Modeling of amyloid-β accumulation in subjects at risk of Alzheimer’s disease under BACE inhibition treatment

Etienne Pigeolet1, Konstantinos Biliouris3, Ulf Neumann3, Alexandra Urusova2, Oleg Demin2 and Tatiana Karelina2

1Pharmacometrics, Novartis, Basel, Switzerland, 2InSysBio, Moscow, Russia, 3Novartis Institute for Biological Research, Cambridge, USA/ Basel, Switzerland

Alzheimer’s disease and Amyloid plaques

• An important pathological feature of Alzheimer’s disease (AD) is the presence of deposits forming amyloid plaques in the brain cortex of affected individuals. These plaques are constituted of aggregated fibrils of amyloid-β (Aβ) peptides that derive from the amyloid precursor protein (APP)[1].
• The amyloid cascade hypothesis states that deposition of (Aβ) is a very early event in the pathogenesis of AD and will ultimately accelerate neurodegeneration and dementia of the Alzheimer type [2].

Beta-site APP-Cleaving Enzyme (BACE)

• BACE-1 is an enzyme involved in the processing of APP to produce Aβ.
• BACE inhibitors are currently under clinical development: by reducing Aβ generation they offer the promise of disease modification in AD.
• Current consensus is that treatment targeting Aβ should be administered well before the clinical diagnosis of the disease but the impact of Aβ reduction on long term progression of plaques is unknown

Objective

• To implement a systems biology model in order to assess what level of BACE inhibition is needed in the long run to slow down the amyloid plaque build up in brain of subjects at risk for AD (ie those who will develop AD whatever the risk factors).

Conclusions

• The results hint to a monotonic slow down of brain insoluble amyloid with increased level of BACE inhibition. Given the underlying assumptions and uncertainty of the model, validation of this prediction warrants further studies.

Model Development

• The model consists of modules describing the synthesis and processing of APP to Aβ species, the distribution of Aβ species between biological compartments, their aggregation process and the long term progression of soluble and insoluble Aβ

Model Evaluation and Selection

• Identifiability assessed by log-likelihood profiling, inter-parameter correlations and re-estimations by fixing one parameter at a time
• Uncertainty assessed through model variants exploration
• Predictability assessed through model’s ability to predict data not used for model calibration
• Seven models variants selected based on different assumptions and goodness of fit.
• Variations applied to processes such as synthesis of Aβ, destruction of insoluble forms, polymerization, age-dependent changes, deposition of Aβ42 feedback on APP production.
• Two final model variants selected for their good fit and for representing model uncertainty

Model Simulations

• Simulations of Aβ42 were performed with 0, 30, 50 and 80% of BACE inhibition for 10 years starting at 65 or 75 years of age

Tools

• DBSolve Optimum software (InSysBio, version 36) with fits performed by the DBSolve Maximum Likelihood Estimation method
• Matlab (R2015b) for simulations

References


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