Results from recent Alzheimer’s disease trials validate the ProMIS approach

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Recent failures in advanced Phase 3 clinical trials by Eli Lilly and Merck have been disappointing for the Alzheimer’s disease (AD) community. However, the results continue to support the ProMIS approach of targeting toxic amyloid-beta (Aβ) oligomers as the primary pathogenic driver of AD.

Much of the clinical focus has been based on the Aβ hypothesis originally put forward in 1992 and positing that, in susceptible individuals, high levels of Aβ monomers in the brain lead to the formation of larger oligomer aggregates that then go on to form fibrils and ultimately plaque deposits which were believed to be responsible for neurotoxicity and brain atrophy. However, more recent experimental and clinical evidence indicates that soluble toxic Aβ oligomers propagating in a prion-like manner, and not plaque, are actually the primary drivers of neurodegeneration and cognitive decline in AD patients.

The lack of clinical success to date is consistent with the fact that none of the tested clinical agents directly or effectively targets toxic oligomers. Solanezumab, the monoclonal antibody developed by Eli Lilly, binds soluble forms of Aβ and was meant to act as a “sink” to capture soluble Aβ monomers and prevent the ensuing cascade of aggregation and plaque formation. The approach failed to produce any significant clinical benefit likely because potential neutralization of soluble toxic oligomers by solanezumab was impeded by binding to the much more abundant non-toxic Aβ monomers.

Merck pursued a similar strategy with verubecestat, a small molecule inhibitor of the beta-secretase 1 (BACE) enzyme involved in the cleavage of amyloid precursor protein (APP), the first step in the generation of Aβ monomers. In this case, the goal was to “turn off the tap” by inhibiting the formation of Aβ monomers. This approach would not be expected to have an effect on the ongoing prion-like propagation of existing toxic oligomers, consistent with the observed lack of efficacy.

By comparison, Biogen’s monoclonal antibody aducanumab, which binds Aβ oligomers and plaque, did provide evidence for a reduction in cognitive decline in a Phase 1b trial. The lack of Aβ monomer binding provided the benefit of reduced competition and potentially more effective neutralization of toxic Aβ oligomers, but binding to plaque was associated with dose-dependent toxicity (brain edema - ARIA-E) which limits the therapeutic window for the antibody.

All of the human clinical data to date are therefore supportive of the ProMIS approach of...
selectively targeting soluble toxic Aβ oligomers to maximize efficacy by avoiding unproductive binding to non-pathogenic Aβ monomers as well as decreasing the risk of edema and vascular adverse events associated with plaque engagement.

References