Enhancing the Utility of Systems Pharmacology Modeling in Pharmaceutical R&D: Lessons from the Development of a PCSK9 Inhibitor Model

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Abstract

Major objective: To contribute insights into systems pharmacology (SP) modeling in developing a PCSK9 inhibitor (PCSK9i) for lowering LDL-C.

Methods: A classical QSP framework was developed to explain variability in clinical response to PCSK9 inhibitors (PCSK9i). The approach, named Virtual Patient Definitions (VPDs), is a novel methodology that develops populations of virtual patients using a QSP framework and a statistical methodology. VPDs are used to inform clinical trial designs, evaluate patient selection criteria, and design the pharmacological dosing regimens.

Results: Several key elements of alirocumab activity were captured in our model (Figure 1). Alirocumab PK (Figure 2). Lipid Metabolism and Plaque Dynamics (Figure 3).

Conclusions

A QSP framework developed to explain variability in clinical response to PCSK9i, and a novel approach to VPDs, was applied to support clinical trial design. The findings provide a proof-of-concept that QSP modeling and VPDs can be used in clinical trials to improve trial design and drug development.

References


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Disclosures

This study was supported by Sanofi and Regeneron. The authors have no other relevant conflicts of interest to declare.

Lipid Metabolism and Plaque Dynamics

- A whole-body systems pharmacology model of lipid metabolism and atherosclerotic plaque dynamics is being developed.
- Goals of systems model:
  -Capture several key elements of alirocumab activity (Figure 1):
  -A QSP framework developed to explain variability in treatment response, and to facilitate QSP simulation capabilities was applied

Lipid Module Major Elements

- Hepatic Lipid Metabolism and recycling.
- Cholesterol output through VLDL-C and EHC.
- Cholesterol input via synthesis, LDL-C/VLDL-C/HDL-C uptake, dietary intake, and EHC.
- Effect of intracellular cholesterol level on SREBP-regulated genes.
- Cholestasis

Alirocumab Multiple-Dose Effect on Lipid Profile (Figure 4)

- Alirocumab dose study performed at Stein et al. (2012) closer towards predictive science.
- Preclinical modeling was used for virtual patients to reflect the diversity of human responses, such as in vitro PK/PD and PK/PD simulation.
- Model improvements were made to alirocumab PK (Figure 2).
- Procedure for generation of VPs for alirocumab: Patient population identifies the largest number of VPs with different age groups, sex, race, weight, height.
- Parameters used for virtual patient definitions

Steps to Virtual Patient Creation and Simulation

- For a given clinical phenotype of interest (e.g., age, gender, race), identify biological and/or environmental factors.
- Essential variables to define virtual populations: age, gender, race, weight, height, baseline lipids.
- Virtual patients of interest can be simulated to monitor the effect of combination therapy in the phenotype represented by the virtual population.

Conclusions

- A QSP framework developed to explain variability in clinical response to PCSK9i, and a novel approach to VPDs, was applied to support clinical trial design. The findings provide a proof-of-concept that QSP modeling and VPDs can be used in clinical trials to improve trial design and drug development.