Quantitative Systems Toxicology Modeling of Otenaproxesul Liver Enzyme Elevations Leads to Prediction of Liver Safety for Acute Otenaproxesul Dosing

Nader Hamzavi[1], Pallavi Bhargava[1], Vinal V. Lakhani[1], David Vaughan[2], Daniel Legault[2], Joseph Stauffer[2], Brett A. Howell[1], Jeffrey L. Woodhead[1]

[1]Simulations Plus, Inc., QSP Solutions Business Unit, RTP, NC [2]Antibe Therapeutics, Inc., Toronto, ON

Contact: jeff.woodhead@simulations-plus.com

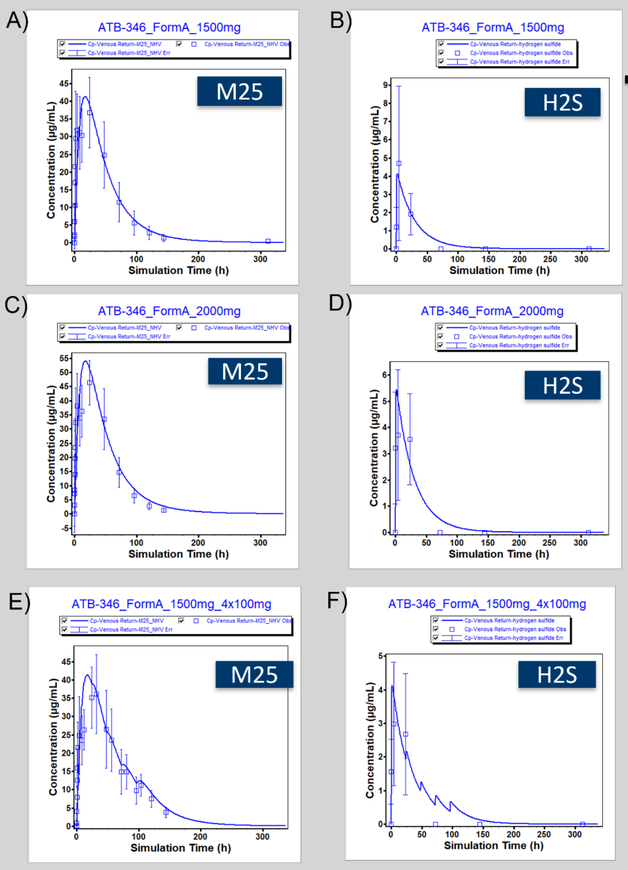
OBJECTIVE

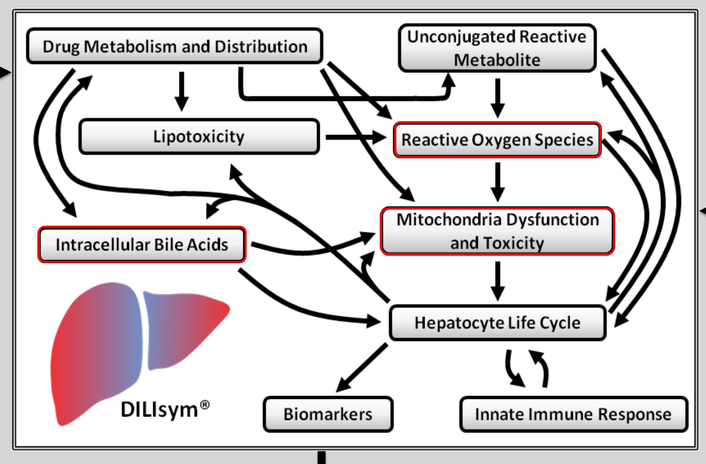
Otenaproxesul (ATB-346), a drug that combines naproxen with a thiobenzamide antioxidant, is being developed as an NSAID that reduces gut toxicity effects. Liver toxicity signals were observed in early clinical studies, mostly after dosing ceased; liver signals appear almost exclusively in individuals with fatty liver. In order to mechanistically explain the observed toxicity and predict potentially safe dosing regimens, a quantitative systems toxicology (QST) representation of otenaproxesul, its main metabolite M25 (naproxen), and the H_2S released by the thiobenzamide moiety was implemented in DILIsym v8A, a QST model of drug-induced liver injury.

METHODS

Otenaproxesul and its metabolites H_2S and naproxen were implemented as compounds in DILIsym v8A, a QST platform model of drug-induced liver injury. A PBPK model for otenaproxesul, naproxen, and H_2S was constructed in GastroPlus 9.8 and used as an input into DILIsym. Otenaproxesul and naproxen (M25) were assessed in a series of *in vitro* experiments that found oxidative stress signals for naproxen; these were translated into inputs into DILIsym as well. H_2S was implemented as a scavenger of both ambient and induced oxidative stress (ROS). Simulations of existing clinical trials in both normal healthy volunteers (NHV), post-menopausal women (PMW), and metabolism-associated fatty liver disease (MAFLD) patients were used as comparators for the model results; for modeling of the rebound effect hypothesis, some of these trials were used as calibration for the de-adaptation effect.

RESULTS

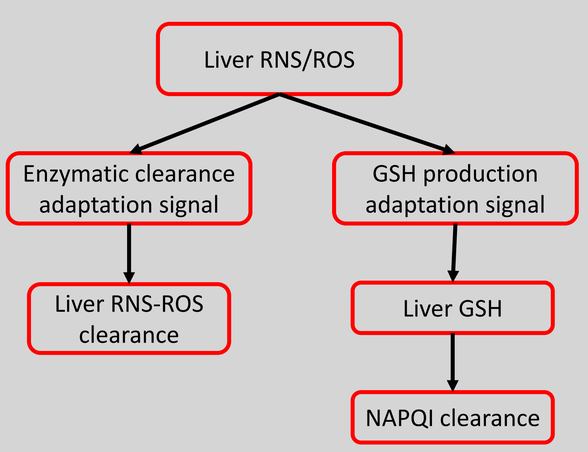




1. PBPK modeling describing liver exposure of otenaproxesul metabolites naproxen (M25) and H_2S and parameters derived from *in vitro* experiments were used as inputs into DILIsym for the representation of otenaproxesul. Otenaproxesul was simulated in both an NHV and a PMW SimPops. The resulting model did not predict any liver injury for otenaproxesul.

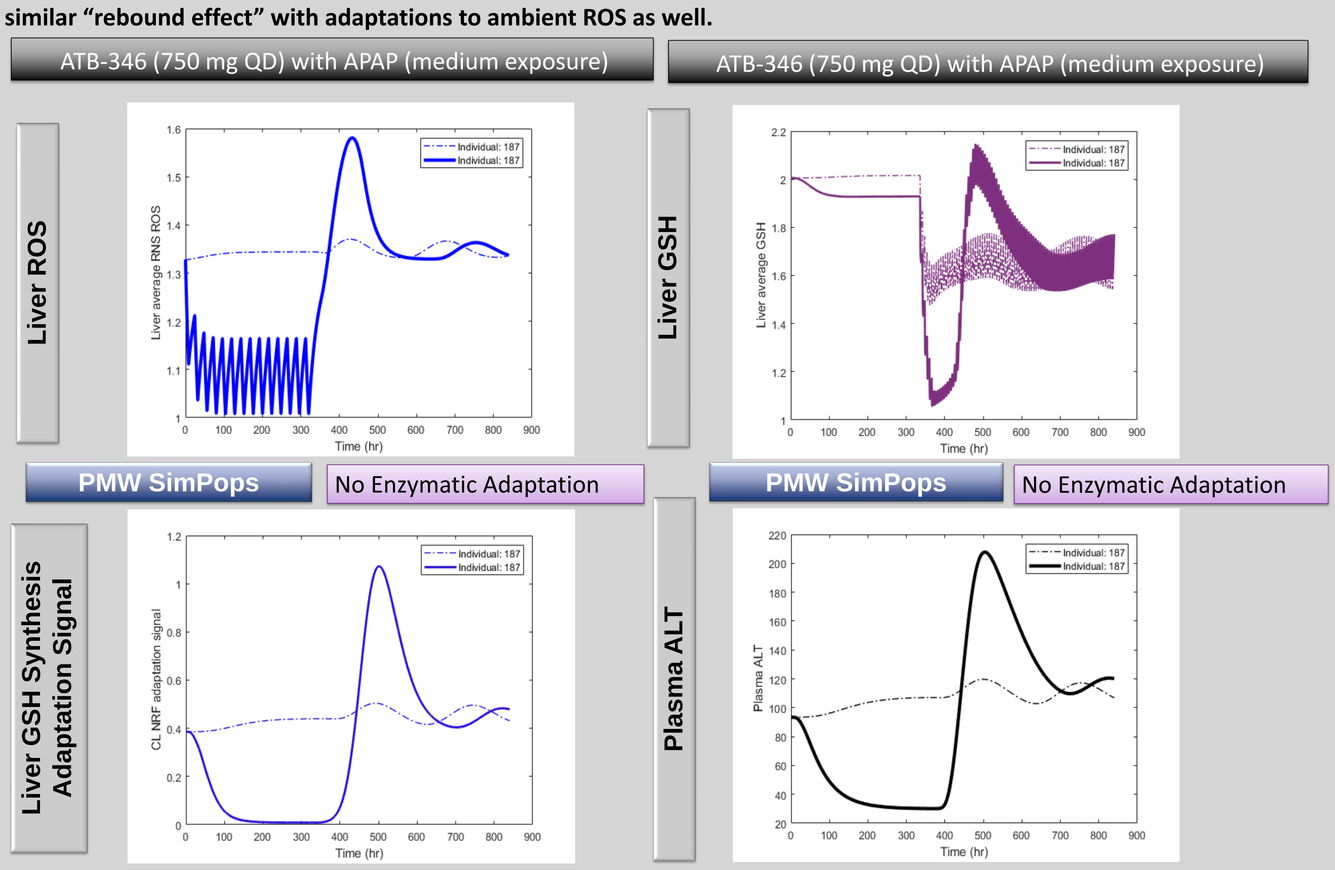
Dosing Protocol	Simulated ALT > 3X ULN*	
	NHV**	PMW***
Placebo	0/285	17/229
Otenaproxesul 150 mg QD for 2 weeks	0/285	19/229
Otenaproxesul 250 mg QD for 2 weeks	0/285	19/229
Otenaproxesul 750 mg QD for 2 weeks	0/285	19/229

Mechanism	Parameter	Unit	Naproxen Value*
BA Transport Inhibition**	Inhibition constant for basolateral efflux	µM	93
Oxidative Stress	Liver RNS/ROS production rate constant 1	mL/nmol/hour	2.8e-05
Mitochondrial Dysfunction	Coefficient for ETC Inhibition 3	µM	347.2
	Max inhibitory effect for ETC inhibition 3	Dimensionless	0.372



3. NRF-2 adaptation is included in DILIsym v8A via two pathways: one featuring glutathione effects that only apply to acetaminophen, and an enzymatic clearance pathway that applies to all forms of ROS. A novel MAFLD population was constructed with individuals that have used enzymatic adaptation to "pre-adapt" to oxidative stress; pre-adapted individuals would have a spike in ROS and thus injury if the adaptation was removed and ambient ROS returned. This model was used to represent the clinical liver injury data, which it did well. The model was used to predict several novel acute clinical protocols, one of which was later demonstrated to be safe in a clinical trial.

2. Simulations with acetaminophen revealed that otenaproxesul potentiated acetaminophen injury after dosing. This was due to the fact that decreased ambient ROS during dosing led to an increase in ROS after the H_2S ROS scavenging was removed; without pre-existing adaptation, acetaminophen toxicity occurred. It was hypothesized that this would lead to a similar "rebound effect" with adaptations to ambient ROS as well.



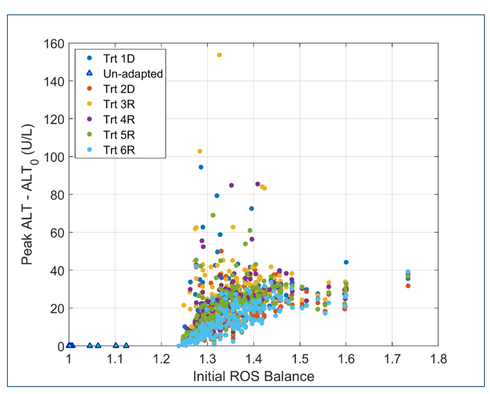
ATB-346 Dose (mg)	Duration (days)	Clinical On-Tx ALT Elevation	Simulated On-Tx ALT Elevation	Clinical ALT Rebound	Simulated ALT Rebound
250 mg QD	7	None Observed	None	Safe	0/261 (0%)
2000 mg QD	1				0/268 (0%)
75 mg QD	21			5% – 10%	7/263 (3%)
250 mg QD	10				163/261 (62%)

Acute ATB-346 Dosing Regimen*	Δ ALT > 120 U/L (n = 275)	
	On-Treatment	Post-Treatment
T_x 1D	0 (0%)	0 (0%)
T_x 2D	0 (0%)	0 (0%)
T_x 3R	0 (0%)	0 (0%)
T_x 4R	0 (0%)	1 (0.4%)
T_x 5R	0 (0%)	0 (0%)
T_x 6R	0 (0%)	0 (0%)

* **Scheme 1D:** Day1: 600 mg and 200 mg q12h, Day2: 200 mg q12h, Day3&4: 100 mg q12h, Day5: 50 mg q12h
Scheme 2D: Day1: 600 mg and 200 mg q12h, Day2: 200 mg q12h, Day3-5: 25 mg q12h
Scheme 3R: Day1: 400 mg and 200 mg q12h, Day2&3: 200 mg q12h, Day4&5: 100 mg q12h
Scheme 4R: Day1: 400 mg and 200 mg q12h, Day2&3: 200 mg q12h, Day4&5: 50 mg q12h
Scheme 5R: Day1: 400 mg and 200 mg q12h, Day2: 200 mg q12h, Day3: 100 mg q12h, Day4&5: 50 mg q12h
Scheme 6R: Day1: 200 mg and 100 mg q12h, Day2: 100 mg q12h, Day3: 50 mg q12h, and Day4&5: 25 mg q12h.
- 17 extra days of no drug were added to all the schemes

CONCLUSION

A QST model for otenaproxesul was successfully constructed in DILIsym and was used to explain the clinically observed post-dosing ALT elevations. The ALT elevations were hypothesized to be due not to the direct actions of naproxen itself but to the fact that the H_2S scavenges enough ambient ROS to cause individuals with high baseline ROS to de-adapt to that baseline ROS, leading to a spike in ROS and liver injury when the drug is removed. This hypothesis was able to explain the observed ALT elevations, and was able to prospectively predict the safety of a novel clinical otenaproxesul dosing protocol. In addition, the model predicted that the most at-risk individuals are those with mild MAFLD-induced ROS (right); these individuals were the ones in which toxicity was observed clinically. This demonstrates the potential for QST modeling to explore novel hypotheses of toxicity and make successful predictions based on those hypotheses.



ACKNOWLEDGEMENTS

The DILI-sim Initiative is responsible for funding the development of DILIsym v8A. For more information on joining the DILI-sim Initiative or gaining access to the DILIsym software platform, visit https://www.simulations-plus.com/software/dilisym/.

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