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PHARMACOKINETICS AND PHARMACODYNAMICS OF MYCOPHENOLIC ACID AND THEIR RELATION TO RESPONSE TO THERAPY OF CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Background—Mycophenolic acid (MPA) is the active form of mycophenolate mofetil (MMF) which is currently used off-label as immunosuppressive therapy in childhood-onset SLE (cSLE). The objectives of this study were to (1) characterize the pharmacokinetics (MPA-PK) and pharmacodynamics (MPA-PD) of MPA and (2) explore the relationship between MPA-PK and cSLE disease activity.

Methods—MPA-PK [area under the curve from 0 to 12 hours (AUC₀₋₁₂)] and MPA-PD [inosine-monophosphate dehydrogenase (IMPDH) activity] were evaluated in cSLE patients on stable MMF dosing. Change in SLE disease activity while on MMF therapy was measured using the British Isles Lupus Activity Group (BILAG) index.

Results—A total of 19 AUC₀₋₁₂ and 10 IMPDH activity profiles were included in the analysis. Large inter-patient variability in MPA exposure (AUC₀₋₁₂) was observed (mean ± SE: 32 ± 4.2 mg*h/L; coefficient of variation: 57%). Maximum MPA serum concentrations coincided with maximum IMPDH inhibition. AUC₀₋₁₂ and weight-adjusted MMF dosing were only moderately correlated (r = 0.56, p=0.01). An AUC₀₋₁₂ of ≥ 30 mg*h/L was associated with decreased BILAG scores while on MMF therapy (p = 0.002).

Conclusion—Weight-adjusted MMF dosing alone does not reliably allow for the prediction of exposure to biologically active MPA in cSLE. Individualized dosing considering MPA-PK

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appears warranted as this allows for better estimation of immunological suppression (IMPDH activity). Additional controlled studies are necessary to confirm that an MPA AUC₀₋₁₂ of at least 30 mg*h/L is required for cSLE improvement.

Keywords

systemic lupus erythematosus; mycophenolic acid; pharmacokinetics; pharmacodynamics; inosine 5'-monophosphate dehydrogenase (IMPDH)

INTRODUCTION

Mycophenolate mofetil (MMF) is an ester pro-drug of mycophenolic acid (MPA), a biologically active immunosuppressant (1). MPA selectively suppresses T-cell and B-cell proliferation, cytotoxic T-cell generation, antibody secretion, and the glycosylation of adhesion molecules by inhibiting *de novo* purine synthesis and by depleting lymphocytes and monocytes of guanosine triphosphate (2-4). In the latter process, MPA acts as a selective and noncompetitive inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH) (5).

MMF is indicated for the prevention of organ rejection in adult and pediatric allogeneic transplantation. Off-label use has also increased in the treatment of lupus nephritis, dermatitis and other manifestations of childhood-onset SLE (cSLE) (6-10). As the optimal MMF dosing to achieve improvement in cSLE is not well-established (11-13), the pediatric renal transplant regimen of 30 mg/kg orally twice daily or 600 mg/m² orally twice daily is currently empirically chosen for cSLE therapy (14-17). Additionally, in cSLE, MMF often is given in combination with other immunosuppressants and corticosteroids, with the latter proposed to contribute to the induction of MPA metabolism, hence decreased exposure of the drug over time (18).

There is a growing body of literature suggesting that weight- or body surface area-based dosing of MMF may be problematic as it neither predicts well MPA-PK nor MPA-PD (19). Pharmacokinetic parameters of MPA (MPA-PK) such as, but not limited to, area under the concentration-time curve (AUC) and clearance have been studied extensively in patients undergoing kidney transplantation. These MPA-PK parameters have been correlated with drug-related toxicity and graft rejection (20-22). In the same patient population, measures of IMPDH activity are also proposed as a pharmacodynamic marker of MPA (MPA-PD) in an effort to further optimize MMF dosing (23-25).

Thus, we hypothesized that there are inter-individual differences in MPA-PK and MPA-PD and that these differences are associated with differences disease control in cSLE.

The objectives of this study in cSLE were to (1) characterize MPA-PK and MPA-PD, and (2) explore the relationship of MPA-PK to MPA-PD and to change in disease activity as measured by the British Isles Lupus Activity Group (BILAG) index.

MATERIALS AND METHODS

Patients

With approval of the institutional review boards of the participating sites, patients diagnosed with cSLE (26) (i.e., SLE with diagnosis prior to or at age 16 years) were studied prospectively after consent and assent had been obtained. To be included in the study, patients were required to have stable renal function, receive MMF at a stable oral dose for at least three weeks, and be on stable doses of other medications for at least 30 days prior to

the study visits. The patients included in this study were representative of our patient population

Data Collection

Medical records were reviewed for relevant demographic data and information such as body weight, cSLE features, and medication regimens. Findings on physical examination, disease course, and standard laboratory testing were recorded. Disease activity was measured using the BILAG index. The index was chosen as it provides a comprehensive evaluation of organ-specific cSLE activity, and thus appeared best suited for the assessment of disease response to treatment (27-28). To determine the relationship between MMF therapy and disease activity, disease activity was serially measured, starting six months prior to MMF commencement until the end of the study period.

Sampling for PK-PD Measurements—To obtain an accurate MMF dosing history, patients completed a drug diary for three days prior to the PK and PD sampling visit. After a fast of at least 8 hours, serial blood samples were collected over a 9 hour time period. Blood samples for MPA-PK testing were taken 1 hour before the morning MMF dose (trough) and at 20, 40 minutes, and at 1, 1.5, 2, 3, 4, 6, and 9 hours afterwards. For MPA-PD, sampling times were as follows: immediately before the morning MMF dose and at 1, 2, 4, 6, and 9 hours thereafter.

Baseline plasma IMPDH activity was measured during a second study visit, which occurred at least one week after the serial blood sampling detailed above. Prior to this second visit, patients were instructed to withhold MMF intake for 4 days, which is equivalent to approximately 5 half-lives of the drug, in an effort to simulate IMPDH activity prior to MMF therapy (29). MPA-PK and MPA-PD measurements were performed at the Pediatric Pharmacology Research Unit of Cincinnati Children's Hospital Medical Center.

Drug Concentration Measurements for Pharmacokinetic Assessments—The concentrations of MPA and its metabolite, MPA glucuronide (MPA-G), in the plasma were measured using a validated high performance liquid chromatography (HPLC) assay (15). In brief, an Agilent 1100 series HPLC system (Agilent Technologies Inc., Palo Alto, CA) with a diode array detector set was used. Separation was achieved using a Synergy 4nm Hydro-RP 80Å (3 × 250 mm) column (Phenomenex, Torrance, CA). The mobile phase consisted of a gradient with solution A (Acetonitrile: 20 mmol/L phosphate buffer, pH 3.0; 24:76, v/v) and solution B (KH₂PO₄:Acetonitrile, pH 4.5; 55:45, v/v) programmed to 100% solution A from 0– 5.5 minutes (min), 100% solution B from 6.0 – 15.2 min and 100% solution A from 15.7– 22 min at a flow rate of 0.5 mL/min. Plasma samples were extracted using solid phase extraction with Oasis HLB 1 mL, 30 mg extraction columns (extraction efficiencies 91–100%; lower limit of quantification 0.25 mg/L for MPA and 1.0 mg/L for MPAG; intra- and inter-day precision and accuracy for quality control samples < 5%, respectively).

Pharmacodynamic Assessments—IMPDH activity, expressed as nmol/mg protein per hour, was measured by the conversion of inosine-monophosphate to xanthosine 5'-monophosphate (XMP) using previously described methods (30-31). In brief, 50 µL peripheral blood mononuclear cell lysate was incubated with 120 µL of a reaction mixture, consisting of 1 mmol/L IMP, 0.5 mmol/L NAD⁺, 40 mmol/L sodium phosphate and 100 mmol/L potassium chloride with a pH of 7.4. After incubation for 2.5 hours at 37°C, the reaction was terminated by the addition of ice-cold perchloric acid. The deproteinized incubation mixture was centrifuged at 15,800 g for 2 minutes, followed by neutralization of the supernatant 5 mol/L potassium carbonate. 15 µL of the supernatant was injected into the HPLC system. As described above, the Agilent 1100 series HPLC system was used.

Separation of XMP was achieved by ion-pair reversed phase HPLC using a 250 mm × 3.1 mm Prontosil AQ column. The mobile phase consisted of a mixture of 5% (v/v) methanol and 94% (v/v) buffer (pH 5.5) containing 50 mmol KH₂PO₄ and 7 mM tetra-n-butyl hydrogen sulfate. Column temperature was kept at 45°C. The method was reproducible with extraction efficiencies at 96 - 100% over the working range of 90-4800 pmol per sample (lower limit of detection for XMP and 11 pmol for AMP; intra-day and inter-day precision for XMP and AMP: 0.5 - 6.7%).

Statistical Analysis

Pharmacokinetic and Pharmacodynamic Analysis—For this pilot study, we estimated that a total of about 20 patients would allow adequate exploratory description of MPA-PK and its variability in this cSLE population (Jadhav PR. Defining the Quality of Pediatric Pharmacokinetic Studies. Personal Communication; April 5, 2010) (32-33). Standard non-compartmental analysis (WinNonlin Pro, version 5.1, Pharsight, Mountain View, CA.) was used to determine the following PK parameters: time to peak MPA concentration (T_{max}); peak MPA concentration (C_{max}); oral clearance CL/F (total body clearance divided by bioavailability, which is the extent or rate at which the active drug reaches its target tissues. To allow for direct comparison to similar published studies, a 12-hour area under the curve (AUC_{0-12}) was extrapolated from the data of the nine-hour serial blood samples by using the trough MPA concentration value as the concentration at the 12-hour time point at steady-state, as is common in pharmacokinetic studies (32,34). Both absolute and dose-normalized and weight-normalized values were determined where appropriate.

For the pharmacodynamic analysis, the following parameters were measured: IMPDH activity at baseline (i.e., after a 4-day washout period), pre-dose IMPDH activity, maximum IMPDH activity, time of the minimum IMPDH activity, percent change from IMPDH activity at baseline to minimum IMPDH activity, and percent change from predose IMPDH activity to minimum IMPDH activity.

Relationship of MPA Pharmacokinetics with cSLE Disease Activity—Numerical variables were summarized as mean ± SD. Binary and categorical variables were summarized by frequency (in %). Pearson correlation coefficients (r) were calculated to assess associations between numerical variables. A Pearson correlation coefficient of <0.4 represents weak correlation, between 0.41 and 0.60 is moderate, whereas between 0.61 and 0.80 is strong to moderate correlation (35). Parametric models were considered primary statistical tools for the study. PK measures were assessed on their associations with MMF response in an analysis of covariance model framework, adjusting for other factors and covariates such as patients' demographic and clinical characteristics. MPA-PK parameters were assessed on their associations using multiple linear regression models, adjusting for other demographic and clinical predictors (such as disease duration, concomitant medication, and renal function). The levels of association were further assessed and compared in subgroups when MMF response was added as an interaction factor to the models. A multiple logistic regression model was used to assess the prediction of odds of MMF response, using PK and PD measures as predictors. Predictors that are highly collinear with other predictors were excluded from the logistic regression models to ensure all unknown parameters are estimable.

Response to treatment was measured as the difference in mean time-adjusted BILAG summary scores up to 6 months prior to MMF therapy ($MTA-BILAG_{Pre-MMF}$) as compared to the time periods between the commencement of MMF treatment and the first study visit ($MTA-BILAG_{Post-MMF}$) (36). Response to therapy was estimated as follows: reduction in

BILAG Score (in percent) = $(\text{MTA-BILAG}_{\text{Pre-MMF}} / \text{MTA-BILAG}_{\text{Post-MMF}}) \times 100\%$. In the analysis of assessing the response to MMF therapy, patients with an MTA-BILAG_{Pre-MMF} of < 5 were excluded (n=4), as they were deemed to have a very low disease activity and thus only a minimal potential gain from MMF therapy (37).

RESULTS

Patients

Data on 19 cSLE patients were available for analysis (17 females, 1 male; 58% African-American, 42% Caucasian, 79% Non-Hispanic), with a mean $\pm$ SD age of 16.9 ± 4 years. Patients' demographics and clinical characteristics at the time of the first study visit are summarized in Table 1. The average $\pm$ SD disease duration of cSLE was 3.3 ± 3 years. The mean $\pm$ SD duration of MMF treatment was 1.5 ± 1.4 years (range: 0.14 - 6.4 years). Indications for starting MMF therapy were lupus nephritis (n=16) and discoid lupus (n=3).

MPA Pharmacokinetics and Pharmacodynamics Analysis

The relationship between weight-adjusted MMF dosing and MPA exposure, as measured by the AUC₀₋₁₂ was no more than moderate ($r = 0.56$, $p=0.01$). Nonetheless, despite adjustments for patient's weight and MMF dose, there was large inter-individual variability in MPA pharmacokinetic parameters. This is shown for the AUC₀₋₁₂ (coefficient of variation 57%) in Figure 1 and Table 2. Peak MPA concentrations ranged from 4 to 32.7 mg/L and occurred between 20 minutes and 1.5 hours after the administration of MMF.

MPA-PD analysis was conducted on available samples ($n = 10$). As expected based on the MPA-PK data and indicated by the large SE bars in Figure 1, there was considerable inter-individual variability in IMPDH activity. IMPDH activity decreased with increasing MPA plasma concentrations, with maximum inhibition of IMPDH coinciding with maximum MPA concentrations. IMPDH activity returned to pre-dose levels as MPA concentration decreased (Figure 1). Table 3 provides a summary of the PD parameters explored in this study.

Relationship of MPA Pharmacokinetics, Pharmacodynamics, and Disease Activity

There were 15 of 19 (79 %) patients with decreased SLE disease activity after commencement of MMF therapy (MTA-BILAG_{Post-MMF}) as compared to the pre-MMF time frame (MTA-BILAG_{Pre-MMF}). The mean $\pm$ SE decrease in disease activity was -5.6 ± 0.84 points. In the remaining four patients (21%) there was a small increase in disease activity (average + 2.2 points). When MMF effectiveness, as measured by the percent-reduction in BILAG score was plotted against drug exposure, patients with MPA AUC₀₋₁₂ levels of at least 30 mg*h/L ($n=5$) had a significantly greater percent-reduction in BILAG scores ($p= 0.002$, Figure 2). Conversely, there was no clear relationship between weight-adjusted MMF dosing and cSLE disease course.

DISCUSSION

We observed significant inter-individual variability in both pharmacokinetics and pharmacodynamics of mycophenolic acid. Additionally, we present initial evidence that personalized cSLE disease control may be related to sufficient exposure to MMF. Both statements support the notion that personalized MMF regimens, based on MPA-PK and/or MPA-PD, may be preferable to the current weight-based approach of MMF dosing in cSLE patients.

Weight-adjusted MMF dosing only moderately correlated with patients' actual exposure to the biologically active drug. Our data support that MPA exposure, as quantified by AUC_{0-12} , is related to maximum IMPDH inhibition, supporting the usefulness of IMPDH as a PD target. To date, IMPDH activity is not routinely assessed in transplant patients and, to the best of our knowledge, has not been studied in cSLE. Although these findings certainly warrant larger studies, we are encouraged as our results are consistent with what is currently known about both MPA-PK and MPA-PD in the field of solid organ transplantation (24-25). If confirmed, IMPDH activity may serve as a biomarker of MPA-PD which may be of significant utility in determining the starting dose of MMF. Given the close relationship of MPA-PK and MPA-PD, MMF dose adjustments based on MPA-PK appear justified during maintenance therapy.

We found weight-based MMF dosing to be only moderately related to exposure to the biologically active MPA. Thus, in contrast to other commonly used anti-inflammatory medications, weight-based MMF dosing does not appear to be useful in estimating the adequacy of MPA exposure in patients with cSLE. Our findings are in line with prior studies in transplant patients and patients with adulthood-onset of SLE which show similar large inter-individual variability in MPA PK (32-33).

We also present initial evidence that disease activity change over time is related to MPA exposure. Although this finding can only be considered as preliminary given the exploratory nature of our study, an MPA AUC_{0-12} level of 30 mg*h/L or higher was associated with improved disease control of cSLE, whereas MPA AUC_{0-12} levels lower than that were not. This tentative AUC_{0-12} target of >30 mg*h/L coincides with the recommended lower MPA AUC_{0-12} target in transplant recipients (24,38-39) and is consistent with reports by Zahr et al in adult SLE (40-41).

Due to its general ability to induce uridine diphosphate glucuronosyltransferase (UGT) (42-44), which is responsible for MPA metabolism, corticosteroids have been proposed to decrease MPA clearance and therefore increase MPA exposure (18). To date, corticosteroid interaction with the specific UGTs involved in MPA metabolism has not been extensively studied (45), and renal transplant studies have concluded that corticosteroids do not influence MPA-PK (45-47). In this study, we did not find a relevant correlation between the prednisone dose and MPA AUC_{0-12} , despite a wide range in prednisone dosing (data not shown). Inter-individual differences in the PK profiles of patients treated with MMF are also likely influenced to an extent by genetic polymorphisms involving the enzymes responsible for transporter-facilitated MPA uptake and metabolism.

The relatively small number of clinically evaluable patients may be construed as a limitation of our study. However, our sample size is consistent with that of other studies assessing MPA pharmacokinetics (32-33). Evaluation of the distribution of the data supported the use of parametric statistics. The use of multivariable linear and logistic regression was done in consideration of the exploratory nature of this initial study, as the investigators assessed that this statistical approach would allow for adjustment for differences between samples at baseline. Another limitation may be that disease activity scores were measured in a retrospective fashion. However, cSLE documentation was done using standard clinic forms and a standardized laboratory panel was ordered during follow-up. This limited the amount of missing data and allowed for more uniform scoring of disease activity, reducing potential measurement errors. Response to MMF may also vary according to cSLE organ involvement. Additionally, all patients enrolled in this study had stable renal function, thus MPA-PK and MPA-PD unlikely changed during the time of MMF therapy.

Given its exploratory nature, the study did not account for concurrent cSLE medications, particularly prednisone, which may influence disease activity, response to MMF, and MPA metabolism. Nonetheless, our findings of the relationship between MPA exposure and response of MMF therapy are well in line with some other studies (24,38-39), supporting the relevance of our findings that this might also be true for cSLE.

Our data may be interpreted as initial evidence that personalized dosing may be preferable in cSLE therapy to optimize response to MMF, thus necessitating a similar method of therapeutic drug monitoring such as that which is in current practice for solid organ transplant recipients. Obviously, such an observation will need to be formally tested under consideration of concurrent medication and patient adherence.

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References

1. Morris RE, Hoyt EG, Murphy MP, Eugui EM, Allison AC. Mycophenolic acid morpholinoethyl ester (RS-61443) is a new immunosuppressant that prevents and halts heart allograft rejection by selective inhibition of T- and B-cell purine synthesis. *Transplant Proc* 1990 Aug;22(4):1659–62. [PubMed: 2389428]
2. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology* 2000 May;47(2-3):85–118. [PubMed: 10878285]
3. Allison AC, Eugui EM. Preferential suppression of lymphocyte proliferation by mycophenolic acid and predicted long-term effects of mycophenolate mofetil in transplantation. *Transplant Proc* 1994 Dec;26(6):3205–10. [PubMed: 7998117]
4. Ransom JT. Mechanism of action of mycophenolate mofetil. *Ther Drug Monit* 1995 Dec;17(6):681–4. [PubMed: 8588241]
5. Chaigne-Delalande B, Guidicelli G, Couzi L, Merville P, Mahfouf W, Bouchet S, et al. The Immunosuppressor Mycophenolic Acid Kills Activated Lymphocytes by Inducing a Nonclassical Actin-Dependent Necrotic Signal. *J Immunol* 2008 Dec 1;181(11):7630–8. [PubMed: 19017951]
6. Alba P, Karim MY, Hunt BJ. Mycophenolate mofetil as a treatment for autoimmune haemolytic anaemia in patients with systemic lupus erythematosus and antiphospholipid syndrome. *Lupus* 2003;12(8):633–5. [PubMed: 12945724]
7. Vasoo S, Thumboo J, Fong KY. Refractory immune thrombocytopenia in systemic lupus erythematosus: response to mycophenolate mofetil. *Lupus* 2003;12(8):630–2. [PubMed: 12945723]
8. Schanz S, Ulmer A, Rassner G, Fierlbeck G. Successful treatment of subacute cutaneous lupus erythematosus with mycophenolate mofetil. *Br J Dermatol* 2002 Jul;147(1):174–8. [PubMed: 12100205]
9. Gaubitz M, Schorat A, Schotte H, Kern P, Domschke W. Mycophenolate mofetil for the treatment of systemic lupus erythematosus: an open pilot trial. *Lupus* 1999;8(9):731–6. [PubMed: 10602445]
10. Falcini F, Capannini C, Martini M, La Torre L, Vitale V, Nacci N, et al. Mycophenolate Mofetil (MMF) for the treatment of juvenile onset systemic lupus erythematosus. *Pediatric Rheumatology* 2008;6(Suppl 1):P234.
11. Tannuri U, Gibelli NE, Maksoud-Filho JG, Santos MM, Pinho-Apezato ML, Velhote MC, et al. Mycophenolate mofetil promotes prolonged improvement of renal dysfunction after pediatric liver transplantation: experience of a single center. *Pediatr Transplant* 2007 Feb;11(1):82–6. [PubMed: 17239128]

12. Jungraithmayr TC, Wiesmayr S, Staskewitz A, Kirste G, Bulla M, Fehrenbach H, et al. Five-year outcome in pediatric patients with mycophenolate mofetil-based renal transplantation. *Transplantation* 2007 Apr 15;83(7):900–5. [PubMed: 17460560]
13. Cransberg K, Cornelissen M, Lilien M, Van Hoeck K, Davin JC, Nauta J. Maintenance immunosuppression with mycophenolate mofetil and corticosteroids in pediatric kidney transplantation: temporary benefit but not without risk. *Transplantation* 2007 Apr 27;83(8):1041–7. [PubMed: 17452893]
14. Ojogho O, Sahney S, Cutler D, Baron PW, Abdelhalim FM, James S, et al. Mycophenolate mofetil in pediatric renal transplantation: non-induction vs induction with basiliximab. *Pediatr Transplant* 2005 Feb;9(1):80–3. [PubMed: 15667617]
15. Lobritto SJ, Rosenthal P, Bouw R, Leung M, Snell P, Mamelok RD. Pharmacokinetics of mycophenolate mofetil in stable pediatric liver transplant recipients receiving mycophenolate mofetil and cyclosporine. *Liver Transpl* 2007 Nov;13(11):1570–5. [PubMed: 17969194]
16. Ettenger R, Cohen A, Nast C, Moulton L, Marik J, Gales B. Mycophenolate mofetil as maintenance immunosuppression in pediatric renal transplantation. *Transplant Proc* 1997 Feb-Mar;29(1-2):340–1. [PubMed: 9123030]
17. Hocker B, Weber LT, Bunchman T, Rashford M, Tonshoff B. Mycophenolate mofetil suspension in pediatric renal transplantation: three-year data from the tricontinental trial. *Pediatr Transplant* 2005 Aug;9(4):504–11. [PubMed: 16048604]
18. Cattaneo D, Perico N, Gaspari F, Gotti E, Remuzzi G. Glucocorticoids interfere with mycophenolate mofetil bioavailability in kidney transplantation. *Kidney Int* 2002 Sep;62(3):1060–7. [PubMed: 12164891]
19. Sherwin C, Fukuda T, Goebel J, Brunner HI, Vinks AA. The evolution of population pharmacokinetic models to describe the enterohepatic recycling of mycophenolic acid in solid organ transplantation and autoimmune disease. *Clin Pharmacokinet*. 2009 in press.
20. Le Meur Y, Buchler M, Thierry A, Caillard S, Villemain F, Lavaud S, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *Am J Transplant* 2007 Nov;7(11):2496–503. [PubMed: 17908276]
21. Jeong H, Kaplan B. Therapeutic monitoring of mycophenolate mofetil. *Clin J Am Soc Nephrol* 2007 Jan;2(1):184–91. [PubMed: 17699403]
22. Lu YP, Zhu YC, Liang MZ, Nan F, Yu Q, Wang L, et al. Therapeutic drug monitoring of mycophenolic acid can be used as predictor of clinical events for kidney transplant recipients treated with mycophenolate mofetil. *Transplant Proc* 2006 Sep;38(7):2048–50. [PubMed: 16979995]
23. Glander P, Hambach P, Braun KP, Fritsche L, Waiser J, Mai I, et al. Effect of mycophenolate mofetil on IMP dehydrogenase after the first dose and after long-term treatment in renal transplant recipients. *Int J Clin Pharmacol Ther* 2003 Oct;41(10):470–6. [PubMed: 14703953]
24. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. *Clin Pharmacokinet* 2007;46(1):13–58. [PubMed: 17201457]
25. Weimert NA, Derotte M, Alloway RR, Woodle ES, Vinks AA. Monitoring of inosine monophosphate dehydrogenase activity as a biomarker for mycophenolic acid effect: potential clinical implications. *Ther Drug Monit* 2007 Apr;29(2):141–9. [PubMed: 17417067]
26. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997 Sep;40(9):1725. [PubMed: 9324032]
27. Hay EM, Bacon PA, Gordon C, Isenberg DA, Maddison P, Snaith ML, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. *Q J Med* 1993 Jul;86(7):447–58. [PubMed: 8210301]
28. Yee CS, Isenberg DA, Prabu A, Sokoll K, Teh LS, Rahman A, et al. BILAG-2004 index captures systemic lupus erythematosus disease activity better than SLEDAI-2000. *Ann Rheum Dis* 2008 Jun;67(6):873–6. [PubMed: 17519277]
29. Cellcept [Package Insert]. Roche Laboratories, Inc.; Nutley, New Jersey, USA: 2009.

30. Glander P, Braun KP, Hambach P, Bauer S, Mai I, Roots I, et al. Non-radioactive determination of inosine 5'-monophosphate dehydro-genase (IMPDH) in peripheral mononuclear cells. *Clin Biochem* 2001 Oct;34(7):543–9. [PubMed: 11738390]
31. Glander P, Sombogaard F, Budde K, van Gelder T, Hambach P, Liefeldt L, et al. Improved assay for the nonradioactive determination of inosine 5'-monophosphate dehydrogenase activity in peripheral blood mononuclear cells. *Ther Drug Monit* 2009 Jun;31(3):351–9. [PubMed: 19333146]
32. Zahr N, Amoura Z, Debord J, Hulot JS, Saint-Marcoux F, Marquet P, et al. Pharmacokinetic study of mycophenolate mofetil in patients with systemic lupus erythematosus and design of Bayesian estimator using limited sampling strategies. *Clin Pharmacokinet* 2008;47(4):277–84. [PubMed: 18336056]
33. Roland M, Barbet C, Paintaud G, Magdelaine-Beuzelin C, Diot E, Halimi JM, et al. Mycophenolate mofetil in patients with systemic lupus erythematosus: a prospective pharmacokinetic study. *Lupus* 2009 Apr;18(5):441–7. [PubMed: 19318398]
34. Kuypers DR, de Jonge H, Naesens M, de Loor H, Halewijck E, Dekens M, et al. Current target ranges of mycophenolic acid exposure and drug-related adverse events: a 5-year, open-label, prospective, clinical follow-up study in renal allograft recipients. *Clin Ther* 2008 Apr;30(4):673–83. [PubMed: 18498916]
35. Franzblau, AN. A primer of statistics for non-statisticians. New York: Harcourt; 1958.
36. Brunner HI, Higgins GC, Wiers K, Lapidus SK, Olson JC, Onel K, et al. Health-related quality of life and its relationship to patient disease course in childhood-onset systemic lupus erythematosus. *J Rheumatol* 2009 Jul;36(7):1536–45. [PubMed: 19487266]
37. Wais T, Fierz W, Stoll T, Villiger PM. Subclinical disease activity in systemic lupus erythematosus: immunoinflammatory markers do not normalize in clinical remission. *J Rheumatol* 2003 Oct;30(10):2133–9. [PubMed: 14528506]
38. van Hest RM. Population-specific limited sampling strategies for therapeutic drug monitoring of mycophenolic acid. *J Postgrad Med* 2006 Oct-Dec;52(4):244. [PubMed: 17191354]
39. Armstrong VW, Shipkova M, Schutz E, Weber L, Tonshoff B, Oellerich M. Monitoring of mycophenolic acid in pediatric renal transplant recipients. *Transplant Proc* 2001 Feb-Mar;33(1-2):1040–3. [PubMed: 11267182]
40. Zahr N, Hulot J, Haroche J, Debord J, Costedoat-Chalumeau N, Cacoub P, et al. Low mycophenolic acid area under the curve is associated with increased systemic lupus erythematosus activity [Abstract]. *Fundam Clin Pharmacol* 2008;22(s1):23. Abstract.
41. Arnaud L, Zahr N, Haroche J, Hulot J, Marquet P, Funck-Brentano C, et al. Low mycophenolic acid area under the curve Is a major parameter of systemic lupus erythematosus activity [Abstract]. *Arthr Rheum* 2009;60(s1)
42. Soars MG, Petullo DM, Eckstein JA, Kasper SC, Wrighton SA. An assessment of udp-glucuronosyltransferase induction using primary human hepatocytes. *Drug Metab Dispos* 2004 Jan;32(1):140–8. [PubMed: 14709631]
43. Kanou M, Usui T, Ueyama H, Sato H, Ohkubo I, Mizutani T. Stimulation of transcriptional expression of human UDP-glucuronosyltransferase 1A1 by dexamethasone. *Mol Biol Rep* 2004 Sep;31(3):151–8. [PubMed: 15560369]
44. Djebli N, Picard N, Rerolle JP, Le Meur Y, Marquet P. Influence of the UGT2B7 promoter region and exon 2 polymorphisms and comedications on Acyl-MPAG production in vitro and in adult renal transplant patients. *Pharmacogenet Genomics* 2007 May;17(5):321–30. [PubMed: 17429314]
45. Lam S, Partovi N, Ting LS, Ensom MH. Corticosteroid interactions with cyclosporine, tacrolimus, mycophenolate, and sirolimus: fact or fiction? *Ann Pharmacother* 2008 Jul;42(7):1037–47. [PubMed: 18594053]
46. Kuypers DR, Claes K, Evenepoel P, Maes B, Coosemans W, Pirenne J, et al. Long-term changes in mycophenolic acid exposure in combination with tacrolimus and corticosteroids are dose dependent and not reflected by trough plasma concentration: a prospective study in 100 de novo renal allograft recipients. *J Clin Pharmacol* 2003 Aug;43(8):866–80. [PubMed: 12953344]

47. Gregoor PJ, de Sevaux RG, Hene RJ, Hesse CJ, Hilbrands LB, Vos P, et al. Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation* 1999 Nov 27;68(10):1603–6. [PubMed: 10589962]

Figure 1.

For ten patients mean concentrations of MPA (mg/L) and IMPDH activity (nmol/h/mg protein) are plotted against specified sampling time points of within 1 hour before the morning MMF dose (trough) and at 20 minutes, 40 minutes, and at 1, 1.5, 2, 3, 4, 6, and 9 hours after the morning MMF dose. Bars indicate standard error (SE).

Large inter-individual variability is evident based on the SE bars. Peak MPA concentrations coincide with the greatest suppression of IMPDH activity.

Figure 2.

Relationship between mycophenolic acid pharmacokinetics expressed as area under the curve (MPA AUC₀₋₁₂) and cSLE disease activity measured by the BILAG index. An MPA AUC level of at least 30 mg*h/L may be ideal for improvement in cSLE disease activity.

Table 1

Demographic and clinical characteristics of patients with childhood-onset SLE at the time of the first study visit. Changes in cSLE disease measures averaged over time using British Isles Lupus Assessment Group (BILAG) index.

	N	% of total	Mean $\pm$ SD	Range
Gender				
Female	18	95		
Male	1	5		
Race				
African-American	11	58		
Caucasian	8	42		
Ethnicity				
Hispanic	4	21		
Non-Hispanic	15	79		
Age (years)			16.9 $\pm$ 4	10.6 - 28.2
Weight (kilograms)			66.6 $\pm$ 15	43.4 - 103
Disease duration (years)			3.3 $\pm$ 3	0.2 - 12.8
Treatment duration with Mycophenolate mofetil (years)			1.5 $\pm$ 1.3	0.14 - 6.4
Medications				
Mycophenolate mofetil (mg/day)	19	100	1973 $\pm$ 634	1000 - 3000
Prednisone (mg/day)	18	95	17.2 $\pm$ 10.4	5 - 40
Methylprednisolone	3	16		
Hydroxychloroquine	17	89		
NSAIDs	11	58		
Antihypertensives	8	42		
Disease activity measures				
MTA-BILAG _{Pre-MMF} [†]			9.8 $\pm$ 5.4	
MTA-BILAG _{Post-MMF} [‡]			5.8 $\pm$ 3.7	

Legend: SD - standard deviation

[†]MTA-BILAG_{Pre-MMF} – time-adjusted mean of BILAG (British Isles Lupus Assessment Group) scores measured up to 6 months prior to initiation of MMF therapy

[‡]MTA-BILAG_{Post-MMF} - time-adjusted mean of BILAG scores measured starting 2 weeks after initiation of MMF therapy

Table 2

Pharmacokinetic parameters in patients with childhood-onset SLE treated with mycophenolate mofetil. Parameter values are reported as means $\pm$ standard deviations.

Pharmacokinetic parameters of mycophenolic acid [‡]	Mean $\pm$ SD	Coefficient of variation (%)	Range
Maximum serum concentration of MPA (C _{max}) [mg/L]	13.5 $\pm$ 6.83	50.7	3.96 – 32.67
Time of the maximum MPA concentration (T _{max}) [hours]	0.92 $\pm$ 0.41	44.8	0.33 – 1.52
12-hour area under the concentration-time curve of MPA [‡] AUC ₀₋₁₂ [mg*h/L]	32 $\pm$ 18.1	56.6	7.48 – 89.3
Dose-normalized MPA AUC _{0-12h} [mg*hour/liter/gram of MPA]	45 $\pm$ 24.1	53.5	16.9 – 120.8
Apparent oral clearance at steady state (CL/F [*]) [liter/hour]	28 $\pm$ 13.7	49.1	8.28 – 59.3

[‡]Units are presented in brackets

[‡]MPA - mycophenolic acid

[‡]Extrapolated to 12 hours (AUC₀₋₁₂) using 9-hour data

^{*}CL/F - apparent oral clearance at steady state.

Table 3

Pharmacodynamic parameters in patients with childhood-onset SLE treated with mycophenolate mofetil. Parameter values are reported as means $\pm$ standard deviations.

Pharmacodynamic parameters [†]	n	Mean $\pm$ SD	CV%	Range
IMPDH activity at baseline (i.e., after drug washout period)	9	3.61 $\pm$ 1.94	53.7	0.43 - 6.63
Predose IMPDH activity	10	1.54 $\pm$ 1.14	74.2	0.38 - 3.91
Maximum IMPDH activity	10	1.9 $\pm$ 1.02	53.6	0.41 - 3.91
Minimum IMPDH activity	10	0.28 $\pm$ 0.15	54.7	0.13 - 0.51
Time of the minimum IMPDH activity [hours]	10	2.02 $\pm$ 1.69	83.9	1 - 6
Change from IMPDH activity at baseline to minimum IMPDH activity [in %]	9	12.1 $\pm$ 10.1	83.4	2.31 - 34.88
Change from predose IMPDH activity to minimum IMPDH activity [in %]	10	29.1 $\pm$ 21.2	72.9	3.32 - 72.19

[†] Values represent nmol/hour/mg protein unless otherwise stated in brackets.