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Neurology's false choice: symptomatic vs. disease-modifying

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Even as many drug developers celebrate anti-amyloid antibodies as the start of a new era of disease-modifying treatments for dementia, a set of up-and-coming biotechs aims to tear down the distinction between symptomatic and disease-modifying therapy.

The conventional wisdom has been that clinical trials of Alzheimer's disease therapies must be long and large if companies want a chance of demonstrating their products can impact the pace of disease progression. Further slowing an already slow process is a tall order. Recent Phase III trials of anti-amyloid therapies enrolled over 1,500 patients apiece and measured their primary outcomes at 18 months.

That, together with the paucity of biomarkers clearly linked to long-term outcomes, means that getting an early efficacy signal — the kind of readout that could be materially de-risking to VCs — prior to a lengthy Phase II study has been challenging.

For two decades, Alzheimer's trials have largely been the purview of big biotechs and pharmas, and nearly all late-stage trials have tested variations of the same hypothesis: lowering β-amyloid levels — whether by cutting off the peptide's production or removing its various aggregated or non-aggregated forms — will slow the inevitable march of the disease.

The recent culmination of that work in the approvals of anti-amyloid therapies from Biogen Inc. (NASDAQ:BIIB) and Eisai Co. Ltd. (Tokyo:4523), and a Phase III win by Eli Lilly and Co. (NYSE:LLY), has been widely heralded as the dawn of a new age in drug development for dementia.

The traditional school of thought is, with disease-modification now possible, why would any company choose to develop a symptomatic treatment?

But what if therapies could do both? Some executives and investors reject the hard line drawn between symptomatic and disease-modifying therapy, arguing that an effective disease-modifying therapy should bring some measure of early symptomatic benefit. After all, what patients want most is a medicine that can relieve their symptoms, help them think and remember more clearly so that they feel and function better. And the sooner they feel the benefits, the better.

Rather than split the world into symptomatic versus disease-modifying, the distinction could be re-conceptualized as a continuum. At one end would be purely symptomatic

treatments that address a specific psychological symptom, such as aggression in Alzheimer's, while purely disease-modifying treatments would slow disease progression but offer no symptom relief.

The wide territory between those two poles would arguably hold the most promise, not only for patients but also for entrepreneurs. A refocusing of the development path to prioritize measurement of early symptomatic benefits — especially cognitive and functional symptoms likely to presage a disease-modifying effect — could change the investment paradigm in dementia.

A faster path to clinical proof of concept would be more palatable for VCs, and assuming the symptoms being measured are important to patients, they could lead to a lucrative drug even if disease modification isn't shown. At the same time, this scenario could make it easier to raise the funds needed to run the longer disease-modifying experiments.

"The Goldilocks mechanism would lead to acute benefits for patients, and then show a disease-modifying effect with more time," Todd Foley, managing director at MPM BioImpact, told BioCentury.

β-amyloid targeting was supposed to offer such a mechanism, given that soluble amyloid oligomers are believed to initially impair synaptic function before neurons die, creating a window for restoring lost function, in addition to slowing progression. The Phase III trials did not bear out the hypothesis, although there is some evidence that earlier treatment might lead to greater efficacy.

The unfolding biology is offering up new mechanisms for near-term symptom relief. For now, these fall into two broad categories: approaches that bolster synaptic function, and ones that improve neuronal health, either via mitochondrial biogenesis or by targeting the astrocytes that nurture neurons. Therapies that alleviate neuroinflammation or target central pathways in both synaptic and neuronal health could straddle both categories.

The new goal: symptomatic and disease-modifying

Rather than prioritizing disease-modification over symptomatic benefit, some companies and investors are embracing a symptom-first paradigm.

"If it's only disease-modifying, it's a weak-acting drug," Gerard Griffioen, CSO of reMYND N.V., told BioCentury. The Belgium-based biotech expects data this year from a Phase IIa trial of its calcium homeostasis regulating therapy ReS19-T, which it believes will improve synaptic function acutely, thereby helping patients think and remember better in the short term. As dysregulated calcium signaling has also been linked to β-amyloid deposition and aberrant tau phosphorylation, the hypothesis is that the approach will also slow disease progression. The company has not yet disclosed the therapy's target.

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John Alam, CEO of CervoMed Inc. (NASDAQ:CRVO), shares similar views. "In neurodegeneration, we're so trapped in this world view — where disease-modifying drugs don't show early symptomatic effects — that we think you can't show a symptomatic effect and be disease-modifying. That's wrong," he told BioCentury.

TNF inhibitors, Alam continued, are disease-modifying for rheumatoid arthritis, "but the reason they get used, and approved, is their profound symptomatic effect. No one says 'it's symptomatic, we're not interested.'"

"Only in neurodegeneration do we assume that that disease modification and symptom treatment are different, that you can't test both," said Alam.

CervoMed raised $50 million in a PIPE last week to fund its ongoing Phase IIb RewinD-LB study of neflamapimod, a small molecule p38 MAPKα inhibitor, to treat dementia with Lewy bodies; data are due this year. Like reMYND's ReS19-T, neflamapimod is expected to improve synaptic function in patients. Neflamapimod should lead to longer-term benefit by slowing degeneration of cholinergic neurons in the basal forebrain. The primary endpoint in the Phase IIb trial is the Clinical Dementia Rating – Sum of Boxes, a standard instrument in dementia trials, and is being measured at 16 weeks.

Other therapeutic mechanisms, such as targeting neuroinflammation or inducing mitophagy, also hold promise.

Chronic neuroinflammation, driven by cytokine release from activated microglia and astrocytes, both damages synapses and is associated with amyloid and tau pathologies. It also represents a mechanism with a high degree of support from human genetics, as many risk variants linked to Alzheimer's disease are immune pathways. Neuroinflammation has become an active area of research in recent years. One of the

leaders, Alector Inc. (NASDAQ:ALEC), expects data from a Phase II trial of TREM2 activator AL002 by year-end.

Mitophagy induction is a newer approach. The cellular process enables degradation of defective mitochondria, activating the biogenesis of new, healthy mitochondria. By restoring cellular energetics and reducing reactive oxygen species, such therapies could improve neuronal function in both the short and long term.

At least five start-ups developing mitophagy inducers list neurodegeneration among their therapeutic areas of interest. Three of these — Vandria S.A., Capacity Bio Inc. and HangZhou PhecdaMed Co. Ltd. — disclosed series A rounds last year, while Mission Therapeutics Ltd., added another $32 million to the $143 million in venture money it had already raised. Mission is nearing the start of a Phase I trial of MTX325, a USP30 inhibitor for Parkinson's disease, and has an Alzheimer's collaboration with AbbVie Inc. (NYSE:ABBV) against undisclosed deubiquitinase (DUB) targets. The partnership is not AbbVie's only mitophagy play. In October, the pharma announced it had exercised its option to acquire Mitokinin, gaining a preclinical Parkinson's program targeting PINK1 on damaged mitochondria.

Investor view

While some investors such as SV Health Investors' Dementia Discovery Fund and EQT's LSP Dementia have been committed to drug development for neurodegenerative diseases, plenty of other VCs have steered clear of the space.

The prospect of a relatively fast development path based on early symptomatic effects has piqued the interest of at least one VC who has historically avoided neurology investments. Foley told BioCentury that long timelines and large trial sizes are largely to blame for keeping MPM away from the neurodegeneration space. "Usually with neurodegenerative diseases, you have to run a multiyear Phase IIb trial to get the first real signal of efficacy, or you hope your mechanism is sexy enough that a pharma will take you out after target engagement. That's hard for a VC."

That changed in October, when the firm participated in the $58 million series A round raised by Alzheimer's play AstronauTx Ltd., a company with two therapeutic hypotheses that Foley believes could hit the sweet spot of dual symptomatic-disease modifying activity.

One of AstronauTx's approaches involves clearing debris from the brain at night, while patients sleep, by increasing glymphatic drainage, movement of fluid through perivascular channels formed by astrocytes. The mechanism should reduce not only β-amyloid, but also tau, α-synuclein and any other soluble misfolded protein in the extracellular space, as well as

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cytokines driving neuroinflammation. "It's essentially doing what you could do with a combination of several antibodies," said Foley.

The biotech's second mechanism is designed to enhance the metabolic support that astrocytes provide to neurons, which should "improve neuronal function acutely because now you've got more gas, more fuel for neuronal activity." The company has not disclosed the targets of either program.

Foley said AstronauTx believes it will be able to observe therapeutic effects in Phase I, noting "a two-week study should be plenty."

The standard clinical scales used to track disease progression in Alzheimer's trials measure symptoms such as impairment in memory, problem solving, and the ability to conduct personal or community affairs. Historically, these scales have been given infrequently, such as every three months, during an office visit. The advent of digital versions of these scales, said Foley, is now allowing patients to take the tests in their homes, and much more frequently, without the results suffering from "training effects" where patients perform better over time simply by becoming familiar with the test. That should enable more fine-grained assessment early in treatment.

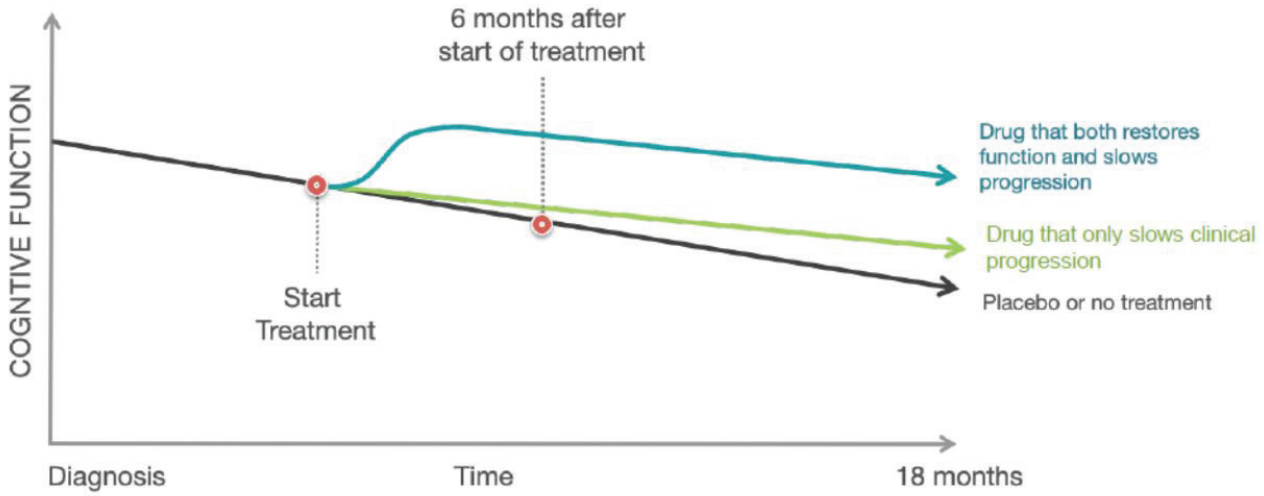
"We think the registration path would center on whatever those benefits are that are shown early," he said. The biotech would confirm the effects are durable "to three or six months" in a Phase II study, at which point, "because you have the path to approval, you can amass the capital to do your longer disease-modifying study."

"As investors, that disease-modifying study is gravy to us," said Foley. "A drug that can noticeably improve patients' symptoms in the first couple of weeks, that's a blockbuster drug by itself. If it also slows disease progression, that's an Ozempic-scale product."

Where amyloid and tau fit in

Another argument maintains that there is no such thing as a purely disease-modifying therapy; all such therapies should be able to improve symptoms acutely if given to the right patients at the right time.

According to Alam, evidence for this view can be found in a post hoc, subgroup analysis from the Phase III trial that supported approval of anti-amyloid therapy Leqembi



Source: CervoMed corporate presentation

lecanemab. The primary endpoint in the study was measured at 18 months, and, in the full trial population, Leqembi appeared only to slow disease progression, not improve cognitive and functional symptoms.

However, a subgroup analysis reported at the 2023 Clinical Trials on Alzheimer's Disease (CTAD) conference suggested the drug may lead to functional improvements if patients are treated early in the course of disease, before much pathological tau aggregation occurs in the brain. In a small subset of patients shown to have little tau pathology at baseline, those in the placebo arm did not meaningfully decline over the study period, with 28% even showing modest improvement in CRD-SB at 18 months. The fraction of patients with improved scores reached 60% in the Leqembi arm.

"I don't think people fully understand the implications of lecanemab and donanemab. As much as they are targeting plaque, the real thing they are targeting is synaptotoxic forms of amyloid," said Alam. For companies looking to restore function by improving the health of synapses, he believes it will be key to deliver therapies at the right phase of disease, when many synapses have become dysfunctional but are still present because substantial degeneration has not yet taken place.

In Alzheimer's disease, tau aggregation may prove useful for identifying such patients, and tau itself remains to be vetted as a therapeutic target. In dementia with Lewy bodies, Alam said the task is a bit easier, as the synaptic dysfunction phase of the disease lasts longer after symptom onset.

He offered a picture of what data from a dual symptomatic/disease-modifying therapy might look like. In CervoMed's theoretical model, a drug that both restores function and slows progression (upper line below) would produce a notable improvement in cognitive function shorty after initiating treatment, resulting in the long-term decline starting from a higher level. In addition, the rate of decline would be slower than for placebo (lowest line below). A drug that only slows clinical progression (middle below) would take much longer to differentiate from placebo, on the order of a year or more.

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