Quantitative Systems Pharmacology (QSP) Model Predicts Lack of Efficacy for Cenicriviroc, a CCR2/5 Antagonist, in NAFLD/NASH Patients

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DIGITAL EXPERIENCE

INTRODUCTION

A phase 3 clinical trial (AURORA) for cenicriviroc (CVC), a CC chemokine receptor 2 and 5 (CCR2/5) antagonist, was recently terminated due to lack of efficacy[1].CVC was thought to suppress the inflammatory response and decrease collagen deposition by reducing recruitment of macrophages and activation of hepatic stellate cells,respectively.[2,3] CVC exposure and its effects were implemented within a quantitative systems pharmacology (QSP) model, NAFLDsym (Figure 1), to see if simulations captured the lack of efficacy observed in the AURORA study and to explore if efficacy was limited by the potency of CVC in NAFLD/NASH patients.

AIM

- Construct a representation for CVC in NAFLDsym using publicly-available *in vivo* and *in vitro* data to predict efficacy of CVC as a treatment for NAFLD/NASH patients
- Determine if CCR2/5 antagonists have the potential to provide therapeutic efficacy
  - Investigate sensitivity of model outcomes to the potency of target effects and determine if a more potent CCR2/5 antagonist may have the potential to improve NAFLD/NASH outcomes

MATERIALS & METHODS

Simulations using *in vitro* estimates for CVC potency

- A physiologically-based pharmacokinetic (PBPK) representation of CVC was constructed (Figure 2)
- Published literature provided *in vitro* estimates for CVC potency on hepatic stellate cell activation and macrophage recruitment[2,3]; *in vitro* derived values were used as inputs for CVC exposure-dependent effects in NAFLDsym
- Simulations were conducted in virtual populations with NASH patients receiving 150mg QD for 104 weeks

Sensitivity analysis

- IC_{50} values derived from literature were scaled to increase potency of CCR2/5 antagonist
- Simulations were conducted in virtual populations with NASH patients receiving 150 mg QD for 104 weeks

RESULTS

NAFLDsym Overview

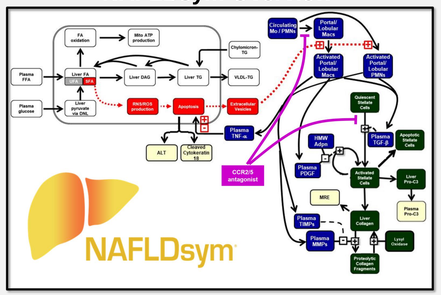
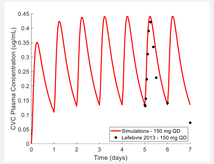


Figure 1. Overview of NASH mechanisms included in NAFLDsym, with CCR2/5 antagonist indicated by magenta lines.

Simulation results using *in vitro* estimates for CVC potency

Simulated CVC 150 mg QD for 2-years	Mean Percent Change from Pre-treatment
Liver fat (%)	0 ± 0
Plasma ALT (U/L)	0 ± 0
NAS (score)	0 ± 0
Fibrosis Score (stage)	-1 ± 8
CPA (%)	0 ± 3
Pro-C3 (ng/mL)	-1 ± 0
Plasma TG (mM)	0 ± 0
Body weight (kg)	0 ± 0

Table 1. Mean percent change from pre-treatment values for NAFLD/NASH outcomes in simulations using *in vitro* estimates of CVC potency. NAFLDsym simulation results from a NAFLD/NASH F3 Cohort (n=73) predict no to minimal improvement in fibrosis or steatosis outcomes.



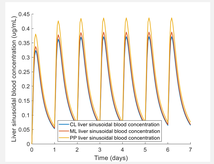


Figure 2. A PBPK model for CVC was constructed using the PBPK submodel in DILIsym®. Parameter values for the PBPK model were derived from literature, where possible, or optimized to published plasma profiles (left).[4,5,6] PBPK predictions for liver sinusoidal concentrations in 3 zones of liver (right) were incorporated into NAFLDsym to drive CVC effects.

Simulations with increased CVC potency

Simulated CVC 150 mg QD for 2-years	Mean Percent Change from Pre-treatment			
	1x potency	2x potency	10x potency	100x potency
Liver fat (%)	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Plasma ALT (U/L)	0 ± 0	0 ± 0	1 ± 0	1 ± 1
NAS (score)	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Fibrosis Score (stage)	-1 ± 8	-1 ± 9	-5 ± 12	-15 ± 17
CPA (%)	0 ± 3	-1 ± 3	-5 ± 3	-18 ± 4
Pro-C3 (ng/mL)	-1 ± 0	-2 ± 1	-5 ± 1	-15 ± 1
Plasma TG (mM)	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Body weight (kg)	0 ± 0	0 ± 0	0 ± 0	0 ± 0

Table 2. Mean percent change from pre-treatment values for NAFLD/NASH outcomes in simulations exploring sensitivity to IC_{50} values affecting CVC potency. Simulation results in NAFLD/NASH F3 cohort (n=73) predict possibility for efficacy with increased potency.

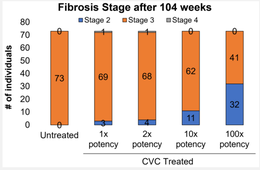


Figure 3. NAFLDsym simulation results indicating an improvement in fibrosis score with an increase in potency, i.e., a reduction in IC_{50} values. Results suggest that pathways targeted by CCR2/5 antagonists can lead to a reduction in fibrosis score with higher potency than estimated for CVC.

CONCLUSION

- Simulations using the *in vitro* estimates of CVC potency reproduced lack of CVC efficacy in NAFLD/NASH patients observed in the AURORA study (Table 1)
  - Although significant changes in clinical fibrosis and inflammatory endpoints were not predicted with CVC simulations, simulations did reflect reductions in recruited macrophages (*not shown*)
- Sensitivity analysis results predict >10x higher potency would have been required to achieve fibrosis stage response rates with CVC (Table 2)
  - Improvement by at least one fibrosis stage in 15% of the simulated population is predicted with a 10x increase in potency (Figure 3)
  - Results suggest that the potency of CVC may have limited its ability to demonstrate efficacy in NAFLD/NASH patients

REFERENCES

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DISCLOSURES

CB, LKMS, GTG, SQS are employees of Simulations Plus.

CONTACT INFORMATION

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