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Individualisation of mycophenolate mofetil therapy - Explaining variability in mycophenolic acid pharmacokinetics and introducing therapeutic drug monitoring

The prodrug mycophenolate mofetil (MMF) contains the active compound mycophenolic acid (MPA), which has immunosuppressive properties. It is used to prevent acute rejection after solid organ transplantation. In renal transplantation, the dose recommendation for MMF is 1000 mg twice daily for adult patients. This fixed dose strategy for MMF is remarkable in the field of transplantation as most other immunosuppressive drugs are used in an individualised dose, often based on drug concentration measurements. During the use of MMF in the past ten years, data have become available which provide four reasons to question the justification of a fixed MMF dose. The first reason is the existence of a concentration-effect relationship: the risk for acute rejection is lower when exposure to MPA is higher. This has led to the adoption of a target exposure range for MPA area-under-the-curve (AUC_{0-12}) values of 30 to 60 mg*h/L. The second reason is the large between-patient variability in MPA pharmacokinetics, reported to be more than 10-fold for MPA AUC_{0-12} . The third reason is that MPA exposure increases over time after transplantation despite a fixed dose. Finally, exposure to MPA is significantly influenced by the use of several other drugs. The result of these four factors is that with the use of a standard dose of MMF, an important subset of renal transplant recipients will have MPA exposure outside the target range, and may therefore be at risk for acute rejection or toxicity. Individualisation of the MMF dose is likely to improve exposure to MPA and may optimise clinical outcome.

The aim of this thesis was to develop recommendations about when and how to individualise the MMF dose. Two hypotheses in this regard were addressed, formulated in chapter 1.2. The first was that demographic factors that contribute to the variability in the pharmacokinetics of MPA may serve as a rationale for MMF dose individualisation (chapters 2.1 to 2.6, and 4.1). The second was that therapeutic drug monitoring of MPA provides a suitable tool for MMF dose individualisation (chapters 3.1 and 3.2).

In chapter 2.1, a population pharmacokinetic model for MPA following oral administration of MMF was developed, and relationships between patient factors and pharmacokinetic parameters were evaluated to quantify and explain variability in the pharmacokinetics of MPA, using non-linear mixed effects modelling (NONMEM). For this purpose, MPA concentration-time data from 140 renal transplant patients were available. The pharmacokinetics of MPA were best described by a two-compartment model with time-lagged first-order absorption. Apparent oral MPA clearance correlated significantly with creatinine clearance, plasma albumin concentration, gender and daily cyclosporine dose ($p < 0.001$), and these relationships could explain 11% and 33% of the observed between- and within-patient variability for apparent oral MPA clearance, respectively.

Chapter 2.2 tried to further elucidate whether renal function, plasma albumin level and the use of cyclosporine are suitable factors to serve as a basis for MMF dose individualisation. This chapter was a population pharmacokinetic analysis including 1894 MPA concentration-time curves obtained from 468 renal transplant recipients with sampling occasions ranging from day 1 to day 3795 (>10 years) after transplantation. The results described in chapter 2.2 show that plasma albumin level and creatinine clearance are important predictors for apparent oral MPA clearance. The latter effect could also explain why patients with delayed graft function had a significantly lower median MPA AUC_{0-12} compared to those with immediate graft function during the first four days after transplantation (23 versus 33 mg*h/L respectively, $p < 0.001$). This observation was likely to be caused by a lower median creatinine clearance in patients with delayed graft function. Nevertheless, renal function and plasma albumin level are not likely to be good candidates to serve directly as a basis for MMF dose individualisation. The reason is that the same change in renal function or plasma albumin level will not have the same effect on apparent oral MPA clearance in every patient, as a result of the estimated large between-patient variability in the effect that renal function and plasma albumin level had on apparent oral MPA clearance (66% and 112%, respectively). A change in both variables merely provides an indication for therapeutic drug monitoring to check whether the MMF dose needs to be adjusted in order to get or keep MPA exposure on target.

Furthermore, the results in chapter 2.2 show that the use of cyclosporine has an important impact on MPA exposure. Patients who were exposed to cyclosporine did not only have lower median dose normalised MPA AUC_{0-12} -values during the study follow-up compared with patients not exposed to

cyclosporine, but half of the patients concurrently treated with cyclosporine had MPA exposure below the recommended target window in the first week after transplantation. Clinical outcome in these patients may be improved by starting with a MMF dose of 1500 mg MMF twice daily instead of the currently recommended 1000 mg twice daily in the immediate post-transplant phase.

In chapter 2.3, it was investigated whether the presence of diabetes mellitus in renal transplant recipients had an impact on the pharmacokinetics of MPA. No significant differences in MPA exposure were found, but renal transplant patients with diabetes mellitus (n=6) had an increased median time to maximum MPA concentration (T_{max}) compared with renal transplant recipients without diabetes mellitus on day 11 after transplantation (1.59 h versus 0.67 h respectively, $p=0.04$). This result implies that patients with diabetes mellitus do not need an adjusted MMF dose. However, the increased T_{max} may cause an underestimation of AUC values calculated from limited sampling strategies. When a limited sampling strategy developed and validated for non-diabetic renal transplant recipients was tested in the population of diabetic renal transplant patients, no significant bias was observed for the estimated AUC (mean bias of -1.5 mg*h/L with 95% confidence interval from -5.7 to 2.7 mg*h/L for 13 pharmacokinetic profiles from 7 diabetic renal transplant patients).

Chapter 2.4 aimed at describing the structural changes of apparent oral MPA clearance over time after transplantation. The data used were the same as in chapter 2.2. It was found that apparent oral clearance typically dropped from 34 L/h (coefficient of variation (CV) =3%) immediately after renal transplantation, to 20 L/h (CV=3%) 165 days (CV=12%) later. The same decrease in apparent oral MPA clearance, from 32 to 19 L/h, corresponded with a simultaneous change, representative for the first 6 months after transplantation, in creatinine clearance from 19 to 71 mL/min, in plasma albumin level from 35 to 40 g/L, in haemoglobin from 9.7 to 12 g/dL and in cyclosporine predose concentration from 225 to 100 ng/mL. These results indicate that by monitoring creatinine clearance, plasma albumin level, haemoglobin and cyclosporine predose concentration, the clinician can get a feeling about changes in apparent oral MPA clearance within a patient over time.

In chapter 3.1, the usefulness of therapeutic drug monitoring was investigated with a computer simulation model. Two dosing regimens were compared: a fixed dosing regimen of 1000 mg MMF twice daily (FD), and a concentration controlled (CC) dosing regimen, targeting MPA exposure at an AUC_{0-12} level of 45 mg*h/L. The simulation was based on the Bayesian parameter estimates for apparent oral MPA clearance from 45 renal transplant recipients on 9 occasions during the first 5 months after renal transplantation who were also treated with cyclosporine, as determined with the population pharmacokinetic model, described in chapter 2.1. The differences between both dosing regimens in percentage of patients with MPA exposure on target was compared. On day 7 after transplantation, significantly more AUC_{0-12} values were on target (AUC_{0-12} range 30-60 mg*h/L) in the CC group than in the FD group: 76% versus 13% respectively, $p<0.001$. To accomplish this improvement, a doubling of MMF dose was necessary in more than half of the patients. The occurrence of extremely high (>85 mg*h/L) or low (<20 mg*h/L) AUC values was prevented in the CC group. It was concluded that therapeutic drug monitoring of MPA is expected to bring a higher proportion of patients to adequate MPA exposure more rapidly.

In chapter 3.2, it was studied whether therapeutic drug monitoring would be feasible with regard to the expected frequency of MPA concentration measurements needed for optimal MPA exposure. For this purpose, the within-patient variability in MPA exposure was analyzed, because variations over time within a patient cannot be controlled and may drive exposure away from the therapeutic window. This may cause the need for frequent monitoring. For 9 occasions during the first 5 months after transplantation, MPA AUC_{0-12} and predose values from 45 renal transplant recipients were divided into quartiles. When AUC_{0-12} or C_0 changed 1, 2 or 3 quartiles within a patient from one occasion to the next, a score of respectively 1, 2 or 3 points was assigned as a measure for within-patient variability. Within-patient variability measured according to this method was found to be low: for AUC_{0-12} , the median overall score was 3.4 of maximal 24. For C_0 measurements this score was significantly higher: 6.0 ($p<0.001$). The higher overall score for C_0 was explained by more quartile changes during the first weeks after transplantation. Based on the observations from this study, it is expected that therapeutic drug monitoring of MPA will be feasible, and that only several measurements of MPA concentrations can already be sufficient to optimise exposure.

Chapter 5 discusses to what extent the combined main findings of the presented studies are in agreement with the specific hypotheses formulated in chapter 1.2. In addition, some comments are

given with regard to the applied methodology in the different chapters, with special attention to population pharmacokinetic modeling. Finally, an individualised MMF dosing regimen is proposed for renal transplant recipients. The proposal comprises 1) a MMF starting dose of 1500 mg twice daily when MMF is combined with cyclosporine, 2) a measurement or estimation of MPA AUC_{0-12} on day 3 after renal transplantation to reduce between-patient variability and achieve target MPA exposure, and 3) a measurement or estimation of MPA AUC_{0-12} when plasma albumin level and renal function have stabilised (presumably around month 1 after transplantation). Further measurements of MPA exposure are proposed in case cyclosporine is tapered or withdrawn, or in case a sudden change in renal function or plasma albumin level occurs.
