

Mycophenolic Acid Pharmacokinetics and Relapse in Children with Steroid–Dependent Idiopathic Nephrotic Syndrome

Stéphanie Tellier,* Aymeric Dallochio,* Vincent Guignonis,[†] Frank Saint-Marcoux,[‡] Brigitte Llanas,[§] Lydia Ichay,^{||} Flavio Bandin,* Astrid Godron,[§] Denis Morin,^{||} Karine Brochard,* Peggy Gandia,[¶] Stéphane Bouchet,** Pierre Marquet,[‡] Stéphane Decramer,* and Jérôme Harambat[§]

Abstract

Background and objectives Therapeutic drug monitoring of mycophenolic acid can improve clinical outcome in organ transplantation and lupus, but data are scarce in idiopathic nephrotic syndrome. The aim of our study was to investigate whether mycophenolic acid pharmacokinetics are associated with disease control in children receiving mycophenolate mofetil for the treatment of steroid–dependent nephrotic syndrome.

Design, setting, participants, & measurements This was a retrospective multicenter study including 95 children with steroid–dependent nephrotic syndrome treated with mycophenolate mofetil with or without steroids. Area under the concentration–time curve of mycophenolic acid was determined in all children on the basis of sampling times at 20, 60, and 180 minutes postdose, using Bayesian estimation. The association between a threshold value of the area under the concentration–time curve of mycophenolic acid and the relapse rate was assessed using a negative binomial model.

Results In total, 140 areas under the concentration–time curve of mycophenolic acid were analyzed. The findings indicate individual dose adaptation in 53 patients (38%) to achieve an area under the concentration–time curve target of 30–60 mg·h/L. In a multivariable negative binomial model including sex, age at disease onset, time to start of mycophenolate mofetil, previous immunomodulatory treatment, and concomitant prednisone dose, a level of area under the concentration–time curve of mycophenolic acid >45 mg·h/L was significantly associated with a lower relapse rate (rate ratio, 0.65; 95% confidence interval, 0.46 to 0.89; $P=0.01$).

Conclusions Therapeutic drug monitoring leading to individualized dosing may improve the efficacy of mycophenolate mofetil in steroid–dependent nephrotic syndrome. Additional prospective studies are warranted to determine the optimal target for area under the concentration–time curve of mycophenolic acid in this population.

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Introduction

Idiopathic nephrotic syndrome (INS) is the most frequent glomerular nephropathy in children. Although most patients initially respond to steroid therapy, around one half of them will relapse, acquire steroid–dependent nephrotic syndrome (SDNS), and require treatment with other immunomodulatory drugs, such as levamisole, cyclophosphamide, calcineurin inhibitors (cyclosporin or tacrolimus), or mycophenolate mofetil (MMF) (1–4). New treatments, such as rituximab, have also emerged (5,6). These immunomodulatory therapies are used to reduce the frequency of relapses and avoid steroid toxicity. Although there is no agreement about the precise timing and order in which a steroid sparing treatment should be introduced, MMF seems to be increasingly used in children with INS, and some studies suggest that it may be considered as a first–line immunomodulatory

therapy in SDNS (7). The recommended daily dose is 1200 mg/m². However, because of the high variability in the dose–concentration relationship, mycophenolic acid (MPA), the active metabolite of MMF, exposure should be measured, and doses should be adjusted accordingly to optimize clinical outcomes. Indeed, too high doses may expose the patient to side effects (abdominal pain, diarrhea, cytopenia, *etc.*), whereas too low doses may lead to reduced efficacy. The potential interest in therapeutic drug monitoring of MMF was first shown in inflammatory diseases, such as SLE, as well as solid organ transplantation (8–14). However, little is known about the role of therapeutic drug monitoring of MPA in INS.

A Bayesian estimator for individual interdose area under the concentration–time curve (AUC) prediction in children with INS has been developed and is used in daily practice by our group (15). However, there

*Service de Pédiatrie, Centre de référence Maladies Rénales Rares du Sud Ouest and [†]Service de Pharmacologie Clinique, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [‡]Service de Pédiatrie, Centre de référence Maladies Rénales Rares du Sud Ouest and [§]Service de Pharmacologie et Toxicologie, Centre Hospitalier Universitaire de Limoges, Limoges, France; ^{||}Service de Pédiatrie, Centre de référence Maladies Rénales Rares du Sud Ouest et Centre d'Investigation Clinique, Centre d'Investigation Clinique 1401, INSERM, and ^{**}Service de Pharmacologie Clinique, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; and [¶]Service de Pédiatrie, Centre de référence Maladies Rénales Rares du Sud Ouest, Centre Hospitalier Universitaire de Montpellier, Montpellier, France

Correspondence:

Dr. Jérôme Harambat, Service de Pédiatrie, Hôpital Pellegrin-Enfants, Place Amélie Raba Léon, 33076 Bordeaux, France. Email: jerome.harambat@chu-bordeaux.fr

is a paucity of data on the relationship between exposure to MPA and clinical outcomes of children with SDNS. The aims of this study were to investigate whether therapeutic drug monitoring of MMF therapy in children with SDNS is associated with (1) therapeutic modifications (dosage adaptations) and (2) clinical consequences (control of the disease and adverse events).

Materials and Methods

Study Population

In this retrospective, multicenter cohort, clinical, biologic, and pharmacokinetic data were collected from pediatric patients with SDNS treated with MMF with or without steroids between 2007 and 2012. All patients treated by MMF (Cellcept; Roche, Basel, Switzerland) in the four participating centers (Bordeaux, Limoges, Montpellier, and Toulouse) had at least one pharmacokinetic profile of MPA during the study period. The database of the Limoges University Hospital Laboratory of Pharmacology, which provided therapeutic drug monitoring reports, was used to track patient enrollment in 2012. Patients who received concomitant immunomodulatory treatment (levamisole, cyclophosphamide, or calcineurin inhibitors) at the time of the first pharmacokinetic study and those treated with rituximab before the introduction of MMF were excluded from the analysis. The timing and the number of pharmacokinetic profiles were at the discretion of the clinicians.

The Institutional Review Board of the University Hospital of Bordeaux (CPP-SOOM3) approved this study and waived the requirement to obtain informed consent. This study was conducted in adherence with the Declaration of Helsinki.

Definitions

All patients were treated according to the guidelines of the French Society for Pediatric Nephrology and had steroid-sensitive nephrotic syndrome (16). SDNS was defined as at least two relapses during alternate day treatment with prednisone or within a month after stopping this treatment. Clinical remission was defined as zero to trace albuminuria on dipstick on 5 consecutive days.

Data Collection

Age at disease onset, number and time of relapses, use of other immunomodulatory treatments before MMF, and dose of prednisone at MMF introduction were collected from patient medical records. Treatment duration, dose, dosage adaptation after the results of the area under the concentration-time curve of mycophenolic acid (MPA-AUC), and patient-reported side effects of MMF at the time of AUC as well as associated treatments were recorded for each pharmacokinetic study using a standardized data collection form. Standard initial dosage of MMF (600 mg/m² twice a day) and additional adaptations were anticipated to achieve an acceptable MPA-AUC target of 30–60 mg·h/L. Only pharmacokinetic studies performed outside relapse were taken into account.

MPA plasma concentrations were determined using a liquid chromatography technique coupled with ultraviolet detection. The methods were the same over the entire study

period, and the four centers had to participate in an external quality control program (Mycophenolate International Proficiency Testing Scheme; available at <http://www.bioanalytics.co.uk>). MPA-AUCs were determined for all children on the basis of samples collected at 20, 60, and 180 minutes after the morning dose using a Bayesian estimator as previously described (15).

Statistical Analyses

Data are presented as medians and interquartile ranges (IQRs) for continuous variables and percentages for categorical variables. Comparisons between groups over the study period (*i.e.*, including all pharmacokinetic studies) were made using the Wilcoxon signed rank test. The association between first MPA-AUC threshold value and prior relapse rate (*i.e.*, number of relapses from start of MMF to the first pharmacokinetic study) was assessed using a negative binomial regression model. A negative binomial model is a model designed to analyze count data (the number of relapses here), which can correct for overdispersion of the data (variance larger than the mean). Variables included as covariables in the model were sex, age at disease onset, time from onset of INS to start of MMF, previous immunomodulatory treatment, and concomitant steroid dose. Statistical analysis was performed using SAS 9.2 software (SAS Institute Inc., Cary, NC).

Results

Population Characteristics

Ninety-five patients with SDNS for whom pharmacokinetic studies of MPA had been performed were included. The characteristics of the population are summarized in Table 1. MMF was introduced either as a first-line steroid-sparing agent ($n=46$; 48%) or after failure or occurrence of side effects of another immunomodulatory treatment ($n=49$; 52%).

Results of MPA-AUC and Clinical Outcome

In total, 140 MPA-AUC measurements were performed in 95 patients (Table 2). Overall, the median value of MPA-AUC was 51.1 mg·h/L (IQR, 37.8–63.6 mg·h/L). The 140 MPA-AUCs performed resulted in 53 MMF dose adjustments (38%) in 43 children. In 21 patients (40%) with median MPA-AUC values of 83 mg·h/L (range, 58–120 mg·h/L; all but one was >60 mg·h/L), MMF was decreased by a median of 21% (range, 11%–50%) from a median dose of 1230 mg/m² per day to a median dose of 940 mg/m² per day. In 32 patients (60%) with a median MPA-AUC value of 28 mg·h/L (range, 17–46 mg·h/L), MMF was increased by a median of 26% (range, 14%–55%) from a median dose of 1110 mg/m² per day to a median dose of 1400 mg/m² per day. In 12 of 32 patients, MMF dose was increased by physicians, despite an MPA-AUC value >30 mg·h/L (range, 31–46 mg·h/L), with the aim of weaning these patients with SDNS from prednisone.

During follow-up, 95 relapses occurred in 48 patients. The relapse rate was lower after the first MPA-AUC (with one relapse in 2.5 patient-years) than before (with one relapse in 1.8 patient-years; $P<0.01$). Among the total of 140 MPA-AUCs, the median MPA-AUC values were 54.0 mg·h/L (IQR, 46.1–63.6 mg·h/L) in nonrelapsers ($n=50$

Table 1. Population characteristics

Parameters	N (%)	Median (IQR)
No. of patients	95 (100)	
Boys	50 (53)	
Age at diagnosis, yr		3.6 (2.5–5.2)
Immunomodulatory therapy before MMF	49 (52)	
Levamisole	25 (26)	
Cyclophosphamide	21 (22)	
Calcineurin inhibitors	20 (21)	
No. of relapses between diagnosis and MMF initiation		4 (3–6)
Time between diagnosis and MMF initiation, yr		2.4 (0.9–5.5)
Follow-up time on MMF, yr		2.2 (1.3–3.1)

IQR, interquartile range; MMF, mycophenolate mofetil.

MPA-AUCs) and 39.5 mg·h/L (IQR, 29.4–56.9 mg·h/L) in relapsers ($n=90$ MPA-AUCs; $P<0.01$) (Figure 1).

When analyzing MPA-AUC values from the first pharmacokinetic study only ($n=95$) and relapser status defined by prior relapses, an MPA-AUC with a cutoff value of 45 mg·h/L yielded a sensitivity of 58% and a specificity of 85% for distinguishing between relapsers and nonrelapsers. In univariable analysis, a value of first MPA-AUC higher than 45 mg·h/L was significantly associated with a lower risk of relapse (rate ratio [RR], 0.51; 95% confidence interval [95% CI], 0.35 to 0.78; $P<0.01$). In the multivariable negative binomial model including sex, age at disease onset, time to start of MMF, previous immunomodulatory treatment, and concomitant prednisone dose, a level of the first MPA-AUC >45 mg·h/L was also significantly associated with a lower relapse rate (RR, 0.65; 95% CI, 0.46 to 0.89; $P=0.01$) (Table 3).

A stratification-based sensitivity analysis was performed to account for the timing of the first pharmacokinetic study of MMF. A significant interaction was seen between time to first AUC and MPA-AUC value ($P=0.04$). Specifically, the effect of an MPA-AUC >45 mg·h/L on relapse rate was more pronounced in children who underwent a first AUC within 6 months after the start of MMF (RR, 0.46; 95% CI, 0.19 to 0.84; $P=0.03$) than among those with first AUC beyond 6 months after start of MMF (RR, 0.80; 95% CI, 0.54 to 1.15; $P=0.14$).

There were 15 adverse events of MMF (11%) noted in 12 patients at the time of the 140 pharmacokinetic analyses. These adverse events included digestive symptoms (abdominal pain and diarrhea) in eight patients, infections in six patients, and hematologic manifestation (leucopenia) in one patient. This led to MMF withdrawal in one patient (meningitis), decreased MMF dose in five patients, unchanged dose in eight patients, and increased dose in one patient with mild viral infections and frequent relapses. The median value of MPA-AUC was not statistically different between patients who experienced adverse events (59.5 mg·h/L) and those who did not (49.3 mg·h/L; $P=0.32$).

Therapeutic changes occurred during follow-up. At last follow-up, steroids were withdrawn in 38 of 76 patients (50%) who received a steroid therapy at the time of the first MPA-AUC. MMF was discontinued in 21 patients (22%) because of long-term stable remission ($n=12$), treatment failure ($n=4$), or side effects ($n=5$; recurrent ear, nose, and throat or bronchial infections, varicella, chronic meningitis, and cerebellar syndrome), irrespective of pharmacokinetic studies. Another immunomodulatory treatment was required in nine patients instead of or in association with MMF.

Discussion

The treatment of SDNS in children frequently requires immunomodulatory therapy to prevent additional relapses and avoid unwanted side effects of long-term use of

Table 2. Mycophenolic acid pharmacokinetic studies

Parameters	N (%)	Median (IQR)
No. of MPA-AUCs	140 (100)	
No. of AUCs per patient		
1 MPA-AUC	61 (64)	
2 MPA-AUC	23 (24)	
≥ 3 MPA-AUC	11 (12)	
Time between MPA-AUC, mo		
From start of MMF to MPA-AUC1, $n=95$		6 (2–15)
From MPA-AUC1 to MPA-AUC2, $n=34$		9 (5–15)
From MPA-AUC2 to MPA-AUC3, $n=11$		9 (6–12)
MMF dosage at MPA-AUC1, mg/m ² per d		1183 (1050–1260)
MMF dosage at MPA-AUC2, mg/m ² per d		1110 (954–1374)
MMF dosage at MPA-AUC3, mg/m ² per d		884 (751–1200)
MPA-AUC value, mg·h/L		51.1 (37.8–63.6)
Associated steroid therapy at time of AUC	103 (74)	
Steroid dosage at time of AUC, mg/m ² per d		10 (4–22)

IQR, interquartile range; MPA, mycophenolic acid; AUC, area under the concentration-time curve; MMF, mycophenolate mofetil.

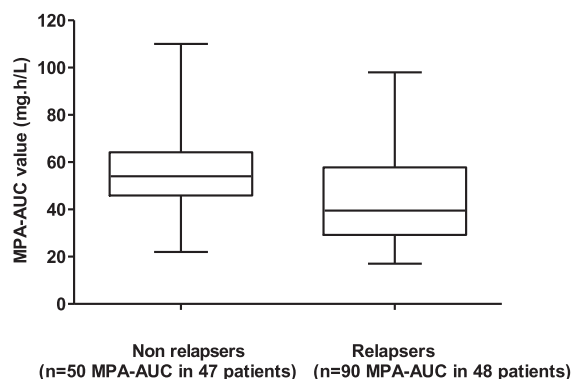


Figure 1. | Area under the concentration-time curve of mycophenolic acid (MPA-AUC) values in relapsers and nonrelapsers in patients with idiopathic nephrotic syndrome ($n=140$ MPA-AUC in 95 patients). Box and whiskers plots show minimums, medians, 25th percentiles, medians, 75th percentiles, and maximums.

steroids, such as osteopenia, growth failure, and cataracts. MMF has been widely used in the treatment of SDNS in the last decade and associated with favorable effect (3,17–24). Despite its increasing clinical use, pharmacokinetic data of MMF and their correlation with therapeutic efficacy are limited. No specific AUC target has been determined to date for MMF in pediatric INS, and we report here the largest study about therapeutic drug monitoring of MMF in children with SDNS.

Our results confirmed in INS the high interindividual variability of MPA-AUC at a given dose of MMF as previously described in solid organ transplant recipients and patients with lupus (10,13,25,26). The variation in the expression of the UDP-glucuronosyltransferases during development is possibly related to the changes in MPA clearance. The differences are apparent, especially in children younger than 10 years of age and adults (27,28). Additionally, the variability of MMF metabolites pharmacokinetics in children may be affected by various factors, such as treatment duration, therapeutic indication, drugs coadministered, and genetic, physiologic, and environmental

factors as well as kidney or liver dysfunction (27,29–33). These data advocate the relevance of therapeutic drug monitoring of MMF in children with INS.

The main finding of our study suggests an association between MPA exposure and the frequency of relapse in children with INS. The proportion of patients without relapse was significantly higher when the AUC value of MPA was >45 mg·h/L. Our results are in accordance with the data of a *post hoc* analysis from a subgroup of 43 children with SDNS treated by MMF in a clinical trial showing a significant decreased relapse rate in those with an MPA-AUC >50 mg·h/L (1.4 versus 0.27 relapses per year) (34). Interestingly, in a recent retrospective, single-center study of 15 children treated by MMF for INS, a similar target of MPA-AUC >45 mg·h/L was proposed by the authors (35). Other studies have reported an association between MPA exposure and the activity of autoimmune disorders. In a population of 19 children with lupus, Sagcal-Gironella *et al.* (36) found that patients with an AUC value >30 mg·h/L had the greatest reduction in disease activity score. In a recent study on patients with active lupus nephritis, MMF was titrated to achieve a stable target of MPA-AUC of 45–60 mg·h/L. A complete renal response was recorded in all patients, no renal flares were observed, and glucocorticoids were withdrawn in all patients (37). In the field of transplantation, a therapeutic window for MPA-AUC of 30–60 mg·h/L has been recommended (25,38,39).

Very little information is available regarding the exposure-toxicity relationship. Higher MPA-AUC was shown to be related to anemia incidence in pediatric liver transplant recipients (27). However, in a study by Sobiak *et al.* (40), 21% of children treated with MMF and corticosteroids for INS or lupus nephritis had an MPA-AUC >60 mg·h/L, with no concomitant increased incidence of adverse effects. In our study, there was no difference in MPA-AUC values between patients with and without MMF adverse events, but the number of observed adverse event was small. Altogether, in our study and others, additional benefit of reaching an MPA-AUC target >60 mg·h/L was not shown.

The role of MMF in the therapeutic strategy of INS remains to be defined. MMF is increasingly used to minimize calcineurin inhibitors toxicity. Two randomized clinical trials compared the efficacy of MMF versus

Table 3. Multivariable model of determinants of relapse rate between start of mycophenolate mofetil and first mycophenolic acid pharmacokinetic study ($n=95$ area under the concentration-time curves of mycophenolic acid in 95 patients)

Parameter	Negative Binomial Model		
	RR	95% CI	P Value
Boys versus girls	2.17	1.02 to 7.53	0.04
Age at INS per yr	0.93	0.75 to 1.17	0.58
Time from INS to MMF per yr	0.94	0.78 to 1.13	0.51
Previous immunomodulatory treatment versus none	2.46	1.30 to 6.37	0.02
Concomitant prednisone dose, mg/m ² per d			
0	1 (reference)		
1–10	2.49	1.09 to 6.96	0.03
>10	3.73	0.81 to 11.34	0.11
MPA-AUC value >45 mg·h/L	0.65	0.46 to 0.89	0.01

RR, rate ratio; 95% CI, 95% confidence interval; INS, idiopathic nephrotic syndrome; MMF, mycophenolate mofetil; MPA-AUC, area under the concentration curve of mycophenolic acid.

cyclosporin A (CsA) in treating children with frequently relapsing INS and concluded that CsA has superior efficacy in preventing relapses (34,41). However, dose adjustment of MMF to MPA-AUC was not systematically performed in these two trials. Given our findings, we believe that one cannot draw conclusions on the superiority of one of these two immunosuppressive drugs without including therapeutic drug monitoring in the study design. Prospective studies comparing patients with prespecified MPA-AUCs with those with AUCs of CsA or trough level targets are needed to appropriately assess the efficacy and tolerance of these treatments in SDNS.

The main limitation of our study was its retrospective design without consistency in indication of MMF prescription, timing of pharmacokinetic analyses, and target AUC values. Moreover, the lack of prespecified dose adjustment as part of a protocol might have led to different changes from the same MPA-AUC value according to physicians' behavior. Finally, this was an observational study without a control group. Randomized clinical trials provide the highest level of evidence for the effect of interventions. However, observational cohort studies, like our study, are useful to corroborate findings from a clinical trial by assessing an intervention in a real life setting. Indeed, our results indicate that management of SDNS from more heterogeneous patient populations may be optimized by routine therapeutic drug monitoring of MMF.

In conclusion, our study suggests that therapeutic drug monitoring leading to individualized dosing may be associated with fewer relapses and improve the efficacy of MMF in childhood SDNS or frequently relapsing nephrotic syndrome. Additional prospective studies are warranted to determine the optimal MPA-AUC target in this population.

Disclosures

None.

References

- Ponticelli C, Edefonti A, Ghio L, Rizzoni G, Rinaldi S, Gusmano R, Lama G, Zaccello G, Confalonieri R, Altieri P, Bettinelli A, Maschio G, Cinotti GA, Fuiano G, Schena FP, Castellani A, Della Casa-Alberighi O: Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: A multicentre randomized controlled trial. *Nephrol Dial Transplant* 8: 1326–1332, 1993
- Ishikura K, Ikeda M, Hattori S, Yoshikawa N, Sasaki S, Iijima K, Nakanishi K, Yata N, Honda M: Effective and safe treatment with cyclosporine in nephrotic children: A prospective, randomized multicenter trial. *Kidney Int* 73: 1167–1173, 2008
- Bagga A, Hari P, Moudgil A, Jordan SC: Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. *Am J Kidney Dis* 42: 1114–1120, 2003
- Hogg RJ, Fitzgibbons L, Bruick J, Bunke M, Ault B, Baqi N, Trachtman H, Swinford R: Mycophenolate mofetil in children with frequently relapsing nephrotic syndrome: A report from the Southwest Pediatric Nephrology Study Group. *Clin J Am Soc Nephrol* 1: 1173–1178, 2006
- Tellier S, Brochard K, Garnier A, Bandin F, Llanas B, Guignonis V, Cailliez M, Pietrement C, Dunand O, Nathanson S, Bertholet-Thomas A, Ichay L, Decramer S: Long-term outcome of children treated with rituximab for idiopathic nephrotic syndrome. *Pediatr Nephrol* 28: 911–918, 2013
- Ravani P, Rossi R, Bonanni A, Quinn RR, Sica F, Bodria M, Pasini A, Montini G, Edefonti A, Belingheri M, De Giovanni D, Barbano G, Degl'Innocenti L, Scolari F, Murer L, Reiser J, Forni A, Ghiggeri GM: Rituximab in children with steroid-dependent nephrotic syndrome: A multicenter, open-label, noninferiority, randomized controlled trial. *J Am Soc Nephrol* 26: 2259–2266, 2015
- Baudouin V, Alberti C, Lapeyraque AL, Bensman A, André JL, Broux F, Cailliez M, Decramer S, Niaudet P, Deschênes G, Jacqz-Aigrain E, Loirat C: Mycophenolate mofetil for steroid-dependent nephrotic syndrome: A phase II Bayesian trial. *Pediatr Nephrol* 27: 389–396, 2012
- Roland M, Barbet C, Paintaud G, Magdelaine-Beuzelin C, Diot E, Halimi JM, Lebranchu Y, Nivet H, Büchler M: Mycophenolate mofetil in patients with systemic lupus erythematosus: A prospective pharmacokinetic study. *Lupus* 18: 441–447, 2009
- Zahr N, Arnaud L, Marquet P, Haroche J, Costedoat-Chalumeau N, Hulot JS, Funck-Brentano C, Piette JC, Amoura Z: Mycophenolic acid area under the curve correlates with disease activity in lupus patients treated with mycophenolate mofetil. *Arthritis Rheum* 62: 2047–2054, 2010
- Djabarouti S, Breilh D, Duffau P, Lazaro E, Greib C, Caubet O, Saux MC, Pellegrin JL, Viillard JF: Steady-state mycophenolate mofetil pharmacokinetic parameters enable prediction of systemic lupus erythematosus clinical flares: An observational cohort study. *Arthritis Res Ther* 12: R217, 2010
- Woillard JB, Bader-Meunier B, Salomon R, Ranchin B, Decramer S, Fischbach M, Berard E, Guignonis V, Harambat J, Dunand O, Tenenbaum J, Marquet P, Saint-Marcoux F: Pharmacokinetics of mycophenolate mofetil in children with lupus and clinical findings in favour of therapeutic drug monitoring. *Br J Clin Pharmacol* 78: 867–876, 2014
- van Gelder T, Silva HT, de Fijter JW, Budde K, Kuypers D, Tyden G, Lohmus A, Sommerer C, Hartmann A, Le Meur Y, Oellerich M, Holt DW, Tönshoff B, Keown P, Campbell S, Mamelok RD: Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: The fixed-dose concentration-controlled trial. *Transplantation* 86: 1043–1051, 2008
- Weber LT, Hoecker B, Armstrong VW, Oellerich M, Tönshoff B: Long-term pharmacokinetics of mycophenolic acid in pediatric renal transplant recipients over 3 years posttransplant. *Ther Drug Monit* 30: 570–575, 2008
- Le Meur Y, Büchler M, Thierry A, Caillard S, Villemain F, Lavaud S, Etienne I, Westeel PF, Hurault de Ligny B, Rostaing L, Therivet E, Szelag JC, Rérolle JP, Rousseau A, Touchard G, Marquet P: Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *Am J Transplant* 7: 2496–2503, 2007
- Saint-Marcoux F, Guignonis V, Decramer S, Gandia P, Ranchin B, Parant F, Bessenay L, Libert F, Harambat J, Bouchet S, Broux F, Compagnon P, Marquet P: Development of a Bayesian estimator for the therapeutic drug monitoring of mycophenolate mofetil in children with idiopathic nephrotic syndrome. *Pharmacol Res* 63: 423–431, 2011
- Bérard E, Broyer M, Dehennault M, Dumas R, Eckart P, Fischbach M, Loirat C, Martinat L; Pediatric Society of Nephrology: [Corticosteroid-sensitive nephrotic syndrome (or nephrosis) in children. Therapeutic guideline proposed by the Pediatric Society of Nephrology]. *Nephrol Ther* 1: 150–156, 2005
- Mendizábal S, Zamora I, Berbel O, Sanahuja MJ, Fuentes J, Simon J: Mycophenolate mofetil in steroid/cyclosporine-dependent/resistant nephrotic syndrome. *Pediatr Nephrol* 20: 914–919, 2005
- Ulinski T, Dubourg L, Saïd MH, Parchoux B, Ranchin B, Cochat P: Switch from cyclosporine A to mycophenolate mofetil in nephrotic children. *Pediatr Nephrol* 20: 482–485, 2005
- Gellermann J, Querfeld U: Frequently relapsing nephrotic syndrome: Treatment with mycophenolate mofetil. *Pediatr Nephrol* 19: 101–104, 2004
- Barletta GM, Smoyer WE, Bunchman TE, Flynn JT, Kershaw DB: Use of mycophenolate mofetil in steroid-dependent and -resistant nephrotic syndrome. *Pediatr Nephrol* 18: 833–837, 2003
- Novak I, Frank R, Vento S, Vergara M, Gauthier B, Trachtman H: Efficacy of mycophenolate mofetil in pediatric patients with steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 20: 1265–1268, 2005
- Bayazit AK, Noyan A, Cengiz N, Anarat A: Mycophenolate mofetil in children with multidrug-resistant nephrotic syndrome. *Clin Nephrol* 61: 25–29, 2004

23. Fujinaga S, Ohtomo Y, Umino D, Takemoto M, Shimizu T, Yamashiro Y, Kaneko K: A prospective study on the use of mycophenolate mofetil in children with cyclosporine-dependent nephrotic syndrome. *Pediatr Nephrol* 22: 71–76, 2007
24. Afzal K, Bagga A, Menon S, Hari P, Jordan SC: Treatment with mycophenolate mofetil and prednisolone for steroid-dependent nephrotic syndrome. *Pediatr Nephrol* 22: 2059–2065, 2007
25. Weber LT, Shipkova M, Armstrong VW, Wagner N, Schütz E, Mehls O, Zimmerhackl LB, Oellerich M, Tönshoff B: The pharmacokinetic-pharmacodynamic relationship for total and free mycophenolic acid in pediatric renal transplant recipients: A report of the German study group on mycophenolate mofetil therapy. *J Am Soc Nephrol* 13: 759–768, 2002
26. Kuypers DR, Le Meur Y, Cantarovich M, Tredger MJ, Tett SE, Cattaneo D, Tönshoff B, Holt DW, Chapman J, Gelder T; Transplantation Society (TTS) Consensus Group on TDM of MPA: Consensus report on therapeutic drug monitoring of mycophenolic acid in solid organ transplantation. *Clin J Am Soc Nephrol* 5: 341–358, 2010
27. Parant F, Rivet C, Bouliou R, Gagnieu MC, Dumortier J, Boillot O, Lachaux A: Age-related variability of mycophenolate mofetil exposure in stable pediatric liver transplant recipients and influences of donor characteristics. *Ther Drug Monit* 31: 727–733, 2009
28. Filler G, Bendrick-Peart J, Christians U: Pharmacokinetics of mycophenolate mofetil and sirolimus in children. *Ther Drug Monit* 30: 138–142, 2008
29. Filler G: Value of therapeutic drug monitoring of MMF therapy in pediatric transplantation. *Pediatr Transplant* 10: 707–711, 2006
30. Filler G: Optimization of immunosuppressive drug monitoring in children. *Transplant Proc* 39: 1241–1243, 2007
31. Brown NW, Aw MM, Mieli-Vergani G, Dhawan A, Tredger JM: Mycophenolic acid and mycophenolic acid glucuronide pharmacokinetics in pediatric liver transplant recipients: Effect of cyclosporine and tacrolimus comedication. *Ther Drug Monit* 24: 598–606, 2002
32. Jacobson P, Huang J, Rydholm N, Tran M, Defor T, Tolar J, Orchard PJ: Higher mycophenolate dose requirements in children undergoing hematopoietic cell transplant (HCT). *J Clin Pharmacol* 48: 485–494, 2008
33. Ghio L, Ferrareso M, Zacchello G, Murer L, Ginevri F, Belingheri M, Peruzzi L, Zanon F, Perfumo F, Berardinelli L, Tirelli S, Dello Strologo L, Fontana I, Valente U, Cardillo M, Edefonti A: Longitudinal evaluation of mycophenolic acid pharmacokinetics in pediatric kidney transplant recipients. The role of post-transplant clinical and therapeutic variables. *Clin Transplant* 23: 264–270, 2009
34. Gellermann J, Weber L, Pape L, Tönshoff B, Hoyer P, Querfeld U; Gesellschaft für Pädiatrische Nephrologie (GPN): Mycophenolate mofetil versus cyclosporin A in children with frequently relapsing nephrotic syndrome. *J Am Soc Nephrol* 24: 1689–1697, 2013
35. Hackl Á, Cseprekál O, Gessner M, Liebau MC, Habbig S, Ehren R, Müller C, Taylan C, Dötsch J, Weber LT: Mycophenolate mofetil therapy in children with idiopathic nephrotic syndrome: Does therapeutic drug monitoring make a difference? *Ther Drug Monit* 38: 274–279, 2016
36. Sagcal-Gironella AC, Fukuda T, Wiers K, Cox S, Nelson S, Dina B, Sherwin CM, Klein-Gitelman MS, Vinks AA, Brunner HI: Pharmacokinetics and pharmacodynamics of mycophenolic acid and their relation to response to therapy of childhood-onset systemic lupus erythematosus. *Semin Arthritis Rheum* 40: 307–313, 2011
37. Zabotti A, Baraldo M, Quartuccio L, Sacco S, De Marchi G, De Vita S: Optimizing the dose of mycophenolate mofetil for the maintenance treatment of lupus nephritis by therapeutic drug monitoring. *Clin Rheumatol* 34: 171–174, 2015
38. Weber LT, Shipkova M, Armstrong VW, Wagner N, Schütz E, Mehls O, Zimmerhackl LB, Oellerich M, Tönshoff B: Comparison of the Emit immunoassay with HPLC for therapeutic drug monitoring of mycophenolic acid in pediatric renal-transplant recipients on mycophenolate mofetil therapy. *Clin Chem* 48: 517–525, 2002
39. van Gelder T, Shaw LM: The rationale for and limitations of therapeutic drug monitoring for mycophenolate mofetil in transplantation. *Transplantation* 80[Suppl]: S244–S253, 2005
40. Sobiak J, Resztak M, Ostalska-Nowicka D, Zachwieja J, Gąsiorowska K, Piechanowska W, Chrzanowska M: Monitoring of mycophenolate mofetil metabolites in children with nephrotic syndrome and the proposed novel target values of pharmacokinetic parameters. *Eur J Pharm Sci* 77: 189–196, 2015
41. Dorresteijn EM, Kist-van Holthe JE, Levchenko EN, Nauta J, Hop WC, van der Heijden AJ: Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. *Pediatr Nephrol* 23: 2013–2020, 2008

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