[] PHARMACOKINETIC-PHARMACODYNAMIC MODELING OF TENOFOVIR EXALIDEX IN HBV SUBJECTS

Robert Foster[1], Michael Conover[2], Carlos Canizres[2], Daniel Trepanier[2], Daren Ure[2], Theresa Matkovits[2], Patrick Mayo[3]

[1]*Drug Development*
[2]*Contravir Pharmaceuticals Inc.; Drug Development*
[3]*University of Alberta; Faculty of Pharmacy and Pharmaceuticals Sciences*

Background and Aims:

Tenofovir Exalidex (TXL), a lipid conjugate of tenofovir (TFV), is designed to mimic lysophosphatidylcholine to take advantage of natural lipid uptake pathways and achieve high intrahepatic concentrations of TFV diphosphate (TFV-PP) while reducing the peripheral TFV concentrations associated with kidney and bone toxicities. As it is not routinely feasible to measure intrahepatic TFV-PP concentrations in patients, a pharmacokinetic-pharmacodynamic (PK-PD) model was developed to aid and optimize further clinical development of TXL.

Method:

TXL was administered to 50 HBV subjects (fasted) at doses ranging from 10–100 mg/day orally. The 50 mg cohort (n = 10) was used to derive PK-PD modeling, as this dose resulted in viral load (VL) reductions (log_{10}) that were not statistically different from Standard-of-Care (SOC, 300 mg, tenofovir disoproxil fumarate). Steady-state PK modeling was generated using linear trapezoidal, linear interpolation, Non-Compartmental Analysis for a 24 hour dosing interval (NCA, Phoenix WinNonLin Ver. 7.0). A linked PK-PD non-linear mixed effects (NLME, Monolix 3.2) model was employed, using an inhibitory Emax model. PK data were also examined using model-dependent analyses. Data after 28 days dosing was used for the current model.

Results:

Maximum VL reductions of up to 3.9 log_{10} were observed with 50 mg/day TXL dosing for 28 days. The prodrug, TXL, rapidly disappeared from plasma, with mean (SD) Cmax, Tmax, AUC_{last}, and $t_{1/2}$ values of 51.28 (39.9) ng/mL, 1.60 (0.7) h, 109.44 (84.9) ng.h/mL, and 2.10 (2.0) h, respectively, at day 28. TFV mean (SD) values for Cmax, Tmax, AUClast, and $t_{1/2}$ were 8.51 (2.0) ng/mL, 4.95 (2.2) h, 136.35 (33.5) ng.h/mL, and 23.3 (3.4) hours, respectively. The VL IC_{50} on Day 29 was 2.92 ng/mL. Additionally, TXL could be described using a one-compartment model, whereas for TFV the model of best-fit was multi-exponential.

Conclusion:

TXL 50 mg VL reductions were not statistically different (p=0.19) from SOC, TDF. The PK-PD relationship after dosing on Day 28 was described using a NCA and inhibitory Emax model for TFV. TXL was rapidly cleared compared with TFV, and the clinical antiviral reduction IC_{50} approximated 3 ng/mL. Modeling promises to be a useful tool for the further clinical development and optimization of TXL.