Pharmacokinetic Modelling and Development of Bayesian Estimators for Therapeutic Drug Monitoring of Mycophenolate Mofetil in Reduced-Intensity Haematopoietic Stem Cell Transplantation

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Abstract

Background: Mycophenolate mofetil, a prodrug of mycophenolic acid (MPA), is used during non-myeloablative and reduced-intensity conditioning haematopoetic stem cell transplantation (HCT) to improve engraftment and reduce graft-versus-host disease (GVHD). However, information about MPA pharmacokinetics is sparse in this context and its use is still empirical.

Objectives: To perform a pilot pharmacokinetic study and to develop maximum *a posteriori* Bayesian estimators (MAP-BEs) for the estimation of MPA exposure in HCT.

Patients and Methods: Fourteen patients administered oral mycophenolate mofetil 15 g/kg three times daily were included. Two consecutive 8-hour pharmacokinetic profiles were performed on the same day, 3 days before and 4 days after the HCT. One 8-hour pharmacokinetic profile was performed on day 27 after transplantation. For these 8-hour pharmacokinetic profiles, blood samples were collected predose and 20, 40, 60, 90 minutes and 2, 4, 6 and 8 hours post-dose.

Using the iterative two-stage (ITS) method, two different one-compartment open pharmacokinetic models with first-order elimination were developed to describe the data: one with two gamma laws and one with three gamma laws to describe the absorption phase. For each pharmacokinetic profile, the Akaike information criterion (AIC) was calculated to evaluate model fitting. On the basis of the population pharmacokinetic parameters, MAP-BEs were developed for the estimation of MPA pharmacokinetics and area under the plasma concentration-time curve (AUC) from 0 to 8 hours at the different studied periods using a limited-sampling strategy. These MAP-BEs were then validated using a data-splitting method.

Results: The ITS approach allowed the development of MAP-BEs based either on 'double-gamma' or 'triple-gamma' models, the combination of which allowed correct estimation of MPA pharmacokinetics and AUC on the basis of a 20 minute-90 minute-240 minute sampling schedule. The mean bias of the Bayesian versus reference (trapezoidal) AUCs was <5% with <16% of the patients with absolute bias on AUC >20%. AIC was systematically calculated for the choice of the most appropriate model fitting the data.

Conclusion: Pharmacokinetic models and MAP-BEs for mycophenolate mofetil when administered to HCT patients have been developed. In the studied population, they allowed the estimation of MPA exposure based on three blood samples, which could be helpful in conducting clinical trials for the optimization of MPA in reduced-intensity HCT. However, prior studies will be needed to validate them in larger populations.

Background

Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA), largely used as an immunosuppressive drug to prevent acute rejection following solid organ transplantation.[1,2] Mycophenolate mofetil is also used in the prophylaxis and treatment of acute and chronic graft-versus-host disease (GVHD) after haematopoietic stem cell transplantation (HCT), or to improve the engraftment in non-myeloablative and reduced-intensity conditioning HCT.[3-15]

The therapeutic drug monitoring (TDM) of mycophenolate mofetil can be recommended in solid organ transplant since it has been demonstrated that the control of exposure to MPA helps to maximize its immunosuppressive effects.[2] However, it is still debated.[16] More precisely, an area under the plasma concentration-time curve (AUC) from 0 to 12 hours (AUC_{12}) of MPA between 30 and 60 mg • h/L is recommended for at least the first 6 months after renal or heart transplantation, when mycophenolate mofetil is used in combination with ciclosporin and corticosteroids.[1,2] Bayesian estimators (BEs), based on pharmacokinetic models and using sparse individual data, have been developed to estimate the dose providing a target AUC value for each patient.[17,18] Some of these BEs, derived from pharmacokinetic models built from large populations of transplanted patients, have been successfully used in a prospective concentration-controlled clinical trial using a limited-sampling strategy (LSS) [20 minutes, 1 hour, 3 hours].[19] These tools are also routinely used by transplantation centres via an expert system available online (https://pharmaco.chu-limoges.fr/abis.htm).[20]

On the other hand, very little information is available about the TDM of mycophenolate mofetil when used in HCT patients. The previous pharmacokinetic studies have reported a wide interpatient variability with a mean total MPA exposure below that recommended in solid organ transplantation.[3,5,7-9,14] Interestingly, mean dose-normalized MPA AUC values observed in HCT patients are almost 50% lower than in renal-transplant patients.[7,14] These observations advocate for mycophenolate mofetil administration three times daily instead of twice daily, as in solid organ transplantation.[10,21] This not only implies dose adjustments in HCT patients, but also strongly suggests that the pharmacokinetic parameters and their associated tools developed for solid organ transplant recipients would not be suitable for HCT. Furthermore, a recent study underlines the importance of MPA TDM in terms of reduction of interpatient variability.[22]

This pilot study aimed at modelling MPA pharmacokinetics and developing maximum *a posteriori* BEs (MAP-BEs) for the estimation of MPA exposure in reduced-intensity HCT patients given mycophenolate mofetil as part of their immunosuppressive regimen.

Patients and Methods

Patients

Fourteen patients were enrolled in the study. The inclusion criteria were as follows: patients who were likely to receive a reduced-intensity HCT as determined by the French Haematological Society; patients who were aged from 18 to 70 years; patients who signed the informed consent form; and absence of inter-current disease that could interfere with the short-term survival of the patient or graft. Exclusion criteria were as follows: hypersensitivity to MPA; contraindications to MPA; severe gastrointestinal disorders; and drug addictions or psychiatric disorders because those patients might not be able to understand the protocol. This clinical trial was designed in accordance with the legal requirements and approved by a local ethics committee.

The reduced-intensity regimen was a combination of fludarabine and melphalan (in eight cases), with total body irradiation (2 Gy in two cases) or with both cyclophosphamide and total-body irradiation (2 Gy in four cases). The immunosuppressive regimen for the prevention of GVHD was a combination of ciclosporin administered orally twice daily (start dose: 5 mg/kg/day; targeted trough concentration: 250 ng/mL) and mycophenolate mofetil administered at the dose of 15 mg/kg three times daily. However, because of the galenic formulation of mycophenolate mofetil (tablets of 500 mg and capsules of 250 mg), the actual dose administered was rounded off to mycophenolate mofetil 1 g three times daily. The two treatments were started 3 days before the HCT.

The supportive care medication was as previously described.[23] Briefly, it consisted in bacterial prophylaxis using phenoxymethylpenicillin (3 MU/day) or spiramycin (3 MU/day). Valaciclovir was administered orally for cytomegalovirus (CMV) prophylaxis: 500 mg twice daily if the donor and recipient were serologically CMV-negative; 1 g three times daily when donor and/or recipient were CMV-positive. Oral itraconazole (400 mg daily) or posaconazole (200 mg three times daily) was administered if fungal prophylaxis was needed.

Pharmacokinetic Profiles

Five profiles were performed during the first month of HCT: two consecutive ones at the beginning of the treatment, 3 days

before the HCT and two others 7 (±1) days later, i.e. 4 days after HCT. During these two sampling periods, the sequence of sampling was predose and 20, 40 and 60 minutes after the first administration in the morning and 2, 4, 6 and 8 hours thereafter; then, 20, 40 and 60 minutes and 2, 4, 6 and 8 hours after the administration of the second daily dose of mycophenolate mofetil. Finally, a single 8-hour pharmacokinetic profile was collected after the morning dose on day 30 (±5).

Bioanalytical Assay

The measurement of total MPA was performed using a validated high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection.[24] Briefly, a mixture of 1 mL whole blood and 4 μg of internal standard (thiopental sodium) were acidified with hydrochloric acid and extracted with 4 mL of dichloromethane. The organic fraction was then evaporated to dryness under a stream of nitrogen. The dry residue was reconstituted with the elution solvent (NaH_2PO_4 buffer/acetonitrile [58/42 v/v] at pH = 2.7). A 30 μL of sample was injected into the HPLC system with an X-Terra column and precolumn (Waters Corporation, Saint Quentin en Yvelines, France) and with a UV detection at 254 nm. This method exhibits a lower limit of quantification of 0.1 mg/L and a coefficient of variation of 6.0% for inter-day precision at the 1 mg/L concentration.

Pharmacokinetic Modelling

The pharmacokinetic profiles were described by one-compartment open models with first-order elimination combined with a gamma model of absorption with either two or three parallel absorption routes. These pharmacokinetic models were previously published to describe pharmacokinetic profiles of MPA in renal transplant patients[17,18] and in patients who have systemic lupus erythematosus.[25] Briefly, in these models, the absorption rate at time t ($V_{abs}(t)$) was described by a sum of gamma distributions (equation 1):

$$V_{abs}(t) = F \bullet D \sum_{i=1}^{m} r_i \bullet f_i(t) \qquad (Eq.\ 1)$$

with (equation 2):

$$f_i(t) = b_i^{a_i} \bullet t^{a_i - 1} \bullet \exp(-b_i \bullet t)/\Gamma(a_i) \quad i = 1...m,\ m = 2\ or\ 3 \qquad (Eq.\ 2)$$

where F is the bioavailability coefficient, D is the administered dose, f_i represents the absorption rate through the ith route, Γ is the gamma function, (a_i, b_i) the parameters of the gamma distributions and r_i is the fraction of drug absorbed through the ith

route. No independent determination of the bioavailability factor F was possible, since there were no intravenous data available for these patients.

The disposition kinetics, i.e. the impulse response I(t) of the system, were described by a one-compartment model, according to equation 3:

$$I(t) = A_{IV} \bullet \exp(-\kappa t) \qquad (Eq.\ 3)$$

where I(t) is the drug concentration at time t following an intravenous bolus of a unit dose D_0, A_{IV} is the initial concentration following an intravenous bolus administration of a unit dose and κ is the apparent elimination rate following the same intravenous bolus administration.

The convolution product of the absorption rate and disposition function was computed analytically as previously described[26,27] (equation 4):

$$C_t = C_0 + F \bullet D \bullet A_{IV} \bullet \exp(-\kappa t) \sum_{i=1}^{m} r_i[b_i/(b_i - \kappa)]^{a_i} \bullet$$
$$P[a_i(b_i - \kappa)t] \qquad (Eq.\ 4)$$

where C_t is the concentration at time t, C_0 the trough concentration and P denotes the incomplete gamma function (equation 5):

$$P(n, x) = [1/\Gamma(n)] \int_0^x z^{n-1} \bullet \exp(-z) \bullet dz \qquad (Eq.\ 5)$$

where n is the exponent of the incomplete gamma function, x is the independent variable (argument of the incomplete gamma function) and z is the integration variable.

Bayesian Estimation of Individual Pharmacokinetic Parameters

The individual parameters (vector θ) for each patient were determined by minimizing the following objective function (equation 6):

$$\Phi(\theta) = \sum_{i=1}^{a} [C_i - f(t_i,\theta)]^2/v_i + (\theta - \mu)^T \bullet \Omega^{-1}(\theta - \mu) \quad (Eq.\ 6)$$

where the symbols have the following meanings:
- Φ: objective function corresponding to the Bayesian posterior distribution
- a: number of experimental points
- C_i: concentration measured at time t_i
- f (t_i,θ): concentration computed at time t_i
- v_i: variance of measured concentration
- θ: vector of model parameters
- μ: mean parameter values in the reference population
- Ω: variance-covariance matrix of parameters in the reference population
- the symbol ^{T} denotes matrix transposition.

The variance-covariance matrix V of the posterior distribution of the parameter estimates for each patient was computed by the classical approximation (equation 7):

$$V = [J^T \mathbf{W} J + \Omega^{-1}]^{-1} \qquad \text{(Eq. 7)}$$

where J denotes the Jacobian matrix ($J_{ij} = \partial f(t_i, \theta)/\partial \theta_j$) and **W** the diagonal matrix of weights ($W_{ii} = 1/v_i$). The determinant of V (detV) was used as a measure of the precision with which parameters were determined (the lower the determinant, the higher the precision).

Population Pharmacokinetics

The population pharmacokinetic parameters were determined by the iterative two-stage (ITS) method,[28,29] using our own programme. At each iteration of the method, the following two steps were performed:

1. Individual estimates θ_k and V_k ($k = 1 \dots N$) for the N patients were obtained by Bayesian estimation as described in the previous section;

2. New estimates of the population mean vector μ and population variance-covariance matrix Ω were computed by equations 8 and 9:

$$\mu = (1/N) \sum_{k=1}^{N} \theta_k \qquad \text{(Eq. 8)}$$

$$\Omega = (1/N) \sum_{k=1}^{N} (\theta_k - \mu)(\theta_k - \mu)^T + (1/N) \sum_{k=1}^{N} V_k \quad \text{(Eq. 9)}$$

The interindividual variability of the pharmacokinetic parameters was assessed by computing the medians and 50% dispersion factors (DF50). DF50 is defined as (Q75 – Q25)/1.32, where Q75 and Q25 are the 25% and 75% quartiles, respectively, and 1.32 represents the width of the interval covering 50% of the observations in the case of a normal distribution. DF50 is equal to the standard deviation for normally distributed parameters and provides a reasonable estimate of the dispersion of a non-Gaussian distribution.[26]

The calibration experiments showed that the standard deviation Si of a measured concentration Ci could be expressed as a polynomial function Si = 0.02 + 0.033 Ci, where Ci and Si are in mg/L. Si was used as the concentration weighting factor.

For each pharmacokinetic profile, the two pharmacokinetic models were applied and the best one was selected based on the lowest Akaike information criterion (AIC),[30] which was calculated as equation 10:

$$\text{AIC} = n \ln \Phi_{\min} + 2p \qquad \text{(Eq. 10)}$$

where $\Phi_{\min}$ is the value of the objective function at minimum,

n is the number of experimental points and p denotes the number of parameters in the model.

Determination of a Limited-Sampling Strategy for the Estimation of the Area under the Plasma Concentration-Time Curve

For each pre- and post-transplantation period, LSSs were tested for Bayesian forecasting with the aim of estimating the AUC from 0 to 8 hours (AUC_8). As previously carried out with renal transplant patients,[17,18] combinations of a maximum of three sampling times within 4 hours post-dose were tested for Bayesian forecasting. Indeed, such a sampling scheme seemed to be a good compromise between the precision of parameter estimates and a possible implementation in clinical practice.

The D-optimality criterion[30] applied to Bayesian estimation was used to compare these candidate LSSs as follows:

- For given sampling times t_1, t_2,... the corresponding concentrations C_1, C_2,... were computed by equation 4, using the population mean vector μ.

- The variance-covariance matrix was then computed with equation 7. The sampling times giving the lowest value of detV were selected as the 'best' sampling times.

The BEs corresponding to each period were evaluated separately, by comparison of observed and estimated AUC_8 estimates obtained using the selected LSS and BE and the linear trapezoidal rule applied to the full profiles (reference values). Additionally, bias and root mean squared error (RMSE) were computed according to the recommendations of Sheiner and Beal.[31]

In a second step, a data-splitting procedure was performed to validate these MAP-BEs, in accordance with previous reports.[32,33] For each period, patients were randomly divided into subsets containing approximately 80% of the patients. To test the robustness of the model, new population parameters were obtained in each '80% subset' and were then compared with those resulting from the entire population. To test the predictive performance of the MAP-BEs, the parameter estimates from each of the subsets were used to estimate the pharmacokinetic parameters and the AUCs of the remaining 20% patients. The predicted AUCs were compared with those obtained using the linear trapezoidal rule by means of the mean bias and RMSE.

Results

The characteristics of the patients are summarized in table I. All pharmacokinetic profiles could be achieved except in two cases: one on day 30 as a result of missing data and one on day 7 because the mycophenolate mofetil treatment was administered

Table I. Patient characteristics at the time of the first pharmacokinetic profile

Characteristic	Value
Age (y) [median (range)]	50.5 (20–60)
Female/male (n)	6/8
Diagnosis (n)	
Hodgkin's lymphoma stage IV	1
myelodysplastic syndrome-refractory anaemia with excess of blasts	1
chronic myeloid leukaemia	1
acute myeloid leukaemia (all types)	7
chronic lymphoblastic leukaemia	1
agnogenic myeloid metaplasia	1

intravenously after the development of an oral mucositis. The mycophenolate mofetil dose was 1000 mg three times daily for all the patients for the first pharmacokinetic profile. On day 7, the mycophenolate mofetil dose was 1000 mg three times daily except in three patients (two at 750 mg three times daily and one at 500 mg three times daily). The reduction of these doses was maintained for the last pharmacokinetic period (day 30) and extended to one additional patient (750 mg three times daily). On day 30, the mycophenolate mofetil dose was increased for one patient (1500 mg three times daily).

The observed concentration-time profiles obtained before transplantation and on day 7 and day 30 are presented in figure 1. Whatever the period, these individual profiles were satisfactorily described using a one-compartment model with either a double- or a triple gamma absorption. Some typical examples illustrating the goodness of fit are provided in supplementary figure 1, Supplemental Digital Content (http://links.adisonline.com/CPZ/A6). The performance of the models is depicted in table II. Interestingly, for each parameter of the models, the precision of the estimation gave satisfactory results (from 5.2% to 32.6%, depending on both the period and pharmacokinetic model). In addition, the medians were very close to the means, the DF50 values were very close to the standard deviations and the Kolmogorov-Smirnov test did not find significant deviations from the normal distribution, as required. Thus, population pharmacokinetic parameters of the two models were used as priors for Bayesian estimation. The AIC was pertinent in discriminating which model best fitted each patient's data. A typical example of the difference in data modelling using a 'double gamma' or a 'triple gamma' model and the corresponding AIC values are presented in figure 2.

With respect to both the AUC_8 estimation performance and the D-optimality criterion, the combination of sampling times at 20 minutes, 90 minutes and 240 minutes post-dose was found to be the best compromise when considering all the pre- and
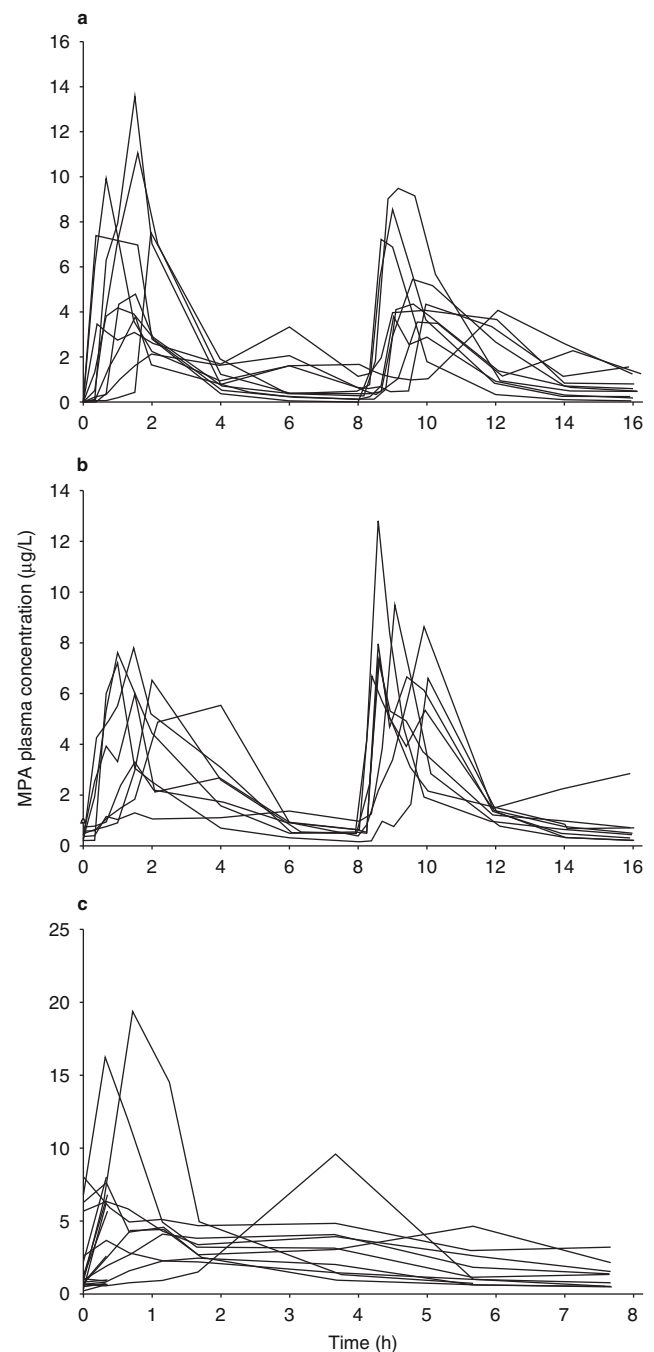

Fig. 1. Observed concentration-time profiles of mycophenolic acid (MPA) in patients given mycophenolate mofetil (MMF) every 8 hours in non-myeloablative haematopoietic stem cell transplantation: (**a**) before transplantation; (**b**) 4 days after the initiation of MMF treatment; and (**c**) 27 days after the initiation of MMF treatment.

Table II. Performance of the pharmacokinetic models and Bayesian estimators[a]

Parameter	Before transplantation		After transplantation	
	first administration	second administration	day 4	day 27
Pharmacokinetic models				
Bias between AUC_{mod} and AUC_{trap}	−0.014 ± 0.068 (−0.082, 0.156)	−0.010 ± 0.049 (−0.081, 0.086)	−0.035 ± 0.049 (−0.108, 0.058)	0.022 ± 0.057 (−0.092, 0.136)
RMSE	0.067	0.048	0.058	0.040
Bayesian estimators based on a 20 min–90 min–240 min sampling schedule				
Bias between AUC_{mod} and AUC_{trap}	−0.008 ± 0.068 (−0.179, 0.195)	−0.060 ± 0.081 (−0.153, 0.078)	−0.025 ± 0.121 (−0.230, 0.281)	0.022 ± 0.06 (−0.092, 0.136)
RMSE	0.010	0.098	0.112	0.040

a   Values are expressed as mean ± SD (range).

AUC = area under the plasma concentration-time curve; **AUC_{mod}** = model-derived AUC; **AUC_{trap}** = AUC calculated by trapezoidal rule; **RMSE** = root mean squared error.

post-transplantation periods. Figure 3 gives four typical examples of MPA pharmacokinetic profiles, estimated using Bayesian fitting. The predictive performance of the different MAP-BEs is summarized in supplementary table I, Supplemental Digital Content. For each period, mean bias between 'calculated' and 'trapezoidal' AUC was <2.5% and the percentage of patients with a bias >20% was <16%. Precisely, on day 7, two of 12 patients were estimated with a bias of −23% and +28%. These last two cases are presented in figure 2.

The MAP-BEs were then validated using a data-splitting strategy. After randomly dividing the patients of the full dataset into subsets containing approximately 20% of the patients, the individual pharmacokinetic parameters of each patient in the remaining '80% subset' were obtained using the final model developed from the whole dataset. In this first step, the mean parameter estimates obtained in each '80% subset' were not statistically different from those resulting from the entire dataset, which showed the robustness of the model. The mean ± SD of the parameter estimates from each '80% subset' were then used to predict the individual AUC values in the remaining '20% subset'. In this second step, the mean bias between individual AUC values estimated using the 20 minute-90 minute-240 minute sampling schedule and the trapezoidal rule was <9%. Whatever the period, <16% of the AUC was estimated with a relative difference of >20% (two of 14 patients on the first administration and two of 14 patients on day 7).

Discussion

In this article, we report on the development of pharmacokinetic models that adequately describe full pharmacokinetic profiles of MPA obtained in patients receiving mycophenolate mofetil three times daily in the context of a reduced-intensity HCT. We also developed BEs allowing for the determination of the MPA AUC_8 on the basis of a three-point LSS within the first 4 hours post-dose.

Patients enrolled in the present study provided full MPA pharmacokinetic profiles before transplantation, then on day 4 and day 27 post-transplantation. When looking at the raw data, we observed that the patients usually exhibited profiles with more than one peak. For this reason, we decided to develop a model able to describe a secondary peak, similar to that previously reported for solid organ transplantation.[17,18] Because of the complexity of some profiles, a model allowing the description of an additional peak was also constructed. Since this leads to an increase in the number of independent estimated parameters, we proposed the use of the AIC to prevent overfitting and to determine the model that best explains all individual data with a minimum of pharmacokinetic parameters. Indeed, AIC reflects not only the goodness of fit, but also
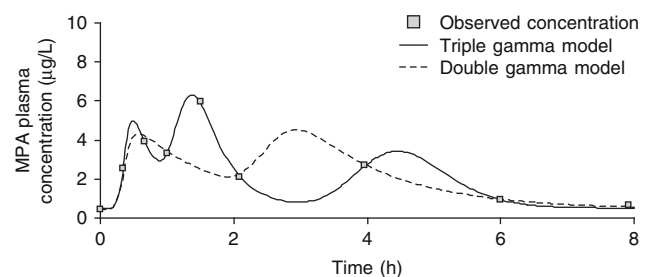

Fig. 2. Modelling of the concentration-time profile of mycophenolic acid (MPA) obtained from a patient given mycophenolate mofetil every 8 hours on day 7 after the initiation of mycophenolate mofetil treatment, using either a 'triple gamma' or a 'double gamma' model. Akaike information criterion values were 20 and 32 for a 'triple gamma' and a 'double gamma' model, respectively.
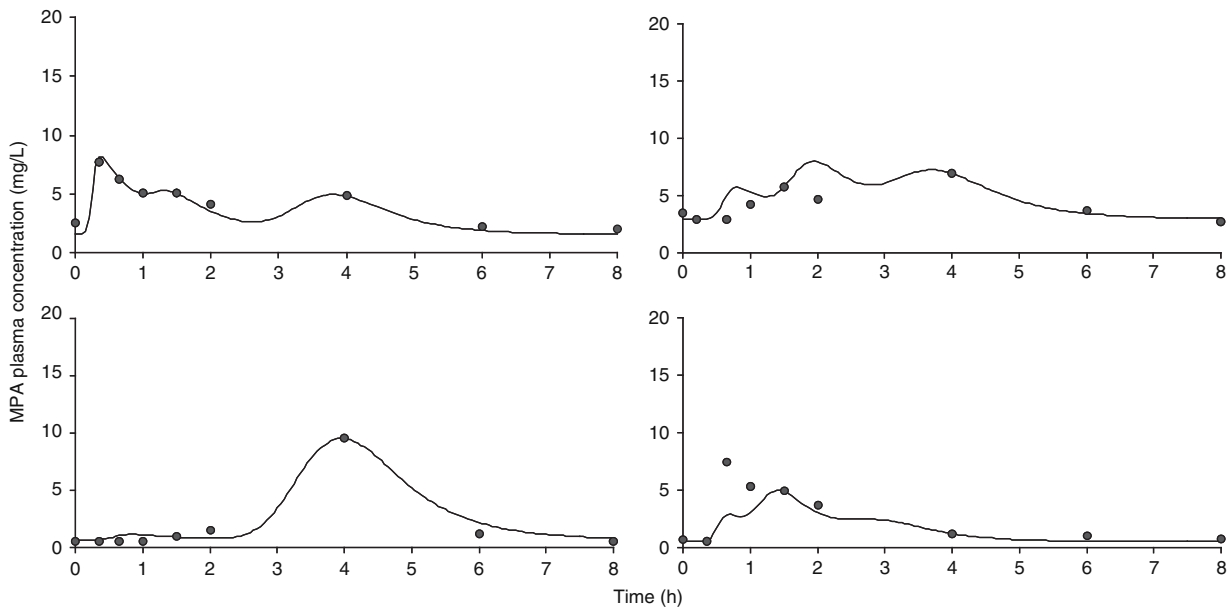
Fig. 3. Bayesian fitting of four mycophenolic acid (MPA) pharmacokinetic profiles using a limited-sampling strategy (20 minutes-90 minutes-240 minutes) in patients receiving mycophenolate mofetil every 8 hours after a haematopoetic stem cell transplantation.

includes a penalty, which is an increasing function of the number of estimated parameters. Therefore, Bayesian fitting was automatically performed for each patient using the two pharmacokinetic models, and only the results corresponding to the lowest AIC value were considered and reported. Of note, such a strategy is routinely performed on the Immuno-Suppressants Bayesian dose Adjustment (ISBA) website (https://pharmaco.chu-limoges.fr/abis.htm) where pharmacokinetic modelling is performed systematically using a one- and a two-gamma absorption model, and the AIC criterion is used to choose which results will be used for dose adjustment of mycophenolate mofetil when used in solid organ transplantation.

Only a few pharmacokinetic studies have been published describing the MPA pharmacokinetic parameters or exposures when mycophenolate mofetil is administered to HCT patients to prevent GVHD, especially after a reduced-intensity regimen.[7,8,12,34] These studies have reported that the mean exposure to MPA (in its total or unbound form) is significantly lower than that observed in solid organ transplantation. The causes of this phenomenon are still controversial. However, to the best of our knowledge, only two MPA pharmacokinetic studies have been performed in HCT patients with the aim of building a tool for improving the TDM of mycophenolate mofetil.[35,36] Using a non-compartmental approach, Ng et al.[36] have developed different equations derived from multi-linear regression models allowing the estimation of total or unbound MPA AUC in HCT patients given mycophenolate mofetil, either orally or intravenously. In the second study,

Huang et al.[35] aimed at developing a pharmacokinetic model able to estimate unbound MPA concentrations from total MPA concentrations. However, the developed multilinear regression equation did not provide satisfactory predictions for clinical assessment. In the present study, we developed BEs able to accurately estimate AUC as well as the relevant pharmacokinetic parameters or exposure indices to MPA using three sampling times. Compared with algorithms using multilinear regression models, the combination of the patient's information and the pharmacokinetic model leads to an accurate estimation of 'unusual' pharmacokinetic profiles and is less sensitive to imprecision in sampling time.

A data-splitting strategy was performed here to validate both the pharmacokinetic models and MAP-BEs. This approach was recommended by the US Department of Health and Human Services of the US FDA.[37] Precisely, although external validation is the 'gold standard' for testing the accuracy of a population model for predictive purposes in clinical practice, this method is hardly usable when the population studied is too small to be divided into a model-building and a model-validation group. This was the case in the present study. In fact, the diminution of the size of the model-building group leads to a decrease in the accuracy of the parameters and variability estimates. However, an external validation of the developed MAP-BEs is required before they can either be proposed to the physicians in charge of HCT patients through the ISBA website, or used to conduct a concentration-controlled trial, such as the one that recently showed a significant improvement for

renal transplant patients using such a strategy[19] and a couple of other ongoing studies in liver transplantation.

Conclusion

Currently, mycophenolate mofetil is widely used in solid organ transplantation. Numerous pharmacokinetic studies and some concentration-controlled trials have led, in the last few years, to a significant improvement of the TDM of mycophenolate mofetil in these patients. Mycophenolate mofetil is also prescribed in HCT; however, prescribed doses are still empirical because target-exposure indices are yet to be defined. In this study, we developed a pharmacokinetic model that satisfactorily described MPA-absorption profiles when given to HCT patients in addition to BEs able to determine the AUC on the basis of a routinely usable LSS. However, further studies are needed to validate these tools in independent groups of patients.

Acknowledgements

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