Introduction

• Variability in patient responses to drugs is a fact of life in the pharmaceutical industry.
• Retrospective analysis may identify covariates associated with response, and population modeling approaches allow for extrapolation under appropriate conditions.
• Only mechanistic modeling enables exploration of the underlying biological drivers of variability retrospectively and prospectively.

Objectives

• Provide an overview of mechanistic modeling and Virtual Patients (VPs) in Rosa’s PhysioPD™ Platforms.
• Show three concrete examples of using VPs to explore responder / non-responder hypotheses.
• Illustrate the utility of this approach to de-risk efficient development of compounds and treatments.

Methods

PhysioPD™ Research Platforms are mechanistic, quantitative models that elucidate the connection between mechanisms and outcomes.

• Rosa’s PhysioPD™ Platforms are graphical, mathematical models of biology, a type of Quantitative Systems Pharmacology (QSP).
• PhysioPD Platforms combine engineering approaches and scientific data analysis to clarify complex physiology and drug interactions.
• PhysioPD Platforms are qualified in accordance with Rosa’s Model Qualification Method™ (MQM) (Figure 1).
• Virtual experiments in VPs can be used to explore the impact of biological variability on response to existing and novel therapy.
• This enables informed extrapolation of existing data to de-risk development.

Results: Atopic Dermatitis

Modeling helped explore possible pathophysiological variability that may explain variable response.

• The client wanted to understand how a novel treatment may compare to dupilumab.
• An Atopic Dermatitis PhysioPD Platform provided a graphical and mathematical model of disease processes.
• A virtual population (VPop) with variability relevant for dupilumab and the novel therapy was developed.
  o Hypotheses for possible mechanistic causes of variable response to dupilumab were generated with client input.
  o All hypotheses were backed by extensive literature investigation.
  o Model-based analysis identified the most sensitive variabilities.
  o VPop virtual trial recapitulated results from Simpson, et al. (Figure 2) and other relevant test therapies.
• Plausible variability relevant for the novel treatment was also explored.
  o Hypotheses were informed by nonclinical data as well as inferences from existing therapies with partially overlapping mechanisms of action (MOAs).
  o Individual VPs and VPop responses to existing therapies were simulated and compared to data.

Results: Cardiovascular Disease

VPs with high / low statin and anti-PCSK9 responses supported investigation of LDL and plaque outcomes.

• A CVD Platform was developed as described in Ming, et al. (Figure 5) to investigate alirocumab effects on different patients.
• A subset of 14 sensitive parameters was identified through biological reasoning and sensitivity analysis.
• VPs differed from each other only in these 14 parameters and featured the desired response profiles (Figure 6).
• Each VP’s parameters were within data constraints, and additional testing included other therapies and comparisons to plaque volume and composition data.
• VPs could then serve to test a range of protocols and predict plaque outcomes not yet available for alirocumab.

Conclusions

• QSP models such as Rosa’s PhysioPD Research Platforms enable exploration of the mechanistic causes of clinical variability.
• Because Platforms draw on dozens of data sources to constrain VP parameters, such analysis can be conducted before clinical data become available.
• Appropriate use of VPs to investigate possible causes of clinical variability reduces development risk.

References


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