# CHAPTER V

# DISCUSSION

Several double-blind, randomized trials have revealed that addition of MMF to an immunosuppressive regimen consisting of CSA and prednisolone results in a significant reduction in the rate of biopsy-proven acute rejection during the first 6 months after kidney transplantation.[1-5] Thereafter, many studies suggested that MPA AUC could explain the efficacy of MMF. However, there were controversial report for prediction the occurrence of toxicities.

Our study was designed to determine the relationship between MPA plasma levels as well as MPA AUC to gastrointestinal adverse event (GAE). Based on actual collected 45 blood samples profiles, we found that the high level of C trough (C0, C12) was best correlated to the occurrence of GAE as compared to MPA plasma levels at other time points including MPA AUC. The C trough levels (C0) which showed serious GAE was 6.2958 $\pm$ 0.5746 mcg/mL (mean $\pm$ SE) and this was significantly higher ($p = 0.001$) than the none experienced group. For mild to serious GAE the C trough levels (C0) which caused side effect was 4.2576 $\pm$ 0.9811 mcg/mL (mean $\pm$ SE) and was significantly higher ($p = 0.037$) than the none side effect group. The study by Mourad et al[13] (B;2001) using the regimen which composed of steroid, MMF 2 gm daily and CSA as triple immunosuppressive regimen suggested that C peak (C0.5) was higher in the experienced side effect group than the none experienced side effect group (C0.5 = 32.99 $\pm$ 12.59 mcg/mL VS 7.45 $\pm$ 5.40 mcg/mL ; $p < 0.0001$, respectively) while C trough in experienced GAE group was 2.22 $\pm$ 1.13 mcg/mL and the none experienced GAE group was 2.17 $\pm$ 1.13 mcg/mL, which was not significantly different ($P > 0.05$). In their

study, they indicated that C peak was C0.5, while in our study, we found that C peak was either appeared at C0.5 (46.51%;N=20) or C1 (51.16 %;N=22) . We found that C0.5 was significantly different between the experienced serious GAE group (C0.5 = 46.4019 $\pm$ 0.0727 mcg/mL) and the none experienced GAE group (C0.5 = 29.6540 $\pm$ 3.8137 mcg/mL). Besides, C0.5 was also significantly different ($P < 0.05$) between the experienced serious combined mild GAE group (C0.5 = 45.9445 $\pm$ 0.4593 mcg/mL) and the none experienced GAE group (C0.5 = 29.2147 $\pm$ 3.8981 mcg/mL). By the way, C trough (C0) and C peak (C0.5) values of the experienced GAE group in our study were higher than those obtained in Mourad study (B;2001). Several reasons could be used to explain these differences. First, in the study of Mourad et al[13] the median time for the first MPA pharmacokinetic measurement after renal transplantation was 8 day (range, 3-26 days) while our study was 9.2 months (range, 1.10-44.13 months). This result supported the report that plasma MPA levels in the first 40 days are less than 50 % of the values measured in patients with an established transplant[28]. There is no good explanation for this; some hypotheses have been put forward, such as Bullingham R, et al (1996)[29] suggested that there might be change in MPA protein binding over time or Behrend M, et al (1997)[30] suggested that there might be an altered enterohepatic recirculation with time. Second, the difference among groups of recipients (Asian versus European), consequence by the difference in pharmacokinetics of MMF. It is known that body (weight and height) of European is bigger than Asian, therefore MPA plasma levels and MPA AUC in Asian should be higher than in European when the same fixed dose had been given. This result supported the study by Brusa P, et al (2000)[28] which indicated that given dosage related to body weight might be better than given fixed MMF dose.

Our results agreed with the study by Gregoor P.J.H. S, et al (1998)[31], which was designed for the patients to receive dual immunosuppressive regimen composed of MMF 2 gm daily and prednisolone. Their results suggested that there were relationship between MPA trough levels and adverse events (all types of toxicities) in kidney allograft recipients. The MPA trough levels were ranged from 1.90 to 9.94 mcg/mL (mean $\pm$ SE = 4.43 $\pm$ 0.38 mcg/mL) in patients with side effects and from 0.66 to 6.03 mcg/mL (mean $\pm$ SE = 2.62 $\pm$ 0.32 mcg/mL) in patients without side effects ($p = 0.0006$ ; Mann-Whitney test). Also from the study by Brusa P, et al (2000)[28], which the patients received triple immunosuppressive regimen included CSA, prednisolone and MMF in a dose ranging from 500 to 2000 mg/day, they found that at plasma trough level higher than 4 mcg/mL some serious toxic effects (all types of toxicities) were observed, whereas C trough less than 2 mcg/mL caused interstitial rejection in some cases.

Our study found that serum creatinine were higher in patients who experienced serious GAE, they were 2.4 mg/dL in patient number 8, 2.7 mg/dL in patient number 10. Serum creatinine of patients who experienced mild GAE was less obviously higher than those who had no GAE. Since nearly 93 % of MMF metabolites were eliminated through renal, therefore serum creatinine which is the parameters which indicated the function of renal may cause some effects on the plasma levels of MPA.

Although, our results suggested that C peak, C trough as well as MPA AUC could explain the occurrence of GAE , it is also known that the C peak plasmatic values showed a wide inter-individual variability while full MPA AUC was inconvenience and more expensive therefore C trough could be used to predict GAE in routine practice. Outcome goal for MMF in prevention of renal rejection were the highest efficacy and the least toxicity. If we could find the optimum points that could be used to predict both

efficacy and toxicity at the same time, this should be useful for future monitoring of MMF in prevention of renal rejection. However, C trough was not the single MPA plasma level which was best correlated to MPA AUC ($R^2$ = 0.425), C0.5 showed better correlation to MPA AUC ($R^2$ = 0.467). This result was similarly to study by Mourad et al (B;2001)[13]($R^2$ = 0.599). Many studies had clearly demonstrated that MPA AUC could predict efficacy for prevention of acute renal rejection. Full MPA AUC was inconvenience and more expensive. Therefore optimum blood sampling strategy is an alternate way for prediction of MPA AUC. Our study suggested that C0, C0.5, C1 and C2 model ($R^2$ = 0.940) was the best model for prediction of MPA AUC and optimum for routine monitoring. Since MPA plasma concentrations-time curve showed obvious two compartment pharmacokinetics within the 12 hours dosing interval, predicted MPA AUC based on abbreviated blood samples using trapezoidal rules might not be as accurated when compared with the regression method.

Although our study was not perfectly designed due to ethical reason and the number of patients participated in the study was quite small, however, our results did suggest the optimum blood sampling time that have a very good trend to predict the occurrence of GAE and found the optimum sampling strategy which may be used as a guideline for prediction of both efficacy and GAE toxicity.

Since the time period was short and the number of patients including in this study was small, further studies in a larger number of patients for a long term period are required to strongly confirm the results obtained.