Mechanistic Modeling Aids in the Interpretation of Alanine Aminotransferase Elevations Associated with Clinical Ischemic Liver Injury

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BACKGROUND

- **DILIsym® software can use serial serum alanine aminotransferase (ALT) assessments to predict hepatocyte loss (HL) and corresponding changes in total bilirubin (TBIL) due to reduction in global liver function as shown in Figure 1.**

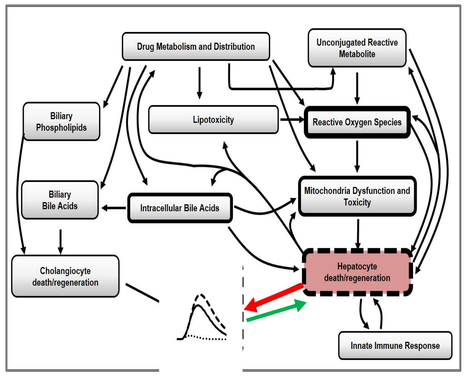

Figure 1. DILIsym is a quantitative systems toxicology software designed to predict drug-induced liver injury. Simulations integrate compound exposure with *in vitro* data regarding the indicated toxicity mechanisms to predict time-dependent hepatocyte loss and resultant serum ALT values (red arrow). When hepatocyte loss is ≥30%, the model predicts elevations in serum TBIL due to global loss of liver function. Conversely, serial serum ALT levels can be used in DILIsym to predict the percent HL (green arrow) and whether observed elevations in serum TBIL reflect loss of global liver function. DILIsym also incorporates inter-patient variability in ALT half life, hepatocyte content of ALT, and liver regeneration and can thereby predict the range of responses observed in patient populations.

- **A mathematical equation, $P_{ALT,}$ has been derived to estimate the maximum HL predicted by DILIsym without access to the software[1]. P_{ALT} predicts a range of maximum hepatocyte loss (Figure 2) associated with the AUC and the peak value of an ALT kinetic profile.**

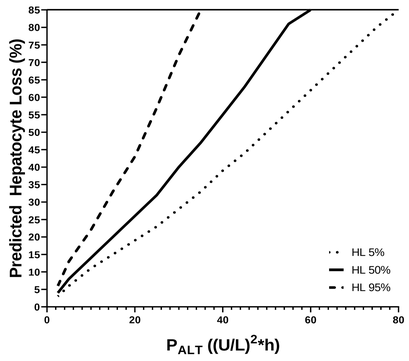

Figure 2. Figure based on data provided in Reference 1. Calculation of P_{ALT} estimates a range of HL based on data from 22,800 simulations generated in DILIsym for four unique kinetic ALT profiles. Lines correspond to the 5th, 50th , and 95th percentiles for maximum HL at any P_{ALT} value. Values stop at 85% hepatocyte loss, as death of an individual is assumed at this point.

- **DILIsym (and hence P_{ALT}) was optimized to estimates of HL (determined by biopsy) and peak serum TBIL levels observed in acetaminophen overdose patients[2]; therefore, it is unclear if the model of P_{ALT} accurately predicts HL and TBIL elevations in other liver injuries.**
- **In this study we tested the ability of DILIsym to predict peak TBIL values associated with ischemic liver injury. Additionally, the maximum HL predicted by DILIsym was compared to P_{ALT}.**

METHODS

- **Serial serum ALT values were curve fit (DILIsym v6A) for N=20 patients who experienced ischemic liver injury.**
- **P_{ALT} was calculated as: P_{ALT}= ALT_AUC*Peak ALT$^{0.18}$/10^5 ((U/L)2*h).**
- **Simulated TBIL values were adjusted so that the baseline value matched the clinically observed value.**
- **Correlations were conducted on log normalized data.**

RESULTS

Table 1. Modeling Results for Ischemic Liver Injury in DILIsym

Patient ID	Peak ALT (U/L)		Peak TBIL (mg/dL)*		Peak HL	
	Observed	Simulated	Observed	Simulated	P_{ALT} 50th Percentile (%)	DILIsym (%)
1	1086	1095.8	0.59	0.45	6	7.09
2	2824	2904.2	0.76	0.94	13	20.35
3	2538	2546.6	0.99	0.75	17	21.96
4	1841	1841.5	0.99	0.69	13	15.57
5	1054	1041.3	0.99	1.1	7	8.19
6	1213	1216.8	0.99	1.13	8	8.13
7	1208	1198.8	1.05	1.38	8	7.26
8	2326	2325.3	1.29	0.99	13	16.05
9	2429	2442.9	1.35	1.26	17	21.22
10	1255	1247.7	1.46	0.75	9	10.12
11	1148	1056.8	1.46	1.18	7	8.37
12	1621	1624.4	1.52	0.7	8	10.77
13	1354	1374.6	1.58	1.44	9	12.96
14	1920	1941.3	1.7	0.9	27	20.87
15	1599	1596.7	1.76	0.78	10	11.55
16	5673	5643.6	2.34	2.99	27	46.35
17	1760	1770.2	3.3	1.01	10	11.80
18	3737	3897.3	3.45	2.49	23	29.80
19	1308	1317.8	4.2	2.48	8	9.37
20	6899	6947.1	7.84	11.67	50	78.00

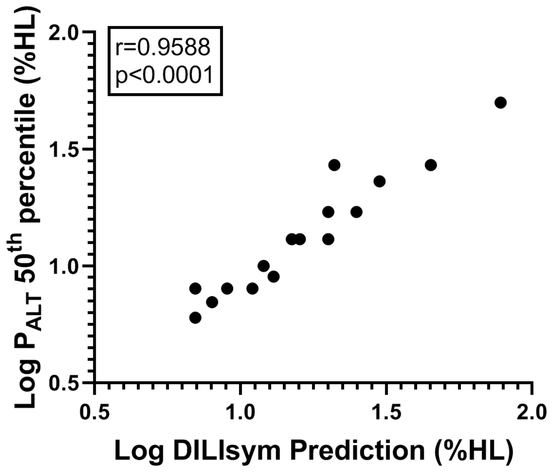

Figure 3. Correlation between maximum HL predicted by DILIsym and the 50th percentile maximum HL predicted by P_{ALT}. Correlation is represented by Pearson's r.

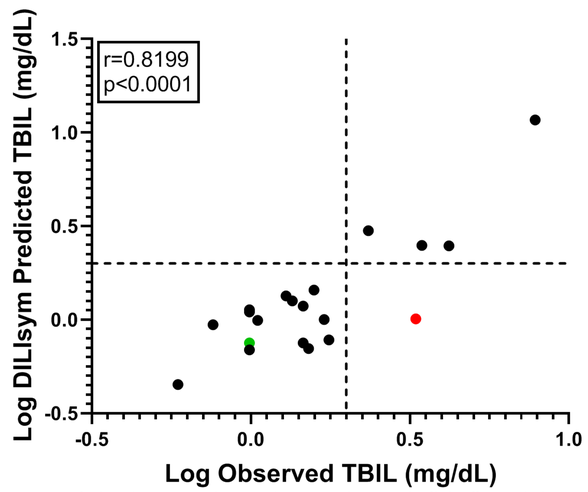

Figure 4. Correlation between the peak TBIL observed clinically and the peak TBIL predicted by DILIsym. Green dot (patient 3) represents a patient that modeled well (see Fig 5). Red dot (patient 17) represents a patient that did not model well (see Fig 5). Dotted lines drawn at log 2 mg/dL, representing a clinically relevant TBIL change. Correlation is represented by Pearson's r.

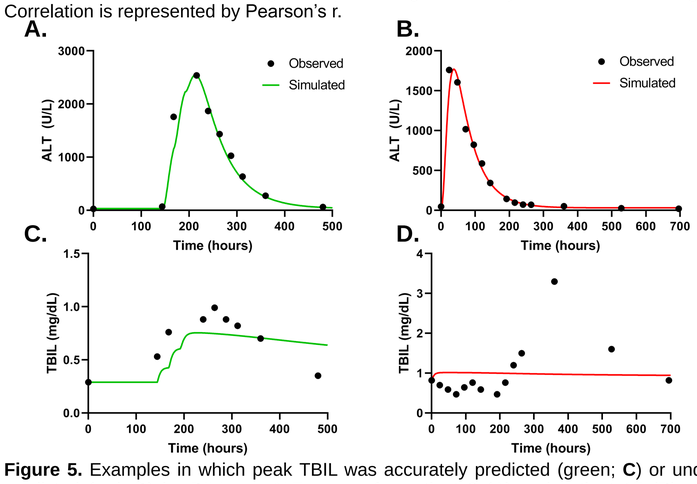

Figure 5. Examples in which peak TBIL was accurately predicted (green; **C**) or under-predicted (red; **D**) by DILIsym. ALT curves for patient 3 (**A**) and patient 17 (**B**) were simulated in DILIsym so that the simulated and clinically observed ALT curves were identical. DILIsym software can simultaneously predict how other parameters, such as TBIL, change concurrently with ALT. The TBIL elevation predicted by DILIsym accurately reflected the peak change observed clinically in patient 3 (**C**) but DILIsym failed to predict the rise in TBIL that was observed clinically in patient 17 (**D**).

CONCLUSIONS/ REFERENCES

- **Maximum HL predicted by P_{ALT} or by DILIsym were highly correlated. P_{ALT} may be useful for estimation of HL in the clinic.**
- **DILIsym only under predicted one significant TBIL change (2 mg/dL) observed clinically. Since this peak occurred about 2 weeks after the peak serum ALT, it may represent an unrelated post-ischemic event.**
- **Further validation of this model should be conducted using data from other acute and more chronic liver injuries including idiosyncratic drug-induced liver injury.**

[1]Chung JY, Longo DM, and Watkins PB. *Clin Pharmacol Ther.* 2019; 105(3): 746-743; [2]Postmann B, Talbot IC, *et al. J Pathol*. 1975; 117(3): 169-81