PEER REVIEWED

Using QSP Modeling to Advance Knowledge and Therapeutics for Alzheimer's and Parkinson's Disease

This article explores the use of quantitative systems pharmacology (QSP) modeling to provide further insights into the mechanism of action of neurodegenerative diseases and the likelihood of success of new drugs in development. This unique approach allows for the prediction of not only biomarkers, but more importantly, clinical outcomes. Here we elaborate on the prospective prediction of lecanemab's Phase 3 CLARITY AD clinical trial using Certara's QSP Alzheimer's disease platform. This prediction was based on the use of a so called "virtual biomarker" and that concept can be applied to other neurodegenerative and rare diseases.

Alzheimer's disease is an irreversible, progressive brain disorder affecting more than 6.5 million Americans.[1] It is characterised by the formation of amyloid beta plaques and neurofibrillary, or tau, tangles in the brain, which result in loss of neurons and their connections.[1]

On July 6, 2023, the U.S. Food and Drug Administration (FDA) granted traditional approval for Eisai's Leqembi (lecanemab-irmb), an amyloid beta-directed antibody indicated to treat patients with Alzheimer's disease.[1] Leqembi was initially approved by the FDA in January 2023 under the Accelerated Approval pathway based on clinical data demonstrating the drug's effect on a surrogate endpoint – reducing amyloid plaques in the brain – that was reasonably likely to predict a clinical benefit to patients. The decision to grant Leqembi traditional approval was made after the CLARITY AD confirmatory trial verified the drug's efficacy.[1] Leqembi became the first approved treatment shown to reduce the rate of disease progression and to slow cognitive and functional decline in adults with Alzheimer's disease.[2]

Early Response

It is widely agreed that the key to success in Alzheimer's disease treatment is early intervention. It is important to identify at-risk patients and start meaningful treatment before they develop symptoms because at that point it is very difficult to reverse the disease.

Therefore, it is especially significant that Certara's quantitative systems pharmacology (QSP) Alzheimer's disease platform was able to predict the successful outcome of Eisai's lecanemab CLARITY AD clinical trial one year before the data became available, when all the previous monoclonal antibodies had failed. Certara's results were presented by BioArctic at AD/PD 2022 the International Conference on Alzheimer's and Parkinson's disease in Barcelona, Spain in March 2022.[3] Eisai licensed lecanemab from BioArctic.

QSP combines computational modelling and experimental data to examine the relationships between a drug, the biological system, and the disease process.

Certara's QSP platform is particularly well suited to studying Alzheimer's disease because it reflects the underlying biology of the amyloid aggregation pathway from the monomeric form to the plaque form. It is a mechanistic, realistic platform that integrates relevant biology and clinical data, and strikes a good balance between data- and mechanism-driven approaches. As this tool helps to replace animal studies, it also enables drug developers to follow the guidance in the FDA Modernization Act 2.0.[4]

In addition, it allows the identification of "virtual biomarkers," which are (currently) inaccessible biomarkers driving the pathology that help to make the link to functional clinical outcomes for amyloid therapeutic agents.

Building Confidence

Eisai's initial goal was to use Certara's QSP Alzheimer's disease platform to create a mechanistic model that would help to ensure it chose the optimal dose for its Phase 3 trial because it had only limited information from its Phase 2 trials on which to base that decision.

Eisai also wanted to gain mechanistic understanding of the biomarker results it could expect to see during that trial and endeavour to identify differentiating factors that would give it confidence that its compound would be successful in the clinic.

Certara and Eisai published the results of their successful collaboration in a paper entitled "A Combined PBPK and QSP Model for Modeling Amyloid Aggregation in Alzheimer's Disease" in CPT: Pharmacometrics & Systems Pharmacology in January 2023.[5]

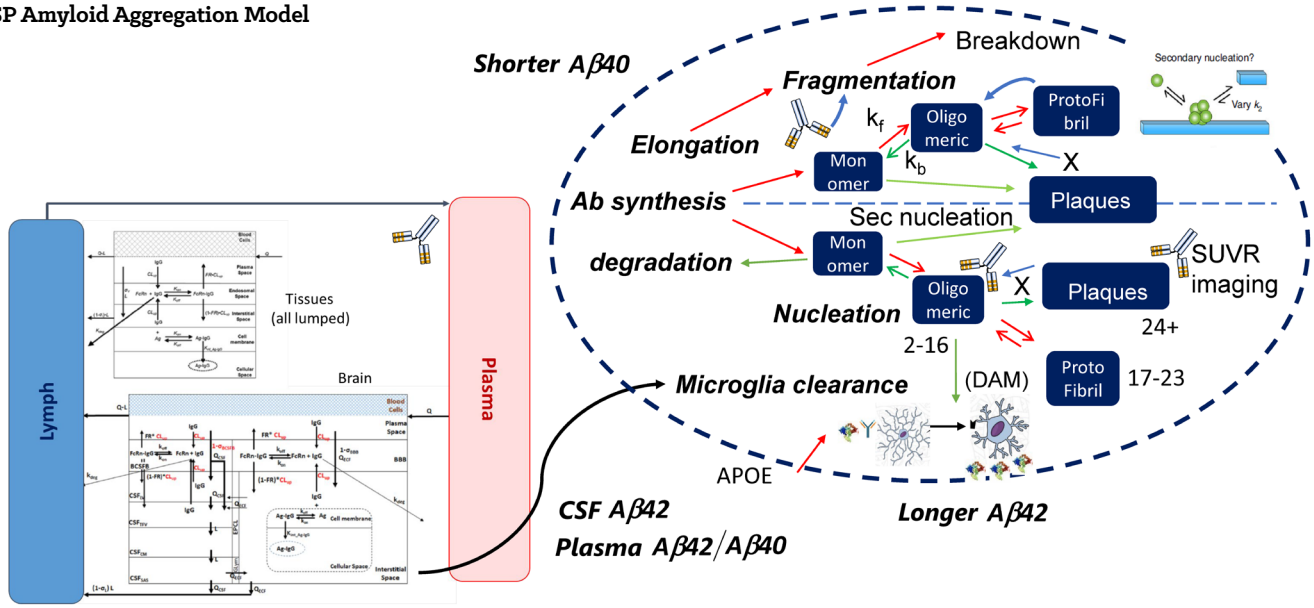
Important Differentiator

At the beginning of the collaboration, a number of amyloid antibodies, all with seemingly similar properties, had failed. Certara integrated its QSP Alzheimer's disease platform with its physiologically based pharmacokinetic (PBPK) platform to investigate the target engagement of the antibodies and explore any differentiators.

Postmortem biospecimens were used to determine the absolute levels and concentrations of different amyloid species, especially intermediate fractions of the pathological beta species, which cannot be evaluated in a living patient. Positron emission tomography (PET) imaging of amyloid load and fluid biomarker data from historical observational studies were all used as input to calibrate the platform.

Lecanemab did not look different from the other antibodies in terms of the measured biomarkers, especially brain amyloid load as reported by Standard-Uptake Value Ratio (SUVR) PET imaging. But this particular biomarker didn't tell the whole story. As the QSP platform demonstrated, the antibodies bind to different subspecies of amyloid, each with their own contribution to the Alzheimer's disease pathology. The slightly different binding profile of lecanemab is key to its success.

QSP Amyloid Aggregation Model



Many of the failed antibodies did not sufficiently reduce the concentration of beta amyloid protofibrils, a key intermediate species, which the scientific community believes is important for functional outcomes in Alzheimer's disease. Even though the effect on amyloid plaque biomarkers were similar for all antibodies, lecanemab had the greatest reduction of those protofibrils.

While it is currently not possible to measure protofibrils in a living human brain, their dynamics after treatment with a candidate compound can now be predicted based on its pharmacology.

This QSP platform is unique in that it involves both the explicit modelling of the intermediate beta amyloid species in the brain and fluid biomarkers of proteins that are generated inside the brain and migrate into the cerebrospinal fluid (CSF) and plasma.

It can also simulate disease progression from birth on, allowing researchers to study the longitudinal and historical progression of the disease, enabling them to explore the impact of different antibodies at different stages of the disease.

Virtual Biomarker

Interestingly, clinical trials reported changes in plasma p-tau levels after amyloid antibodies removed beta amyloid from the human brain. However, there was only a weak correlation between changes in brain amyloid load, measured with SUVR and changes in plasma phospho-tau levels, suggesting a more complex relationship.

The QSP platform identified the brain Abeta monomer level as a virtual biomarker that had a better correlation with the changes in plasma phospho-tau. The model provided a mechanistic and biological rationale as to why the Aβ42 monomer level dynamics inside the human brain drive this plasma phospho-tau biomarker. That has important implications for the drug's clinical rollout, because a plasma sample is much easier to obtain than CSF samples or a PET scan.

Minimising Side Effects

The biggest challenge in clinical practice is to manage the delicate balance between efficacy and side effects. A major side effect with all amyloid antibodies is amyloid-related imaging abnormalities with edema (ARIA-E), a very serious and potential lethal side effect. It is hypothesized to be due to microbleeds in the brain vasculature and is also often accompanied by haemorrhage (ARIA-H).

Certara's QSP Alzheimer's disease platform can predict both the compound's efficacy and the likelihood of it producing this type of side effect. Therefore, it is possible to optimise the drug's outcome by adjusting the titration dosing regimen.

These advances echo some of the legacy modelling work that Certara conducted with COVID-19 vaccines during the pandemic, studying different dosing intervals to optimise the immune response. While the COVID-19 vaccine modelling focused mainly on efficacy, the focus here is on how to best balance efficacy and side effects. The Alzheimer's disease modelling suggests that it is possible to minimise but not eliminate the side effects.

The Alzheimer's disease platform has now been applied to several customers' projects.

Clinical Repository

A long-term monitoring initiative that is currently underway is the National Institutes of Health Alzheimer's Disease Preclinical Efficacy Database (AlzPED),[6] which is a repository of the clinical trajectory of patients who are treated with anti-amyloid antibodies. It was initiated by the Alzheimer's Association to look at the impact of anti-amyloid antibodies in real-world clinical practice.

The goal of this database is to better understand why specific patient populations respond better or do not respond at all to certain anti-amyloid therapies, and to streamline, optimise and personalise treatment.

For instance, Roche's gantenerumab only failed due to a lack of clinical efficacy in females, whereas the treatment shows clear benefit in the male population, despite a similar reduction in the amyloid biomarker. Nobody understands yet why females and males respond so differently in this particular trial. The hope is that the Alzheimer's disease QSP platform might be able to generate hypotheses about this and other observations.

Regulatory Interest

The FDA takes an active interest in QSP modelling advances. The Certara team was invited to present its Alzheimer's disease work to the FDA a few months ago and the Agency is in the process of obtaining a license. It also gave webinars to the Agency on its immunogenicity, vaccine, and immuno-oncology simulators earlier this year.

Tackling Tau
Tau is the next major target in Alzheimer's disease. The Certara team is combining its amyloid and tau QSP models to facilitate investigation of combination therapy in living patients. It is also starting to examine neuro-inflammation in Alzheimer's disease.[7]

A QSP Model for Parkinson's Disease
The tau progression model, which can be used as a template for an a-synuclein (α-Syn) progression model after appropriate parameter modifications, can be applied to candidate drugs for Parkinson's disease. Aggregation of α-Syn is associated with the dysfunctionality and degeneration of dopamine neurons in Parkinson's disease.[8]

Certara's CNS platform also allows it to estimate the functional clinical outcomes for Parkinson's disease patients in terms of the clinical scales of rigidity (stiffness), tremor and bradykinesia (slow movement), which are well calibrated using the symptomatic treatments that are available.

This is important because even disease-modifying therapies in Parkinson's disease need to be administered on top of the existing standard of care, (various formulations of L-dopa), and different dopamine modulators often mask to a different degree some of the functional benefits of the disease modifying therapy.

Creating Virtual Twins
This highlights the need for Certara's concept of virtual twins. Here an individualised QSP model for each patient in the active treatment arm is created, complete with baseline genotypes, comedications and disease state, allowing it to simulate the untreated (placebo) trajectory and subsequently compare with the actual treatment outcome on a per-patient basis. This will reduce the variability and increase the clinical signal of any novel therapeutic intervention. Such an approach can increase the probability of success and reduce the number of placebo patients required in clinical trials for common neurodegenerative diseases.

Other applications include rare neurological diseases, where significant challenges for developing new therapies include the limited number of patients with the condition and sometimes the invasive nature of the intervention. Consequently, it is close to impossible to conduct a double-blind, placebo-controlled study. In most cases, sponsors need to demonstrate the benefits of their candidate drug in a single-arm trial comparing it with the standard of care or historical controls which are hypothesized to be well matched with the treatment population. However, because of the limited number of patients and the variability of the functional trajectories due to baseline conditions, not only is such a selection somewhat arbitrary, but it is difficult to achieve clear statistical significance.

The use of external controls or synthetic controls is an important area for regulators. For example, of course no parent will sign up their child with a rare disease for a placebo study. Those children need treatment and regulatory agencies are exploring new guidelines for these single-arm trials.

Simulating the clinical trajectory of untreated computer-generated virtual twins allows one to compare the outcome for each individual patient with and without the active treatment, enabling each patient to serve as their own external placebo control. By taking this virtual twin QSP approach, a sponsor can additionally generate evidence of a positive difference between their active treatment and the standard of care.

Future Applications
New developments to Certara's CNS QSP platforms will enable the investigation of frontotemporal dementia[9] and rare diseases, such as progressive supranuclear palsy[10] or corticobasal degeneration.[11]

Conclusion
QSP modelling can be used to predict a candidate drug's efficacy both in biomarker and clinical readouts and optimise its side effects profile. These advances are showing potential to improve new therapies not only for Alzheimer's and Parkinson's disease but also for other forms of dementia and rare neurological diseases.

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