A step-wise analysis of multiple biomarkers drives the development of a Semi-Mechanistic Comprehensive Model. Application to modulation of Amyloid-β.

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Background

•Technical challenges

Integrating different biomarkers to model a biological cascade of responses results in technical challenges in NONMEM, such as model stability issues and parameter identifiably.

•Alzheimer's Disease (AD): The Amyloid Hypothesis

Build-up of amyloid-β-peptide and its associated plaques in brain is hypothesized to lead to development of AD. Aβ peptides are generated by sequential cleavage from amyloid precursor protein (APP) by β-site APP-cleaving enzyme and γ-secretase in the amyloidogenic pathway. Aβ peptide concentration in CSF is a therapeutic target for AD, with the potential for disease modifying effect by reducing Aβ levels.

Objective

- To develop an approach to build a comprehensive model describing biomarker inter-relationships and their responses.
- Describe the Aβ response to 2 inhibitors acting on different sequence in the Aβ processing pathway in a comprehensive model, as an aid to drug development targeting AD.

Methods

A step-wise modeling approach was followed:

I. Each biomarker-inhibitor combination was evaluated by separate models.

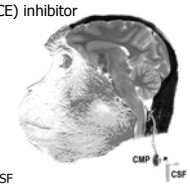
II. By sequentially adding each biomarker (sAPPβ, Aβ40, Aβ42, sAPPα), a comprehensive biomarker model was developed for BACE inhibitor, using one drug effect term to account for response of all 4 biomarkers.

III. Aβ40 and Aβ42 response to GS and BACE inhibitor were investigated simultaneously.

IV. Aβ40 and Aβ42 response to GS inhibitor was integrated into the comprehensive model.

Compounds

- β-site APP-cleaving enzyme (BACE) inhibitor
- γ-secretase (GS) inhibitor



Data

Study 1 Compound: BACE inhibitor

- Measured:
  - PK: plasma and CSF concentrations
  - PD: sAPPβ, Aβ40, Aβ42, sAPPα in CSF
- Dose-ranging SD, 4 period cross-over
  - Vehicle and active treatment (3 different doses)
- Cisterna-magna-ported rhesus monkeys (n=6)

Study 2 [1] Compound: GS inhibitor

- Measured:
  - PK: plasma and CSF concentrations
  - PD: Aβ40 and Aβ42 in CSF
- Dose-ranging SD, 3 period cross-over
  - Vehicle and active treatment (2 different doses)
- Cisterna-magna-ported rhesus monkeys (n=6)

Study 3 [1] Compound: GS inhibitor

- Measured:
  - PK: plasma and CSF concentrations
  - PD: Aβ40 and Aβ42 in CSF
- SD, longer term sample collection
- Cisterna-magna-ported rhesus monkeys (n=6)

Additional baseline data

- Measured:
  - PD: Aβ40, Aβ42, sAPPβ, sAPPα in CSF
- Vehicle
- Cisterna-magna-ported rhesus monkeys (n=6)

Model

- Brain-concentration profiles, derived from individual plasma PK scaled by the ratio AUC_{csf}/AUC_{plasma}, were used as driver of biomarker response.
- Drugs act on different steps in the cascade:
  - GS inhibitor blocks Aβ40 and Aβ42 production
  - BACE inhibitor blocks sAPPβ and C99 production

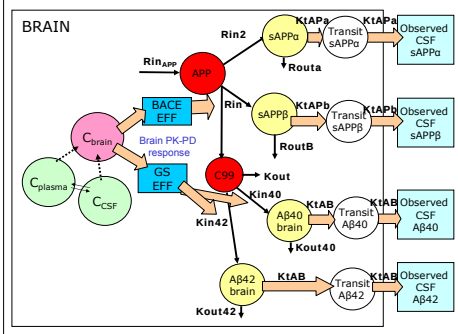


Figure 1. Semi-mechanistic comprehensive model to describe the modulation of Aβ.

Abbreviations:

APP: amyloid-β precursor protein; *Aβ:* amyloid-β-peptide; *Ccsf:* drug concentration in CSF; *Cbrain:* drug concentration in brain; *Cplasma:* drug concentration in plasma; *Kin40:* Aβ40 formation rate; *Kin42:* Aβ42 formation rate; *Kout:* "C99" degradation rate; *Kout40:* Aβ40 degradation rate; *Kout42:* Aβ42 degradation rate; *KtAPa:* transit rate sAPPα from brain to CSF; *KtAPb:* transit rate sAPPβ from brain to CSF; *KtAB:* transit rate Aβ from brain to CSF; *RinAPP:* production flux of new APP; *Rin:* sAPPβ and C99 formation rate; *Rin2:* sAPPα formation rate; *Routa:* sAPPα degradation rate; *Routb:* sAPPβ degradation rate

Results

I. For each biomarker-inhibitor combination comparable model structures and IC50 estimates were obtained (results not shown).

II. An indirect response model described sAPPβ response to BACE inhibitor. The sAPPβ pool was then used as moderator to describe the baseline and behavior of Aβ40 and Aβ42 in presence of BACE inhibitor. Next, sAPPα was incorporated in the model. A precursor pool APP, shared by sAPPα and sAPPβ, was introduced to describe all 4 biomarkers with one common drug effect. The effect of BACE inhibitor was build-in the model as inhibition of loss of this precursor pool. Incorporating different transit rates for transit compartments from brain to CSF allowed the rate of onset of response to differ for each biomarker. Drug-specific and system-specific parameters were not correlated and all system-specific parameters could be estimated with good precision. An adequate description of all 4 biomarkers was obtained *(figure 2)*.

III. Using a subset of the data Aβ40 and Aβ42 response to GS and BACE inhibitor were described by a model with a sAPPβ precursor pool. Introduction of a C99 compartment allowed simultaneous description of response to both inhibitors. The effect of BACE inhibitor was built in the model as inhibition of production of sAPPβ and C99 precursor pool. The effect of GS inhibitor was incorporated as inhibition of formation of Aβ from C99. An adequate description of Aβ42 response was obtained. Aβ40 response to BACE inhibitor was slightly under predicted, which is hypothesized to be related to study differences. Not all parameters could be identified on this subset of the data (results not shown).

IV. The response of Aβ40 and Aβ42 to GS was built-in the comprehensive model of step II, with inclusion of a C99 compartment as identified in step III. Additional baseline data was added to the dataset to enhance model stability. The data from studies 1, 2, and 3 could be described by the model as depicted in figure 1 *(figure 4)*. The under prediction of Aβ40 response to BACE inhibitor is similar as was observed in step III. The dynamics of APP and C99 in the comprehensive model were investigated in a simulation *(figure 3)*, which shows a built-up of APP in response to BACE inhibitor and a built-up of C99 in response to GS inhibitor.

Step II: Description study 1

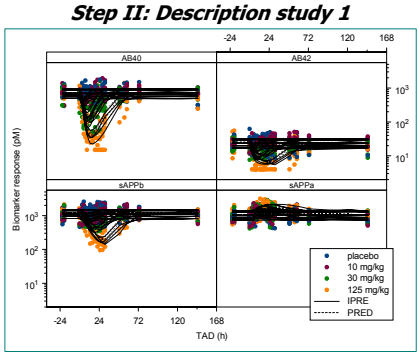


Figure 2. Description of Aβ40, Aβ42, sAPPβ and sAPPα response to BACE inhibitor by the comprehensive BACE model from step II.

Step IV: Simulation

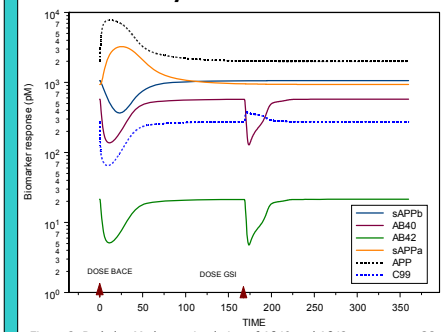


Figure 3. Berkeley Madonna simulation of Aβ40 and Aβ42 response to GS inhibitor and Aβ40, Aβ42, sAPPβ and sAPPα response to BACE inhibitor with the model as depicted in figure 1.

Step IV: Description studies 1, 2 and 3

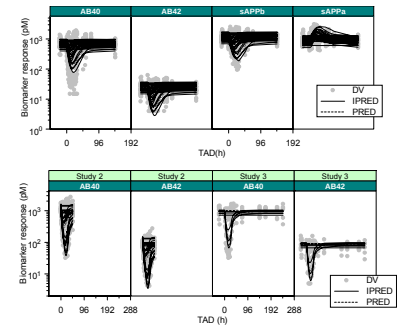


Figure 4. Description of Aβ40 and Aβ42 response to GS inhibitor (bottom, studies 2 and 3) and Aβ40, Aβ42, sAPPβ and sAPPα response to BACE inhibitor (top, study 1) by the semi-mechanistic comprehensive model.

Conclusions & Perspectives

- A step-wise modeling approach was developed to facilitate the build of a comprehensive model for describing a biological cascade of responses.
- By analyzing effects of inhibitors acting on different steps in the cascade the dynamics of the inter-relationship between biomarkers could be characterized.
- The comprehensive Aβ model quantified the response of the biomarkers and gives insight into the mechanism of the system.
- Drug- and system-specific parameters could be distinguished. Thus, it is anticipated that the comprehensive Aβ model will aid further development of drugs targeting AD.
- The comprehensive Aβ model forms the first step in developing a translational platform model to predict possible Aβ response in human using preclinical data.

Find the poster here:

References

[1] Cook, J.J., Wildsmith, K.R., Gilberto, D.B., Holahan, M.A., Kinney, G.G., Mathers, P.D., Michener, M.S., Price, E.A., Shearman, M.S., Simon, A.J., Wang, J.X., Wu,G.,Yarasheski, K.E., Bateman, R.J. (2010) Acute γ-Secretase Inhibition of Nonhuman Primate CNS Shifts Amyloid Precursor Protein (APP) Metabolism from Amyloid-β Production to Alternative APP Fragments without Amyloid-β Rebound. J. Neuroscience 30 (19):6743-6750