Mechanistic modeling of biologics-induced liver injury (BILI) predicts hepatotoxicity of Tocilizumab through both on- and off-target effects

Lara Clemens[1], James J. Beaudoin[1], Lawrence A. Vernetti[2], D. Lansing Taylor[2], Albert Gough[2], Christina Battista[1], Scott Q. Siler[1], Lisl K.M. Shoda[1], Brett A. Howell[1] and Kyunghee Yang[1]

[1]DILIsym Services Division, Simulations Plus Inc., Research Triangle Park, North Carolina;
[2]Drug Discovery Institute, University of Pittsburgh, Pittsburgh, Pennsylvania

Abstract: 4057

ABSTRACT

BACKGROUND:

Biologics address a range of unmet medical needs. However, there are increasing numbers of BILI cases which slow therapeutic development or require frequent monitoring of liver function.

METHODS:

To assess the potential clinical BILI liability of biologics, a novel quantitative systems toxicology (QST) platform, BIOLOGXsym™, was developed incorporating relevant liver biochemistry, mechanistic representations of key pathophysiologic pathways, and assay data from a human biomimetic liver microphysiology system.

Tocilizumab (TCZ), a human anti-interleukin (IL)-6 receptor antagonist biologic used for treating inflammatory diseases, can lead to transient elevations in alanine aminotransferase (ALT), a biomarker of liver injury. Within BIOLOGXsym, a mechanistic model of TCZ was developed including direct representation of IL-6, IL-6 receptor, and specific on-target (CYP expression, hepatocyte regeneration) and off-target (TCZ-induced reactive oxygen species, [ROS]) effects.

Exposure of human (vascularized) liver acinus microphysiology system ([v]LAMPS) to 1.6 µM TCZ demonstrated TCZ-induced ROS and recovery of IL-6 inhibited CYP activity, offering insights into potential hepatotoxic effects of TCZ. These data, along with data from the literature and TCZ exposure predictions from GastroPlus®, were used to parameterize the model and run proof-of-concept simulations.

RESULTS:

Simulated TCZ administration (8 mg/kg Q4W for 12 weeks) to a small cohort (n=4) of individuals with elevated IL-6 demonstrates ALT above three times the upper limit of normal in one individual. When TCZ is co-administered with repeat therapeutic doses of acetaminophen, a medication with CYP-dependent hepatotoxicity, all individuals in the cohort show significant ALT elevations. Mechanistic analysis of these responses indicates persistent ALT elevations during co-medication when either off-target or on-target effects are excluded from the simulation.

CONCLUSION:

These results demonstrate the potential of BIOLOGXsym to predict BILI, identify key toxicity mechanisms, and evaluate drug-drug interactions for developing biologics.

INTRODUCTION

Biologics can address many unmet clinical needs. However, BILI cases can slow therapeutic development or require frequent monitoring of liver function. Here we developed BIOLOGXsym, a novel QST model, to predict the potential BILI liability of new biologics.

We use TCZ as an exemplar compound to demonstrate the ability to predict liver toxicity with BIOLOGXsym. TCZ is an IL-6 receptor antagonist monoclonal antibody commonly used to treat inflammatory diseases, including rheumatoid arthritis. Elevations in the liver injury biomarker ALT are commonly seen in patients administered TCZ.

	ALT > 1-3xULN	ALT > 3-5xULN	ALT > 5xULN
TCZ 8 mg/kg (n=269)[1]	33.8%	1.1%	0.7%

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RESULTS

Exposure predictions for Tocilizumab

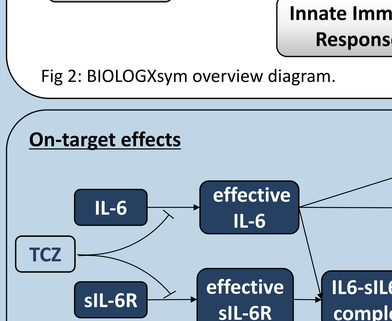


Fig. 1: Simulated plasma (solid blue line) and liver interstitium (dashed red line) concentration of 8 mg/kg TCZ administered intravenously (i.v.) every four weeks (Q4W).

To account for exposure, we predict the interstitial liver concentration for 8 mg/kg i.v. TCZ Q4W using GastroPlus (Fig. 1).

Mechanistic Model of Tocilizumab Effects on Liver

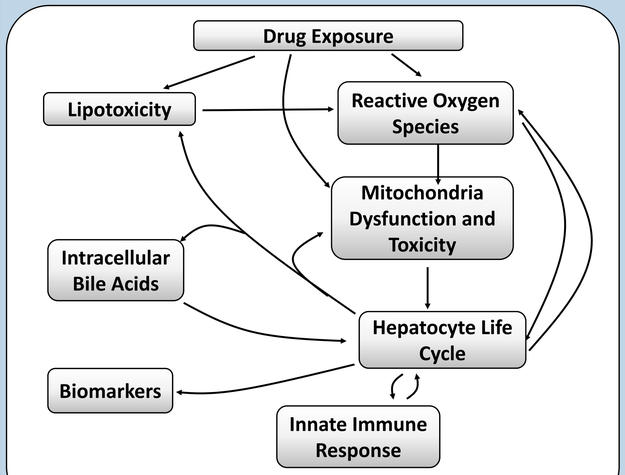


Fig 2: BIOLOGXsym overview diagram.

Fig 3: Network of on- and off- target effects included in BIOLOGXsym model of TCZ. On-target effects include major downstream effects of IL-6 signaling through both membrane and soluble IL-6 receptor. Off-target effects include elevations in reactive oxygen species (ROS) and steatosis.

Simulation Scheme

To predict the hepatotoxicity of TCZ, we determine the peak ALT level during treatment with 8 mg/kg i.v. TCZ Q4W for twelve weeks. In addition, we evaluate how TCZ-driven changes in CYP activity could impact toxicity during drug co-administration. To do this, we simulate co-administration of TCZ with 1 g acetaminophen (APAP), a compound with CYP-dependent toxicity, given four times daily. We also investigate how on- vs off-target effects of TCZ drive hepatotoxicity by simulating TCZ+APAP with only on-target or only off-target effects (defined in Fig. 3). In each case, we evaluate four simulated individuals (SimCohorts™) with elevated IL-6 compared to healthy levels, to mimic an inflammatory disease state.

Hepatotoxicity of Tocilizumab

We simulated 8 mg/kg i.v. TCZ administration in a cohort (n=4) of individuals with elevated IL-6 levels at baseline. Alone, TCZ led to mild ALT elevations. Co-administered with APAP, TCZ led to ALT elevations in all patients. Simulating only on-target effects or only off-target effects from TCZ also demonstrates ALT elevations in most patients.

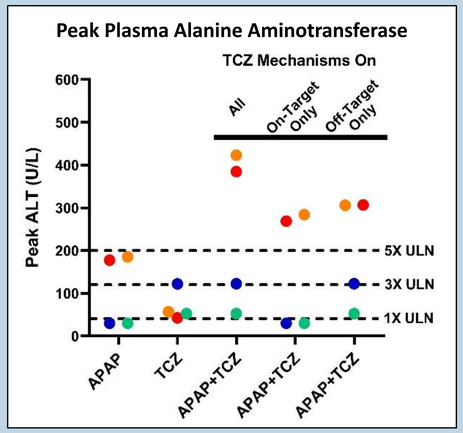
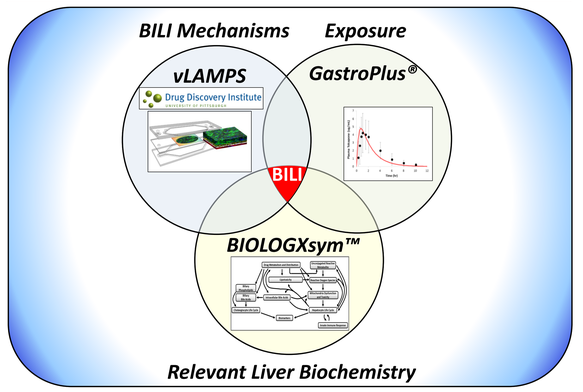


Fig 4: Simulated peak ALT responses in the SimCohorts (n=4) administered APAP alone, TCZ alone, or APAP+TCZ. The impact of on-target and off-target TCZ mechanisms was explored for APAP+TCZ simulations. Dotted horizontal lines indicate upper limit of normal (ULN) multiples (1x, 3x and 5x) of ALT.

Summary

- Developed BIOLOGXsym to predict BILI liability
- Modeled on- and off-target effects of TCZ, supported by outputs from a microphysiology system
- Simulations of TCZ in individuals with elevated IL-6 show modest ALT increases, consistent with clinical data
- Co-administration of TCZ with APAP unmasks APAP toxicity, leading to more significant ALT elevations in all simulated individuals compared to either compound alone
- Simulations including only on- or off-target effects of TCZ also produce ALT increases during co-administration with APAP
  - Supports both changes in CYP activity and ROS accumulation as mechanisms

METHODS



BILI Mechanisms

- 1.6 µM TCZ +/- 3 ng/mL IL-6 applied to human vascularized Liver Acinus MicroPhysiology Systems (vLAMPS) for 10 days
- Key outputs, including ROS and CYP3A4 activity, were quantified at Day 7
- Steatosis measured at Day 10 of 1.6 µM TCZ administration

Relevant Liver Biochemistry

- Constructed BIOLOGXsym, a QST model, representing relevant liver biochemistry and toxicity mechanisms
- Modeled IL-6 signaling through both soluble and membrane-bound receptors, including key downstream effects pertaining to hepatocytes
- Parameterized major on- and off-target effects of TCZ using data available from vLAMPS and literature[2-4]

Exposure

- PBPK model for TCZ constructed in biologics module of GastroPlus to predict exposure in liver interstitium[2-3]

For more details, visit:

- Poster 4445/P445 (vLAMPS overview)
- Poster 4661/P707 (GGF2 representation in BIOLOGXsym)

CONCLUSION

Our QST model, BIOLOGXsym, can predict potential hepatotoxicity of biologics. The methods used here are generalizable, offering an approach to rapidly evaluate the liver safety of new biologics. In addition, we can gain insights into main mechanisms of toxicity and potential drug-drug interactions.

REFERENCES

[1] Schiff 2011, [2] Nishimoto 2003, [3] Nishimoto 2008, [4] Long 2016

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