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Summary in English

The investigation described in this thesis focused on assessing the role of genotype differences in explaining inter-individual variability in drug metabolism and the impact of these differences on both the clinical response and the selection of the appropriate dosing scheme. In Chapter 1 this thesis starts with an overview of the current applications of Pharmacogenomics (PGx) across drug development with an emphasis on the implications of polymorphisms 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 oral glucose lowering drug, sipoglitazar which undergoes phase II biotransformation by conjugation catalyzed by UDP-glucuronosyltransferase (UGT). Clinical data from four phase I studies in healthy volunteers and from two phase II trials in subjects with type 2 diabetes mellitus (T2D patients) were utilized in the analysis. PGx samples for determination of UGT genotype were collected for all subjects enrolled in the trials

Clinical relevance of genetic variants in pharmacokinetic properties

Exploratory preliminary evaluation of genotype during Phase I clinical 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 differences in exposure between genotypes. The analysis in Chapter 3 was conducted using data from a trio of phase I clinical pharmacology studies in healthy volunteers (n=82). The dose range for sipoglitazar was 0.2-64mg. Statistical analysis of area under the plasma concentration–time curve from time 0 to infinity (AUC) revealed dose proportionality across the dose range (slope = 0.99; 95% confidence interval 0.92-1.05), (Chapter 3). As a first step in the PGx investigation, the contribution of each genotype to the variation in dose normalized AUC was assessed using Analysis of variance (ANOVA). Results of this investigation revealed that variation in UGT2B15 accounted for approximately two-thirds of the variability in

sipoglitazar plasma exposure, while no relationship between sipoglitazar plasma exposure and variants of the other UGT enzymes could be identified. Considerable exposure overlap was observed between genotype groups, particularly between the UGT2B15*1/*1 and UGT2B15*1/*2 genotypes and the exposure was found to be approximately two- to three-fold higher in the UGT2B15*2/*2 genotype than either UGT2B15*1/*1 or UGT2B15*1/*2. Two outlier subjects were identified. These subjects, which were genotyped as UGT2B15*1/*1 and UGT2B15*1/*2, had considerably higher exposure than expected based on their genotype. This analysis showed that across the population UGT2B15, genotype could explain 66% of the variability of sipoglitazar exposure as determined by dose-normalized AUC. Other factors such as age, body mass index or sex appeared to contribute little to explaining the additional variability or outlying subjects in this healthy volunteer population.

Development of a population PK model for sipoglitazar in T2D patients

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 A population PK analysis was conducted with the aim to quantify the differences in exposure in the target population between UGT2B15 genotype, to evaluate other potential sources of variability and to derive exposure values by dose. The model estimated median clearance values for UGT2B15*2/*2 genotype were found to be approximately 2-fold and 3-fold higher than those subjects with the UGT2B15*1/*2 or UGT2B15*1/*1 genotypes, respectively. Before accounting for any covariates (including genotype), inter-individual variability (IIV) on clearance was 60%; however, after including genotype as a covariate, the IIV of clearance was reduced to 40%. Only one other covariate (fat free mass) was found to be significant during the covariate analysis and accounted for an additional 2% of the IIV. This analysis confirmed the earlier findings of the relationship of UGT2B15 genotype to sipoglitazar exposure in the target population. Post-hoc CL values

were then used to determine individual exposure over the dose interval at steady state (AUC24). These exposure values were then were used as the input into the PK-PD model to evaluate the exposure response relationship described in Chapter 5.

Evaluating the clinical relevance of genotype differences in exposure

Evaluating the influence of genotype on clinical response through disease progression analysis

In Chapter 5, the approach was taken to develop a population PK-PD model to describe the changes in FPG and HbA1c as a function of individual exposure, whilst PD response data from rosiglitazone at a therapeutic dose of 8mg QD were incorporated into the analysis as a reference group The developed PK-PD model could describe the individual and median profiles for all dose levels (8-64 mg total daily dose of sipoglitazar) and no differences in the shape of the exposure response relationship were found between genotypes. The PK-PD model was used to simulate the expected FPG and HbA1c change from baseline at 6 months (duration of a Phase III trial) by UGT2B15 genotype. The simulation showed that for sipoglitazar, a dose of 32 mg in the UGT2B15*2/*2 genotype would be expected to provide an equivalent result to the reference treatment rosiglitazone. The results of the simulation also show that for a dose of 32 mg, the change in HbA1c was less than proportional relative to the changes in drug exposure across genotypes. In the phase II population, approximately a 3.3-fold difference in CL is observed between UGT2B15*1/*1 and UGT2B15*2/*2 genotypes, however this results in only a 1.8-fold difference in HbA1c drop relative to the baseline. Although a dose of 32 mg in the UGT2B15*2/*2 subjects can achieve reductions in HbA1c equivalent to rosiglitazone, the reduction in HbA1c was significantly less in the UGT2B15*1/*1 genotype as compared to the UGT2B15*2/*2 genotype.

It was therefore postulated that genotyped based dosing could contribute to the normalization of response across individuals by achieving comparable exposure levels across genotype groups. Simulations were performed evaluating three different approaches, (1) a single dose level for all subjects, (2) genotype-based dose adjustment (where genotype is

used to estimate the starting dose) or (3), titration based on therapeutic response. The percentage of subjects achieving HbA1c reduction >0.7% at 6 months was used for evaluation. Based on these results to achieve equivalence to rosiglitazone (73%), for all subjects irrespective of genotype, a dose of 96mg of sipoglitazar would be required (a single dose level for all subjects). However using genotype based dosing uniform response rates could be achieved with lower doses for the UGT2B15*2/*2 and UGT2B15*1/*2 groups (UGT2B15*1/*1=96mg, UGT2B15*1/*2=64mg and UGT2B15*2/*2=32mg).

Although a genotype-based dosing approach could be used to normalize response between the genetic subgroups, in T2D a titration approach based on efficacy/safety is routinely applied. A comparison was therefore simulated between genotyped-based dosing and titration based on therapeutic response, with all subjects in the titration group starting at 32mg. The results of this simulation highlight two key points. The magnitude of reduction in FPG or HbA1c between the genotype and titration approaches would be expected to be the same but the time taken to eventually achieve that maximum response would be shorter when pre-selection of dose was based on genotype. The difference in the time to 90% of steady state between genotyped and titration-based dosing was approximately 1 and 2 months for the UGT2B15*1/*2 and UGT2B15*1/*1 genotypes.

Application of a PD model based approach in Japanese T2D subjects to describe the drug and disease effects on FPG and HbA1c for pioglitazone over 2.5-4 years

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 either pioglitazone (+/-oral glucose-lowering drugs) or oral glucose-lowering drugs alone (control group). Treatment was adjusted to achieve HbA1c<6.9% and all subjects included in the trial were treatment experienced. A simultaneous cascading indirect response model structure was applied to describe the time

course of FPG and HbA1c. HbA1c levels were described using both an FPG-dependent and an FPG-independent function. To account for titration, drug effects for both treatment groups were implemented using a time dependent Emax model.

Differences in the effect due to maximum drug exposure on FPG were observed between the two treatment groups. The model derived Emax values for pioglitazone and the control group were 17% and 8%, respectively and resulted in approximately 2-fold greater reduction in FPG for pioglitazone as compared to the control treatment. Disease progression was parameterized as a proportional increase over time relative to the FPG baseline. The model predicted increases resulting from disease progression were estimated at approximately 2 mg/ml/per year for FPG and 0.2%/per year for HbA1c. Simulations of FPG and HbA1c over 5 years were performed. The maximum drug effect for FPG was forecasted to occur earlier (11 months) for pioglitazone than the control group (14 months). The simulated additional reduction in FPG and HbA1c achieved with pioglitazone was predicted to be maintained beyond the currently observed study duration. Through the development of a model on this long term data (>2years) simulation can be used to hypothesize how PGx in T2D may be used to influence drug response through both symptomatic and disease modifying effects.

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. The implementation of a population PK-PD model based approach to evaluate the influence of genotype provides a more comprehensive link between the observed changes in the pharmacokinetics and its influence on the magnitude of response. Thus enabling a comparison of the differences observed between the magnitude of change in the PK due to genotype and the magnitude of this change on clinical response. As PGx sample collection becomes routine in clinical studies, the possibility to integrate this into our understanding of drug effects should only increase. Evaluating this impact early in the

development phase is important to appropriately design future clinical studies and to ensure that the exposure response relationship can be appropriately determined for all genetic subgroups. Such a comprehensive approach should only improve study design and patient outcomes and ultimately help to reduce drug attrition across the pharmaceutical industry.