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Solanezumab—prospects for meaningful interventions in AD?

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Abstract

A treatment trial of the monoclonal anti-amyloid antibody solanezumab showed slight benefits in people with dementia due to mild Alzheimer disease. Drug effects on several neuropsychological testing outcomes were statistically significant, but the effect sizes were unlikely to manifest as meaningful functional benefits. Here, we discuss the implications and possible molecular underpinnings.

Solanezumab is a therapeutic monoclonal anti-amyloid- β (A β) peptide antibody, and is at an advanced stage of clinical development: the drug has now been examined in two phase III clinical trials involving over 2,000 participants with mild to moderate Alzheimer disease (AD). Although solanezumab did not meet its primary outcomes across these large studies, a new subgroup analysis by Eric Siemers and colleagues, focusing on the participants with mild AD, suggests that the drug could be effective if administered sufficiently early in the disease process.¹

Bapineuzumab, the first anti-A β antibody to be studied in patients with AD, produced robust reduction of fibrillar brain amyloid, as demonstrated by amyloid imaging, yet no clinical benefit was observed.² One interpretation of these results is that A β clearance was initiated too late in the clinical course. Siemers *et al.* used data from the two solanezumab trials—EXPEDITION and EXPEDITION2—to test this hypothesis.¹ When participants with mild to moderate AD were analysed in aggregate, the primary cognitive efficacy end points were missed, that is, the solanezumab-treated group continued to progress at similar rates to the group that received placebo. When the 1,322 participants with mild AD were pooled and analysed, however, three of six prespecified end points were met at the $P < 0.001$ level of statistical significance, one was met at $P < 0.05$, one was a near miss at $P < 0.057$, and two were non-significant. Among the neuropsychological testing parameters that demonstrated improvement, the reduction in cognitive decline was estimated at 34% in the solanezumab-treated patients.

An important issue to raise here is the difference between statistically significant and clinically meaningful. Of the parameters measured, the ones that showed the least benefit

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Competing interests

Within the past 5 years, S.G. has provided consultation to the Janssen Pfizer Immunotherapy Alliance and has held grants from Baxter, Amicus and Constellation/Polyphenolics. M.S. has provided consultation to Janssen Pharmaceuticals, Eli Lilly, Eisai, Medivation, Sanofi Aventis, Biogen and Takeda. She has also consulted for Merck and Nutricia without any compensation.

from solanezumab were those associated with activities of daily living. In practice, this means that within the duration of the trial, scores on tests were slightly improved in the solanezumab-treated group, but the benefits would be unlikely to have a meaningful impact on the patients' everyday lives. The plotted data suggest, however, that some of these parameters might have diverged to a larger extent had the trial continued past 18 months.

Cerebral amyloidosis—that is, deposition of A β in the brain in the form of amyloid plaques—is a key pathological feature that is required for the neuropathological diagnosis of AD. Genetic evidence indicates that mutations in a host of structurally disparate familial AD (FAD)-related genes promote the development of cerebral amyloidosis, supporting an important role for this process in the pathogenesis of clinical AD, and providing the rationale for the development of therapeutic anti-A β monoclonal antibodies, such as bapineuzumab² and solanezumab.¹ However, the relationship between cerebral amyloidosis and clinical AD is far from clear: brain amyloid imaging-positive cerebral amyloidosis can precede clinical AD by up to 30 years³ and, conversely, about one-third of patients with clinical AD lack demonstrable amyloid- positive imaging, despite hippocampal atrophy and/or impaired brain glucose metabolism.⁴ Also, in addition to amyloid plaques, the A β peptide exists in a variety of forms in the brain, including an α -helical soluble form that is believed to be a normally generated neuromodulator, and A β oligomers-amorphous submicroscopic clumps of A β that are believed to be key neurotoxins.⁵

The clinical relevance of A β oligomers is illustrated by patients with FAD who harbour an amyloid precursor protein mutation known as the Arctic mutation. Arctic mutation-containing A β forms oligomers rather than fibrils, yet patients with Arctic-mutant FAD show a clinical AD phenotype indistinguishable from that of other forms of AD. Therefore, despite florid clinical dementia, amyloid imaging is negative in patients with Arctic FAD.⁶ Thus, as we reflect on the development of solanezumab for the more common sporadic forms of AD, it is important to keep in mind that at least one crucial variable—brain levels of oligomeric A β —remains unmeasurable during life.

The importance of cerebral amyloidosis in identifying those individuals at greatest risk of clinical dementia is highly controversial. Clinical studies indicate that healthy amyloid imaging-positive older individuals exhibit minimal evidence of conversion to AD, even after 3 years of follow-up.⁷ Although average cognitive performance of the amyloid imaging-positive individuals was below that of their amyloid imaging-negative counterparts, the magnitude of the diminished performance was minuscule. Nevertheless, the amyloid-positive patients would, according to new criteria, probably be diagnosed as having 'preclinical' or 'asymptomatic' AD.

A new study of the genetic underpinnings of progressive cognitive decline in individuals with asymptomatic cerebral amyloidosis identified an immune receptor component, IL1RAP, as the key factor associated with conversion from asymptomatic amyloidosis to cognitive impairment.⁸ This finding supports the notion that AD can be divided into an amyloid accumulation phase that might be silent, and an immune-inflammatory phase that drives cognitive decline. In the largest genome-wide association study of sporadic AD to date,⁹ involving over 74,000 participants, immune-inflammatory genes were overrepresented, reinforcing the importance of these pathways, and raising the possibility that some forms of AD are driven by ‘hyperinflammation’ that begins and/or propagates independently of fibrillar amyloidosis. The most important implication of this line of reasoning is that A β reduction may not be beneficial in all forms of AD, as defined by classic clinical criteria. In some cases, therefore, drug failure would be attributable not to ‘intervening too late’ but, rather, to the fact that, in some patients, A β is the wrong target.

Despite these caveats, additional trials are ongoing in individuals without dementia who show biomarker evidence of brain amyloid accumulation. In the A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer’s) Study,¹⁰ 1,000 individuals with no or very mild symptoms are being screened by amyloid imaging, and those with positive amyloid scans and no contraindications are randomly assigned to a 3-year course of monthly infusion of solanezumab or placebo. A4 is a highly ambitious study, and confounding factors—both ‘known unknowns’ and ‘unknown unknowns’—may be encountered. For example, the presence of radiologically detectable fibrillar amyloid implies that peptide oligomers and/or microaggregates might have been present inside and between neurons for years or decades before reaching the sensitivity of the imaging modality. Many molecular events (for example, transcriptomic pathology) could have been set in motion by this unvisualizable molecular pathology, and it is unclear how many of these processes can be interrupted or reversed by removal of fibrils or oligomers.

The outcome from the A4 Study is not expected for at least three more years. Given the modest benefit of solanezumab reported to date,¹ the prospect that this drug alone will have a meaningful impact on the progression of most forms of sporadic AD is, in our estimation, unlikely. Even with the most optimistic of predicted outcomes for solanezumab, an enormous need still exists to elucidate the causes of AD and evaluate new interventions.

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