PHARMACOKINETIC AND PHARMACODYNAMIC MODEL FOR DRUG INDUCED TRANSIENT TRANSAMINITIS

Ricardo Nalda-Molina[1] (jnalda@umh.es), Amelia Ramón-López[1], Belén Valenzuela[1], Bernardo Miguel-Lillo[2], Maria José Duart[1], Arturo Soto-Matos[2]

Pharmacy and Pharmaceutics Division, Department of Engineering, Faculty of Pharmacy, Miguel Hernández University, Spain.

[2] Pharma Mar. Madrid, Spain.

OBJECTIVE: Reversible transient elevations in transaminases have been observed after the administration of several drugs. The objectives of this analysis were to characterize the time course of ALT concentrations after Drug X administration following different dosing schedules, including the tolerance to this drug effect, and evaluate, through simulations, the clinical impact of dose-intensity, dose-density and duration of the infusion on Drug X pharmacodynamics.

METHODS:

✓ **Analysis dataset:** The analysis dataset comprised 475 subjects and 4756 ALT measurements. The drug was administered as monotherapy (dose range: 1x–100x mg) as 1- or 24-h infusions on days 1, 8, and 15 every 28 days; 3- or 24-h infusions on days 1 and 15 every 28 days; 1-h infusions daily for five consecutive days every 21 days; or 3- or 24-h infusions every 14 days. ALT measurements were obtained weakly, although in Phase 1 studies, 2 to 3 ALT measurements were collected during the first week of treatment samples.

✓**Model Development:** The development of the PKPD model was performed using a sequential process. Initially, an open three compartment disposition model, with linear elimination and linear distribution to deep and shallow compartments was used to described the pharmacokinetics of drug X in plasma. Bayesian estimates of individual PK parameters were used to predicted individual drug X concentration-time profiles, which were used as input functions into the PD model.

A previously developed precursor-dependent indirect pharmacodynamic response model was used as the structural model[1]. The schematic of the model is depicted in figure 1. The covariates included in the analysis were demographic factors, biochemical tests and other covariates related to the disease. Stepwise approach and the likelihood ratio test were used for the covariate analysis. The analysis was conducted with NONMEM V Level 1.1, using nonlinear mixed-effects modelling by extended least squares regression with the first order conditional estimation (FOCE) approximation method.

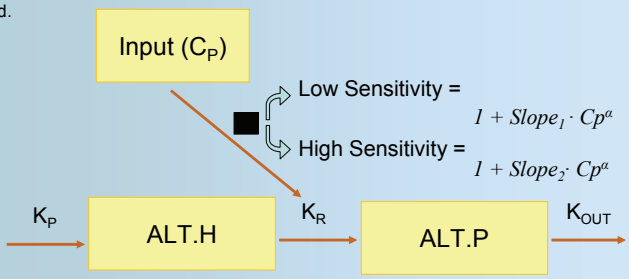


Figure 1. Precursor-dependent indirect pharmacodynamic response model for ALT. ALT.H and ALT.P are the concentration of ALT in hepatocyte and plasma, respectively; k_P is the production rate constant of ALT in hepatocytes; k_R is the release rate constant of ALT from hepatocyte to plasma; k_{OUT} is the removal rate constant of ALT from plasma; C_P is the Drug X plasma concentration; Slope is the relationship of the stimulatory effect of Drug X on ALT elevation.

Validation: A posterior predictive check (PPC) was performed to assess the predictive performance of the incidence of transaminitis grade 3 and 4. One-hundred data sets with the same design as the original data set were simulated using the estimated parameters obtained from the PK/PD model. The observed incidence of transaminitis was then compared with the 95% confidence intervals of the simulated incidences of transaminitis.

✓**Simulation:** Deterministic simulations were performed to evaluate the impact of dose intensity, dose density and infusion duration on the time course of ALT. The accumulated doses used in the deterministic simulations ranged from 10800 to 28800 µg per month. Stochastic simulations of weekly ALT measurements were performed to assess the clinical impact of dose intensity, dose density and infusion duration on the incidence of grade 3 and grade 4 hepatic toxicity. The accumulated doses used in the stochastic simulations ranged from 4500 to 19500 µg per month. Three different schedules were included in the simulations: Schedule 1: Infusions on Days 1, 8, and 15 every 28 days. Schedule 2: infusions on Day 1 every 15 days. Schedule 3: infusions on Days 1, 8, every 21 days. The infusion durations included in the simulations were 1h, 3h and 24 h.

Results:

A precursor dependent indirect response model is suitable to describe the drug mediated toxicity on liver transaminase (Table 1, Figure 1). The model accounts for the tolerance phenomena observed in transaminases after multiple dose and is able to distinguish between subjects with high and low sensitivity to Drug X in terms of transaminase elevation. No covariate effect were found to be statistically significant. PKPD parameters were consistent across different dosing schedules evaluated. Simulations indicated that Drug X dose and schedule were the main determinants of the incidence on hepatic toxicity. The duration of the infusion had negligible impact on the ALT time course.

Table 1: Fixed and random parameter estimates of Drug X of the PKPD model. $ALT.H_0$ and $ALT.H_0$ are the ALT baseline in hepatocyte and plasma, respectively. High and low slope are the relationship of the stimulatory effect of Drug X on ALT elevation for high and low sensitive population, respectively.

	Central Tendency (RSE%)	Between Subject Variability % (RSE%)
$ALT.H_0$ (xULN)	25.4 (17.2)	-
$ALT.P_0$ (xULN)	0.458 (3.3)	55.7
Kout (h^{-1})	$2.43 \cdot 10^{-3}$ (11.9)	135
High Slope (L/µg)	10 (24.9)	164
Low Slope (L/µg)	0.945 (30.1)	
α	1.19 (7.1)	-
Percentage of High Sensitivity Population (%)	12.5 (22.7)	-

Residual Variability % (RSE%) : 39.9 (4.53)

Figure 2. Diagnostic plots (upper panels) of the final PKPD model fit of the ALT measurement after drug X administration. Posterior predictive check (lower panels) of the hepatic toxicity grade 3 and 4: Red lines represents observed incidence of hepatic toxicity, blue lines represent 2.5, 50 and 97.5 percentiles of the incidence of toxicity from 100 simulated datasets.

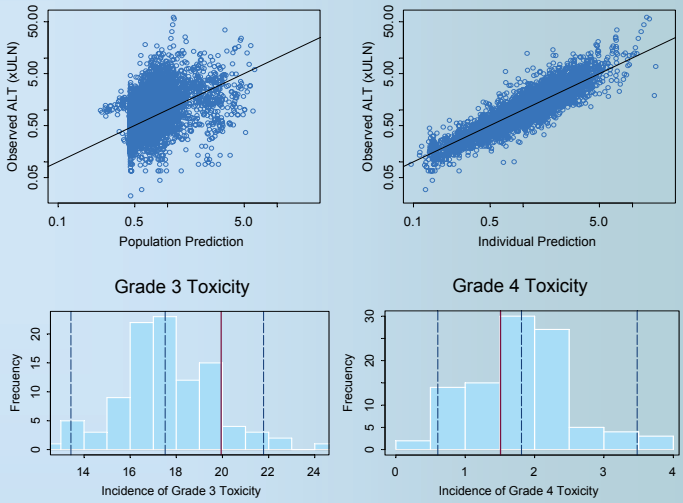
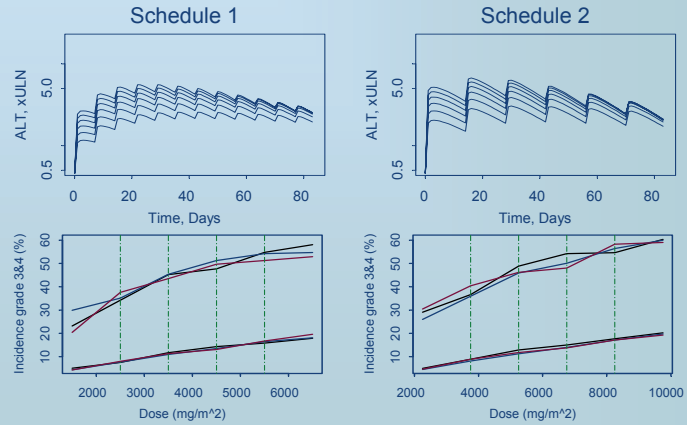


Figure 3. Deterministic simulations to evaluating the impact of dose-intensity of weekly (upper left panel) and biweekly (upper right panel) on the ALT time course for a 3h i.v. infusion (upper panels). Summary results of the stochastic simulations evaluating the the incidence of liver toxicity grade 3 and grade 4 as a function of the dose-intensity and infusion duration for weekly (lower left pannel) and biweekly (lower right pannel) dosing. Black, blue and red line correspond to 1h, 3h and 24h infusion, respectively. The incidence of liver toxicity was stratified by high sensitive population (upper lines) and low sensitive population (lower lines) in each graph.



REFERENCE: Fetterly GJ, Owen JS, Stuyckens K, Passarell JA, Zannikos P, Soto-Matos A, Izquierdo MA, Perez-Ruixo JJ., Cancer Chemother Pharmacol. 2008 Jun;62(1):135-47

Conclusion:

A PKPD modeling has been used to analyze the hepatic toxicity during drug development. Simulation techniques were employed to understand the exposure versus toxicity relationship and to make decisions on dose selection for future clinical trials.