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Preventive Alzheimer’s trials keep amyloid hope alive

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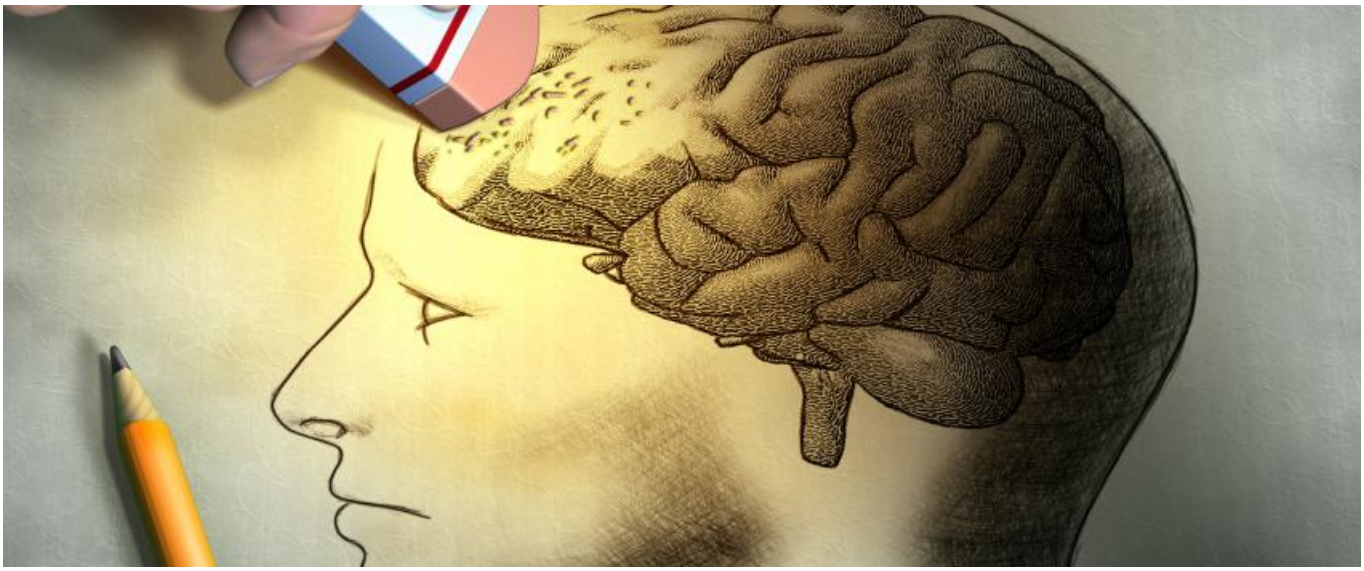

Drugs have so far failed to make an impact in established Alzheimer's disease, so research is moving towards efforts to prevent the disorder.

With the amyloid hypothesis perhaps drawing its last breath in symptomatic Alzheimer’s disease, the sector’s attention is turning to preventing or slowing Alzheimer’s onset in people genetically predisposed to the condition.

Researchers have yet to stray far from the hypothesis that amyloid beta brain plaques are the culprits in cognitive degeneration, but they believe that the insights from these trials could allow patients to be identified earlier, as well as giving clues to new treatments. They make a comparison with heart disease, in which the early work in familial cholesterolaemia led to drugs like statins that have broadly prevented death and cardiovascular complications.

“When somebody has dementia they’re really in that late stage of disease – the brain has seen significant injury by plaques and tangles,” says Michael Rafii, clinical director of the Alzheimer's Therapeutic Research Institute at the University of Southern California. With the prevention trials, “the idea is to go as early as possible”.

The difficulty for researchers is how to identify patients in whom the disorder is early enough that accumulation of amyloid plaques can be arrested. The cost and invasiveness of the procedures used to identify patients make mass screening impractical; however, by working with patients genetically predisposed to Alzheimer’s the hope is that biomarkers can be discovered that will lead to an inexpensive test for sporadic disease, the non-genetic type.

Amyloid for now

So much effort has been sunk into treatments seeking to disrupt amyloid accumulation that researchers seem reluctant to abandon them just yet. Instead they are seeking to identify a patient population in whom anti-amyloid therapies might yield a statistically significant benefit. The lack of a plausible alternative hypothesis also weighs heavily in this debate.

The “will they ever work?” question breaks down into two: does the agent in question target the right species of amyloid beta, and can it change the course of the disease? Monomer-targeting agents – solanezumab largely hit soluble monomers in the bloodstream – have been disproven in patients with early signs of disease,

and the signs are not strong for projects targeting the more complex soluble protofibrils, like Biogen's BAN2401 and Roche's crenezumab. Data due mid-year should reveal their promise.

More optimism surrounds Biogen's aducanumab, which can bind to and remove the solid form of amyloid beta in brain plaques. It is believed that this might be a more effective way to alter the normal rate of degeneration. Even here, though, the struggles of a similarly acting agent, Roche's gantenerumab, should trigger some caution – that project has already failed in phase III trials, one in Alzheimer's patients with the earliest signs of cognitive impairment and a second in those with mild dementia.

Biogen disturbed Alzheimer's followers earlier this year when it expanded the size of the phase III programme for aducanumab because of "variability" in the primary endpoints, which are two measures of cognitive impairment – the fear being that aducanumab was struggling to show a statistically significant benefit. The two trials will read out in 2019 and 2020.

Do you remember?

With uninterrupted failure in this space at least in symptomatic patients, and enough doubt remaining on the agents that have yet to report a definitive finding, researchers have been forced to chase another possibility – that targeting amyloid beta might alter the course of disease if patients receive treatment before they show symptoms.

This is where the prevention trials come in. Patients genetically predisposed to early-onset Alzheimer's or in the earliest stages of disease pathology are being enrolled into six different trials, with the earliest glimpses of data expected in late 2019.

Alzheimer's disease preventive trials

Study	Project	Phase	Enrolment	Population	Completion	Trial ID
DIAN-TU	Solanezumab	Phase III	438	PSEN1, PSEN2 and APP mutations	2019/20	NCT01760005
	Gantenerumab				2019/20	
	JNJ-54861911				2023	
A4	Solanezumab	Phase III	1,150	Patients with evidence of amyloid pathology on PET scan	2022	NCT02008357
EARLY	JNJ-54861911	Phase III	1,650	Apo E4 mutation with evidence of amyloid pathology	2024	NCT02569398
Generation S1	CAD106	Phase II/III	1,340	Apo E4 mutation	2024	NCT02565511
	CNP520				2024	
Generation S2	CNP520	Phase II/III	2,000	Apo E4 mutation with evidence of amyloid pathology	2024	NCT03131453
API-ADAD	Crenezumab	Phase II	252	Patients with with PSEN1 E280A mutation	2022	NCT01998841

Source: Clinicaltrials.gov.

By necessity these studies involve projects that have either failed or shown mixed results. Solanezumab is in two trials, with the A4 study being run by the University of Southern California's medical school having quadrupled the dose from the Lilly-run trials to 1,600mg every four weeks.

Dr Rafii noted that sola had a fairly clean safety profile in the Lilly-run trials, justifying an increase in dose. "If we have a drug that could be just as safe at a higher dose, we should attempt to maximise the chance of success with this drug."

The DIAN-TU trial is also using a higher dose of solanezumab. Lead investigator Randall Bateman, a neurology professor at Washington University in St Louis, tells *EP Vantage* that this had been done in conjunction with A4, although he did not specify the dose.

Right dose, right drugs, right patients

This strategy of boosting the dose of amyloid beta antibodies is endorsed by Professor Philip Scheltens, the director of the Alzheimer Center at the VU University Medical Center in Amsterdam, who has previously told *EP Vantage* that trials of solanezumab and Roche's gantenerumab have not hit the peptide hard enough.

"I don't think we've done the right trials with the right drugs and the right dose," he said (*Interview – Probiodrug hopes to avoid Alzheimer's amyloid abyss, April 16, 2018*).

No studies are looking at novel mechanisms of action. Amyloid-beta antibodies and Bace inhibitors similar to Merck & Co's failed verubecestat (MK-8931) dominate, although Novartis's anti-amyloid beta vaccine CAD106 (amilomotide) is being tested in the Generation S1 trial alongside the Bace inhibitor CNP520.

In addition to solanezumab and gantenerumab, DIAN-TU has recently made use of its adaptive trial design and added Johnson & Johnson's Bace inhibitor JNJ-54861911. Professor Bateman says he is interested in adding a tau inhibitor and combination projects.

As for the population being enrolled, all are cognitively normal patients predisposed to Alzheimer's by family history or because of specific mutations. DIAN-TU is enrolling patients with confirmed or high probability of having a genetic profile that leads to autosomal dominant Alzheimer's disease, while Generation S1 and S2 enrollees must be homozygous for the Apo E4 genotype.

While these prevention trials are focusing on patients with elevated risk of developing Alzheimer's dementia because of their genetic profile or family history, the findings can be translated into patients with sporadic disease, Professor Bateman says: "These are two forms of the same disease."

But this translation might only be able to happen if there is an easy way to screen for elevated levels of amyloid beta besides expensive PET scans or invasive spinal taps – something Professor Bateman says is close.

At last year's Alzheimer's Association International Conference, he reported on a mass spectrometry-based test that can help identify people who are accumulating amyloid plaques in the brain – this is based on the ratio of amyloid beta 40 to amyloid beta 42, the latter of which is associated with plaques, in the blood.

"We need a validated blood test and preventive treatment," Professor Bateman says. "We haven't had highly effective treatments in terms of changing the disease process. That's the thing that's changed over the past couple of years. There are several key things converging that give me optimism."

This optimism can perhaps only be sustained if researchers are correct that it is amyloid beta that destroys cognition in Alzheimer's: despite repeated failure, that is what the sector remains focused on. If it is wrong the prevention trials will be no more successful.

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