Pharmacokinetic evaluation of MFF in combinations with tacrolimus and cyclosporine. Findings of $C_0$ and AUC

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Abstract
We hypothesized that area under the concentration time curve (AUC$_{(0-12)}$) is more accurate pharmacokinetic predictor vs trough level of mycophenolic acid ($C_0$).

Study was performed at the University Hospital of Limoges (France) and included 238 renal recipients aged 22 to 82 years. Risk of nephropathy was evaluated by analyzing data of protocol biopsies according to the Banff 97 classification.

Assessment of immunosuppressants’ exposures was based on the calculation of the mean of AUC$_{(0-12)}$. The AUC$_{(0-12)}$ was estimated using a Bayesian estimator and a 3-point limited sampling strategy. Cyclosporine and tacrolimus analyses were performed using liquid chromatography–mass spectrometry method. The measurement of total mycophenolic acid was performed using a validated high-performance liquid chromatography method with ultraviolet detection. IBM SPSS 20.0 was used for statistical analysis.

The most accurate dosing of mycophenolate mofetil (MMF) was observed in patients receiving MMF with tacrolimus, 70.6% of patients’ AUC$_{(0-12)}$ exposures were within the therapeutic range. The highest rates of low dosing were observed in patients receiving MMF with cyclosporine, 30.9% of patients had AUC$_{(0-12)}$ exposures below the therapeutic range. The assessment of AUC$_{(0-12)}$ revealed 38% of chronic nephropathy cases, while $C_0$ enables to identify only 20% of chronic nephropathy cases.

Probability test results showed that more likely AUC$_{(0-12)}$ and $C_0$ will be maintained within the therapeutic width if patients receive MMF with tacrolimus vs MMF with cyclosporine: 0.6320 vs 0.6410 for AUC$_{(0-12)}$ determination and 0.8415 vs 0.4827 for $C_0$ determination.

Combination of MMF with tacrolimus is dosed more precisely vs dosing of MMF with cyclosporine. 72 (70.6%) patients AUC$_{(0-12)}$ and 79 (77.5%) patients $C_0$ out of 102 patients were within the therapeutic range. The AUC$_{(0-12)}$ monitoring of mycophenolic acid in patients receiving MMF with tacrolimus or in patients receiving MMF with cyclosporine enabled to identify more overdosing and possible risky cases.

Study results show that standard MMF dosing without monitoring and with mycophenolic acid level within the therapeutic width is possible and demonstrates less risky cases in patients receiving MMF with tacrolimus, while patients receiving MMF with cyclosporine should be intensively monitored to achieve the highest safety. However, AUC$_{(0-12)}$ monitoring is advised showing better compliance vs $C_0$ monitoring.

Abbreviations: AUC = the area under the concentration time curve, BID = twice-daily dosing, $C_0$ = trough level, CNI = calcineurin inhibitor, CsA = cyclosporine, LSSs = limited sampling strategies, MMF = mycophenolate mofetil, MPA = mycophenolic acid, SD = standard deviation, Tacro = tacrolimus, TDM = the therapeutic drug monitoring.

Keywords: cyclosporine, immunosuppression, MMF, pharmacokinetics, tacrolimus
1. Introduction

Mycophenolate mofetil, a pro-drug for mycophenolic acid, used in combination with calcineurin inhibitors (CNI) reduces the likelihood of allograft rejection after renal transplantation. Early adequate mycophenolic acid (MPA) exposure is associated with less rejection in kidney transplantation and monitoring of MPA levels may be useful for effective mycophenolate mofetil (MMF) dosing. However, the bioavailability of MMF increases with time, such that exposure measured later in the post-transplant period may not reflect drug exposure in the first week. In addition recipients who reach therapeutic targets late may still be at a greater risk of rejection from inadequate inhibition of early immune activation responses.

Risk increases with MMF administration at a fixed dose without MPA (the active constituent of MMF) monitoring routinely. Conflicting results from randomized controlled trials regarding the benefits of therapeutic drug monitoring guided dosing over standardized dosing raise even more questions. Nevertheless, studies have shown 10-fold variation in dose-normalized MPA exposure, suggesting that adequate exposure may not be achieved in all individuals with standardized dosing. In addition, multiple studies have linked low drug concentrations with acute rejection, and TDM techniques have been discussed. Trough concentration monitoring (C0) and single concentration time points (e.g., C2 or C4) analyses were assumed as not accurate, due to vary in timing from the “ideal” 12-hour dose interval and weak concentration time points association to full AUC. Full AUC (AUC0 to 12h) does not require patient to be available for the complete dosing interval (12 hours) sometimes hardly achievable. Multiple concentration time points (several specific timed points after dosing, also called limited sampling strategies (LSSs)) requires longer stay for multiple samples and errors in timing may lead to errors in estimations. Extrapolations can be used with accuracy only in the population in which the regressions have been developed. Single or multiple concentration time points used for Bayesian analysis are mathematically more complex technique, requires preexisting population pharmacokinetic model and knowledge of covariates. This is computer model based and requires interpretation for dosing advice.

In the consensus report on therapeutic drug monitoring (TDM) of mycophenolic acid in solid organ transplantation TDM techniques have been discussed. Trough concentration (C0) and single concentration time points (e.g., C2 or C4) analyses were assumed as not accurate, due to vary in timing from the “ideal” 12-hour dose interval and weak concentration time points association to full AUC. Full AUC (AUC0 to 12h) does not require patient to be available for the complete dosing interval (12 hours) sometimes hardly achievable. Multiple concentration time points (several specific timed points after dosing, also called limited sampling strategies (LSSs)) requires longer stay for multiple samples and errors in timing may lead to errors in estimations. Extrapolations can be used with accuracy only in the population in which the regressions have been developed. Single or multiple concentration time points used for Bayesian analysis are mathematically more complex technique, requires preexisting population pharmacokinetic model and knowledge of covariates. This is computer model based and requires interpretation for dosing advice.

Table 1

Table presenting reason for AUC0–12h and C0 assessment.

| Motive                                      | MMF + CsA | MMF + Tacro | Total |
|---------------------------------------------|-----------|-------------|-------|
| Control of drug adaptation                   | 44 (32.4%)| 19 (16.6%)  | 63 (26.5%)|
| Systematic observation                      | 63 (46.3%)| 57 (55.9%)  | 120 (50.4%)|
| Chronic nephropathy have been reported      | 29 (21.3%)| 56 (23.1%)  | 85 (22.5%)|
| Total                                       | 136 (100.0%)| 102 (100.0%)| 238 (100.0%)|

2. Materials and methods

2.1. Characteristics of study patients

The study was performed at the University Hospital of Limoges, in France. Renal transplant recipients aged from 22 to 82 years who underwent MMF monitoring in the university hospital of Limoges during 1-year period were included in the study. In total 238 patients were enrolled: 136 patients receiving MMF with cyclosporine (CsA) and 102 patients receiving MMF with tacrolimus (Tacro), with post-transplantation time >1 year, 2 BID regimen. Motive for assessment is presented in Table 1. MMF and CsA receiving study group consisted of patients aged from 23 to 82 years, mean 56.97 ± 12.97 SD years; MMF and Tacro receiving patients were 22 to 79 years, mean 54.34 ± 11.56 SD years. All patients were stable kidney recipients with post-transplantation time more than 1 year: 1.0 to 26.24 years, mean 7.37 ± 4.81 SD years in MMF + CsA study group; 1.0 to 18.01 years, mean 4.31 ± 3.41 SD years in MMF + Tacro study group (data presented in Table 2).

The inclusion criteria were age of more than 18 years, kidney transplant, and immunosuppression with MMF and either cyclosporine or tacrolimus. Patients were excluded if they received immunosuppression with other medications and / or underwent transplantation of the other organs. MMF dose varied from 500 to 4000mg/day, mean 1825.11 ± 669.30 SD mg/day in MMF + CsA group; from 500 to 3000mg/day, mean 1406.86 ± 510.92 SD mg/day in MMF + Tacro group (data presented in Table 2). MMF was given two times daily to all subjects receiving either MMF and CsA or either MMF and Tacro. Accordingly, AUC0–12h was calculated and the therapeutic latency was from 30 to 60 mg h/L. Therapeutic latency for assessment of C0 was 1.0–3.0 mcg/mL for all patients. Prednisolone was prescribed in accordance with the standard hospital practice.

T-test results showed that variability of MMF doses and age among patients (all groups) was similar (P > 0.05; same conditions).

The work described was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Determination of MPA

Blood samples were collected in EDTA tubes at 20 minutes, 1 and 3 hours after the use of an MMF dose. Plasma was separated by
centrifugation. The measurement of total MPA was performed using a validated high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection. Blood serum (500 µL), an internal standard (50 µL) (thiopental in methanol 1 g/L diluted with deproteinized water to 25 mg/L) and calibrators were acidified with hydrochloric acid and extracted with dichloromethane (5 mL). Calibrators were prepared in drug-free plasma and their concentrations were 0, 0.5, 1, 5, 10, and 20 µg/L for MPA. The organic fraction was then evaporated to dryness under a stream of nitrogen. The dry residue was reconstituted with 100 µL elution solvent (KH₂PO₄ buffer/acetonitrile [70/30 v/v] at pH 2.6). Then, the sample (40 µL) was injected into the HPLC system with a steel column Nucleosil C18, 5 µm (250 × 4.6 mm, i.d.) and with UV detection at 300 nm. The limits of detection (LOD) and quantification (LOQ) were respectively 50 µg/L and 200 µg/L, and calibration curves obtained using quadratic regression from the LOQ to 20,000 µg/L yielded r² > 0.999.

2.3. Pharmacokinetic analysis

The NONMEM version VI (GloboMax LLC) non-linear mixed-effects population pharmacokinetic model and the Bayesian estimator of a 3-point limited sampling strategy developed at Limoges University Hospital were used to determine MPA area under the blood concentration-time curve (AUC₀₋₁₂).

2.4. Statistical analysis

The G*Power 3.1.9.4 version has been used to calculate the sample size. Statistical test MANOVA with effect size of f²(V) = 0.0625 was used. Total calculated sample size was 171 patients with an actual power of 0.95.

Statistical analysis was performed using IBM SPSS 20.0. Pharmacokinetic parameters (AUC₀₋₁₂ and C₀) of MPA were assessed (compliance within therapeutic ranges) and compared between the patients’ groups. The unpaired t test was used to compare the study groups (GraphPad software, available online: http://www.graphpad.com/quickcalcstests1.cfm). Probability values of less than .05 were considered significant.

3. Results

3.1. Comparison of AUC₀₋₁₂ and C₀ methods for assessing MPA concentrations in MMF receiving subjects

Dissemination of average AUC₀₋₁₂ values is presented in Table 3. The non-compliance rates are accepted as AUC₀₋₁₂ exposures not within the therapeutic ranges and demonstrate cases of MMF overdosing or too low dosing.

The most accurate dosing of MMF was observed in patients receiving MMF with tacrolimus, 70.6% (72 cases) of patients’ AUC₀₋₁₂ exposures were within the therapeutic range. The highest rates of low dosing were observed in patients receiving MMF with CsA, 30.9% (42 cases) of patients had AUC₀₋₁₂ exposures below the therapeutic range. 10 (7.4%) cases of overdose were observed when subjects received MMF with CsA, and slightly more 11 (10.8%) cases of overdose were observed in subjects receiving MMF with Tacro. The data is presented in Table 3.

The mean AUC₀₋₁₂ value of MPA for the patients receiving MMF with CsA was 37.86 ± 14.65 mg h/L; for the subjects receiving MMF with Tacro was 41.95 ± 16.38 mg h/L (Table 2). Independent Sample T-test showed statistically significant difference between these study groups, patients receiving MMF with CsA vs patients receiving MMF with Tacro. These results show that AUC₀₋₁₂ of MPA depends on the drug being taken together.

The non-compliance rates of C₀ are presented in Table 3. Data analyses showed high non-compliance rates in patients receiving MMF with CsA, 58.8% (80 patients) of patients MPA concentrations were below the therapeutic latitude, while high rates of compliances are seen in patients receiving MMF with Tacro, 77.5% (79 patients). According to the above-mentioned results C₀ of MPA was highly influenced by the co-administrated drug.

Based on the results obtained, we can state that AUC₀₋₁₂ was more appropriate evaluation method for the MPA pharmacokinetic parameters. The AUC₀₋₁₂ exposures of MPA were within the therapeutic latitude for 84 (61.8%) patients who received MMF with CsA, and for 72 (70.6%) patients who received MMF with Tacro. Moreover, AUC₀₋₁₂ correlate with C₀ and can be good pharmacokinetic predictor with correlation coefficients of 0.851 in MMF with Tacro and 0.371 in MMF with CsA receiving patients (Persons correlation is significant at the 0.01 level (2-tailed)).

Table 2

| Demographical data of two study groups: MMF + CsA and MMF + Tacro. |
|---------------------|---------------------|---------------------|---------------------|---------------------|
| MMF + CsA | MMF + Tacro | P value |
| Age ± SD (years) | 56.97 ± 12.37 | 54.34 ± 11.56 | <0.05 |
| (23–82) | (22–79) |
| MMF dose ± SD (mg) | 1825.00 ± 669.30 | 1406.86 ± 510.92 | >0.05 |
| (500–4000) | (500–3000) |
| Post-transplantation time ± SD (years) | 7.37 ± 4.81 | 4.31 ± 4.1 | Not applicable |
| (1.0–26.24) | (1.0–18.01) |
| C₀ (µg/L) | 0.98 ± 0.45 | 1.91 ± 0.82 | >0.05 |
| (0.10–2.60) | (0.30–4.36) |
| AUC₀₋₁₂ (mg h/L) | 37.86 ± 14.05 | 41.95 ± 16.38 | >0.05 |
| (3.21–64.48) | (5.94–97.60) |
| Number of patients | 136 | 102 |

Table 3

Comparative table of MPA AUC₀₋₁₂ exposure and C₀ values compliances within therapeutic ranges.

| Therapeutic range for AUC₀₋₁₂ evaluation | MMF + CsA | MMF + Tacro |
|----------------------------------------|----------|------------|
| <30 mg h/L | 42 (30.8%) | 19 (18.6%) |
| 30–60 mg h / L | 84 (61.8%) | 72 (70.6%) |
| >60 mg h/L | 10 (7.4%) | 11 (10.8%) |
| Number of patients | 136 | 102 |

| Therapeutic range for C₀ evaluation | MMF + CsA | MMF + Tacro |
|------------------------------------|----------|------------|
| <1.0 mcg/mL | 80 (58.8%) | 12 (11.8%) |
| 1.0 – 3.0 mcg/mL | 56 (41.2%) | 79 (77.5%) |
| >3.0 mcg/mL | - | 11 (10.8%) |
| Number of patients | 136 | 102 |

CsA = cyclosporine, MMF = mycophenolate mofetil, Tacro = tacrolimus.
Results show that standard MMF dosing without monitoring and with mycophenolic acid level within the therapeutic width is possible and demonstrates less risky cases in patients receiving MMF with tacrolimus, while patients receiving MMF with cyclosporine should be intensively monitored to achieve the highest safety. This data acknowledge results obtained in clinical trials showing that the best results were achieved with tacrolimus + MMF dosing.[14,15]

3.2. Analyses of overdose cases
Assessment of C₀ demonstrated good compliance within estimated therapeutic range, no cases of overdose was identified in patients receiving MMF with CsA, while 11 cases of overdose was observed in patients receiving MMF with Tacro. Assessment of AUC₀ revealed 10 cases of overdose in patients receiving MMF with CsA and 11 cases of overdose in patients receiving MMF with Tacro. Demographical data of patients is presented in Table 4, non-compliance data is presented in Table 5.

Assessment of AUC₀ revealed 38% of chronic nephropathy cases (21 patients out of 55 patients with chronic nephropathy were determined by using AUC₀ method). C₀ enabled to identify 20% of chronic nephropathy cases (11 patients out of 55 patients with chronic nephropathy were determined by using C₀ method). The biggest part of patients determined as having AUC₀ > 60 mg h/L showed C₀ values compliance within the therapeutic range in rates of 80.0% in MMF + CsA receiving patients and overdose in rates of 72.7% in MMF + Tacro receiving patients (Table 5). Table 6 presents the data demonstrating reasons of assessment.

3.3. Analyses of patients with reported outcomes of chronic nephropathy
Data is provided in Tables 7 and 8. Most of the patients AUC₀ and C₀ values were obtained below or within the therapeutic ranges. Analysis of compliance showed that C₀ values were below the therapeutic width in patients receiving MMF with CsA (20 cases, 69.0%) and within the therapeutic range for AUC₀ assessment (16 cases; 55.2%) in the majority of patients. Mean C₀ value in patients receiving MMF with CsA was below the therapeutic range (C₀ 0.87 ± 0.45); AUC₀ mean value was within the therapeutic range in a lowest bound.

AUC₀ and C₀ values were highly maintained within the therapeutic range 65.4% (17 cases) and 69.2% (18 cases) for patients receiving MMF with tacrolimus. AUC₀ mean value in patients receiving MMF with Tacro was also within the therapeutic range in a lowest bound. Results of this one-dimensional study showed that MPA levels in patients with chronic nephropathy were well-controlled and reduced to the lowest levels to avoid even greater influence on the kidneys.

However, a large distribution between the lowest and the highest values of AUC₀ and C₀ was observed. No other special features with available variables have been noticed in patients with reported chronic nephropathy presuming that not only AUC₀ or C₀ of MPA are acquired and other prescribed medicaments play an important role.

3.4. Probability analyses
Probability test results showed that more likely AUC₀ and C₀ will be maintained within the therapeutic width if patients receive MMF with Tacro vs MMF with CsA: 0.6320 vs 0.6410 for AUC₀ determination and 0.8415 vs 0.4827 for C₀ determination.

4. Limitations
Risk of nephropathy was evaluated by analyzing data of protocol biopsies according to the Banff 97 classification. The Banff 97 classification had been used since the transplantations were...
performed from 1985. There are several revisions to the Banff classification since 1997. The Banff 97 classification is old and might limit the applicability of the data presented in current clinical practice.

5. Discussion

Based on the data available in the public domain, the contribution of MPA trough level monitoring during MMF therapy in solid organ transplant recipients remains contradictory. Studies have limitations and report conflicting results. There is a lack of prospective randomized trials, particularly in pediatric renal transplant recipients, cardiac and liver transplantation. The majority of studies showed no correlation between MPA plasma concentrations and adverse effects, regarding suggestion that there may be a relationship between efficacy and MPA trough levels.\(^{[16,17]}\)

Other researchers demonstrated that MPA AUC\(_{(0-12)}\) is useful predictor of outcome in renal recipients within first 6 months after renal transplantation\(^{[18]}\) or MPA AUC with 4-point sampling provide an effective approach for estimating full MPA AUC\(_{(0-12)}\) in renal recipients on enteric-coated mycophenolate sodium plus tacrolimus or cyclosporin A.\(^{[19]}\) The Bayesian method used in this study takes into account MPA AUC\(_{(0-4)}\) profile and approaches estimation for full MPA AUC\(_{(0-12)}\) as well. High variability between MPA AUC\(_{(0-12)}\), levels were observed between the 2 studies: MPA AUC\(_{(0-12)}\) levels 14-67 mg h/L (mean: 37 ± 14)\(^{[19]}\) vs 3-84 mg h/L (mean: 38 ± 15) in patients on MMF plus cyclosporine therapy and 6 to 98 mg h/L (mean: 42 ± 16) in patients on MMF plus tacrolimus therapy. Both studies demonstrated no correlation between MPA AUC\(_{(0-12)}\) and MPA trough level \(C_0\). However, in this study better AUC\(_{(0-12)}\), compliance within therapeutic range was obtained in patients on MMF plus tacrolimus therapy. Moreover, in 100 de novo renal allograft recipients was demonstrated that the dynamics of long-term MPA pharmacokinetics in combination with tacrolimus differ according to the daily MMF dose and that this effect is not adequately reflected by MPA trough concentrations and using the latter as a routine measure for therapeutic drug monitoring might mislead clinicians into drawing wrong conclusions in terms of relating questions of efficacy or toxicity to MPA exposure.\(^{[20]}\)

Tacrolimus and cyclosporine A may have different effects on exposure to concomitantly administered mycophenolate mofetil (MMF), measured as the mycophenolic acid (MPA) dose interval area under the plasma concentration vs time curve (AUC\(_{(0-12)}\)) or the plasma MPA predose concentration \(C_0\). This has led to recommendations in using a 50% lower dose of MMF in combination with tacrolimus compared to cyclosporin A.\(^{[20]}\) This study did not analyze the CsA or tacrolimus influence on MMF dose, however data showed that patients on MMF plus tacrolimus therapy received 23% lower MMF dose than patients on MMF plus cyclosporine therapy (Table 2).

Although LSSs and Bayesian techniques are difficult and requires staff competences these techniques remains preferable for MPA monitoring. Our study data shows that assessment of AUC\(_{(0-12)}\) helps to maintain MMF dosing within the therapeutic range of MPA, compliance within therapeutic range in patients receiving MMF with CsA was 87.5% and in patients receiving MMF with Tacrolimus was 70.6%.

However, some studies still use the through level for MPA monitoring. Therapeutic trough level between 3 and 4.5 mg/L\(^{[12,13,15]}\) is recommended to decrease the risk of treatment failure in patients with lupus nephritis treated with MMF. Others state that MPA trough level monitoring may be a feasible monitoring option to improve renal transplant recipients exposure and possibly outcomes.\(^{[24]}\) Nonparametric correlation in patients receiving MMF with CsA showed that link between \(C_0\) and MPA monitoring might exists \((r = 0.171, P < 0.05)\). Whether MPA trough level monitoring leads to improved efficacy and less toxicity is currently subject to a large randomized trial; final results are eagerly awaited. But for now AUC for MPA monitoring is strongly advised.

6. Conclusion

Combination of MMF with Tacrolimus is dosed more precisely vs dosing of MMF with CsA. 72 (70.6%) patients AUC\(_{(0-12)}\) and 85 (83.3%) patients \(C_0\) out of 102 patients were within the therapeutic range. The AUC\(_{(0-12)}\) monitoring of MPA in patients receiving MMF with Tacrolimus was 34.8% and in patients receiving MMF with Cyclosporine was 87.5%. This enabled to identify more overdosing and possible risky cases.

Study results show that standard MMF dosing without monitoring and with mycophenolic acid level within the therapeutic width is possible and demonstrates less risky cases in patients receiving MMF with tacrolimus, while patients receiving MMF with cyclosporine should be intensively monitored to achieve the highest safety. However, AUC\(_{(0-12)}\) monitoring is advised showing better compliance vs \(C_0\) monitoring.

**Author contributions**

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**Formal analysis:** Aurelija Radzevičienė.

**Funding acquisition:** Aurelija Radzevičienė.

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**Table 8**

Comparative table of MPA AUC\(_{(0-12)}\) exposure and \(C_0\) values compliances within therapeutic ranges in patients with reported chronic nephropathy.

| Therapeutic range for AUC\(_{(0-12)}\) evaluation | MMF + CsA | MMF + Tacro |
|-----------------------------------------------|-----------|-------------|
| \(<30\text{ mg h/L}\)                       | 11 (37.9%)| 8 (30.8%)   |
| \(30-60\text{ mg h/L}\)                     | 16 (55.2%)| 17 (65.4%)  |
| \(> 60\text{ mg h/L}\)                     | 2 (6.9%)  | 1 (3.8%)    |
| Number of patients                           | 29        | 26          |

| Therapeutic range for \(C_0\) evaluation     | MMF + CsA | MMF + Tacro |
|----------------------------------------------|-----------|-------------|
| \(<1.0 \text{ mcg/mL}\)                     | 20 (69.0%)| 6 (23.1%)   |
| \(1.0 - 3.0 \text{ mcg/mL}\)               | 9 (31.0%) | 18 (69.2%)  |
| \(> 3.0 \text{ mcg/mL}\)                   | -         | 2 (7.7%)    |
| Number of patients                           | 29        | 26          |

CsA = cyclosporine, MMF = mycophenolate mofetil, Tacrolimus.
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