How cyclosporine reduces mycophenolic acid exposure by 40% while other calcineurin inhibitors do not

Gelder, T. van

How cyclosporine reduces mycophenolic acid exposure by 40% while other calcineurin inhibitors do not

Teun van Gelder[1]

[1]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, the Netherlands

The most frequently used immunosuppressive treatment in kidney transplant recipients is the combination therapy of a calcineurin inhibitor (CNI) and mycophenolate mofetil, with or without corticosteroids. Cyclosporine and tacrolimus are the 2 CNIs registered for this indication. Also, in the treatment of glomerular diseases, CNIs and mycophenolate are being used on a worldwide scale, either alone or as combined treatment. In January 2021, the US Food and Drug Administration approved voclosporin, a novel CNI, for the treatment of adult patients with active lupus nephritis. There is a clinically relevant drug–drug interaction between cyclosporine and mycophenolate. As a result of cyclosporine-induced inhibition of the enterohepatic recirculation of mycophenolate, the mycophenolic acid area under the curve is significantly lower (40%) in case of cyclosporine coadministration compared with cotreatment with either tacrolimus or voclosporin (or no CNI cotreatment). The aim of this mini review is to summarize this potential drug–drug interaction and explain how cyclosporine affects the pharmacokinetics of mycophenolate. The optimal dose of mycophenolate mofetil is likely to depend on the CNI with which it is coadministered. Furthermore, clinical implications are discussed, including the potential emergence of mycophenolic acid–related adverse effects after discontinuation of cyclosporine cotreatment.

Kidney International (2021) **100,** 1185–1189; https://doi.org/10.1016/j.kint.2021.06.036

KEYWORDS: calcineurin inhibition; cyclosporine; lupus nephritis; mycophenolic acid; tacrolimus; transplantation; voclosporin

Correspondence: *Teun van Gelder, Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. E-mail: T.van_Gelder1@lumc.nl*

Received 24 March 2021; revised 8 June 2021; accepted 17 June 2021; published online 17 July 2021

Mycophenolic acid (MPA) was developed as an immunosuppressive drug by Anthony Allison and Elsie Eugui.[1] MPA inhibits inosine monophosphate dehydrogenase, the rate-limiting enzyme in the *de novo* synthesis of guanosine nucleotides. MPA has a relatively strong effect on lymphocytes because it is a more potent inhibitor of the type II isoform of inosine monophosphate dehydrogenase. The type II isoform is more expressed in activated lymphocytes than the type I isoform of inosine monophosphate dehydrogenase, which is expressed in most other cell types. MPA has poor bioavailability, but this was solved by addition of the morpholinoethyl ester. The resulting mycophenolate mofetil (MMF) proved suitable for pharmaceutical formulation. Clinical development started after demonstration of treatment of heart transplant rejection in an experimental model.[2] MMF is a prodrug, and the active metabolite is MPA.

Three phase 3 randomized clinical trials led to the registration of MMF for the prevention of kidney allograft rejection in the mid-1990s.[3] In all 3 studies, a standard dose of 1000 mg twice a day (bid) MMF was combined with cyclosporine. Within a couple of years, MMF had almost completely replaced azathioprine as an antiproliferative immunosuppressive drug for this indication. Also in the mid-1990s, tacrolimus was introduced as a new calcineurin inhibitor (CNI). A meta-analysis of 30 randomized trials reported that at 1 year post-transplant, tacrolimus-treated patients had 31% less acute rejection (relative risk, 0.69; 95% confidence interval, 0.60–0.79), less steroid-resistant rejection (relative risk, 0.49; 95% confidence interval, 0.37–0.64), and better graft survival with tacrolimus compared with cyclosporine.[4] After the publication of the Efficacy Limiting Toxicity Elimination (ELITE)–Symphony study, tacrolimus gradually took over from cyclosporine.[5] Two years later, the Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommended tacrolimus as the first-choice CNI in kidney transplant recipients.[6] At present, the combined use of tacrolimus and MMF is the most frequently used maintenance treatment after solid organ transplantation.

In the recent KDIGO clinical practice guideline on glomerular diseases, CNIs are suggested as treatment options in children with steroid-resistant nephrotic syndrome, and in adults with treatment-resistant membranous nephropathy, minimal change nephropathy, and focal segmental glomerulosclerosis.[7] Although tacrolimus is the first-choice CNI in

organ transplantation, cyclosporine is widely used in the treatment of several forms of glomerulonephritis. In January 2021, voclosporin was the first CNI to be approved by the US Food and Drug Administration for treatment of adult patients with active lupus nephritis. In the phase 2 and phase 3 studies, the addition of voclosporin on top of the standard of care (MMF and steroids) significantly increased renal response at 1 year.[8,9]

A comparison of the efficacy and safety of tacrolimus and cyclosporine, if combined with MMF, is not just a comparison of 2 CNIs. The exposure to the active metabolite of MMF, MPA, differs substantially between the 2 regimens. The higher MPA concentrations associated with the use of tacrolimus will certainly contribute to the overall success of the combined treatment.

There is a clinically relevant drug–drug interaction between MMF and the CNIs. With new treatment options entering the market, this mini review aims to highlight the existence of this drug–drug interaction, with emphasis on the underlying molecular mechanism and the clinical consequences.

Tacrolimus + MMF versus cyclosporine + MMF

In 1997, a study in kidney transplant patients reported that MPA concentrations differed between tacrolimus and cyclosporine cotreatment.[10] Besides higher MPA concentrations in the tacrolimus-treated patients, significantly lower levels of the glucuronide metabolite of MPA (MPAG) were also found. The authors suggested that tacrolimus had an inhibitory effect on the glucuronidation of MPA. A couple of years thereafter, it was shown that it was not tacrolimus that increased MPA exposure, but in fact cyclosporine that caused a decrease in MPA concentrations.[11] Increasing cyclosporine daily doses are associated with lower MPA concentrations, whereas discontinuation of cyclosporine leads to an increase in MPA trough concentrations.[12,13] In a pharmacokinetic substudy of the ELITE–Symphony study, the effect of cyclosporine on MPA concentrations was observed as well.[14]

The pharmacokinetics of MPA are complex, and involve enterohepatic recirculation.[15] In the liver, MPA is glucuronidated to MPAG, which is then excreted into bile. The bile subsequently reaches the gut, where it is deglucuronidated by bowel flora and is again reabsorbed as MPA (Figure 1). This enterohepatic recirculation contributes significantly to overall MPA exposure. Interruption of the enterohepatic recirculation leads to a decrease in area under the curve (AUC) of ≈40%.[16] The enterohepatic recirculation leads to a second peak in the concentration-time profile of MPA at approximately 8 to 12 hours after the administration of MMF.[17] In this review, the focus is on the impact of cyclosporine on the pharmacokinetics of MPA. An external bile drain (not unusual after liver transplantation) or broad-spectrum antibiotics (eliminating the glucuronidase activity on the gut flora) can also interrupt the enterohepatic recirculation and lead to a decrease in MPA concentrations.[18]

The biliary excretion of MPAG into bile is an active process, in which the transporter protein multidrug resistance-

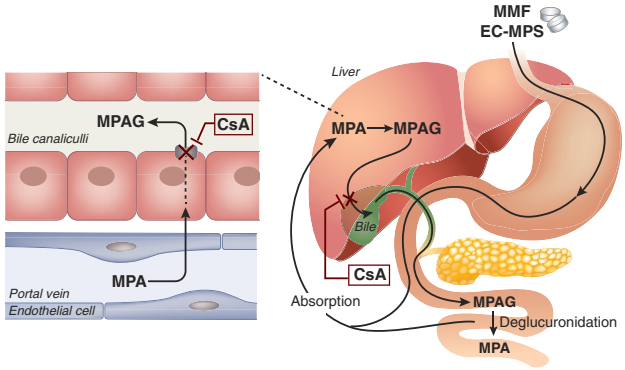

Figure 1 | The enterohepatic recirculation of mycophenolic acid (MPA). Following oral administration, mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS) is absorbed from the gut. The active metabolite, MPA, is glucuronidated in the liver, and excreted in bile as mycophenolic acid glucuronide (MPAG). In the gut, MPAG is deglucuronidated by bowel flora and MPA is reabsorbed, reflecting the enterohepatic recirculation. The biliary excretion of MPAG from the hepatocyte into bile is an active process, and the involved transporter protein (multidrug resistance-associated protein-2) is inhibited by cyclosporine (CsA). As a result, the recirculation is interrupted and exposure of MPA in plasma is reduced.

associated protein (mrp)–2 (currently also known as ABCC2) is involved.[19] In the past, this protein was also referred to as canalicular multispecific organic anion transporter. This name refers to its role in the biliary excretion of glutathione conjugates, glucuronides, and other organic anions. The mrp-2 transporter protein, present in the hepatobiliary membrane, is responsible for the excretion of MPAG into bile. The mrp-2 transporter protein is inhibited by cyclosporine, resulting in interruption of the recirculation.[20,21] Evidence that this is the mechanism by which cyclosporine causes its effect comes from an experimental study performed in rats deficient for this transporter protein.[22] Clinical evidence, among others, comes from a population pharmacokinetic model published in this journal in 2014, which showed how increasing cyclosporine trough concentrations gradually cause more and more inhibition of the enterohepatic recirculation of MPA.[23]

The elevated MPAG concentrations in patients cotreated with cyclosporine may be due to accumulation of MPAG in the liver, where it is formed in the hepatocytes, but not excreted into bile. However, the mrp-2 protein is not only present in the canalicular membrane of hepatocytes but also in the luminal membrane of proximal renal tubular cells.[24] Inhibition of the renal mrp-2 may also play a role in the accumulation of MPAG in plasma, due to reduced renal clearance.[25] As MPAG is an inactive metabolite, such high MPAG concentrations do not result in additional toxicity.

Voclosporin

Voclosporin is a novel CNI, structurally similar to cyclosporine except for a modification of a functional group on amino acid 1 of the molecule. This modification has changed

the binding of voclosporin to calcineurin and has been shown both *in vitro* and *in vivo* to increase the potency by 2-fold to 5-fold compared with cyclosporine.[26] In January 2021, the US Food and Drug Administration approved voclosporin, in combination with a background immunosuppressive therapy regimen consisting of steroids and MMF, for treatment of lupus nephritis. In view of the frequent coadministration of voclosporin and MMF in the lupus nephritis patient population, a formal drug–drug interaction study was performed. This study showed that adding voclosporin to MMF does not change MPA AUC (40.8 vs. 39.1 μg*h/L).[27] More evidence for lack of a drug–drug interaction between voclosporin and MMF comes from a phase 2 study in renal transplantation, where MPA exposure was found to be similar in voclosporin- and tacrolimus-treated patients.[28] Apparently, with the registered voclosporin, 23.7 mg bid, dose found to be effective in the treatment of lupus nephritis, no clinically relevant inhibition of the enterohepatic recirculation of MPA is observed.

Does the same interaction exist for enteric-coated mycophenolate sodium?

Enteric-coated mycophenolate sodium (EC-MPS) and MMF are both prodrugs, producing the same active drug moiety, MPA.[29] An equivalent dose of MMF and EC-MPS (1000 and 720 mg bid, respectively) provides a similar MPA AUC. The delayed release coating of EC-MPS will result in more variable trough concentrations and more variable time to the maximum plasma concentration.[30] Also, for EC-MPS, there is an enterohepatic recirculation of MPA, and thus the same drug–drug interaction with cyclosporine can be expected. There are several studies that confirm this mechanism.[31–33] More recently, in a population pharmacokinetic study in Chinese kidney transplant patients treated with EC-MPS, it was shown that MPA AUC was significantly lower in patients cotreated with cyclosporine compared with tacrolimus (52.7 $\pm$ 25.1 and 86.6 $\pm$ 44.3 mg*h/L; $P < .001$).[34] The correlation between the MPA predose concentrations and the AUC is poor in patients treated with MMF, and even worse in those on EC-MPS treatment.[30]

Clinical implications of the drug–drug interaction

In kidney transplant recipients, it has been shown that the risk of acute rejection is higher if MPA AUC is below the therapeutic range of 30 to 60 mg*h/L.[35,36] The evidence for this therapeutic window is stronger for the combined treatment of MMF and cyclosporine, but this same range of MPA exposure is used also for MMF-tacrolimus treatment. Although MMF was introduced as a "one-size-fits-all" drug, the 40% difference in MPA AUC between cyclosporine- and non–cyclosporine-based regimens suggests that the 1000 mg bid dose may not be the best dose for all patients.[37] With the 1000 mg bid dose, MPA AUC in kidney transplant patients cotreated with cyclosporine is more often below the therapeutic window compared with patients with tacrolimus or sirolimus.[38–40] Le Meur *et al.* showed that, in cyclosporine-treated patients, temporary dose increases up to 2000 mg bid are necessary to reach the target MPA AUC, and that this results in a lower incidence of rejection.[41] A German group recommended "intensified dosing" during the first 6 weeks after transplantation.[42] Compared with standard EC-MPS dosing (1440 mg/d) with an intensified dosing group (days 0–14, 2880 mg/d; days 15–42, 2160 mg/d), more patients reached an MPA AUC of >40 mg*h/L in the first week. MMF has conventionally been administered at a fixed dose without routinely monitoring MPA blood levels, and intensified dosing of MMF or EC-MPS is not recommended in treatment guidelines.[6] To reach similar MPA exposure in longer-term maintenance treatment, the MMF/EC-MPS dose will be lower in non–cyclosporine-based compared with cyclosporine-based treatment regimens. For patients cotreated with tacrolimus or voclosporin, a starting dose of 1000 mg MMF bid seems to be the best choice, with dose reductions after the first 2 to 4 weeks based on either therapeutic drug monitoring or tolerability.[43]

Another important clinical implication of the interaction is that, after discontinuation of cyclosporine, the MPA concentrations will increase and can cause MPA-related adverse effects, such as leukopenia, although the MMF dose was not changed. This has been observed in patients with a "creeping creatinine" in whom, due to deteriorating renal function, it was decided to discontinue cyclosporine treatment.[44] In patients in whom the MMF dose has been stable for years, the emergence of adverse effects may then not always be linked to MMF, especially if MPA drug concentrations are not monitored.

Conclusions

In the treatment of organ transplant recipients and of patients with lupus nephritis, combination therapy with a CNI and MMF/EC-MPS is daily practice. In contrast to tacrolimus and voclosporin, there is a significant decrease in the MPA AUC when cyclosporine and MMF/EC-MPS are combined. Cyclosporine-mediated inhibition of the enterohepatic recirculation of MPA is the mechanism behind this drug–drug interaction. Therefore, to reach similar MPA exposure, the dose of MMF/EC-MPS will need to be higher if combined with cyclosporine. Furthermore, discontinuation of cyclosporine, or switching from cyclosporine to another CNI, may cause MPA-related adverse effects, despite an unchanged MMF/EC-MPS dose.

DISCLOSURE

In the last 3 years, TvG has received lecture fees and study grants from Chiesi and Astellas, in addition to consulting fees from Roche Diagnostics, Vitaeris, CSL Behring, Hikma, Astellas, Aurinia Pharma, and Novartis. In all cases, money has been transferred to hospital accounts, and none has been paid to his personal bank accounts. TvG does not have employment or stock ownership at any of these companies, and neither does he have patents or patent applications.

ACKNOWLEDGMENTS

The author thanks Manon Zuurmond for creating the figure.

REFERENCES

1. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology*. 2000;47:85–118.
2. Morris RE, Hoyt EG, Murphy MP, et al. Mycophenolic acid morpholinoethylester (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;22:1659–1662.
3. Halloran P, Mathew T, Tomlanovich S, et al. The International Mycophenolate Mofetil Renal Transplant Study Groups. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. *Transplantation*. 1997;63:39–47.
4. Webster AC, Woodroffe RC, Taylor RS, et al. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ*. 2005;331:810.
5. Ekberg H, Tedesco-Silva H, Demirbas A, et al., ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med*. 2007;357:2562–2575.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9(suppl 3):S1–S155.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Disease Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. 2021;100:S1–S276.
8. Rovin BH, Solomons N, Pendergraft WF 3rd, et al., AURA-LV Study Group. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int*. 2019;95:219–231.
9. Rovin BH, Teng YKO, Ginzler EM, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2021;397:2070–2080.
10. Zucker K, Rosen A, Tsaroucha A, et al. Unexpected augmentation of mycophenolic acid pharmacokinetics in renal transplant patients receiving tacrolimus and mycophenolate mofetil in combination therapy, and analogous in vitro findings. *Transpl Immunol*. 1997;5:225–232.
11. van Gelder T, Klupp J, Barten MJ, et al. Comparison of the effects of tacrolimus and cyclosporine on the pharmacokinetics of mycophenolic acid. *Ther Drug Monit*. 2001;23:119–128.
12. Gregoor PJ, de Sévaux RG, Hené RJ, et al. Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation*. 1999;68:1603–1606.
13. van Hest RM, van Gelder T, Vulto AG, Mathot RA. Population pharmacokinetics of mycophenolic acid in renal transplant recipients. *Clin Pharmacokinet*. 2005;44:1083–1096.
14. Grinyó JM, Ekberg H, Mamelok RD, et al. The pharmacokinetics of mycophenolate mofetil in renal transplant recipients receiving standard-dose or low-dose cyclosporine, low-dose tacrolimus or low-dose sirolimus: the Symphony pharmacokinetic substudy. *Nephrol Dial Transplant*. 2009;24:2269–2276.
15. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. *Clin Pharmacokinet*. 2007;46:13–58.
16. Cremers S, Schoemaker R, Scholten E, et al. Characterizing the role of enterohepatic recycling in the interactions between mycophenolate mofetil and calcineurin inhibitors in renal transplant patients by pharmacokinetic modelling. *Br J Clin Pharmacol*. 2005;60:249–256.
17. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet*. 1998;34:429–455.
18. Bergan S, Brunet M, Hesselink DA, et al. Personalized therapy for mycophenolate: consensus report by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology. *Ther Drug Monit*. 2021;43:150–200.
19. König J, Nies AT, Cui Y, et al. Conjugate export pumps of the multidrug resistance protein (MRP) family: localization, substrate specificity, and MRP2-mediated drug resistance. *Biochim Biophys Acta*. 1999;1461:377–394.
20. Kobayashi M, Saitoh H, Kobayashi M, et al. Cyclosporin A, but not tacrolimus, inhibits the biliary excretion of mycophenolic acid glucuronide possibly mediated by multidrug resistance-associated protein 2 in rats. *J Pharmacol Exp Ther*. 2004;309:1029–1035.
21. Westley IS, Brogan LR, Morris RG, et al. Role of Mrp2 in the hepatic disposition of mycophenolic acid and its glucuronide metabolites: effect of cyclosporine. *Drug Metab Dispos*. 2006;34:261–266.
22. Hesselink DA, van Hest RM, Mathot RA, et al. Cyclosporine interacts with mycophenolic acid by inhibiting the multidrug resistance-associated protein 2. *Am J Transplant*. 2005;5:987–994.
23. Colom H, Lloberas N, Andreu F, et al. Pharmacokinetic modeling of enterohepatic circulation of mycophenolic acid in renal transplant recipients. *Kidney Int*. 2014;85:1434–1443.
24. Masereeuw R, Notenboom S, Smeets PH, et al. Impaired renal secretion of substrates for the multidrug resistance protein 2 in mutant transport-deficient (TR-) rats. *J Am Soc Nephrol*. 2003;14:2741–2749.
25. El-Sheikh AA, Koenderink JB, Wouterse AC, et al. Renal glucuronidation and multidrug resistance protein 2-/ multidrug resistance protein 4-mediated efflux of mycophenolic acid: interaction with cyclosporine and tacrolimus. *Transl Res*. 2014;164:46–56.
26. Kuglstatter A, Mueller F, Kusznir E, et al. Structural basis for the cyclophilin A binding affinity and immunosuppressive potency of E-ISA247 (voclosporin). *Acta Crystallogr D Biol Crystallogr*. 2011;67(pt 2):119–123.
27. van Gelder T, Huizinga RB, Lisk L, Solomons N. Voclosporin: a novel calcineurin inhibitor without impact on mycophenolic acid in patients with SLE [e-pub ahead of print]. *Nephrol Dial Transplant*. 2021:gfab022.
28. Busque S, Cantarovich M, Mulgaonkar S, et al. The PROMISE study: a phase 2b multicenter study of voclosporin (ISA247) versus tacrolimus in de novo kidney transplantation. *Am J Transplant*. 2011;11:2675–2684.
29. Budde K, Glander P, Diekmann F, et al. Review of the immunosuppressant enteric-coated mycophenolate sodium. *Expert Opin Pharmacother*. 2004;5:1333–1345.
30. de Winter BC, van Gelder T, Glander P, et al. Population pharmacokinetics of mycophenolic acid: a comparison between enteric-coated mycophenolate sodium and mycophenolate mofetil in renal transplant recipients. *Clin Pharmacokinet*. 2008;47:827–838.
31. Kaplan B, Meier-Kriesche HU, Minnick P, et al. Randomized calcineurin inhibitor cross over study to measure the pharmacokinetics of co-administered enteric-coated mycophenolate sodium. *Clin Transplant*. 2005;19:551–558.
32. Tedesco-Silva H Jr, Felipe CR, Slade A, et al. Chronopharmacokinetics of mycophenolic acid and its glucuronide and acyl glucuronide metabolites in kidney transplant recipients converted from cyclosporine to everolimus. *Ther Drug Monit*. 2012;34:652–659.
33. Huang HF, Yao X, Chen Y, et al. Cyclosporine A and tacrolimus combined with enteric-coated mycophenolate sodium influence the plasma mycophenolic acid concentration - a randomised controlled trial in Chinese live related donor kidney transplant recipients. *Int J Clin Pract Suppl*. 2014;(181):4–9.
34. Chen B, Shao K, An HM, et al. Population pharmacokinetics and bayesian estimation of mycophenolic acid exposure in Chinese renal allograft recipients after administration of EC-MPS. *J Clin Pharmacol*. 2019;59:578–589.
35. Hale MD, Nicholls AJ, Bullingham RE, et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. *Clin Pharmacol Ther*. 1998;64:672–683.
36. van Gelder T, Tedesco Silva H, de Fijter JW, et al. Renal transplant patients at high risk of acute rejection benefit from adequate exposure to mycophenolic acid. *Transplantation*. 2010;89:595–599.
37. Kuypers DR, Le Meur Y, Cantarovich M, et al. 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*. 2010;5:341–358.
38. Picard N, Prémaud A, Rousseau A, et al. A comparison of the effect of ciclosporin and sirolimus on the pharmokinetics of mycophenolate in renal transplant patients. *Br J Clin Pharmacol*. 2006;62:477–484.
39. van Gelder T, Silva HT, de Fijter JW, et al. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. *Transplantation*. 2008;86:1043–1051.
40. Musuamba FT, Rousseau A, Bosmans JL, et al. Limited sampling models and Bbayesian estimation for mycophenolic acid area under the curve prediction in stable renal transplant patients co-medicated with ciclosporin or sirolimus. *Clin Pharmacokinet*. 2009;48:745–758.

41. Le Meur Y, Büchler M, Thierry A, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *Am J Transplant*. 2007;7:2496–2503.
42. Glander P, Sommerer C, Arns W, et al. Pharmacokinetics and pharmacodynamics of intensified versus standard dosing of mycophenolate sodium in renal transplant patients. *Clin J Am Soc Nephrol*. 2010;5:503–511.
43. van Gelder T, Bouamar R, Shuker N, et al. The optimal MMF dose in tacrolimus treated patients. *Am J Transplant*. 2014;14:1221.
44. Shipkova M, Armstrong VW, Kuypers D, et al., MMF Creeping Creatinine Study Group. Effect of cyclosporine withdrawal on mycophenolic acid pharmacokinetics in kidney transplant recipients with deteriorating renal function: preliminary report. *Ther Drug Monit*. 2001;23:717–721.