A Tale of Tangles Chapter Three: The Desert Expanse

In chapters one and two of our series, we reviewed the early history and theories behind Alzheimer's Disease (AD) which preceded meaningful progress for symptomatic treatments in the early 2000s. Four new drugs were approved by the FDA in quick succession between 1996 and 2003. After initial progress, the collective consciousness shifted towards addressing the cause of AD and developing disease modifying therapies. Despite a concerted effort by leading pharmaceutical companies, 2003 to 2021 were barren years for new Alzheimer's drugs. We track at least 36 mid-to late stage candidates that failed in clinical trials since 2010 and other sources identify 146 failed attempts from 1998 to 2017.[1] The failed candidates span a broad range of mechanisms from BACE inhibitors, to β-amyloid and tau targeting monoclonal antibodies among others. The candidates either failed to show any clinical efficacy or were associated with side effects that halted advancement. While much of the hope in disease modifying therapies was a mirage, an oasis across the sands materialized with the 2021 approval of a therapy with disease modifying potential.

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[1] A Long Line of Alzheimer's Failures: Roche Drops Two Drug Trials. January 30, 2019

Parched in the Desert

The most visible AD failures over the last decades include small molecule BACE inhibitors aimed at inhibiting generation of amyloid-β monomers as well as several amyloid-β-directed antibodies. Crenezumab, solanezumab and bapineuzumab were all Phase III assets that enrolled thousands of subjects and consumed billions in investment but were abandoned due to lack of safety or efficacy.

Crenezumab, from Roche was dropped after an interim analysis showed it was safe but unlikely to meet the primary endpoint of improvement in Clinical Dementia Rating-Sum of Boxes (CDR-SB) Score.

Lilly's solanezumab showed no evidence of slowing cognitive decline in a large pivotal trial despite early data showing positive trends in cognition and function. It was later found that up to 35% of patients did not even have amyloid-β plaques.

Bapineuzumab was advanced by Johnson & Johnson, Elan and Pfizer, but failed in several late stage studies including two specifically enrolling ApoE4 carriers. The sponsors ran four large trials enrolling almost 4,500 individuals but found no clinical benefit. A review of six bapineuzumab studies showed no benefit for patients on drug compared with the placebo group using the AD assessment scale.

Failure was so common, with a rate exceeding 99%, that many large pharmaceutical companies slowed or stopped their programs in neurodegeneration. In early 2018, Pfizer (PFE) decided to shutter its neuroscience drug discovery division and eliminate 300 related positions.

Some of the reasons for the failures may be attributed to a late treatment start, inadequate understanding of AD mechanisms and failure to use combination approaches. While these programs came up dry, they did meaningfully contribute to the community's understanding of Alzheimer's disease biology. For example, it became clear that non-selective antibodies targeting all forms of amyloid-β including monomers and plaques are ineffective approaches.

Aducanumab: A Mirage or Effective?

Despite numerous setbacks, Biogen held on to its most promising candidate, aducanumab. In 2019 it appeared that the drug would advance no further; however, after a tumultuous 27 months of ups and downs, the FDA finally sanctioned the monoclonal antibody in 2021.

The process and decision to allow the drug to be marketed was controversial as it was approved on surrogate endpoints that have not been directly tied to clinical benefit. As a condition of approval, aducanumab must undergo a post-marketing confirmatory study that will examine direct measures of efficacy. The trial is expected to take four years to complete.

Despite a number of missteps by Biogen, post-approval safety concerns and CMS' limitation of Medicare coverage to aducanumab clinical studies, the approval of the drug has stimulated interest and investment in AD. FDA actions have shown that there is a regulatory pathway forward and that the agency is committed to working with sponsors to advance new therapies in neurological diseases with few alternatives.

While aducanumab was not the unequivocal success that everyone wanted, the development process helped identify a number of important elements for success. Some of the key learnings are the realization that toxic oligomers of amyloid-β are the underlying cause of AD, that biomarkers serve an

important role in rapidly and efficiently identifying successful candidates and that the structure of the antibody is key to driving an immune response.

Just Deserts

Despite a bleak two decades, much has been learned. The focus has centered on amyloid-β; however, views have evolved to recognize the specific cause of AD as toxic amyloid-β oligomers. Candidates that bind to the toxic oligomers such as aducanumab perform better than others, such as solanezumab, which do not. Binding to insoluble fibrils can not only cause damaging side effects (ARIA-E),[2] it can also dilute a drug's effect.

As new approaches build on past learning, second generation candidates that focus on the right target, possess effector function, and influence biomarkers that measure neuronal cell death are in development. Three candidates that stand out include Eli Lilly's (NYSE: LLY) donanemab, Acumen Pharma's (NASDAQ: ABOS) ACU193 and ProMIS Neurosciences' (TSE: PMN.TO) PMN310, each of which addresses disadvantages of earlier amyloid β programs.

Join us next time for chapter four of our series to look at some of the active research in AD and see what the future may bring.

[2] Amyloid-related imaging abnormalities, edema (ARIA-E) are abnormal differences seen in magnetic resonance imaging of the brain of Alzheimer's disease patients, associated with amyloid-modifying therapies.