Simulations using BIOLOGXsym demonstrate hepatotoxic potential of Tocilizumab through both on- and off-target effects

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MIDD+22 Model Informed Drug Development +

PURPOSE

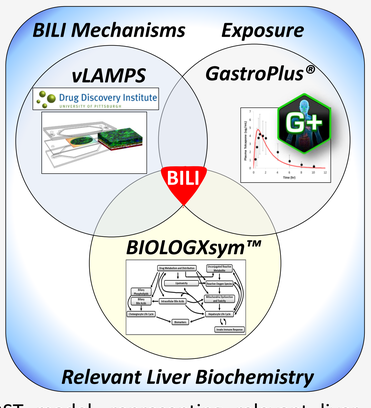
Biologics can address many unmet clinical needs. However, biologic-induced liver injury (BILI) cases can slow therapeutic development or require frequent monitoring of liver function. Here we developed BIOLOGXsym™, a novel quantitative systems toxicology (QST) platform, to predict the potential BILI liability of new biologics.

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

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

METHODS

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



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

RESULTS

Exposure predictions for Tocilizumab

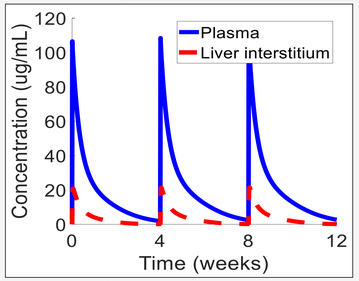


Fig. 1: Simulated plasma (solid blue line) and liver interstitium (dashed red line) concentration of 8 mg/kg TCZ administered intravenously every four weeks (Q4W).

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

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) 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.

Mechanistic Model of Tocilizumab Effects on Liver

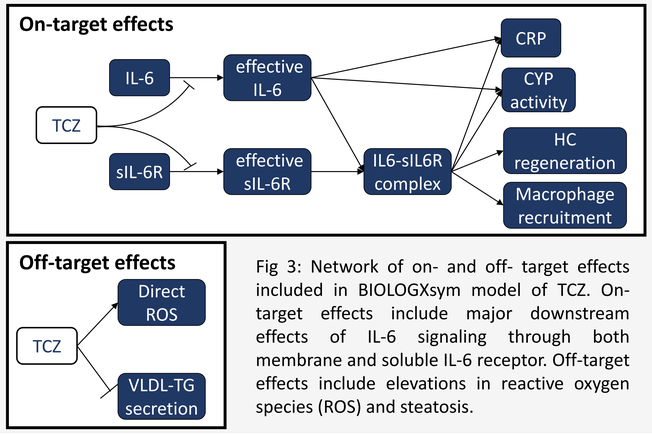


Fig 3: Network of on- and off- target effects included in BIOLOGXsym model of TCZ. On-target effects include major downstream effects of IL-6 signaling through both membrane and soluble IL-6 receptor. Off-target effects include elevations in reactive oxygen species (ROS) and steatosis.

vLAMPS

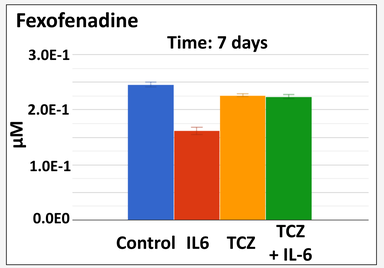


Fig 2: CYP3A4 activity, measured by fexofenadine production, in vLAMPS in response to TCZ +/- IL-6 after 7 days. CYP3A4 activity decreases with added IL-6 compared to control. Adding TCZ restores activity.

Experiments using vLAMPS provided data to parameterize key TCZ effects on hepatocytes, including CYP3A4 activity (Fig. 2). Additional outputs include ROS and steatosis (data presentation SOT 2022, presentation available upon request March 27, 2022).

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.

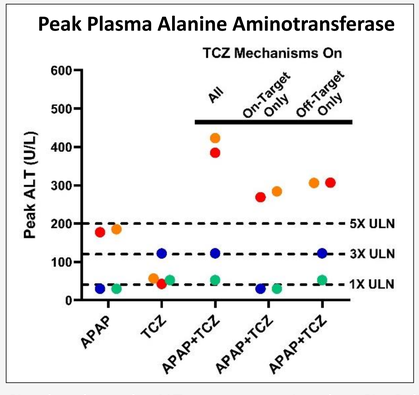


Fig 4: Simulated peak ALT responses in the SimCohorts (n=4) administered APAP alone, TCZ alone, or APAP+TCZ. The impact of on-target and off-target TCZ mechanisms was explored for APAP+TCZ simulations. Dotted horizontal lines indicate upper limit of normal (ULN) multiples (1x, 3x and 5x) of peak ALT.

SUMMARY

- Developed BIOLOGXsym to predict BILI for new biologics
- 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 leads 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 buildup as mechanisms

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

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[2] Nishimoto 2003
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[4] Long 2016

FUNDING

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