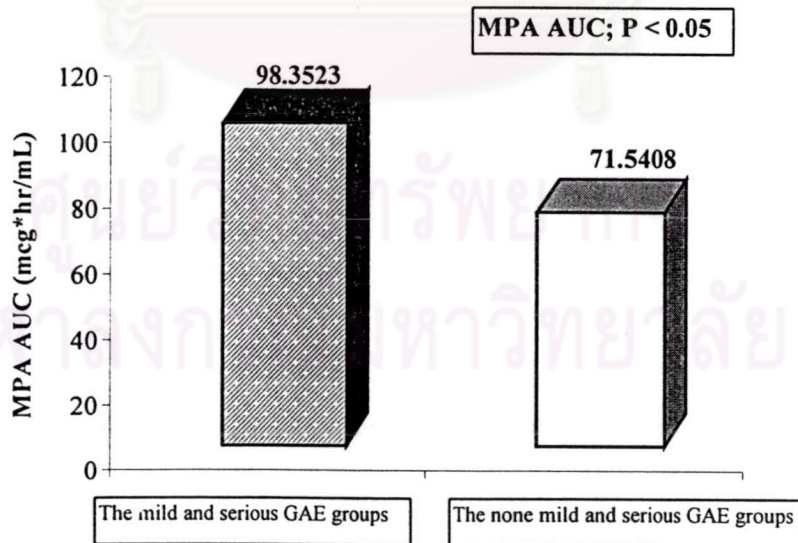
**Figure 13: Mean of MPA plasma concentrations between the serious GAE groups and the none serious GAE groups (based on actual collected plus predicted data)**



**Figure 14: Mean of MPA AUC between the serious GAE groups and the none serious GAE groups (based on actual collected plus predicted data)**



**Figure 15:** Mean of MPA plasma concentrations between the mild and serious GAE groups and the none mild and serious GAE groups (based on actual collected plus predicted data)



**Figure 16:** Mean of MPA AUC between the mild and serious GAE groups and the none mild and serious GAE groups (based on actual collected plus predicted data)



### 3. Optimum sampling time points for prediction of 12-hours MPA AUC

Early clinical studies suggested that MPA AUC could be used to predict efficacy for the prevention of renal rejection. In a therapeutic monitoring program, the full MPA AUC had been impractical and expensive. So a few optimum sampling time points were the alternative way for routine monitoring MMF. There were significant relationship between MPA AUC and GAE even though MPA AUC could not explain GAE as good as C trough alone. However, if we could find a minimum optimum sampling time points which could be used for prediction of both MPA efficacy and toxicity, that would be clinically beneficial. Therefore, minimum optimum sampling time points that could most accurately predicted 12-hours MPA AUC were determined. Only 23 complete plasma concentrations-time profiles were used for MPA AUC evaluation (table B1 in appendix B).

When only 1- sampling time points (1-STP) was used to predict MPA AUC based on regression equations, the MPA plasma level measured at half-hours after MMF administration (C0.5) was best correlated ( $R^2 = 0.467$ , absolute prediction error (APE) =  $27.171 \pm 5.684$  %) when the prediction was based on trapezoidal calculations, the MPA plasma level at 1 hour after MMF administration (C1) was best correlated ( $R^2 = 0.555$ , APE =  $39.365 \pm 15.695$  %). The 1-STP model which included only C0 showed  $R^2$  equaled to 0.425 and APE equaled to  $27.864 \pm 6.964$  % using regression equations while based on trapezoidal equations the  $R^2$  was equaled to 0.425 and APE was equaled to  $46.975 \pm 4.172$  %. The detailed were demonstrated in table 4.3 a (1.1), 4.3 a (1.2), 4.3 b (1) and 4.3 b (2).

For 2-STP, the model including C0.25 and C4 showed highest correlation ( $R^2 = 0.762$  and APE =  $15.209 \pm 2.591$  %) when was predicted by regression equations while C0.25 and C3 presented highest correlation ( $R^2 = 0.716$  and APE =  $42.976 \pm 3.325$  %) when was predicted by trapezoidal equations. The best correlated 2-STP model between MPA AUC and plasma level MPA which included C trough (C0) were composed of C0 and C0.5 with  $R^2$  equal to 0.713 and APE equaled to  $17.732 \pm 3.554$  % based on regression equation while using trapezoidal equations the  $R^2$  was equaled to 0.546 and APE was equaled to  $165.129 \pm 17.762$  % were composed of C0 and C1. The other 2-STP models were presented in table 4.3 a (2.1), 4.3 a (2.2), 4.3 b (1) and 4.3 b (2).

Three MPA plasma levels models could better explain MPA AUC. These results were similar to previous reported studies. The 3-STP models could predict more than 80 % of the MPA AUC. The best correlated model which included C0 for 3-STP was composed of C0, C0.5 and C1 based on regression equations ( $R^2 = 0.866$  and  $APE = 12.060 \pm 2.189$  %), which this models including C0, while based on trapezoidal equations, C0.5, C1 and C3 showed highest correlation ( $R^2 = 0.802$  and  $APE = 12.110 \pm 2.095$  %). The other 3-STP models were shown in table 4.3 a (3.1), 4.3 a (3.2), 4.3 b (1) and 4.3 b (2).

The 4-STP models could predict more than 90 % of the MPA AUC. The best correlated 4-STP model composed of C0.5, C1, C6 and C12 ( $R^2 = 0.959$  and  $APE = 7.652 \pm 1.321$ %) based on regression equations. When trapezoidal equations were considered, C0.5, C1, C3 and C12 model showed highest correlation with MPA AUC ( $R^2 = 0.918$  and  $APE = 15.923 \pm 2.223$  %). The best correlated model which included C trough (C0) was C0, C0.5, C1 and C2 model ( $R^2 = 0.940$  and  $APE = 9.308 \pm 1.495$  %) based on regression equations while using trapezoidal equations the based model composed of C0, C0.5, C1, and C3 ( $R^2 = 0.812$  and  $APE = 11.664 \pm 2.103$  %). All other models were presented in table 4.3 a (4.1), 4.3 a (4.2), 4.3 b (1) and 4.3 b (2).

Our study suggested that C trough was the best MPA plasma level which could be used to predict the occurrence of GAE. As mentioned in other previous studies, MPA AUC could explain efficacy for prevention of acute renal rejection. APE when using regression equations was lower than using trapezoidal equations. Therefore the best optimum sampling time points which could relate for both efficacy and toxicity of MMF were 4-STP at C0, C0.5, C1, and C2 model ( $R^2 = 0.940$  and  $APE = 9.308 \pm 1.495$  %). This model showed the R-square ( $R^2$ ) and APE which was nearly as high as the best correlated model for 4-STP (C0.5, C1, C6, and C12 model;  $R^2 = 0.959$  and  $APE = 7.652 \pm 1.321$  %). This C0, C0.5, C1, and C2 model was convenient for routine clinical practice since the blood samples could be taken within the short period of time (within 2 hours after MMF has been given). If less samples are requested for economical reason, the 3-STP, C0, C0.5 and C1 model with  $R^2 = 0.866$  and  $APE = 12.060 \pm 2.189$  % may satisfy.



**Table 4.3a(1.1) Regression equations for prediction of MPA AUC from single MPA plasma level**

Selected time points (hr after MMF dosing)	Regression Equations : Predicted 12 hr-AUC =	Absolute prediction error (%) (APE) Mean $\pm$ SE	R-square
0	$47.271 + 8.808 * C_0$	$27.864 \pm 6.964$	0.425
0.25	$52.108 + 1.305 * C_{0.25}$	$27.016 \pm 5.385$	0.456
0.5	$49.038 + 0.726 * C_{0.5}$	$27.171 \pm 5.684$	0.467
1	$34.429 + 1.320 * C_1$	$27.795 \pm 5.252$	0.460
2	$50.419 + 2.407 * C_2$	$34.596 \pm 7.563$	0.147
3	$47.889 + 6.472 * C_3$	$32.845 \pm 7.043$	0.184
4	$44.812 + 8.987 * C_4$	$29.351 \pm 5.612$	0.271
6	$55.117 + 6.087 * C_6$	$33.385 \pm 7.813$	0.143
12	$49.450 + 7.441 * C_{12}$	$27.057 \pm 5.514$	0.353

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Table 4.3 a(1.2) Trapezoidal equations for prediction of MPA AUC from single MPA plasma level

Selected time points (hr after MMF dosing)	Trapezoidal Equations : Predicted 12 hr-AUC =	Absolute prediction error (%) (APE) Mean $\pm$ SE	R-square
0 !	$C_0 * 12$	$46.975 \pm 4.172$	0.425
0.25	$(0.5 * C_{0.25} * 0.25) + (0.5 * C_{0.25} * (12 - 0.25))$	$67.842 \pm 12.034$	0.493
0.5	$(0.5 * C_{0.5} * 0.5) + (0.5 * C_{0.5} * (12 - 0.5))$	$163.687 \pm 31.517$	0.515
1	$(0.5 * C_1 * 1) + (0.5 * C_1 * (12 - 1))$	$39.365 \pm 15.695$	0.555
2	$(0.5 * C_2 * 2) + (0.5 * C_2 * (12 - 2))$	$31.064 \pm 3.747$	0.324
3	$(0.5 * C_3 * 3) + (0.5 * C_3 * (12 - 3))$	$59.825 \pm 3.180$	0.424
4	$(0.5 * C_4 * 4) + (0.5 * C_4 * (12 - 4))$	$68.338 \pm 2.597$	0.513
6	$(0.5 * C_6 * 6) + (0.5 * C_6 * (12 - 6))$	$77.370 \pm 1.598$	0.456
12 !!	$C_{12} * 12$	$55.236 \pm 5.264$	0.353

Abbreviations ; ! :  $C_{12} = C_0$

!! :  $C_0 = C_{12}$

Others :  $C_0 = C_{12} = 0$

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Table 4.3 a (2.1) Regression equations for prediction of MPA AUC from two MPA plasma levels

Selected time points (hr after MMF dosing)	Regression Equations : Predicted 12 hr-AUC =	Absolute prediction error (%) (APE) Mean $\pm$ SE	R-square
0, 0.5	$30.971 + 0.589 * C_{0.5} + 6.922 * C_0$	$17.732 \pm 3.554$	0.713
0, 1	$18.815 + 1.074 * C_1 + 6.989 * C_0$	$19.757 \pm 3.162$	0.712
0.25, 1	$30.090 + 0.982 * C_1 + 0.967 * C_{0.25}$	$19.381 \pm 3.854$	0.680
0.25, 2	$22.547 + 1.484 * C_{0.25} + 3.262 * C_2$	$16.916 \pm 3.616$	0.718
0.25, 3	$21.812 + 1.455 * C_{0.25} + 8.109 * C_3$	$17.180 \pm 2.799$	0.739
0.25, 4	$24.182 + 1.356 * C_{0.25} + 9.560 * C_4$	$15.209 \pm 2.591$	0.762
0.25, 6	$36.678 + 1.320 * C_{0.25} + 6.303 * C_6$	$20.840 \pm 4.570$	0.610
0.5, 1	$27.852 + 0.541 * C_{0.5} + 0.976 * C_1$	$20.318 \pm 3.571$	0.689
0.5, 2	$19.955 + 0.814 * C_{0.5} + 3.192 * C_2$	$16.380 \pm 3.704$	0.719
0.5, 3	$23.654 + 0.753 * C_{0.5} + 7.066 * C_3$	$17.896 \pm 3.541$	0.686
0.5, 4	$26.593 + 0.692 * C_{0.5} + 8.235 * C_4$	$17.224 \pm 3.209$	0.694
0.5, 12	$35.977 + 0.614 * C_{0.5} + 5.804 * C_{12}$	$18.690 \pm 3.481$	0.671
1, 3	$1.209 * C_1 + 4.789 * C_3$	$27.822 \pm 3.916$	0.557
1, 4	$22.063 + 1.125 * C_1 + 6.210 * C_4$	$23.050 \pm 2.984$	0.579
1, 6	$1.385 * C_1 + 6.977 * C_6$	$22.622 \pm 3.077$	0.647
1, 12	$20.573 + 1.175 * C_1 + 6.327 * C_{12}$	$18.520 \pm 2.672$	0.710
4, 12	$32.391 + 6.325 * C_{12} + 7.096 * C_4$	$22.054 \pm 3.922$	0.514



Table 4.3 a(2.2) Trapezoidal equations for prediction of MPA AUC from two MPA plasma levels

Selected time points (hr after MMF dosing)	Trapezoidal Equations : Predicted 12 hr-AUC =	Absolute prediction error (%) (APE) Mean $\pm$ SE	R-square
0, 0.5 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_0)*(12-0.5)$	173.958 $\pm$ 33.578	0.516
0, 1 !	$0.5*(C_0+C_1)*1 + 0.5*(C_1+C_0)*(12-1)$	165.129 $\pm$ 17.762	0.546
0.25, 1	$0.5*C_{0.25}*0.25 + 0.5*(C_{0.25}+C_1)*(1-0.25)+0.5*C_1*(12-1)$	142.146 $\pm$ 17.480	0.508
0.25, 2	$0.5*C_{0.25}*0.25 + 0.5*(C_{0.25}+C_2)*(2-0.25)+0.5*C_2*(12-2)$	23.830 $\pm$ 3.420	0.516
0.25, 3	$0.5*C_{0.25}*0.25 + 0.5*(C_{0.25}+C_3)*(3-0.25)+0.5*C_3*(12-3)$	42.976 $\pm$ 3.325	0.716
0.25, 4	$0.5*C_{0.25}*0.25 + 0.5*(C_{0.25}+C_4)*(4-0.25)+0.5*C_4*(12-4)$	42.225 $\pm$ 4.763	0.666
0.25, 6	$0.5*C_{0.25}*0.25 + 0.5*(C_{0.25}+C_6)*(6-0.25)+0.5*C_6*(12-6)$	41.060 $\pm$ 4.480	0.559
0.5, 1	$0.5*C_{0.5}*0.5 + 0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*C_1*(12-1)$	147.635 $\pm$ 16.611	0.545
0.5, 2	$0.5*C_{0.5}*0.5 + 0.5*(C_{0.5}+C_2)*(2-0.5)+0.5*C_2*(12-2)$	20.530 $\pm$ 3.640	0.685
0.5, 3	$0.5*C_{0.5}*0.5 + 0.5*(C_{0.5}+C_3)*(3-0.5)+0.5*C_3*(12-3)$	30.512 $\pm$ 5.288	0.612
0.5, 4	$0.5*C_{0.5}*0.5 + 0.5*(C_{0.5}+C_4)*(4-0.5)+0.5*C_4*(12-4)$	40.460 $\pm$ 8.145	0.570
0.5, 12 !!	$0.5*(C_{12}+C_{0.5})*0.5 + 0.5*(C_{0.5}+C_{12})*(12-0.5)$	173.262 $\pm$ 33.211	0.515
1, 3	$0.5*C_1*1 + 0.5*(C_1+C_3)*(3-1)+0.5*C_3*(12-3)$	22.578 $\pm$ 2.995	0.557
1, 4	$0.5*C_1*1 + 0.5*(C_1+C_4)*(4-1)+0.5*C_4*(12-4)$	23.130 $\pm$ 3.157	0.556
1, 6	$0.5*C_1*1 + 0.5*(C_1+C_6)*(6-1)+0.5*C_6*(12-6)$	43.973 $\pm$ 8.288	0.520
1, 12 !!	$0.5*(C_{12}+C_1)*1 + 0.5*(C_1+C_{12})*(12-1)$	161.126 $\pm$ 17.121	0.555
4, 12 !!	$0.5*(C_{12}+C_4)*4 + 0.5*(C_4+C_{12})*(12-4)$	60.103 $\pm$ 3.159	0.513

Abbreviations ; ! :  $C_{12} = C_0$

!! :  $C_0 = C_{12}$

Others :  $C_0 = C_{12} = 0$

**Table 4.3 a(3.1) Regression equations for prediction of MPA AUC from three MPA plasma levels**

Selected time points (hr after MMF dosing)	Regression Equations: Predicted 12-hr MPA AUC=	Absolute prediction error (%) (APE) Mean $\pm$ SE	R-square
0,0.25,1	$20.546 + 0.931 * C1 + 4.994 * C0 + 0.609 * C0.25$	$15.739 \pm 2.929$	0.778
0,0.5,1	$15.610 + 0.452 * C0.5 + 0.823 * C1 + 5.965 * C0$	$12.060 \pm 2.189$	0.866
0,0.5,2	$0.688 * C0.5 + 2.515 * C2 + 5.406 * C0$	$18.791 \pm 2.643$	0.858
0,0.5,3	$17.668 + 0.642 * C0.5 + 4.948 * C3 + 5.209 * C0$	$13.839 \pm 2.661$	0.805
0,0.5,4	$17.480 + 0.591 * C0.5 + 6.322 * C4 + 5.489 * C0$	$12.735 \pm 2.054$	0.836
0,1,6	$1.165 * C1 + 5.145 * C6 + 5.772 * C0$	$15.866 \pm 2.067$	0.806
0.25,0.5,2	$17.482 + 0.461 * C0.5 + 3.333 * C2 + 0.835 * C0.25$	$14.396 \pm 2.807$	0.792
0.5,1,2	$0.661 * C0.5 + 2.456 * C2 + 0.703 * C1$	$17.332 \pm 2.291$	0.820
0.5,1,3	$0.596 * C0.5 + 5.818 * C3 + 0.807 * C1$	$15.930 \pm 2.274$	0.830
0.5,1,4	$14.751 + 0.555 * C0.5 + 6.498 * C4 + 0.764 * C1$	$12.444 \pm 1.797$	0.819
0.5,1,6	$0.454 * C0.5 + 1.084 * C1 + 5.512 * C6$	$20.232 \pm 2.655$	0.800
0.5,1,12	$17.180 + 0.451 * C0.5 + 0.911 * C1 + 5.376 * C12$	$11.224 \pm 1.738$	0.863

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**Table 4.3 a(3.2) Trapezoidal equations for prediction of MPA AUC from three MPA plasma levels**

Selected time points (hr after MMF dosing)	Trapezoidal Equations : Predicted 12 hr-AUC =	Absolute prediction error (%) (APE) Mean $\pm$ SE	R-square
0,0.25,1 !	$0.5*(C_0+C_{0.25})*0.25+0.5*(C_{0.25}+C_1)*(1-0.25)+0.5*(C_1+C_0)*(12-1)$	167.261 $\pm$ 17.063	0.585
0,0.5,1 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_0)*(12-1)$	173.308 $\pm$ 16.041	0.627
0,0.5,2 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_2)*(2-0.5)+0.5*(C_2+C_0)*(12-2)$	48.600 $\pm$ 5.222	0.786
0,0.5,3 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_3)*(3-0.5)+0.5*(C_3+C_0)*(12-3)$	26.225 $\pm$ 5.460	0.724
0,0.5,4 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_4)*(4-0.5)+0.5*(C_4+C_0)*(12-4)$	42.224 $\pm$ 8.117	0.661
0,1,6 !	$0.5*(C_0+C_1)*1+0.5*(C_1+C_6)*(6-1)+0.5*(C_6+C_0)*(12-6)$	56.164 $\pm$ 8.075	0.665
0.25,0.5,2	$0.5*C_0*0.25+0.5*(C_{0.25}+C_{0.5})*(0.5-0.25)+0.5*(C_{0.5}+C_2)*(2-0.5)+0.5*C_2*(12-2)$	19.495 $\pm$ 3.437	0.711
0.5,1,2	$0.5*C_0*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_2)*(2-1)+0.5*C_2*(12-2)$	24.581 $\pm$ 4.164	0.648
0.5,1,3	$0.5*C_0*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_3)*(3-1)+0.5*C_3*(12-3)$	12.110 $\pm$ 2.095	0.802
0.5,1,4	$0.5*C_0*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_4)*(4-1)+0.5*C_4*(12-4)$	18.418 $\pm$ 3.101	0.751
0.5,1,6	$0.5*C_0*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_6)*(6-1)+0.5*C_6*(12-6)$	49.303 $\pm$ 7.033	0.715
0.5,1,12 !!	$0.5*C_0*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_{12})*(12-1)$	169.472 $\pm$ 15.409	0.636

Abbreviations ! :  $C_{12} = C_0$

!! :  $C_0 = C_{12}$

Others :  $C_0 = C_{12} = 0$

**Table 4.3a (4.1) Regression equations for prediction of MPA AUC from four MPA plasma levels**

Selected time points (hr after MMF dosing)	Regression Equations: Predicted 12-hr MPA AUC=	Absolute prediction error (%) (APE) Mean + SE	R-square
0, 0.5, 1, 2	0.558 * C0.5 + 1.896 * C2 + 0.636 * C1 + 5.041 * C0	9.308 ± 1.495	0.940
0, 0.5, 1, 3	0.509 * C0.5 + 4.024 * C3 + 0.739 * C1 + 4.669 * C0	11.446 ± 1.526	0.925
0, 0.5, 1, 4	0.477 * C0.5 + 4.929 * C4 + 0.687 * C1 + 5.006 * C0	12.663 ± 1.607	0.937
0, 0.5, 1, 6	0.400 * C0.5 + 0.924 * C1 + 5.122 * C0 + 4.060 * C6	11.512 ± 1.766	0.923
0.25, 0.5, 1, 2	0.389 * C0.5 + 2.660 * C2 + 0.619 * C1 + 0.687 * C0.25	15.580 ± 2.111	0.869
0.25, 0.5, 1, 3	0.284 * C0.5 + 6.575 * C3 + 0.716 * C1 + 0.779 * C0.25	13.450 ± 1.940	0.891
0.25, 1, 3, 6	0.873 * C1 + 4.750 * C6 + 1.101 * C0.25 + 4.605 * C3	8.205 ± 1.610	0.932
0.25, 1, 4, 6	0.832 * C1 + 4.667 * C6 + 1.057 * C0.25 + 5.165 * C4	12.254 ± 1.701	0.925
0.25, 1, 6, 12	1.074 * C1 + 6.487 * C6 + 0.632 * C0.25 + 3.765 * C12	9.440 ± 1.874	0.926
0.5, 1, 2, 6	0.573 * C0.5 + 1.849 * C2 + 0.842 * C1 + 3.691 * C6	11.113 ± 1.786	0.862
0.5, 1, 2, 12	0.558 * C0.5 + 1.938 * C2 + 0.705 * C1 + 4.581 * C12	9.226 ± 1.620	0.941
0.5, 1, 3, 12	0.509 * C0.5 + 4.370 * C3 + 0.796 * C1 + 4.372 * C12	10.484 ± 1.674	0.936
0.5, 1, 4, 12	0.474 * C0.5 + 5.236 * C4 + 0.748 * C1 + 4.645 * C12	13.216 ± 2.160	0.944
0.5, 1, 6, 12	0.373 * C0.5 + 1.014 * C1 + 5.156 * C6 + 5.160 * C12	7.652 ± 1.321	0.959

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Table 4.3 a (4.2) Trapezoidal equations for prediction of MPA AUC from four MPA plasma levels

Selected time points (hr after MMF dosing)	Trapezoidal Equations : Predicted 12 hr-AUC =	Absolute prediction error (%) (APE) Mean $\pm$ SE	R-square
0, 0.5, 1, 2 !	$0.5*(C_0+C_0.5)*0.5+0.5*(C_0.5+C_1)*(1-0.5)+0.5*(C_1+C_2)*(2-1)+0.5*(C_2+C_0)*(12-2)$	42.195 $\pm$ 5.380	0.777
0, 0.5, 1, 3 !	$0.5*(C_0+C_0.5)*0.5+0.5*(C_0.5+C_1)*(1-0.5)+0.5*(C_1+C_3)*(3-1)+0.5*(C_3+C_0)*(12-3)$	20.068 $\pm$ 2.630	0.902
0, 0.5, 1, 4 !	$0.5*(C_0+C_0.5)*0.5+0.5*(C_0.5+C_1)*(1-0.5)+0.5*(C_1+C_4)*(4-1)+0.5*(C_4+C_0)*(12-4)$	30.366 $\pm$ 3.762	0.860
0, 0.5, 1, 6 !	$0.5*(C_0+C_0.5)*0.5+0.5*(C_0.5+C_1)*(1-0.5)+0.5*(C_1+C_6)*(6-1)+0.5*(C_6+C_0)*(12-6)$	63.578 $\pm$ 6.633	0.791
0.25, 0.5, 1, 2	$0.5*C_0.25*0.25+0.5*(C_0.25+C_0.5)*(0.5-0.25)+0.5*(C_0.5+C_1)*(1-0.5)+$ $0.5*(C_1+C_2)*(2-1)+0.5*C_2*(12-2)$	48.724 $\pm$ 7.007	0.726
0.25, 0.5, 1, 3	$0.5*C_0.25*0.25+0.5*(C_0.25+C_0.5)*(0.5-0.25)+0.5*(C_0.5+C_1)*(1-0.5)+$ $0.5*(C_1+C_3)*(3-1)+0.5*C_3*(12-3)$	11.513 $\pm$ 2.015	0.824
0.25, 1, 3, 6	$0.5*C_0.25*0.25+0.5*(C_0.25+C_1)*(1-0.25)+0.5*(C_1+C_3)*(3-1)+$ $0.5*(C_6+C_3)*(6-3)+0.5*C_6*(12-6)$	14.248 $\pm$ 2.087	0.828
0.25, 1, 4, 6	$0.5*C_0.25*0.25+0.5*(C_0.25+C_1)*(1-0.25)+0.5*(C_1+C_4)*(4-1)+$ $0.5*(C_6+C_4)*(6-4)+0.5*C_6*(12-6)$	53.787 $\pm$ 2.697	0.752
0.25, 1, 6, 12 !!	$0.5*(C_{12}+C_0.25)*0.25+0.5*(C_0.25+C_1)*(1-0.25)+0.5*(C_1+C_6)*(6-1)+0.5*(C_6+C_{12})*(12-6)$	55.446 $\pm$ 7.096	0.754
0.5, 1, 2, 6	$0.5*C_0.5*0.5+0.5*(C_0.5+C_1)*(1-0.5)+0.5*(C_1+C_2)*(2-1)+0.5*(C_2+C_6)*(6-2)+0.5*C_6*(12-6)$	8.760 $\pm$ 2.088	0.834
0.5, 1, 2, 12 !!	$0.5*(C_{12}+C_0.5)*0.5+0.5*(C_0.5+C_1)*(1-0.5)+0.5*(C_1+C_2)*(2-1)+0.5*(C_2+C_{12})*(12-2)$	38.823 $\pm$ 4.904	0.780
0.5, 1, 3, 12 !!	$0.5*(C_{12}+C_0.5)*0.5+0.5*(C_0.5+C_1)*(1-0.5)+0.5*(C_1+C_3)*(3-1)+0.5*(C_3+C_{12})*(12-3)$	16.480 $\pm$ 2.337	0.920
0.5, 1, 4, 12 !!	$0.5*(C_{12}+C_0.5)*0.5+0.5*(C_0.5+C_1)*(1-0.5)+0.5*(C_1+C_4)*(4-1)+0.5*(C_4+C_{12})*(12-4)$	27.897 $\pm$ 3.425	0.875
0.5, 1, 6, 12 !!	$0.5*(C_{12}+C_0.5)*0.5+0.5*(C_0.5+C_1)*(1-0.5)+0.5*(C_1+C_6)*(6-1)+0.5*(C_6+C_{12})*(12-6)$	61.410 $\pm$ 6.173	0.808

Abbreviations ; ! :  $C_{12} = C_0$

!! :  $C_0 = C_{12}$

Others :  $C_0 = C_{12} = 0$

**Table 4.3 b (1) Regression equations for prediction of MPA AUC using various MPA plasma which including C0 in models**

Selected time points (hr after MMF dosing)	Regression Equations : Predicted 12 hr-AUC =	Absolute prediction error (%) (APE) Mean $\pm$ SE	R-square
0	47.271 + 8.808 * C0	27.864 $\pm$ 6.964	0.425
0, 0.5	30.971 + 0.589 * C0.5 + 6.922 * C0	17.732 $\pm$ 3.554	0.713
0, 1	18.815 + 1.074 * C1 + 6.989 * C0	19.757 $\pm$ 3.162	0.712
0,0.25,1	20.546 + 0.931 * C1 + 4.994 * C0 + 0.609 * C0.25	15.739 $\pm$ 2.929	0.778
0,0.5,1	15.610 + 0.452 * C0.5 + 0.823 * C1 + 5.965 * C0	12.060 $\pm$ 2.189	0.866
0,0.5,2	0.688 * C0.5 + 2.515 * C2 + 5.406 * C0	18.791 $\pm$ 2.643	0.858
0,0.5,3	17.668 + 0.642 * C0.5 + 4.948 * C3 + 5.209 * C0	13.839 $\pm$ 2.661	0.805
0,0.5,4	17.480 + 0.591 * C0.5 + 6.322 * C4 + 5.489 * C0	12.735 $\pm$ 2.054	0.836
0,1,6	1.165 * C1 + 5.145 * C6 + 5.772 * C0	15.866 $\pm$ 2.067	0.806
0, 0.5, 1, 2	0.558 * C0.5 + 1.896 * C2 + 0.636 * C1 + 5.041 * C0	9.308 $\pm$ 1.495	0.940
0, 0.5, 1, 3	0.509 * C0.5 + 4.024 * C3 + 0.739 * C1 + 4.669 * C0	11.446 $\pm$ 1.526	0.925
0, 0.5, 1, 4	0.477 * C0.5 + 4.929 * C4 + 0.687 * C1 + 5.006 * C0	12.663 $\pm$ 1.607	0.937
0, 0.5, 1, 6	0.400 * C0.5 + 0.924 * C1 + 5.122 * C0 + 4.060 * C6	11.512 $\pm$ 1.766	0.923



**Table 4.3 b (2) Trapezoidal equations for prediction of MPA AUC using various MPA plasma levels which including C0 in models**

Selected time points (hr after MMF dosing)	Trapezoidal Equations : Predicted 12 hr-MPA AUC =	Absolute prediction error (%) Mean $\pm$ SE	R-square
0 !	$C_0 * 12$	$46.975 \pm 4.172$	0.425
0, 0.5 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_0)*(12-0.5)$	$173.958 \pm 33.578$	0.516
0, 1 !	$0.5*(C_0+C_1)*1 + 0.5*(C_1+C_0)*(12-1)$	$165.129 \pm 17.762$	0.546
0,0.25,1 !	$0.5*(C_0+C_{0.25})*0.25+0.5*(C_{0.25}+C_1)*(1-0.25)+0.5*(C_1+C_0)*(12-1)$	$167.261 \pm 17.063$	0.585
0,0.5,1 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_0)*(12-1)$	$173.308 \pm 16.041$	0.627
0,0.5,2 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_2)*(2-0.5)+0.5*(C_2+C_0)*(12-2)$	$48.600 \pm 5.222$	0.786
0,0.5,3 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_3)*(3-0.5)+0.5*(C_3+C_0)*(12-3)$	$26.225 \pm 5.460$	0.724
0,0.5,4 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_4)*(4-0.5)+0.5*(C_4+C_0)*(12-4)$	$42.224 \pm 8.117$	0.661
0,1,6 !	$0.5*(C_0+C_1)*1+0.5*(C_1+C_6)*(6-1)+0.5*(C_6+C_0)*(12-6)$	$56.164 \pm 8.075$	0.665
0, 0.5, 1, 2 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_2)*(2-1)+0.5*(C_2+C_0)*(12-2)$	$42.195 \pm 5.380$	0.777
0, 0.5, 1, 3 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_3)*(3-1)+0.5*(C_3+C_0)*(12-3)$	$20.068 \pm 2.630$	0.902
0, 0.5, 1, 4 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_4)*(4-1)+0.5*(C_4+C_0)*(12-4)$	$30.366 \pm 3.762$	0.860
0, 0.5, 1, 6 !	$0.5*(C_0+C_{0.5})*0.5+0.5*(C_{0.5}+C_1)*(1-0.5)+0.5*(C_1+C_6)*(6-1)+0.5*(C_6+C_0)*(12-6)$	$63.578 \pm 6.633$	0.791

Abbreviations ; ! :  $C_{12} = C_0$

#### 4. The optimum MMF dose for individual Thai renal transplanted patients

**Table 4.4 a Individual MPA AUC of the patients and their optimum dose**

Patient Name	12 hour MPA AUC (mcg*hr /mL)			Optimum MMF dose (mg/day)
	MMF 1000 (N=13) (mg/day)	MMF 1500 (N=20) (mg/day)	MMF 2000 (N=12) (mg/day)	
1. PROJ *	23.4947	47.2958*	56.9977	1500
2. TP	xxx	69.5611	93.4048	1000
3. AN	xxx	74.9054	86.313	1000
4. SW	49.7664	79.0461	xxx	1000
5. PIRAT	xxx	xxx	104.1716	1000
6. SPN	xxx	49.5951	61.6633	1500
7. JVD	82.7237	78.3962	122.1017	1000
8. NVR **	xxx	104.9503**	xxx	1000
9. AR	xxx	84.5851	96.2267	1000
10. VN **	xxx	45.1587	102.8979**	1500
11. JR *	71.3272	79.0461*	139.0493	1000
12. VB **	62.4519	75.4664	xxx**	1000
13. JP *	65.5461	99.6862	126.6462*	1000
14. PCN	53.9078	78.1307	73.7355	1000
15. BM	50.5501	87.1344	93.1208	1000
16. CHAN	65.2595	114.9413	xxx	1000
17. NP	50.5119	70.5923	xxx	1000
18. DK	35.5306	59.6287	xxx	1500
19. PCR **	xxx	88.6376	xxx **	1000
20. ANS	45.7661	xxx	xxx	1000
21. PP	72.8737	xxx	xxx	1000
22. SK	xxx	75.7574	xxx	1000
23. NRL	xxx	36.3629	xxx	1500
Mean	56.1315	74.8421	96.3607	1109
SD	16.1644	20.2351	25.0297	211
SE	4.4832	4.5247	7.2254	44
Min	23.4947	36.3629	56.9977	1000
Max	82.7237	114.9413	139.0493	1500

Abbreviations ; \*\* = serious GAE ; \* = mild GAE  
; xxx = missing data

Based on Western studies, the reference range of MPA AUC for prevention of renal acute rejection was mentioned to be 30 to 60 mcg\*hr/mL, the optimum MMF dose

for Thai renal transplanted patients which participated in our study were calculated and demonstrated in table 4.4 a. The most common optimum MMF dose was 1000 mg / day and for some patients the optimum dose was 1500 mg / day. When the patients received MMF 2000 mg / day, their MPA AUC were all higher than the reference range, therefore, none of our patients required to receive a dose as high as 2000 mg/day.

The MPA AUC found in Thai patients in our study were much higher than those reported in Western studies for the same MMF dose. The comparisons were presented in table 4.4 b.

**Table 4.4 b** Comparison between MPA AUC reported in Western studies, previous Thai study and this study

Study	MMF dose (mg per day)	12-hrMPA AUC (mcg*hr/mL)
1. Western studies	2000	30-60
2. Previous Thai study	1000	37.46 ± 3.46
3. This study	1000 1500 2000	56.13 ± 4.48 74.84 ± 4.52 96.36 ± 7.23