Quantitative systems pharmacology model of amyloid pathology allows for clinical endpoint prediction and hypothesis testing
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Objectives: Different treatments of Alzheimer’s disease (AD) targeting amyloid (Ab) are under development and in clinical trials now. We apply QSP model of amyloid pathology for quantitative simulation of longitudinal biomarker dynamics for validation of different Ab toxicity hypothesis using trial data.

Methods: The translational model of Ab pathology describes Ab production, clearance and distribution in brain, CSF, plasma and other tissues, as well as aggregation in brain. It was calibrated and validated on multiple dynamic and steady state data for mouse, monkey and human. PET data were used for external verification. Three assumptions of relationship between Ab and Adas-cog score are used: (i) proportional or (ii) threshold Ab influence on Adas-cog score and (iii) Ab functional obligatoriness for neurons [1]. Formulation of hypotheses as explicit algebraic functions of model predicted Ab concentration allows for description of the disease progression corresponding to the observed longitudinal sporadic AD data.

Results: Amyloid secretion inhibition (SI) by 20 and 50 % and activation of insoluble Ab destruction (DA) to 150% were simulated for two ages of therapy start: 70 (early) and 75 (late) years. Model predictions revealed that for early therapy start no significant difference with placebo group would be seen for at least two years for all toxicity hypotheses. Amyloid obligatoriness assumption predict cognitive decline at the beginning of late start SI compensated only after two years with toxic form depletion. Destruction activation is less dangerous in this respect, but requires a year to observe at least 4 points of Adas-cog score diff vs placebo. Under the proportional toxicity and Ab obligatoriness hypothesis model predictions approximately correspond to the published results of avagacestat [2] and bapineusumab [3] trials.

Conclusions: Mechanistic model allows framework for amyloid toxicity hypothesis formulation and prediction of clinical trial results.

References:

![Graph showing biomarker value differences and treatment effects](image-url)
Figure 1: Comparison of model simulations (validation) with bapineumab trial results: 95% confidence intervals for observations and model simulations.