CHAPTER I

INTRODUCTION

Mycophenolate mofetil (MMF) is the 2-morpholino-ethyl ester of Mycophenolic acid (MPA). It is a prodrug immunosuppressant which is widely used in organ transplantation to prevent acute allograft rejection (AR)[1-3]. MPA inhibits inosine monophosphate dehydrogenase (IMPDH), a key enzyme in the *de novo* pathway of purine synthesis, acting against the proliferation of T and B lymphocytes. In general, MMF is given orally on a twice daily schedule in combination with cyclosporin (CSA) and corticosteroids in the triple immunosuppressive regimen.

Currently, MMF is widely used in organ transplantation to prevent acute AR, because MMF is more selectively inhibits the lymphocytes than azathioprine (AZA). Large clinical trials[2-5]have revealed that the efficacy of MMF in preventing acute AR was superior to AZA, MMF significantly decreased incidence of acute renal AR and adverse events (AEs) as compared to AZA, especially the bone marrow suppression. However, gastrointestinal adverse event (GAE), including diarrhea, abdominal pain, nausea and vomiting, are a major concern in MMF treatment. The most common occurrence of GAEs is diarrhea (41.8-47%).[6] Furthermore the other AEs are anemia, neutropenia and infections such as cytomegalovirus (CMV), *Pneumocystic carinii* pneumonia (PCP). Sollinger HW et al (1995)[2] investigated an experiment using randomized, double-blind, multicenter design 499 patients, in their first post-renal transplantation from cadaveric donors were followed up for 6 months. They reported the incidence of biopsy-proven AR, treatment failure such as death, graft loss and noncompliance in the AZA group and MMF 2 gm daily group and MMF 3 gm daily group to be 47.6 % , 31.1 % and 31.3 % , respectively. These results were the same as these reported by Ojo AO et al.[7]

Clinical efficacy and toxicity of MMF were evaluated in patients who showed no occurrence of acute renal AR and could tolerate to MMF. Many studies [8-11] reported that the efficacy of MMF can be predicted by the MPA AUC. It is known that the difference in individual pharmacokinetics, therefore trough and peak concentrations can not

accurately predict the efficacy of MMF. The recommended dose of MMF for the prevention of acute renal AR is 2 or 3 gm daily. In Western, MMF is usually given not more than 3 gm daily. In Thailand[12], experiment using retrospective trial reported that only 1 gm daily dose should be used in order to avoid GAE, especially diarrhea and /or abdominal pain. At Rajavithi Hospital, standard treatment of MMF administration to prevent acute renal AR is started with 1 gm daily dose in normal body weight patients, then gradually increased 500 mg daily each time up to 2 gm daily, if no incidence of GAE. On the other hand, when patients experienced GAE, then MMF dose was gradually decreased 500 mg daily each time until no sign of GAE.

Blood levels and AUC of MMF are varied any patients due to difference in pharmacokinetics. Many studies[8-11] reported that the incidence of AR can be predicted by MPA AUC, such as Hale MD et al[10] which performed a randomized, double-blind, controlled trial, found relationship between MPA AUC and the incidence of AR ($P < 0.001$), the higher AUC contribute to the lower incidence of AR (MPA AUC 15, 25 and 40 mcg*hr/mL gave a yield of maximum achievable efficacy 50 %, 75 % and 90 %, respectively.). Efficacy of MMF must obtain by follow up the patients for a long period, i.e., not less than 6 months. By the way, Shaw LM et al[11] investigated in heart and renal transplanted patients, which received MMF, CSA and corticosteroids in the early 2 weeks, found the relationship between MPA AUC and AE but not found the relationship between MMF dose and the incidence of GAE. They reported that MPA AUC which were higher than the upper limit AUC (AUC > 60 mcg*hr/mL) had increased the risk for AEs while this interval of MPA AUC has not been approved in generally strategy. In agreement with Mourad M et al[13] who investigated prospective trial in 51 patients, reported that there were high correlation between MPA plasma concentrations and its toxicity after MMF administration, therefore optimal dose should be given. Many studies, reported that the MPA plasma concentrations and MPA AUC can be used to predict the efficacy and safety of MMF.

This study was designed to investigate relationships between MPA plasma levels, MPA AUC and incidence of GAE, including diarrhea and / or abdominal pain (occurred within 7 days) after MMF was given, when GAE occurs then some other AEs such as CMV infection[16] will be lead to occur since gastrointestinal tract (GIT) is the best region for the growth of CMV. Besides, GAE also contributes to noncompliance[17] and it

disturbs life style. Since full AUC are laborious and expensive[18-19], require multiple blood sampling, therefore, the second purpose of this study was to find the best blood sampling strategy for MMF monitoring which could be used to predict both MMF efficacy and GAE toxicity. And the third purpose was to determine the MPA plasma concentrations and / or MPA AUC which could cause GAE.

In Thailand, limited pharmacokinetics data are available, there was only one study by Julasareekul et al[20], who investigated the pharmacokinetics of MMF after 1 gm daily dose had been given. There was no study on the maximum MPA AUC or concentrations which the patients could tolerate without suffering from GAE, which in turn could lead to the estimation of the optimal dose of MMF that could cause the best clinical outcome in renal transplanted Thai patients.

Objectives

The present study was performed with the following objectives:

1. To find the relationship between GAE and MPA plasma concentrations at different sampling time points including MPA AUC.
2. To determine the MPA plasma concentrations and /or MPA AUC which could have a high risk of causing GAE.
3. To find a minimum optimum sampling time points which could be used to predict both MMF efficacy and GAE toxicity.

The significant of the study

1. The study will provide information about the best sampling time points to obtain MPA plasma concentrations which could be used to predict GAE in renal transplanted Thai patients.
2. Information about the range of MPA plasma concentrations and / or MPA AUC which have a high risk of causing GAE could be used to calculate an optimum dose for individual patient once his / her MPA plasma concentrations and / or MPA AUC after any dose are known.
3. The study will provide the best sampling strategy of MMF, which could predict both efficacy and GAE toxicity.