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PHARMACOKINETICS AND PHARMACODYNAMICS OF INFLIXIMAB, AN ANTI-TUMOR NECROSIS FACTOR-ALPHA MONOCLONAL ANTIBODY, FOLLOWING SINGLE SUBCUTANEOUS ADMINISTRATIONS IN RHEUMATOID ARTHRITIS PATIENTS. Y. W. Zhu, PhD, C. Pendley, PhD, D. Sisco, R. Westhovens, MD, PhD, P. Durez, MD, E. Bouman-Thio, MD, B. van Hartingsveldt, D. E. Everitt, MD, M. A. Graham, PhD, Centocor, Inc., University Hospitals KU, Université Catholique de Louvain, Radnor, PA.

AIMS: To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of infliximab (INFX) prepared in a new highly concentrated formulation following single subcutaneous (SC) injections in rheumatoid arthritis (RA) patients.

METHODS: Patients with active RA were enrolled in a Phase I, open-label, randomized study with single SC doses of INFX (0.5, 1.5 and 3.0 mg/kg, n = 5 per group). Serum INFX levels were measured using ELISA. Non-compartmental analysis was employed to calculate PK parameters. The absolute bioavailability (BA) of INFX was estimated from the dose-normalized AUC following SC injection and a previous clinical trail of INFX as IV infusion. The relationships between PK and the tender joint count (TJC), swollen joint count (SJC) and C-reactive protein (CRP) were also investigated.

RESULTS: INFX was slowly absorbed into the systemic circulation (median T_{max} = 7.0 days) and slowly eliminated from the serum (median $T_{1/2}$ = 8.1 days). The C_{max} and AUC increased in a dose-proportional manner, and the $T_{1/2}$ and CL/F were dose-independent. The BA of INFX was approximately 71.1%. Rapid reductions in TJC, SJC and CRP were seen at all dose levels at week 2 through week 4. The reduction in TJC at week 4 appeared to be a function of the dose and AUC.

CONCLUSIONS: PK of INFX following single SC doses were linear and dose-independent. SC administration is feasible in terms of its BA and clinical response. Note: This new formulation of INFX has not been approved by the FDA or other regulatory agencies for human therapeutic use.

PI-135

PREDICT RECEPTOR OCCUPANCY FOR COMPOUND A AT RECEPTOR R2 BASED ON ITS OCCUPANCY AT RECEPTOR R1. S. Mu, PhD, S. Mitchell, PhD, W. Ebling, Eli Lilly and Company, Pharsight Corporation, Indianapolis, IN.

PURPOSE: To illustrate a new method for calculating receptor occupancy (RO) for compound (A) that binds to two receptors R1 and R2.

METHODS: Compound A is a competitive inhibitor for an endogenous brain chemical S at two functionally distinct receptors R1 and R2 in the central neural system. The receptor occupancy can be quantitated through neuro-imaging for R1, but not for R2. Analytical solution of RO at R2 at given RO at R1 was derived as a function of binding affinities of A and S to both receptors, and concentration of S at the site of action. Major assumptions in the derivation include: fraction of radiotracer that binds to R2 is negligible; stoichiometry of binding between A and receptors R1 and R2, and between S and R1 and R2, respectively, is 1:1; S is the only significant competitor with A for both receptors. RO at R2 was generated under 3 binding affinity scenarios: a) A binds to R1 and R2 equally; b) A binds R1 > R2; c) A binds R2>R1.

RESULTS: Exposure-RO relationships were generated which allowed evaluation under different scenarios. The robustness of the assumptions was also tested.

CONCLUSION: This method allows the estimation of RO for a receptor conditional on RO information at another receptor. Simulated exposure-RO relationship helps dose selection for compound A that maximizes its occupancy at both receptors while avoiding undesirable effects.

PI-136

POPULATION PHARMACOKINETIC ANALYSIS OF RIMONABANT IN HEALTHY SUBJECTS. G. M. Ferron, PharmD, PhD, M. Grandison, PhD, G. Lockwood, PhD, Sanofi-Aventis, Malvern, PA.

BACKGROUND: The purpose of this analysis was to investigate the influence of dose and key demographic parameters on the population pharmacokinetics (PPK) of rimonabant.

METHODS: PK data were combined from 7 similar phase I studies consisting of 141 young healthy subjects (3874 observations), including 52 Japanese, 89 non Japanese, 8 female, 133 male, obese and non obese [body mass index (BMI): 18.2 - 41.6 kg/m^2, body weight: 50.4 - 135 kg] and doses of 3 to 120 mg. Subjects received either a single dose or once-daily doses for 21 days of rimonabant. The PPK model was developed using a non-linear mixed effect model (WinNonMix, v2.0.1). Model verification was performed by an examination of the goodness of fit plots, mean weighted residuals and by estimation of the prediction error and its 95% confidence interval.

RESULTS: Rimonabant PPK was described by a two-compartment model in terms of volume (Vc/F and Vp/F) and clearance (CL/F and CLd/F) parameters with a first-order absorption rate constant (ka) and a lag time (t_{lag}). Individual parameter values were log-normally distributed. The final model included significant relationship between BMI and Vp/F, between rimonabant dose and ka, Vc/F, CL/F, and Vp/F, and between dose regimen and t_{lag}. No effect of race was observed.

CONCLUSIONS: BMI appears to be the major determinant of rimonabant PK within the doses used in phase III trials, reflecting extensive distribution in the peripheral target tissues.

PI-137

EFFECT OF FEBUXOSTAT ON PHARMACOKINETICS OF DESIPRAMINE, A CYP2D6 SUBSTRATE, IN HEALTHY SUBJECTS. R. Khosravan, PhD, K. Erdman, BS, L. Vernillet, PharmD, PhD, J. T. Wu, PhD, N. Joseph-Ridge, MD, S. Umeda, PhD, D. Mulford, PhD, TAP Pharmaceutical Products Inc., Teijin Ltd, Lake Forest, IL.

Febuxostat is a novel non-purine selective inhibitor of xanthine oxidase (NP-SIXO) being developed for the management of hyperuricemia in patients with gout.

BACKGROUND: *In-vitro* data showed that febuxostat had no significant effect on CYP1A2, CYP2C9, CYP2C19 or CYP3A4 activity (K_i>100 μM), and a weak inhibitory effect on CYP2D6 (K_i=40 μM).

AIM: The effect of febuxostat on desipramine pharmacokinetics (PK) was evaluated.

METHODS: A phase-1, two-period, crossover, double-blind study was conducted in 18 CYP2D6 extensive-metabolizer subjects. Each subject received a single 25 mg oral dose of desipramine (DES) after multiple oral dosing with febuxostat (FBX) 120 mg or placebo (PLA) once daily. Blood samples were collected to assess the PK of DES and 2-hydroxydesipramine (2-HD).

RESULTS: The results are shown in the table below.

Mean±SD Plasma PK for DES and 2-HD, Point Estimates (PE) and Confidence Intervals (CI)

Parameter	DES + FBX	DES + PLA	PE (90% CI)[1]
DES			
C_{max} (ng/mL)	9.6 ± 3.5	8.4 ± 3.2	1.16 (1.10-1.23)
AUC_∞ (ng h/mL)	295 ± 194	263 ± 249	1.22 (1.11-1.35)
2-HD			
C_{max} (ng/mL)	6.2 ± 2.0	6.6 ± 2.3	0.96 (0.90-1.02)
AUC_∞ (ng h/mL)	163 ± 30	166 ± 62	1.02 (0.93-1.11)
AUC Ratio[2]	0.74 ± 0.40	0.88 ± 0.49	0.83 (0.76-0.91}

[1]Ratio of DES+FBX to DES+PLA; [2]AUC Ratio: 2-HD/DES AUC ratio.

The increase in total exposure to DES and the concomitant decrease in the 2-HD/DES AUC ratio suggest that the metabolism of DES to 2-HD via CYP2D6 was mildly inhibited. However, this effect was not considered to be clinically significant. The incidence of adverse events was similar between treatment regimens with the majority being mild and moderate in severity.

CONCLUSION: No dose adjustment is expected for CYP2D6 substrates when co-administered with febuxostat.