Simulated CD8⁺ T Cell-Mediated Liver Injury During Ipilimumab Administration in a Simulated Population (SimPops®) Demonstrates Profiles Consistent with Observed Clinical Data

Conner Sandefur, Lara Clemens, Michael Kelley, James J. Beaudoin, Christina Battista, Scott Q. Siler, Lisl K.M. Shoda, Brett A. Howell, Kyunghee Yang
Quantitative Systems Pharmacology Solutions, Simulations Plus Inc., Research Triangle Park, NC
Contact: conner.sandefur@simulations-plus.com

OBJECTIVE

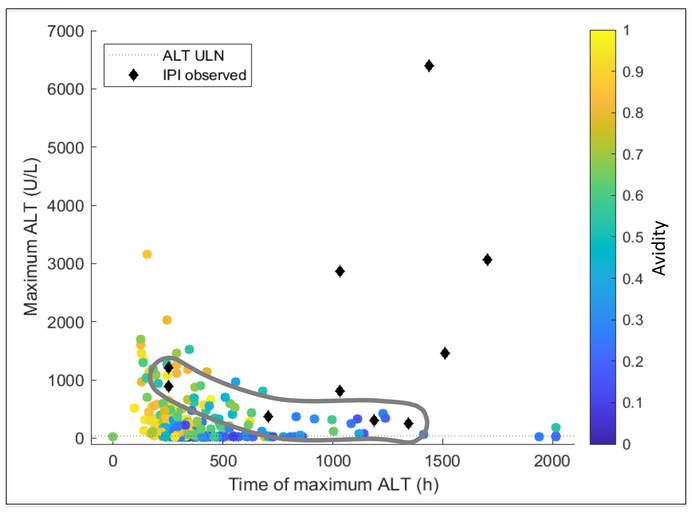
Immune checkpoint inhibitors (ICIs) have revolutionized treatment of various cancers. They act by releasing the brakes on immune responses to permit immune-mediated tumor cell killing. Many ICIs are also associated with immune-related adverse events (irAEs), including liver injury[1]. Of patients treated with the ICI ipilimumab, 7% exhibit signs of liver injury, e.g., alanine aminotransferase (ALT) elevations[2]. Ipilimumab targets CTLA-4, an inhibitory cell surface protein expressed on activated T cells. One hypothesis for ipilimumab-mediated liver injury is that CTLA-4 inhibition is permissive for normally suppressed de novo T cell responses to liver antigens. We applied a quantitative systems toxicology (QST) model of biologics-mediated liver injury (BIOLOGXsym™) to investigate this hypothesis.

METHODS

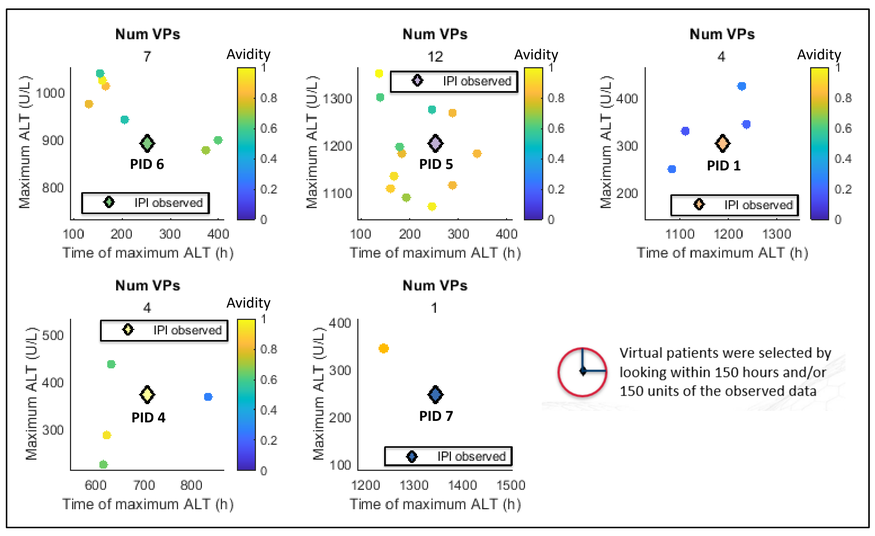
- BIOLOGXsym represents liver parenchymal and nonparenchymal cell dynamics, such as innate and adaptive immune responses. The modeled adaptive immune response leverages CD8⁺ T cell responses specific for hepatocyte-expressed antigen as previously described[3,4].
- Ipilimumab was modeled as inhibiting early regulatory signaling in the T cell activation cascade, leading to a net increase in T cell avidity for hepatocyte-expressed antigen and aberrant expansion of hepatocyte specific CD8⁺ T cells.
- Variability in ipilimumab pharmacokinetics, patient anthropometric characteristics, and liver biochemistry were not included.

RESULTS

1 ALT results of simulated ipilimumab administration in a SimPops (N>500) developed to capture variability in CD8⁺ T cell numbers, differentiation and killing rates, regulatory inhibition of CD8⁺ proliferation, antigen presentation, and T cell receptor avidity, including overrepresentation of susceptible patients.

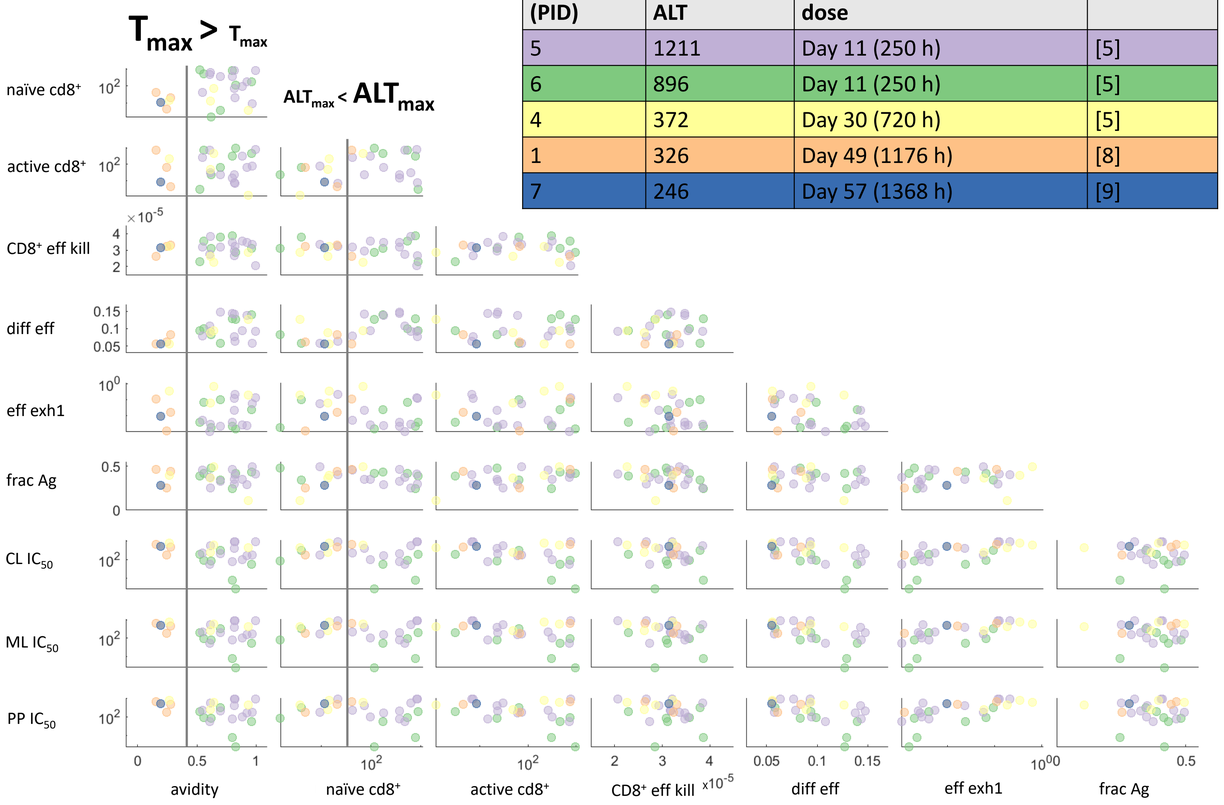


2 Virtual patients (VPs) recapitulating five clinically reported cases of ipilimumab (IPI) liver injury were identified.

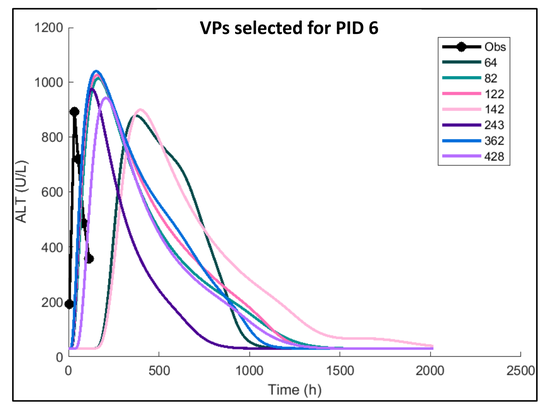


3 Pairwise analysis of VP parameters demonstrated associations between lower avidity and delayed peak ALT and higher initial naïve CD8⁺ T cell numbers and higher peak ALT.

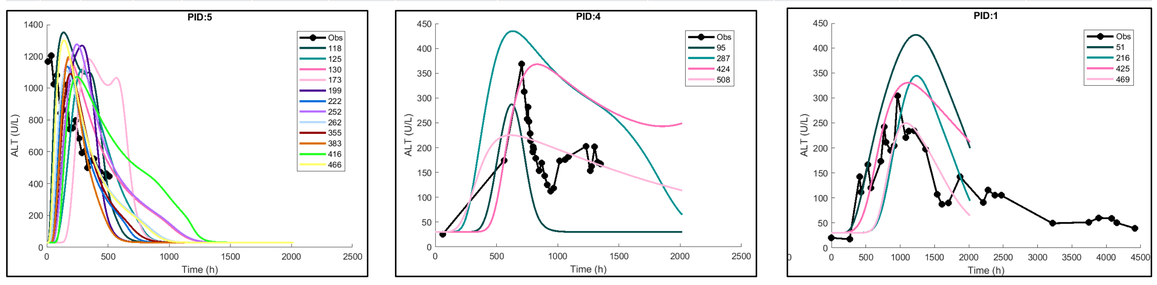
Patient Identifier (PID)	Patient Maximum ALT	Time of Maximum ALT (T_{max}) from first ipilimumab dose	Reference
5	1211	Day 11 (250 h)	[5]
6	896	Day 11 (250 h)	[5]
4	372	Day 30 (720 h)	[5]
1	326	Day 49 (1176 h)	[8]
7	246	Day 57 (1368 h)	[9]



4 Simulated ALT dynamics were confirmed to be similar to reported observations, where dynamic variability can be interrogated by parameter analysis.



PID	VP ID	Max ALT (U/L)	T_{max} (h)	Avidity	CD8⁺ T Cell Baseline Fold Change		CD8⁺ killing scalar (*cd8 eff kill*)	CD8⁺ effector differentiation scalar (*diff eff*)	CD8⁺ conversion rate scalar of effector to exhausted 1 (*eff exh1*)	CD8⁺ killing scalar (*cd8 eff kill*)	Fraction Antigen Presenting Hepatocytes	Regional CD8⁺ proliferation feedback IC_{50} (1e3 cells)
					Naïve	Active						
6	64	877	374	0.70	3.9	65	3.8E-5	0.06	0.095	3.8E-5	0.35	317
6	82	1013	165	0.88	115	952	2.8E-5	0.13	0.002	2.8E-5	0.42	2.6
6	122	1025	159	0.96	174	455	3.1E-5	0.14	0.024	3.1E-5	0.43	55
6	142	899	398	0.62	1.5	23	3.1E-5	0.08	0.002	3.1E-5	0.48	80
6	243	974	130	0.80	771	306	3.9E-5	0.13	0.002	3.9E-5	0.25	7.8
6	362	1039	153	0.57	535	748	3.6E-5	0.01	0.066	3.6E-5	0.42	93
6	428	942	206	0.53	874	3.1	2.3E-5	0.09	0.004	2.3E-5	0.39	196



CONCLUSION

The undeniable benefit of ICIs is tempered by the risk of irAEs, which are poorly understood and therefore difficult to avoid. These results provide an initial demonstration of how QST can be applied to explore mechanistic hypotheses and identify key drivers of ICI liver injury. Further, these results set the stage for collaborations to generate additional data to inform key parameters, confirm/refute assumptions, and improve our understanding of these important safety concerns. Supported by NIH-R44TR003535.

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