Chapter 2

PKPD Modeling of Pharmacogenomics in Early Drug Development. Scope and Motivation of the Investigations

Introduction

Phase I studies conducted early in the clinical development program provide the first opportunity to assess not only the pharmacokinetic (PK) profile of a drug but also to evaluate the extent of differences between individuals. Evaluating the basis for differences between individuals considers a range of factors including, routes and rates of elimination, permeability/solubility data or covariates such as age or gender. Identification of the enzymes catalyzing the in-vitro-metabolism is a key component in determining the source and possible clinical relevance of this variation. For drugs in which in-vitro studies show that a polymorphic gene is central to the metabolism of the drug (in vitro data predict >50% of the drug be cleared by a single polymorphic enzyme) [1], it is important to consider the role of this enzyme to the PK variability. The implementation of genetic factors into the development program has three key aims 1) to understand how genetic factors contribute to inter-individual variability in PK and PD 2) to inform the optimal design of phase 2/3 studies 3) to provide evidence/information to support the labeling [2].

Application of model based approaches in PK

The role of polymorphic changes in variability of drug exposure should be considered relative to the other intrinsic or extrinsic factors. The understanding of specific covariates (e.g., age and race) and gene-covariate interactions on the variability in drug response is useful in understanding the relative impact of genetics, versus other nongenetic factors on the both the PK and safety/efficacy of the drug [3]. This is important to consider when evaluating if dose individualization and/or therapeutic drug monitoring (TDM) could actually be used to improve patient outcomes. Population PK models are a powerful tool to quantify and identify sources of variability both within and between subjects [4]. By implementing a model based approach, differentiation between variability both within and between subjects can enhance the statistical power to identify the different factors influencing the pharmacokinetic profile [5]. The value of a applying a model based approach was demonstrated for tacrolimus where studies investigating the effect of CYP3A4*22 genotype on tacrolimus PK had been limited in their approach by only considering the trough concentrations and not fully evaluating the use of co-medication [5]. Moes et al quantified the effect of CYP3A4*22 genotype for cyclosporine, everolimus, and tacrolimus clearance and found that the effect was a reduction

in clearance of less than 20%. They therefore concluded that dose adjustments based on CYP-3A4*22 were not required. The study further confirmed the role of CYP-3A5*3 genotype and found this was a suitable predictive marker for tacrolimus clearance, but close TDM remains essential due to the remaining variability between patients within the same genotype group.

Other sources of variability were also incorporated into the population PK analysis of the HIV-1 protease inhibitor, Atazanavir [6]. The drug exhibits high inter- and intrapatient variability and sources of variation between individuals were attributed to a number of sources not only related to pharmacogenetic (CYP3A5) factors but also including the effect of food on the bioavailability and adherence to therapy. An integrated population PK analysis revealed that a 28% increase in clearance was observed in subjects with at least one CYP3A5*1 allele, however the between subject variability decreased by an additional 40% when adherence was also considered in the model. This approach was able to delineate the effects resulting from genotype whilst considering the other components contributing to the variability in exposure. Such a comprehensive model based approach can then be used to further evaluate the necessity of individualized dosing.

Application of model based approaches in PK-PD

Whilst population PK models can be used to characterize the PK properties of a drug, they can also be linked either directly or indirectly with pharmacodynamic (PD) response. Through the use of a PK-PD model based approach to evaluate the influence of genotype a more comprehensive link between changes in the PK and its influence on the magnitude of response can be established. This is an important consideration to assess the clinical relevance of these changes in exposure as a direct result of genotype since overall variability in the PD, which appears random until relevant covariates have been identified, can be much greater than that observed in the PK [7]. Currently, the application of a model based approach to evaluate the influence of different genotypes, by linking pharmacokinetic changes with response seems limited to only a few drugs. Many studies have evaluated the effect of pharmacogenetics for warfarin and several models have been published describing the relationship between PK and the PD marker, International Normalized Ratio (INR) [8]. The application of a PK-PD model based approach for warfarin has not only been limited to adults where both age and CYP-2C9/VKORC1 genotypes were included as covariates for

clinical response (INR), but this was recently extended to evaluate if the same relationships could be identified in children [9]. Hamberg et al applied a PK-PD model based approach to a data set on 163 children. They evaluated if another genetic covariate (CYP-4F2 genotype), which had recently been shown to influence warfarin dose requirement should be included in the current pharmacogenetic dosing algorithms. The PK-PD analysis showed that variability in children was found to be comparable with that reported in adults and that CYP-2C9 genotype could explain up to a four-fold difference in dose with VKORC1 genotype explaining up to a two-fold difference in dose. The analysis also found that bodyweight, age, baseline and target INR, time since initiation of therapy, but not CYP-4F2 genotype, were found to influence significantly typical warfarin dose requirements in children. This model based approach can now be further utilized to improve the improving efficacy and safety of warfarin therapy in children.

Furthermore physiologically based pharmacokinetic (PBPK) models have been linked to PD response integrated to estimate the drug concentration at the site of action. This may offer a better understanding of true PD variability vs. variability resulting from drug disposition at the site of action [10]. Through the development of a PBPK-PD model, Rose et al demonstrated that by using the local concentration at the effect site to drive the PD response they were able to explain why there was a disconnect observed between the effect of (organic anion-transporting polypeptide) OATP1B1 polymorphism on rosuvastatin plasma concentration and the lack of impact observed on the PD response. They show that plasma concentration is different between individuals due to genotype, but a significant proportional reduction in the PD marker (mevalonic acid) does not occur as the concentration at the effect site has already reached Emax. Such an approach is able to describe the physiological implications behind these differences and enhance the understanding of the eventual impact of genotype on clinical response.

Genotype influences on model based approaches in disease progression analysis

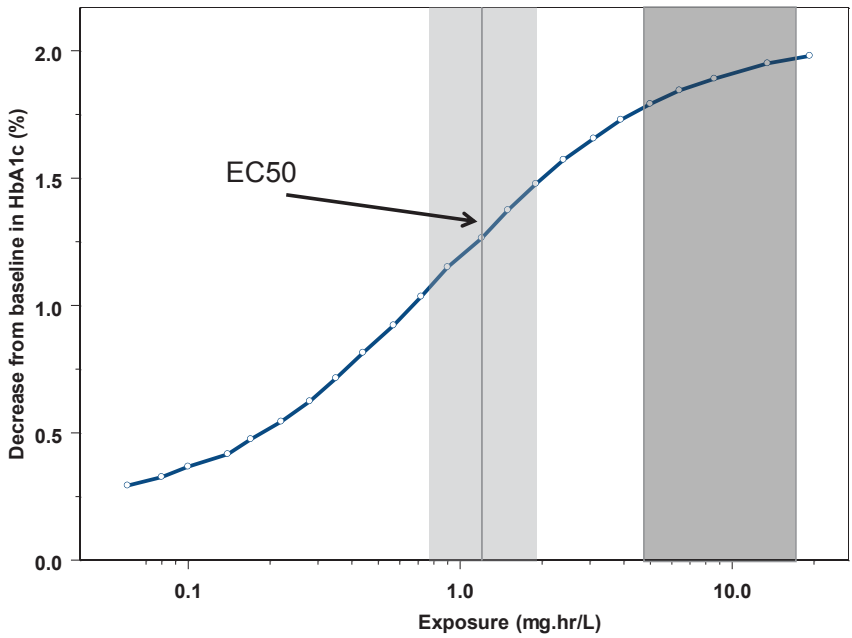
Disease progression analysis is a model based approach applied to describe and explain changes in disease status as a function of time and drug therapy [11]. The advantage of implementing a model based approach being the key characterization of the relationship between treatment and the physiology of the disease over time. Many of the published

models evaluating disease progression have focused in the areas of Type 2 Diabetes (T2D), Parkinson's and Alzheimer's disease [12, 13]. Recently the application of the genome wide association study (GWAS) has emerged as a powerful tool for identifying disease-related genes for many common human disorders. The application of these studies have identified eleven new susceptibility loci for late-onset Alzheimer's disease, in T2D significant associations were identified for more than 35 independent loci and in Parkinson's disease many GWAS are currently on-going to evaluate susceptibility to the disease [14, 15, 16]. Data from these GWAS could also be an important covariate as an extension of the current model based approaches applied in these disease areas. Such an approach would enable treatment specific effects to be evaluated on the time course of the disease profile and enable evaluation of disease modifying drug effects in the different genetic populations. This comprehensive approach could then be used to evaluate if specific genetic sub-populations respond differently to drug treatment.

Understanding the dose response relationship relative to genotype

Genotype difference should be considered relative to the dose response relationship [3]. For example, for a drug which has a steep dose response curve, small changes in exposure resulting from genotype differences will have a greater impact depending on where the therapeutic dose sits on the curve. Whilst for a drug at which the therapeutic dose is given close to the Emax these differences resulting from genotype will be less apparent. Figure 1 shows how these changes in exposure can be related to the drug response and how the therapeutic dose should be evaluated relative to the exposure response relationship. The magnitude of the influence of exposure changes on response (i.e. decrease from baseline in HbA1c) is different depending on the drug exposure.

Figure 1 Exposure response relationship for the decrease from baseline in HbA1c (%) at 3 months, light grade shade shows exposure range between EM and PM subjects at 64mg, dark grey shade shows exposure range for EM and PM at 400mg



When the drug exposure is close to the EC50, greater changes in HbA1c between different genotypes would be observed. The influence of this is illustrated in Figure 2a and Figure 2b.

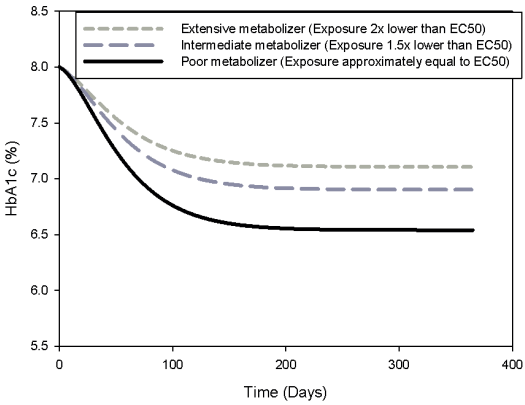


Figure 2a. HbA1c simulation over time for a dose of 64mg

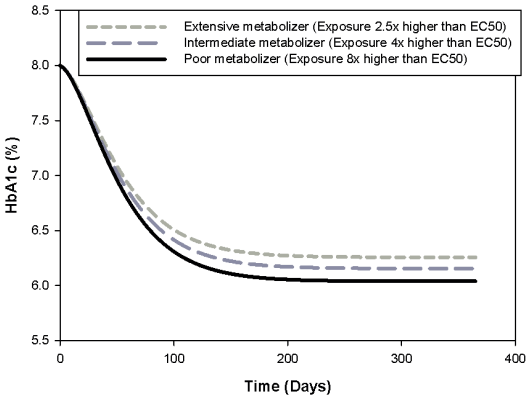


Figure 2b. HbA1c simulation over time for a dose of 400mg

When the genotype influence is simulated for a dose close to the EC50 (light graded shaded area on Figure 1), the difference in the change from baseline in HbA1c between extensive (EM) and poor metabolizers (PM) is -0.6%. However, when a higher dose is given (dark gray shaded area on Figure 1), a large change in exposure results in a less than proportional change in the clinical response. The difference in the change from baseline in HbA1c between EM and PM subjects is now only -0.2%. Therefore this genotype difference would not be clinically relevant when a higher dose was given. Whilst increasing the exposure can negate the influence of genotype, this should routinely be considered on balance to the safety/efficacy margin. A comprehensive model based approach would incorporate not only PD response related to efficacy but also including safety. Often in clinical development the relationship between drug exposures and efficacy can be well defined, but the relationship between drug exposure and safety may only be defined as linear as dose escalation would be limited by exposure margins or would be stopped before the maximum effects are reached. This could have an influence for subjects who are poor metabolizers as these subjects would be expected to have higher exposure than the average population. Additional studies at higher doses than previously studied in Phase I may be needed to cover the exposure range for the

subjects who are poor metabolizers. This may be the case if the frequency distribution/ratio of genotypes for EM/PM is highly unbalanced and no poor metabolizers had been enrolled at the top dose level in phase I or II.

Evaluating the clinical consequence of genetic differences

Dosing recommendations should ensure that a patient receives a drug that is both safe and effective [1]. Genotype based dosing recommendations are expected to follow the same expected level of evidence as other adjustments made for subpopulations where dose adjustment are made based on renal function or weight. Different routes for dose recommendations may include dose titration, optional gene based dosing or dosing based on genotype [1]. Since dose titration approaches are widely applied in many therapeutic areas, for existing therapies dose titration approaches should be compared with genotype based dosing to evaluate the additional utility of implementing a genetic dosing algorithm. As such the application of a model based approach can be used to simulate different scenarios and address clinical questions such as the time to reach maximum effect or the % of subjects achieving a certain target for both genotyped-based dosing vs. titration-based approaches. Clinical trial simulation can also be used to look at clinical outcomes in each of the genotype sub-populations for upcoming pivotal studies.

Conclusions

The application of model based approaches to evaluate the influence of genotype, have primarily focused on the use of genotype as a covariate on drug exposure. These models should preferably also be extended during the drug development program to include clinical response, evaluating safety or efficacy markers to design the appropriate genetic based dosing algorithms or compare different study designs i.e. genotype-based dosing vs. a single dose level for all subjects. Further extension has focused on the use of PB-PK models which can be developed during the non-clinical stage and combined with PD models for safety or efficacy. Ultimately these model based approaches can be used to determine if covariate-based dose individualization would be required to normalize exposure and minimize variability in clinical outcomes across population subgroups and inform label recommendations that can improve individual patient outcomes [17].

Outline of the investigations in this thesis

This thesis starts with an overview of the current applications of Pharmacogenomics (PGx) across drug development with an emphasis on the implications of polymorphism in drug metabolizing enzymes and transporters. The second section (Chapter 2) focuses on the application of model based approaches to evaluate differences in drug exposure and response as a result of these genetic differences between individuals.

In Chapters 3, 4 and 5 the focus for this thesis is on a clinical example for the T2D drug, sipoglitazar. Sipoglitazar undergoes phase II biotransformation by conjugation catalyzed by UDP-glucuronosyltransferase (UGT) [18]. Clinical data from four phase I studies in healthy volunteers and two phase II trials in T2D subjects were utilized in the analysis. PGx samples for determination of UGT genotype were collected for all subjects enrolled in the trials. The objectives of the investigation in Chapters 3-5 was to evaluate the role of UGT genotype differences in explaining inter-individual variability for sipoglitazar and to then investigate the impact of these differences on both the clinical response and the selection of the appropriate dosing scheme for future trials.

In Chapter 3, an investigation was conducted to evaluate the enzymes that were contributing to the inter-individual variability of sipoglitazar and to then quantify the resulting exposure differences between genotype. Here the importance of considering genotype relative to other intrinsic and extrinsic factors is investigated and discussed. The analysis in Chapter 3 was conducted using data from a trio of phase I clinical pharmacology studies in healthy volunteers. The studies included a single ascending dose (n=39), multiple ascending dose (n=19) and a single dose age/gender study (n=30). The dose range for sipoglitazar was 0.2-64mg.

The investigation and analysis conducted in Chapter 4 was then focused on evaluating genotype influences in the target population, T2D patients. In this chapter data from two phase II randomized, double-blind studies (sipoglitazar once daily: 8, 16, 32, or 64 mg; sipoglitazar twice daily: 16 or 32 mg; rosiglitazone 8 mg once daily and placebo for 13 weeks; n = 780) were included in the analysis. For evaluation of the exposure data the phase II trials were combined with a large phase I single dose (64mg) study in a diverse ethnic study population of 524 healthy male and female subjects. The magnitude of exposure

differences resulting from polymorphic differences in the UGT2B15 enzyme were quantified and considered relative to other covariates in the target population using pharmacokinetic modelling. The predictability of the genotype-exposure relationship was investigated and an approach to evaluate the predictability of this relationship is then described. The consequences of disconnect between genotype and exposure are discussed. In addition, a preliminary analysis was conducted to evaluate the relationship between genotype and efficacy, using change from baseline in HbA1c at 3 months by dose and genotype as a pharmacodynamic endpoint. Exposure data were then reviewed relative to the safety margin and discussed in context to the therapeutic dose.

This analysis was extended in Chapter 5 and a population PK-PD model was implemented to evaluate the relationship between exposure differences resulting from genotype and its magnitude of impact on the clinical response (FPG and HbA1c). This analysis showed how the development of PK-PD model can be used to test different dosing scenarios to appropriately plan future clinical studies and to evaluate the impact of genotype on dosing relative to current dosing practices in T2D.

The next section (Chapter 6) focusses on PD model based approaches in T2D over a much longer time period (>2.5 years). Since T2D is a slowly progressing disease, the importance of considering both the drug and disease effects on the time course of the relevant biomarkers is investigated. A phase IV study that was conducted in Japanese T2D subjects was used for the analysis. In this study (n=587) subjects received pioglitazone in combination with other oral glucose-lowering drugs or oral glucose-lowering drugs excluding thiazolidinedione (control group). Treatment was adjusted to achieve HbA1c<6.9% following the standard treatment guidelines for T2D in Japan. In the control group, either the dosage of the current therapy was increased, or a concomitant oral glucose-lowering drug was added. In the pioglitazone group, the preferred adjustment was to increase the dose of pioglitazone. The study was conducted over a period of 2.5-4 years and all subjects included in the trial were treatment experienced. Throughout the study biomarker samples for FPG and HbA1c were collected. A population PD model simultaneously incorporating FPG and HbA1c was developed to describe the time course of the drug and disease effects in both treatment groups. The aim of this analysis was to further enhance the understanding of the treatment and time course effects on FPG and

HbA1c and the development of the PD model enabled simulations to be performed to compare the longer term glycemic durability between treatment groups.

In Chapter 7 the investigations are reviewed and discussed with a focus on the application of model based approaches across clinical drug development to evaluate and understand genotype differences in enzymes and transporters. Furthermore the applications of PGx in treatment approaches to T2D over the long term are hypothesized. The future perspectives on the applications of model based approaches to evaluate the impact of genotype in clinical development are presented. The focus for discussion is on the utilization of PBPK models throughout clinical development in understanding the role of genotype relative to the other intrinsic and extrinsic factors and for considerations in study design.

References

1. Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products, April 2010. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000411.jsp&mid=WC0b01ac058002958e&murl=menus/regulations/regulations.jsp&jsenabled=true. Accessed 21 July 2014.
2. Lesko, L. Application of PGx in PK at FDA: Experience and Expectations. Presentation EMEA-EFPIA Workshop. 2008. http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500010650.pdf. Accessed 10 August 2014.
3. Guidance for Industry: Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies, Jan 2013 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf. Accessed 21 July 2014.
4. Mould DR and Upton RN. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development—Part 2: Introduction to Pharmacokinetic Modeling Methods. CPT Pharmacometrics Syst Pharmacol. Apr 2013; 2(4): e38.
5. Moes DJ, Swen JJ, den Hartigh J et al. Effect of CYP3A4*22, CYP3A5*3, and CYP3A Combined Genotypes on Cyclosporine, Everolimus, and Tacrolimus Pharmacokinetics in

Renal Transplantation. CPT Pharmacometrics Syst Pharmacol. 2014 Feb 12;3:e100. doi: 10.1038/psp.2013.78.

6. Savic RM, Barrail-Tran A, Duval X et al. Effect of adherence as measured by MEMS, ritonavir boosting, and CYP3A5 genotype on atazanavir pharmacokinetics in treatment-naive HIV-infected patients. Clin Pharmacol Ther. 2012 Nov;92(5):575-83.
7. Levy, G. Predicting effective drug concentrations for individual patients. Determinants of pharmacodynamic variability. Clin. Pharmacokinet. 1998; 34, 323–333.
8. Hamberg AK, Wadelius M, Lindh JD et al. A Pharmacometric Model Describing the Relationship Between Warfarin Dose and INR Response With Respect to Variations in CYP2C9, VKORC1, and Age. Clin Pharmacol Ther. 2010 Jun;87(6):727-34.
9. Hamberg AK, Wadelius M, Friberg LE, Biss TT, Kamali F, Jonsson EN. Characterizing variability in warfarin dose requirements in children using modelling and simulation. Br J Clin Pharmacol. 2014 Jul;78(1):158-69.
10. Rose RH, Neuhoff S, Abduljalil K, Chetty M, Rostami-Hodjegan A, Jamei M. Application of a Physiologically Based Pharmacokinetic Model to Predict OATP1B1-Related Variability in Pharmacodynamics of Rosuvastatin. CPT Pharmacometrics Syst Pharmacol. 2014 Jul 9;3:e124. doi: 10.1038/psp.2014.24.
11. Post TM, Freijer JI, DeJongh J, Danhof M. Disease system analysis: basic disease progression models in degenerative disease. Pharm Res. 2005 Jul;22(7):1038-49
12. de Winter W, DeJongh J, Post T et al. A mechanism-based disease progression model for comparison of long-term effects of pioglitazone, metformin and gliclazide on disease processes underlying Type 2 Diabetes Mellitus. J Pharmacokinet Pharmacodyn. 2006 Jun;33(3):313-43.
13. Ploeger BA, Holford NH. Washout and delayed start designs for identifying disease modifying effects in slowly progressive diseases using disease progression analysis. Pharm Stat. 2009 Jul-Sep;8(3):225-38.
14. Voight BF, Scott LJ, Steinthorsdottir V et al. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat Genet. 2010 Jul;42(7):579-89.

15. Lambert JC, Ibrahim-Verbaas CA, Harold D et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013 Dec;45(12):1452-8.

16. Simón-Sánchez J, Schulte C, Bras JM et al .Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet. 2009 Dec;41(12):1308-12.

17. Joerger M. Covariate Pharmacokinetic Model Building in Oncology and its Potential Clinical Relevance. AAPS J. Mar 2012; 14(1): 119–132.

18. Nishihara M, Sudo M, Kawaguchi N et al. An unusual metabolic pathway of sipoglitazar, a novel antidiabetic agent: cytochrome P450-catalyzed oxidation of sipoglitazar acyl glucuronide. Drug Metab Dispos. 2012 Feb;40(2):249-58.