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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 = through 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

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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.[1] Early adequate mycophenolic acid (MPA) exposure is associated with less rejection in kidney transplantation[2] and monitoring of MPA levels may be useful for effective mycophenolate mofetil (MMF) dosing.[3] 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.[2]

Risk increases with MMF administration at a fixed dose without MPA (the active constituent of MMF) monitoring routinely.[4] Conflicting results from randomized controlled trials regarding the benefits of therapeutic drug monitoring guided dosing over standardized dosing raise even more questions.[5–7] Nevertheless, studies have shown 10-fold variation in dose-normalized MPA exposure,[8] 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,[1,5–7,9,10] highlighting the clinical significance of underexposure. These data suggest that individualized dosing may be advantageous.

In the consensus report on therapeutic drug monitoring (TDM) of mycophenolic acid in solid organ transplantation TDM techniques have been discussed. Trough concentration (C_0) and single concentration time points (e.g., C_2 or C_4) 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.[11] Full AUC ($AUC_{0\ to\ 12\,h}$, dose-interval AUC) requires 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.[11]

Consensus report agreed that TDM of MPA based on LSSs is preferred in solid organ transplantation vs drug dosing that is based on single MPA (trough) concentrations. LSSs provide a good estimation of the MPA dose-interval AUC, which is associated with early postoperative efficacy (avoidance of acute rejection) but less clearly with drug-related toxicity. Using LSSs can improve early graft outcome in terms of acute rejection, although avoidance of drug-related adverse events has not been shown.[11]

Although, whether commonly obtained through levels are an acceptable method of surveillance remains debatable. We hypothesized that area under the concentration time curve ($AUC_{(0\text{-}12)}$) is more accurate pharmacokinetic predictor vs trough levels of MPA.

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 medicaments and / or underwent transplantation of the other organs. MMF dose varied from 500 to 4000 mg/day, mean 1825.11 ± 669.30 SD mg/day in MMF + CsA group; from 500 to 3000 mg/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, $AUC_{(0\text{-}12)}$ was calculated and the therapeutic latitude was from 30 to 60 mg h/L.[11] Therapeutic latitude for assessment of C_0 was 1.0–3.0 mcg/mL for all patients.[11] 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 ($P > .05$; 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

Table 1

Table presenting reason for $AUC_{(0\text{-}12)}$ and C_0 assessment.

Motive	MMF + CsA	MMF + Tacro	Total
Control of drug adaptation	44 (32.4%)	19 (18.6%)	63 (26.5%)
Systematic observation	63 (46.3%)	57 (55.9%)	120 (50.4%)
Chronic nephropathy have been reported	29 (21.3%)	26 (25.5%)	55 (23.1%)
Total	136 (100.0%)	102 (100.0%)	238 (100.0%)

Table 2

Demographical data of two study groups: MMF + CsA and MMF + Tacro.

	MMF + CsA	MMF + Tacro	*P* value
Age ± SD (years)	56.97 ± 12.97 (23–82)	54.34 ± 11.56 (22–79)	.106
MMF dose ± SD (mg)	1825.00 ± 669.30 (500–4000)	1406.86 ± 510.92 (500–3000)	.000
Post-transplantation time ± SD (years)	7.37 ± 4.81 (1.0–26.24)	4.31 ± 3.41 (1.0–18.01)	Not applicable
C_0 (mg/L)	0.98 ± 0.45 (0.10–2.80)	1.91 ± 0.82 (0.30–4.36)	.000
$AUC_{(0\text{-}12)}$ (mg h/L)	37.86 ± 14.65 (3.21–84.48)	41.95 ± 16.38 (5.94–97.69)	.047
Number of patients	136	102	

centrifugation. The measurement of total MPA was performed using a validated high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection.[12] 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 (KH_2PO_4 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 $\mu g l^{-1}$ and 200 $\mu g l^{-1}$, and calibration curves obtained using quadratic regression from the LOQ to 20,000 $\mu g l^{-1}$ yielded $r^2 > 0.999$.

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[13] area under the blood concentration-time curve ($AUC_{(0\text{-}12)}$).

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 $f^2(V) = 0.0625$ 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 ($AUC_{(0\text{-}12)}$ and C_0) 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/quickcalcs/ttest1.cfm). Probability values of less than .05 were considered significant.

3. Results

3.1. Comparison of $AUC_{(0\text{-}12)}$ and C_0 methods for assessing MPA concentrations in MMF receiving subjects

Dissemination of average $AUC_{(0\text{-}12)}$ values is presented in Table 3. The non-compliance rates are accepted as $AUC_{(0\text{-}12)}$ 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' $AUC_{(0\text{-}12)}$ 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 $AUC_{(0\text{-}12)}$ 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 $AUC_{(0\text{–}12)}$ 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 $AUC_{(0\text{-}12)}$ of MPA depends on the drug being taken together.

The non-compliance rates of C_0 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 C_0 of MPA was highly influenced by the co-administrated drug.

Based on the results obtained, we can state that $AUC_{(0\text{-}12)}$ was more appropriate evaluation method for the MPA pharmacokinetic parameters. The $AUC_{(0\text{-}12)}$ 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, $AUC_{(0\text{-}12)}$ correlate with C_0 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 3

Comparative table of MPA $AUC_{(0\text{-}12)}$ exposure and C_0 values compliances within therapeutic ranges.

Therapeutic range for $AUC_{(0\text{-}12)}$ evaluation	MMF + CsA	MMF + Tacro	Therapeutic range for C_0 evaluation	MMF + CsA	MMF + Tacro
<30 mg h/L	42 (30.9%)	19 (18.6%)	<1.0 mcg/mL	80 (58.8%)	12 (11.8%)
30–60 mg h / L	84 (61.8%)	72 (70.6%)	1.0 – 3.0 mcg/mL	56 (41.2%)	79 (77.5%)
>60 mg h/L	10 (7.4%)	11 (10.8%)	>3.0 mcg/mL	-	11 (10.8%)
Number of patients	136	102	Number of patients	136	102

CsA = cyclosporine, MMF = mycophenolate mofetil, Tacro = tacrolimus.

Table 4

Demographical data of patients with $AUC_{(0-12)} > 60$ mg h/L.

	MMF + CsA	MMF + Tacro
Age ± SD (years)	59.65 ± 11.90 (43–82)	58.57 ± 12.78 (36–72)
MMF dose ± SD (mg)	2050.00 ± 598.61 (1000–3000)	2000.00 ± 447.21 (1500–3000)
Post-transplantation time ± SD (years)	7.74 ± 5.15 (1.88–19.12)	2.79 ± 1.00 (1.98–4.99)
C_0 (mg/L)	1.29 ± 0.46 (0.41–2.20)	3.33 ± 0.60 (2.52–4.36)
Number of patients	10	11

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 C_0 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 $AUC_{(0-12)}$ 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 $AUC_{(0-12)}$ revealed 38% of chronic nephropathy cases (21 patients out of 55 patients with chronic nephropathy were determined by using $AUC_{(0-12)}$ method). C_0 enabled to identify 20% of chronic nephropathy cases (11 patients out of 55 patients with chronic nephropathy were determined by using C_0 method). The biggest part of patients determined as having $AUC_{(0-12)} > 60$ mg h/L showed C_0 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 $AUC_{(0-12)}$ and C_0 values were obtained below or within the therapeutic ranges. Analysis of compliance showed that C_0 values were below

Table 5

Comparative table of MPA C_0 values compliance within therapeutic range for patients with $AUC_{(0-12)} > 60$ mg h/L.

	MMF + CsA	MMF + Tacro
<1.0 mcg/mL	2 (20.0%)	-
1.0–3.0 mcg/mL	8 (80.0%)	3 (27.3%)
>3.0 mcg/mL	-	8 (72.7%)
Number of patients	10	11

CsA = cyclosporine, MMF = mycophenolate mofetil, Tacro = tacrolimus.

Table 6

Table presenting reason for the $AUC_{(0-12)}$ assessment in patients with $AUC_{(0-12)} > 60$ mg h/L.

Motive	MMF + CsA	MMF + Tacro	Total
Control of drug adaptation	2 (20.0%)	2 (18.2%)	4 (19.0%)
Systematic observation	6 (60.0%)	8 (72.7%)	14 (66.7%)
Chronic nephropathy have been reported	2 (20.03%)	1 (9.1%)	3 (14.3%)
Total	10 (100.0%)	11 (100.0%)	21 (100.0%)

the therapeutic width in patients receiving MMF with CsA (20 cases, 69.0%) and within the therapeutic range for $AUC_{(0-12)}$ assessment (16 cases; 55.2%) in the majority of patients. Mean C_0 value in patients receiving MMF with CsA was below the therapeutic range (C_0 0.87 ± 0.45); $AUC_{(0-12)}$ mean value was within the therapeutic range in a lowest bound.

$AUC_{(0-12)}$ and C_0 values were highly maintained within the therapeutic range 65.4% (17 cases) and 69.2% (18 cases) for patients receiving MMF with tacrolimus. $AUC_{(0-12)}$ 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 $AUC_{(0-12)}$ and C_0 was observed. No other special features with available variables have been noticed in patients with reported chronic nephropathy presuming that not only $AUC_{(0-12)}$ or C_0 of MPA are acquired and other prescribed medicaments play an important role.

3.4. Probability analyses

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 Tacro vs MMF with CsA: 0.6320 vs 0.6410 for $AUC_{(0-12)}$ determination and 0.8415 vs 0.4827 for C_0 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

Table 7

Demographical data of patients with reported chronic nephropathy.

	MMF + CsA	MMF + Tacro	*P* value
Age ± SD (years)	54.98 ± 14.00 (23–75)	53.45 ± 11.76 (23–79)	.664
MMF dose ± SD (mg)	1575.86 ± 450.12 (1000–2000)	1326.92 ± 582.11 (500–3000)	.080
Post-transplantation time ± SD (years)	8.33 ± 4.85 (1.00–21.16)	3.32 ± 2.35 (1.00–9.95)	Not applicable
C_0 (mg / L)	0.87 ± 0.45 (0.10–2.10)	1.75 ± 0.77 (0.66–3.58)	.000
$AUC_{(0-12)}$ (mg h / L)	34.70 ± 12.47 (15.09–68.78)	36.51 ± 13.36 (15.32–63.58)	.605
Number of patients	29	26	

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	Therapeutic range for C_0 evaluation	MMF + CsA	MMF + Tacro
<30 mg h/L	11 (37.9%)	8 (30.8%)	<1.0 mcg/mL	20 (69.0%)	6 (23.1%)
30–60 mg h/L	16 (55.2%)	17 (65.4%)	1.0 – 3.0 mcg/mL	9 (31.0%)	18 (69.2%)
> 60 mg h/L	2 (6.9%)	1 (3.8%)	> 3.0 mcg/mL	-	2 (7.7%)
Number of patients	29	26	Number of patients	29	26

CsA = cyclosporine, MMF = mycophenolate mofetil, Tacro = tacrolimus.

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 $AUC_{(0-4)}$ 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 (Tale 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 61.8% and in patients receiving MMF with Tacro was 70.6%.

However, some studies still use the through level for MPA monitoring. Therapeutic trough level between 3 and 4.5 mg/L[21–23] 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 motive for MMF monitoring might exists ($r_s = 0.171$, $P < 0.05$). 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 Tacro 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 Tacro or in patients receiving MMF with CsA 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.

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