

PI-24

MODELING & SIMULATION OF PHARMACOKINETICS (PK), PHARMACODYNAMICS (PD) AND TUMOR KINETICS (TUK) TO OPTIMIZE ANTICANCER DOSE REGIMENS. C. DiLea, PharmD, Novartis Pharmaceuticals Corp, Florham Park, NJ.

BACKGROUND/AIM: Pharmacologic activity (biochemical & functional) and toxicity observed in animal models with anticancer agents result from exposure driven mechanisms. Drug treatment is terminated due to lack of an acceptable therapeutic index (toxicity/efficacy ratio) for the indication and patient population. Ideally an optimum dose regimen (dose & schedule) would have a larger therapeutic index that could be achieved with equal or better anti-tumor activity, reduced toxicity, dose and/or exposure. Modeling PK, PD & TUK can be used to control exposure profiles and provide the rationale for dose regimens that maximize pharmacologic activity and minimize toxicity. It is intended to demonstrate, through modeling & simulation, the importance of PK, PD and TUK parameters to optimize dose regimens of anticancer agents in the typical Xenograft tumor bearing mouse model.

METHODS: A PK-PD-TUK model describing drug concentrations in plasma (Cp), tumor (Ctu), tumor volume (tv) growth and drug effects in a Xenograft mouse was formulated. Parameters consist of: [PK] volumes, first order transfer rate constants with elimination from plasma; [TUK] first order growth and death rate constants (Kg & Kd) with Michaelis Menten feedback on Kg from tv; [PD] maximum inhibition of Kg (Emax), Ctu inhibiting Kg by 50% (IC50), hill coefficient (HC). This model has evolved after using abbreviated versions to analyze *in vitro* and *in vivo* data. Dose regimens were simulated with varied PK, PD, TUK parameters; Ctu half lives ranged from 1–6 hours, HC ranged 1–4 and tv doubling times ranged 24–96 hours. Plots of simulated Cp, Ctu and tv vs time were used to evaluate dose regimen performance. The more efficient (optimum) regimen is considered to inhibit tumor growth (Kg=Kd) during a dose interval with the least amount of input (dose rate) and or exposure.

RESULTS: Dose regimens were optimized by exploiting PK, PD, and TUK parameters. Each parameter has a different affect on the exposure and activity profiles. Optimum dose regimens maintain tumor stasis during the dose interval, avoid unnecessary high Ctu, reduce the time below a critical effective Ctu, minimize the Cmax: Cmin ratio in Ctu and in some cases require lower doses.

CONCLUSIONS: This approach requires further evaluation/confirmation with anti-tumor and safety data in xenograft mouse models.

PI-25

POPULATION PHARMACOKINETICS AND PHARMACODYNAMICS OF VALPROIC ACID IN MANIA ASSOCIATED WITH BIPOLAR DISORDER FOLLOWING ONCE-DAILY ADMINISTRATION OF EXTENDED-RELEASE DIVALPROEX SODIUM. S. Dutta, PhD, P. M. Diderichsen, PhD, Abbott Laboratories, Abbott Park, IL.

AIM: Characterize the population pharmacokinetics (PK) and pharmacodynamics (PD) of valproic acid (VPA) in mania associated with bipolar disorder following once-daily administration of extended-release divalproex sodium (divalproex-ER).

METHODS: The efficacy and safety of divalproex-ER in the treatment of the acute manic or mixed phase of bipolar disorder were evaluated in a double-blind, placebo-controlled, parallel-group, multi-center study. Subjects (N = 370) were randomly assigned in a 1:1 ratio to receive either divalproex-ER, initiated at 25 mg/kg/day rounded up to the nearest 500 mg, or placebo, in a once daily regimen for up to 21 days. On Day 3, doses were increased by 500 mg for all subjects; subsequently subjects received dosage adjustments of study medication on Days 7, 12, and 17 at the discretion of the investigator based on clinical effect,

safety and plasma concentrations (Cp) of VPA (from unblinded central laboratory). The primary efficacy variable, change from baseline in the Mania Rating Scale (CMRS) score and VPA Cp were assessed on 4 to 6 occasions over the 21-day trial. The relationship between CMRS and VPA Cp was assessed using mixed effects models (variations of linear, exponential and Emax) that accounted for the placebo effect time-course (linear and exponential models with/without baseline MRS [BMRS] score as a covariate) in NONMEM.

RESULTS: VPA PK was optimally characterized by 1-compartment model with 0-order absorption. The estimated duration of absorption, CL/F and V/F were 17.8 h, 0.845 (intersubject CV = 40%) L/h, 20.7 L, respectively. The final PD model that optimally characterized the VPA concentration-CMRS effect relationship was $CMRS = (\beta_1 * BMRS + \eta + \beta_2 * Cp[time]) * (1 - \exp[-3 * time])$. The estimated PD parameters were: $\beta_1 = -0.364$, $\beta_2 = -0.0628$, $\beta_3 = 0.00445$, and intersubject SD on CMRS = 16.6.

CONCLUSIONS: A population PK/PD model was developed to characterize VPA PK and concentration-effect relationship in subjects with mania following once-daily divalproex-ER administration. An exponential time course model optimally described the placebo effect. A statistically significant linear relationship between VPA Cp and CMRS was established after accounting for the placebo effect and differences in BMRS across subjects.

PI-26

POPULATION PHARMACOKINETIC ANALYSIS OF VARENICLINE IN ADULT SMOKERS. H. M. Faessel, P. Ravva, M. R. Gastonguay, K. D. Rohrbacher, T. G. Tensfeldt, Pfizer Clinical R&D, Metrum Research Group LLC, Groton, CT.

BACKGROUND: The objectives of this analysis were to characterize the population pharmacokinetic (PPK) of varenicline and identify factors leading to its exposure variability in adult smokers. PK information was then utilized in subsequent PPK-pharmacodynamic analyses of efficacy and tolerability endpoints.

METHODS: Data were pooled from 9 clinical studies consisting of 1878 adult smokers (954 males, 924 females). A 2-compartment model with 1st-order absorption and elimination adequately described the concentration-time data (11935 observations). Covariates were assessed using a full model approach; parameters and bootstrapped 95% confidence intervals (CI) were estimated using nonlinear mixed effects modeling. Covariate effects for renal function [16-268 mL/min, Cockcroft-Gault method] and race [81.0% White; 12.6% Black and 6.44% Other] on apparent clearance (CL/F), and for bodyweight [41.0-129 kg], age [18-76 yrs] and race on central volume of distribution (V2/F) were estimated. Model performance was assessed with a predictive check (PC).

RESULTS: The typical PPK parameter estimates and their 95% CI's for the final varenicline model were: CL/F, 10.4 L/hr [10.2-10.6]; V2/F, 337 L [309-364]; V3/F, 78.1 L [61.9-98.9]; Q/F, 2.08 L/hr [1.39-3.79]; Ka 1.69 hr⁻¹ [1.27-2.00]; and Alag 0.43 hr [0.37-0.46]. Random interindividual variances were estimated for Ka (70% CV), CL/F (25% CV), and V2/F (50% CV) using a block covariance matrix. All fixed effect parameters were precise (most with %RSE <10% and all with %RSE <25%) and PC indicated adequate model performance. Renal function had the greatest effect on varenicline PK. CL/F decreased from 10.4 L/hr for a typical subject with normal renal function (CLcr = 100 mL/min) to 4.4 L/hr (CLcr = 20 mL/min) for a typical subject with severe renal impairment, which corresponds to a 2.4-fold increase in daily steady-state exposure. Bodyweight was the primary predictor of variability in volume of distribution. After accounting for renal function, there was no apparent effect of age, gender and race on varenicline PK.

CONCLUSIONS: Renal function was the clinically important factor leading to interindividual variability in varenicline exposure.

A dose reduction to 1 mg/day, which is half the recommended dose, is indicated for patients with severe renal impairment.

PI-27

FACILITATE DOSE SELECTION VIA EXPOSURE-CLINICAL OUTCOME MODELING AND SIMULATION. Y. Feng, PhD, L. Zhang, PhD, M. Pfister, MD, FCP, Bristol-Myers Squibb Co., Princeton, NJ.

BACKGROUND: Selecting Phase III dose(s) of a new molecular entity based on its Phase II exposure, efficacy, and safety information, via a population-based model and simulation approach (M&S).

METHODS: M&S is a useful prognostic tool to facilitate decision making in drug development. More than 500 subjects have been tested in the phase II trial of Drug X. The collected data included Drug X plasma concentration, efficacy, and safety response rates. Mixed-effect modeling was used to characterize the time-concentration profiles and the model-predicted exposure level was linked to efficacy and safety outcomes by logistic regression. One thousand trials over a wide dose range were simulated based on the modeled exposure-clinical outcome relationships. Clinical utility functions were applied to select the doses that yield preferred benefit/risk balance. The sensitivity of selected doses toward the exposure/clinical outcome model and utility functions were examined.

RESULTS: A one-compartment pharmacokinetic model with first order absorption characterized the Drug X's time-concentration profile adequately. Creatinine clearance was identified as a clinically significant covariate on exposure. The variance and the uncertainty in modeled parameters were quantified. Model-predicted individual steady state AUC was shown to be a significant predictor for efficacy and safety outcomes. Doses with favorable efficacy/safety profiles were identified for testing in phase III subjects with normal and impaired renal function.

CONCLUSIONS: The impact of strategic application of M&S on decision making in drug development was demonstrated in this case study, in which M&S provided scientific and quantitative rational for Phase III dose selection.

PI-28

A POPULATION PHARMACOKINETIC (PK) ANALYSIS TO EVALUATE THE POTENTIAL EFFECT OF THE UGT1A1*28 GENOTYPE ON THE PK OF AG-013736, AN ANTI-ANGIOGENIC AGENT. M. Garrett, B. E. Houk, S. P. Myrand, B. Hee, J. Mota, Y. K. Pithavala, Pfizer Global Research & Development, La Jolla, CA.

BACKGROUND: AG-013736, an investigational anti-cancer drug currently in clinical development, is a potent inhibitor of vascular endothelial growth factor receptors (VEGFRs) with picomolar (IC_{50}) activity and also an inhibitor of platelet-derived growth factor receptor (PDGFR) and KIT with nanomolar (IC_{50}) activity. AG-013736 is primarily metabolized by cytochrome P450 (CYP) 3A4 and uridine glucuronosyltransferase (UGT). Due to polymorphism in UGT1A1*28, subjects homozygous for the variant form ($7_{(TA)}/7_{(TA)}$) have a potential for reduced glucuronidation of AG-013736. The objective of this analysis was to quantitate the potential effects of the UGT1A1*28 genotype on AG-013736 PK.

METHODS: PK concentration data from four healthy volunteer studies was used to construct a population PK model. All subjects ($n=82$) received a single 5 mg oral dose of AG-013736 in the fasted state. Nonlinear mixed effects modeling (NONMEM) was performed with first-order conditional estimation (FOCE). The potential effect of UGT1A1*28 genotype was assessed as a covariate on oral clearance (CL/F). Clinical trial simulations were performed to predict the distribution of steady-state AG-013736 exposures at doses of greater than 5 mg BID (twice daily).

RESULTS: A 2-compartment, first-order absorption model was used to describe the PK data. Subjects homozygous ($7_{(TA)}/7_{(TA)}$) and

heterozygous ($6_{(TA)}/7_{(TA)}$) for the UGT1A1*28 genotype had reductions in mean CL/F of 36% and 20%, respectively, compared to homozygous wild-type ($6_{(TA)}/6_{(TA)}$). Inter-individual variability on CL/F decreased from 52% to 48% with inclusion of the UGT1A1*28 genotype as a covariate in the model. However, substantial overlap in the simulated plasma concentration-time curves for doses of 5 mg BID or greater was shown among all genotypes and doses.

CONCLUSION: The results indicate that the UGT1A1*28 genotype contributes to only 8% of overall inter-individual variability in AG-013736 PK. Additionally, at the highest simulated dose (10 mg BID), the upper 90% bound for the predicted AUC distribution in homozygous variant patients was lower than the plasma exposure associated with unacceptable toxicity in the first in human study.

PI-29

IMPACT OF TRANSCRIPTION ERRORS ON THE OUTCOME OF A CLINICAL TRIAL. A. E. Grahnen, PhD, K. Karlsson, MSc, F. Bragazzi, Msc, Quintiles Nordic Region, Uppsala University, Uppsala, Sweden.

BACKGROUND: The process of repeated inspections of source data stem from the belief that perfection in data (no errors) improves the quality of a clinical trial. The purpose of this investigation was to assess the impact of random errors on the outcome of a clinical trial using clinical trial simulation.

METHODS: The basis for the simulation was a powered, randomized, parallel group, double-blind, placebo controlled exposure-response trial (4 active doses). Two group sizes were investigated (corresponding to a power of approximately 80 and 90% respectively). The clinical endpoint of the trial was a continuous variable. Impacts of random errors in the recorded clinical endpoint of the trial were investigated. The magnitude and frequency of the random errors (in both directions) was 10 times (one magnitude) the true value, occurring at 1% and 5%. Outcome of the introduced errors was assessed by comparing the power of the trials (with and without errors) using model-based statistics (log likelihood ratio test). Simulations were performed in NONMEM.

The models in the simulations included a pharmacokinetic (PK) and pharmacokinetic-clinical endpoint (PK-CE) model. The PK-model was a one compartment, infusion model. The PK-CE model was an E_{max} model.

RESULTS: Despite the fact that the introduced errors were large in magnitude, the results showed that the impact of the introduced errors was insignificant. The outcome of the trial was only marginally affected.

CONCLUSIONS: The result of this simulation study indicates that the influence of random errors (of a fairly large magnitude) at frequencies of 1 to 5% do not have any significant influence on the outcome of the clinical trial in case. It should be emphasized that this simulation study is limited in its scope, dealing primarily with random errors and a continuous clinical endpoint described by a traditional E_{max} model. However, the outcome of the study indicates that the impact of random errors is by far less damaging to the outcome of a trial than traditionally believed. The current paradigm of repeated inspections (to strive for perfection) is questioned and a call for a truly evidence based quality system is made.

PI-30

USE OF MIXED EFFECTS MODELING TO EVALUATE THE CONTRIBUTION OF GENETICS TO PHARMACOKINETIC VARIABILITY IN A TWINS STUDY. N. C. Sambol, PharmD, T. Lam, T. D. Nguyen, PhD, D. L. Kroetz, PhD, University of California San Francisco, San Francisco, CA.

BACKGROUND/AIM: Twin studies are sometimes used to evaluate the influence of genetics on pharmacokinetic (PK) and pharmacodynamic variability. Analysis of the resulting data typically