Review

Optimization of Mycophenolic Acid Therapy Using Clinical Pharmacometrics

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Summary: Novel approaches applying quantitative clinical pharmacology or pharmacometrics have been increasingly embraced by the drug development community in the last decade. State-of-the-art population modeling and simulation enable better characterization and prediction of drug exposure. For narrow therapeutic index drugs such as mycophenolic acid (MPA) which exhibit large inter-individual variation in drug exposure, pharmacometric analysis can be of great clinical benefit. This review aims to summarize the recent progress of using pharmacometric tools toward individualized MPA therapeutics. The population pharmacokinetic models including those developed for special populations and Bayesian estimators for therapeutic drug management will be reviewed. Special attention will be given to new methodologies such as nonparametric population modeling and the physiological-based pharmacokinetics modeling (PBPK) that emerged recently as alternatives to the parametric population approach to predict MPA exposure. D-Optimal design strategies applied in clinical study design will also be reviewed. Lastly, the potential of using a pharmacodynamic based optimal treatment strategy by focusing on MPA’s target enzyme inosine monophosphate dehydrogenase (IMPDH) will be discussed.

Keywords: mycophenolic acid; pharmacometrics; therapeutic drug monitoring; D-optimality; pharmacokinetics; pharmacodynamics; physiologically based pharmacokinetic modeling; nonparametric; inosine monophosphate dehydrogenase (IMPDH)

Introduction

Pharmacometrics is a branch of science which entails the “development and application of mathematical and statistical methods to characterize, understand, and predict a drug’s pharmacokinetic, pharmacodynamic, and biomarker–outcomes behavior.” Since its emergence in the early 1980’s, the field of pharmacometrics has grown dramatically. This can be attributed to the advances in mathematics and statistics as well as to the vast progress in computer power and technology. The core components of pharmacometrics are population modeling and simulation. Population modeling defines appropriate mathematical models to describe the time courses of drug exposure and response, including the description of both population average and individual variability. Using the developed models, new data can be simulated to predict “what if” situations. The application of pharmacometrics covers the entire drug development process from health risk assessment to In Vitro–In Vivo Extrapolation (IVIVE) and from first-in-man study to clinical trial design. Both the pharmaceutical industry and regulatory agencies have greatly embraced these approaches: in a survey performed by the US Food and Drug Administration (FDA), more than 60% of new drug application submissions between 2000 and 2008 were informed by pharmacometric analyses in drug approval and labeling decisions. For pediatric drug development, the FDA predicts pharmacometrics to be an important part of every pediatric drug application and has set targets such that 50% of all pediatric trials will be using simulations in the design by 2015 and 100% by 2020.

These approaches are also increasingly appreciated in translational and clinical research in the clinical setting to facilitate individualized pharmacotherapy. A good example of its use is in the development of individualized dosing strategies for mycophenolic acid (MPA). MPA is a cornerstone immunosuppressive drug widely used in solid organ transplantation typically in combination with a calcineurin inhibitor such as tacrolimus. MPA has a narrow therapeutic window yet a poorly predicted dose-exposure profile...
due to large inter- and intra-individual variability in its pharmacokinetics. To overcome some of these complexities, pharmacometric approaches have been applied to better capture and predict the between patient variability of MPA pharmacokinetics. Especially, therapeutic drug monitoring (TDM) strategies using maximum a posteriori (MAP) Bayesian estimation in combination with sparse sampling have been developed and are increasingly applied in clinic. Given its importance, specific topics related to the optimization of MPA therapy using pharmacometric approaches have been previously summarized elsewhere, including MPA population PK modeling, prediction of MPA exposure using Bayesian estimators, and pharmacokinetics/pharmacodynamics of MPA in the treatment of autoimmune diseases. The current review intends to provide an updated overview of these topics with an emphasis on recent developments.

Clinical Pharmacokinetics/Pharmacodynamics of MPA

MPA is a cornerstone immunosuppressant used to prevent allograft rejection after solid organ transplantation. It is also used off-label in the treatment of various autoimmune diseases, such as lupus nephritis and lupus erythematosus. Currently, two different forms of MPA are available on the market: mycophenolate mofetil (MMF) and enteric-coated, delayed-release mycophenolate sodium (EC-MPS). After oral administration, MMF is quickly and almost entirely absorbed and hydrolyzed by carboxylesterases to MPA, the active moiety. MPA is predominantly metabolized by uridine 5'-diphosphate glucuronyltransferases (UGTs) in the liver, intestine, and kidney into the inactive 7-O-glucuronide (MPAG) and to a much lesser extent into an active metabolite acyl-glucuronide MPA (AcMPAG). Although pharmacologically inactive, MPAG plays a critical role in MPA pharmacokinetics due to its enterohepatic recycling (and subsequent conversion back to MPA in the gut) and its ability to compete with MPA for protein binding sites. The major side effects of MPA include leucopenia, gastrointestinal (GI) discomfort and diarrhea. To reduce the frequency of GI side effects, an enteric-coated mycophenolate sodium salt (EC-MPS) was developed. EC-MPS pharmacokinetics are characterized by a delayed onset of effect and atypical absorption profiles with a decrease in mean plasma concentration during the early absorption phase, sometimes resulting in U-shaped concentration-time profiles. The overall exposure after EC-MPS administration, however, was comparable to MMF after administration of equimolar dosages. The complex pharmacokinetic characteristics of EC-MPS have hampered the development of straightforward therapeutic drug monitoring strategies for patient receiving this formulation.

MPA pharmacokinetics exhibit large inter- and intra-individual variability with a more than 10-fold difference in drug exposure as measured by the area under the curve (AUC) in adult after kidney, liver and heart transplant patients. It has also been shown that MPA drug exposure gradually changes over time after transplantation, most notably during the first 3 months. The relationship between MPA dose and drug exposure is reported to be nonlinear in both adult and pediatric patients, presumably due to saturation of transporters and variable enterohepatic circulation. In consensus reports for the adult and pediatric kidney transplant population, the area under the plasma concentration-time curve (AUC) but not the trough concentration is the most clinically useful parameter for optimal therapeutic drug monitoring (TDM). The consensus target exposure range for MPA has been proposed as AUC_{0-12h} 30–60 mg·h/L.

MPA exposure may be impacted by drug-drug interactions as co-administration of multiple drugs is common in organ transplant patients. For example, co-administration of the calcineurin inhibitor (CNI), cyclosporine (CsA), results in significant reduction of MPA exposure through inhibition of multi-drug resistance-associated protein 2 (MRP2/ABCC2) which mediates excretion of MPAG into the bile. Proton pump inhibitors (PPIs) have also been reported to reduce MPA concentration presumably due to an inhibitory effect on MMF hydrolysis. Finally, patients on nonsteroidal anti-inflammatory drugs (NSAIDs) showed lower MPA exposure most likely caused by reduced enterohepatic circulation.

Population Pharmacokinetics Modeling of MPA: Recent Advances

To date, most MPA population pharmacokinetic models have been developed by nonlinear mixed-effect modeling using NONMEM. With this approach, the pharmacokinetic parameter estimates are described as the mean or typical population values (the “fixed effects”) with inter- and intra-individual variability within the population described as “random effects.” Certain assumptions, usually normal distribution or log-normal distribution, are used to describe the random effects. Covariate factors such as patient demographic data (age, weight, gender), genetic information and laboratory test results are used to predict (some of) the inter-individual variability. One of the major advantages of nonlinear mixed-effect modeling is the ability of using sparse data across many subjects to estimate population parameter estimates and their variability. This approach is particularly useful when analyzing data obtained in routine clinical settings where sample sizes usually are small, sparse sampling is common and patient demographics are highly variable.

Recently, Sherwin et al. published a comprehensive overview of earlier work on MPA population modeling and the development of enterohepatic circulation models. For an overview on the most recent advances in MPA population modeling, we conducted a literature search using the online database and search engine PubMed (visited September 2013). Publication dates were restrained from 2010/01/01 to 2013/09/12 and searches were limited to the English language. The keywords for searching were “mycophenol*” in combination with “population pharmacokinetic*” and/or “NONMEM.” The results were then filtered to only include those studies using the non-linear mixed effect modeling approach. The results of this recent search are summarized in Table 1. In summary, significantly more recent studies were conducted in special populations such as pediatric patients. Also, as MMF is increasingly being prescribed in hematopoietic stem cell transplant recipients and in patients with autoimmune diseases, several population PK models have been established to describe MPA PK in these conditions. As noted before, MPA pharmacokinetics shows substantial differences across these patient populations. For instance, MPA clearance is higher in adult
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<th>Study</th>
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<tr>
<td>Li et al. (2013)</td>
<td>Allogeneic hematopoietic cell transplantation (HCT)</td>
<td>Adult</td>
<td>4,496 samples from 408 patients</td>
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<td>Total</td>
<td>Two-compartment model with first order absorption and lag time</td>
<td>CL/F = 24.2L/h Ve/F = 36.4L</td>
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<td>Frymoyer et al. (2013)</td>
<td>Allogeneic hematopoietic cell transplantation (HCT)</td>
<td>Adult</td>
<td>1,171 samples from 132 patients</td>
<td>NONMEM</td>
<td>Unbound</td>
<td>Two-compartment model with first order absorption</td>
<td>CL/F = 1,610L/h Ve/F = 1,230 L Q/F = 541L/h Vp/F = 6,140L</td>
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<td>Punyawudho et al. (2013)</td>
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<td>122 samples from 14 patients</td>
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<td>Two-compartment model with first order absorption and a lag time</td>
<td>CL/F = 14.5L/h Ve/F = 12.1L Q/F = 21.1L Vp/F = 237L fixed</td>
<td>None</td>
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<td>Barau et al. (2012)</td>
<td>Liver transplantation</td>
<td>Pediatric</td>
<td>112 samples from 16 patients</td>
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<td>One-compartment model with first-order absorption</td>
<td>CL/F = 12.7L/h Ve/F = 64.7L</td>
<td>Age on Ka;</td>
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<td>Kim et al. (2012)</td>
<td>Allogeneic hematopoietic cell transplantation (HCT)</td>
<td>Pediatric and young adult</td>
<td>417 samples from 36 patients</td>
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<td>Unbound</td>
<td>Two-compartment model with first order absorption</td>
<td>CL/F = 25.3L/h Ve/F = 11.9L Q/F = 15.3L Vp/F = 182L</td>
<td>WT; creatinine clearance and total bilirubin on CL/F</td>
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<tr>
<td>Sherwin et al. (2012)</td>
<td>Childhood-onset systemic lupus erythematosus</td>
<td>Pediatric and young adult</td>
<td>186 samples from 19 patients</td>
<td>NONMEM</td>
<td>Total</td>
<td>Two-compartment model and transit absorption with enterohepatic circulation</td>
<td>CL/F = 36.9L/h Ve/F = 11.9L Q/F = 15.3L Vp/F = 182L</td>
<td>None</td>
</tr>
<tr>
<td>Li et al. (2012)</td>
<td>Allogeneic hematopoietic cell transplantation (HCT)</td>
<td>Adult</td>
<td>955 samples from 77 patients</td>
<td>NONMEM</td>
<td>Total</td>
<td>Two-compartment model</td>
<td>CL/F = 36.9L/h Ve/F = 11.9L Q/F = 15.3L Vp/F = 182L</td>
<td>Concomitant calcineurin inhibitor on CL/F &amp; Ve/F;</td>
</tr>
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<td>de Winter et al. (2011)</td>
<td>Kidney transplantation</td>
<td>Adult</td>
<td>7,739 samples from 241 patients</td>
<td>NONMEM</td>
<td>Total</td>
<td>Two-compartment model with first order absorption and lag-time</td>
<td>CL/F = 17L/h Ve/F = 68 L Q/F = 38 L Vp/F = 229 L</td>
<td>Dose on relative bioavailability</td>
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<td>Zhao et al. (2010)</td>
<td>Idiopathic nephrotic syndrome</td>
<td>Pediatric</td>
<td>285 samples from 23 patients</td>
<td>NONMEM</td>
<td>Total</td>
<td>Two-compartment model with first order absorption and lag-time</td>
<td>CL/F = 9.7L/h Ve/F = 22.3 L Q/F = 18.8 L Vp/F = 250 L</td>
<td>WT on CL/F;</td>
</tr>
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<td>Renal transplantation</td>
<td>Pediatric</td>
<td>497 samples from 89 patients</td>
<td>NONMEM</td>
<td>Total</td>
<td>Two-compartment model with erlang distribution for absorption</td>
<td>CL/F = 12.9L/h Ve/F = 23.0 L Q/F = 25.6 L Vp/F = 158 L</td>
<td>WT on CL/F;</td>
</tr>
<tr>
<td>Sam &amp; Joy (2010)</td>
<td>Glomerulonephritis</td>
<td>Adult</td>
<td>444 samples from 39 patients</td>
<td>NONMEM</td>
<td>Total</td>
<td>Two-compartment model with first order absorption and enterohepatic circulation</td>
<td>CL/F = 36.9L/h Ve/F = 11.9L Q/F = 15.3L Vp/F = 182L</td>
<td>Concomitant immunosuppressive medication on CL/F</td>
</tr>
<tr>
<td>Zeng et al. (2010)</td>
<td>Blood or marrow, kidney and liver transplantation</td>
<td>Children and young adult</td>
<td>859 samples from 38 patients</td>
<td>NONMEM</td>
<td>Total</td>
<td>Two-compartment model with first order absorption</td>
<td>CL/F = 6.42L/h Ve/F = 7.24L Q/F = 3.74 L Vp/F = 16.8 L</td>
<td>Creatinine clearance &amp; albumin</td>
</tr>
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hematopoietic stem cell transplant recipients but lower in patients suffering from HIV/AIDS as compared to renal transplant recipients. It is noteworthy that several studies used semi-mechanistic models to describe the complex MPA absorption and enterohepatic circulation processes as they were shown to provide a better prediction of overall MPA drug exposure.

**Nonparametric Modeling and Its Application in MPA Pharmacokinetic Analysis**

The large variability in individual MPA pharmacokinetic profiles raises the question of whether a parametric modeling approach is optimal for describing the population variability. In contrast to the more frequently used parametric population modeling, nonparametric pharmacokinetic analysis is based on algorithms that do not make any assumptions about the shape of the parameter distributions. It is considered to be theoretically superior to parametric analyses as it can better accommodate unexpected, outlying observations that might be problematic when using a parametric approach. A full discussion of pros and cons of parametric and nonparametric methods can be found in a series of excellent overviews by Jelliffe et al.

Rousseau and the Limoges group used both nonlinear mixed-effect modeling (NONMEM) and the nonparametric adaptive grid (NPAG) approaches to analyze pharmacokinetic data from pediatric renal transplant patients, and compared the predictive performance of the two methods with data from a separate group of patients. This comparative study demonstrated that the mean population Bayesian parameter estimates were higher using NPAG, especially the elimination rate. This might be expected as the NPAG algorithm does not assume a distribution and considers outlying values more likely whereas in NONMEM the individual parameter estimates are more likely to “shrink” back toward the population mean (i.e. $\eta$-shrinkage) depending on the information content. In addition, the predictive performance of NPAG was more favorable than that with NONMEM in describing individual MPA pharmacokinetics. These authors concluded that nonparametric analysis is preferable to NONMEM in case of non-normal distribution of any one of the pharmacokinetic parameters of interest and is more suitable for clinical applications such as model-based therapeutic drug management.

**PBPK Modeling and Its Application in MPA Pharmacokinetic Analysis**

In recent years, physiologically based pharmacokinetic (PBPK) modeling has become available and is increasingly being utilized in drug development. PBPK is a mechanism based “bottom-up” modeling approach that integrates drug physiochemical properties, (patho)physiology, and trial design as part of the modeling (Fig. 1). Having initially been applied mostly for compound toxicity evaluations, this approach has recently being propagated as an alternative to describe drug behavior in situations where data-drive pharmacokinetic modeling is more difficult to execute or has significant limitations. In contrast to the classical “top-down” empiric compartmental pharmacokinetic modeling, PBPK uses compartments which represent true organs/tissues connected by realistic representations of arterial and venous blood vessel systems.

The top-down compartmental pharmacokinetic analysis does have limitations to capture MPA’s variable absorption and entero-hepatic recycling process, and typically requires complicated
models with large numbers of parameters.\cite{24,40} PBPK represents a powerful tool to characterize the complex absorption process of MPA in a mechanistic fashion. Although this type of PBPK modeling has been used in describing the pharmacokinetics of other immunosuppressive drugs such as sirolimus and tacrolimus,\cite{41,42} no peer-reviewed studies on its application to MPA pharmacokinetic analysis have been published. We recently developed a PBPK model for the prediction of MPA exposure with an emphasis on the absorption phase. Using literature in vitro enzymatic activity values in combination with default settings in GastroPlus\textsuperscript{TM}, one of the commercially available PBPK platforms, was used in our pilot study for the PBPK modeling as it is particularly suited to describe the complicated gastrointestinal absorption process mechanically.\cite{44,45} Physiochemical properties of MMF/MPA (pKa’s, LogP, solubility and permeability) were estimated by the ADMET Predictor\textsuperscript{TM} 6.0 (Simulations Plus) supplemented with data from the literature. The advanced compartmental absorption and transit (ACAT\textsuperscript{TM}) model in GastroPlus\textsuperscript{TM} was used to simulate the absorption phase. Using literature in vitro enzymatic activity values in combination with default settings in GastroPlus\textsuperscript{TM} for blood flow and tissue volumes allowed simulation of realistic MPA and MPAG pharmacokinetic concentration-time curves. Predictive performance was evaluated by comparing simulated profiles to reported values in healthy volunteers following intravenous (IV) and oral dosing of MMF.\cite{46} Although the current model needs further validation and refinement using patient data, our preliminary results show a good predictive performance.\cite{45} Challenges remain as only limited information is available on some of the elements in the model development. For instance, there are no data on enzymatic activity of the MPAG conversion to MPA. Nevertheless, the PBPK modeling approach holds great promise to predict MPA exposure at the level of the individual patient, and has advantages when studying the influence of drug-drug interactions on MPA pharmacokinetics and the more erratic pharmacokinetic profiles of enteric coated mycophenolic acid-sodium (EC-MPS).

\textbf{Bayesian Estimation and Dose Individualization}

One of the powerful clinical applications of population models is their use as part of Bayesian adaptive control strategies.\cite{24,47} This allows the estimation of the area under the concentration-time curve (AUC) e.g. of immunosuppressive drugs using sparse and D-optimally sampled data.\cite{7} In transplantation the AUC of MPA is a better predictor of clinical outcomes than single trough concentration measurements (C\textsubscript{0}).\cite{12} Before population based approaches were introduced, clinical drug therapy used limited sampling strategies to predict AUC. Bayesian algorithm based sampling strategies provide flexible sampling windows which are much more practical than a strictly fixed sampling plan. For a summary of recently developed Bayesian MPA estimation algorithms, the reader is referred to the review by Staatz and Tett in 2011.\cite{7}

Researcher at the University Hospital, Limoges, France have developed and validated multiple population models and Bayesian estimators for all of the immunosuppressants including MMF used in solid organ transplantation and lupus patients. These Bayesian estimators are accessible via a web based service (https://pharmaco.chu-limoges.fr/). For instance for MPA dose individualization, pharmacokinetic parameters and the AUC\textsubscript{0-12} are estimated based on patients’ demographic, co-medication records, dosing regimen, and drug concentrations sampled at 3 specific time windows (20 ± 10 min, 60 ± 15 min and 180 ± 30 min post-dose). The service has been well received by the transplantation community, and has handled almost 14,000 requests from more than 30 transplantation centers worldwide over a 5-year period.\cite{48} The impact of the service was evaluated in a retrospective study which looked at the efficacy of MMF dose adjustment based on Bayesian estimation of AUC\textsubscript{0-12}. It showed that 72–80% of the estimated AUC values were within the desired 30–60 mg/L-h range, compared to only 39–57% of the estimated AUCs within that range when dose adjustment was recommended but was not clinically applied.\cite{49} These results nicely showcase the benefits of using a pharmacometric approach in MPA therapeutic management.

A new pharmacometric approach was also used in the evaluation of MPA exposure and clinical outcomes in kidney transplantation. Previously, the association between MPA exposure and clinical outcomes has been evaluated using single or few selected post-transplantation time points which do not consider the evolving changes in MPA exposure over time. Daher Abdi \textit{et al}. used a joint modeling approach to study the impact of longitudinal MPA exposure on acute rejection episodes in renal transplant patients.\cite{50} Joint modeling has been considered the gold standard to assess the effects of longitudinal time varying covariates in a time-to-event analysis of a clinical endpoint.\cite{51} In their study, the MPA AUC time-course data from at least five follow-up visits during the first 12 months post-transplantation period in 490 adult renal-transplant recipients were described by a mixed-effects sub-model while the rejection-free survival data were described by a Weibull survival sub-model. The study showed a significant association between longitudinal MPA exposure and the incidence of acute rejection. This joint model can account for the intra-patient pharmacokinetic variability over time and offers a new perspective to look at the relationship between MPA exposure and clinical outcome.

\textbf{Model-based Clinical Trial Design for MPA}

Knowledge gained from pharmacometrics analyses can facilitate efficient study design, especially when the enrollment of target patients is anticipated to be difficult, e.g. rare diseases or special populations such as neonatal or infant. The application of pharmacometrics in trial design typically includes the determination of the required number of subjects and the sampling strategy as defined by the number of samples and best times of sampling.
Clinical trial simulations based on prior pharmacokinetic information and optimal design methodology based on pharmacometrics in study design are advocated by the regulatory agencies and have been adopted within the pharmaceutical industry. To date, optimal design has facilitated the selection of most informative sampling times in MPA pharmacokinetic studies. For example, in a recent published study by Musuamba et al., D-optimality was used as the design criterion to identify the most appropriate sampling windows. Based on population pharmacokinetic models and using statistical criteria, D-optimal design identifies the sampling times that provide the maximum information about the pharmacokinetic parameter of interest. For more in-depth discussion about D-optimal design, readers are encouraged to review articles specifically related to this topic. The design in the study by Musuamba et al. was based on six previously published MPA population pharmacokinetic models in patients on concomitant tacrolimus treatment, and included prior information from several absorption and disposition models. The design then was applied to a clinical study to evaluate MPA and tacrolimus pharmacokinetics. According to the authors, the application of the D-optimality criterion was successful and resulted in reasonable precision of pharmacokinetic estimates. The implementation of D-optimal design in combination with robust sample size estimation will help to improve the efficiency and cost-effectiveness of MPA pharmacokinetic/pharmacodynamic studies.

**Drug Monitoring Strategy Based on IMPDH Activity**

As MPA is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), targeting IMPDH activity as a surrogate pharmacodynamic marker of MPA induced immunosuppression may provide an attractive strategy for individualized dosing to improve clinical outcomes. The philosophy behind such a strategy is attractive: by directly monitoring MPA-induced IMPDH inhibition, both drug exposure and the response to the drug can be followed. However, although several studies have demonstrated that the level of IMPDH inhibition can be used as a reliable biomarker to tailor the level of immunosuppression and clinical outcome are scant, and the target range of IMPDH inhibition to achieve desired efficacy is currently not well defined. Nevertheless, pharmacometric tools hold great promise to facilitate the development of pharmacodynamic-based MPA dosing strategies. For example, if the area under the IMPDH enzyme activity curve (AEC) could be identified as a predictive parameter for clinical outcomes, model based Bayesian estimation could be implemented to predict AEC. Recently, an integrated pharmacokinetic/pharmacodynamic population model was developed by our group. In the model the relationship between MPA concentration and IMPDH enzyme activity could be well described by an inhibitory $E_{\text{max}}$ model. However, further prospective clinical studies to determine the relationship between the level of IMPDH inhibition and clinical outcome will be necessary to identify the optimal target range of IMPDH inhibition.

**Conclusions and Future Directions**

In conclusion, MPA exhibits large inter- and intra-patient pharmacokinetic variability. Therapeutic drug monitoring is used to tailor MPA exposure, but the complex pharmacokinetics of MPA has partly hampered efficient use of pharmacokinetic assisted dosing. Optimally sampled AUC monitoring using Bayesian algorithms has shown to improve clinical outcomes and has been implementation as a “personalized” MPA treatment strategy. More research will be needed in areas such as pharmacodynamically-based drug management strategies. Emerging pharmacometric methodologies will provide us with new venues for further research on the optimization of MPA therapy.

However, even though applying pharmacometrics into clinical practice is promising to improve therapeutic outcome, it will also be challenging due to insufficient pharmacometrics training and education amongst clinical providers. Clinical pharmacometrists will be needed to bridge this gap. In addition, further clinical proof to demonstrate the utility of these tools would be warranted. As many MPA pharmacokinetic/pharmacodynamic studies are hampered by small subject numbers, especially studies in special populations, a systematic review of available studies in combination with mechanism based PBPK will improve our understanding of the relations between MPA dose, drug exposure, and clinical outcome. Finally, the ultimate integration of all this information will be through user-friendly tools that are intuitive and report actionable results to physicians. We envision a one-stop “dashboard” that in real time and as part of the electronic health record provides pharmacogenetic and adherence information with pharmacokinetic interpretation, using an integrated Bayesian algorithm to facilitate clinical decision making related to individualized MPA dosing.

**References**


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