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

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INTRODUCTION

A phase 3 clinical trial (AURORA) for cenirciviroc (CVC), a CC chemokine receptor 2 and 5 (CCR2/5) antagonist, was recently terminated due to lack of efficacy. CVC was thought to suppress the inflammatory responses and decrease collagen deposition by reducing recruitment of macrophages and activation of hepatic stellate cells respectively.1-3 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 recruitment2; 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
- IC50 values derived from literature were scaled to increase potency of CCR2/5 antagonist
- Simulations were conducted in virtual populations with NASH patients receiving 150mg QD for 104 weeks

RESULTS

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=79) predict no to minimal improvement in fibrosis or steatosis outcomes.

Table 2. Mean percent change from pre-treatment values for NAFLD/NASH outcomes in simulations exploring sensitivity to IC50 values affecting CVC potency. Simulation results in NAFLD/NASH F3 Cohort (n=73) predict possibility for efficacy with increased potency.

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 be 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


DISCLOSURES

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

CONTACT INFORMATION

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