Beginning a New Era of Precision Alzheimer's Therapy - rethinking the amyloid hypothesis from the pharmacological perspective

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Alzheimer's disease (AD) is the most rapidly growing neurodegenerative disorder, with nearly 140 million cases projected by 2050 (WHO). For the past two decades, the field has struggled with the lack of approval of disease-modifying therapies. The only real options were acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonist, none of which had a large impact on AD symptoms.

Since last year, interest has increased, and different companies have decided to target diverse parts of the amyloid plaque formation in the hope of stopping neurodegeneration. Despite past criticism of the so-called "amyloid hypothesis" due to failing numerous clinical trials, it gained support with the approval of lecanemab and donanemab in the U.S., although EU approval is still pending. These IgG1 monoclonal antibodies target aggregated soluble and insoluble forms of amyloid beta (Aβ) to reduce plaque buildup, slowing early-stage AD progression.

However, concerns remain about its modest and limited efficacy and serious side effects, such as amyloid-related imaging abnormalities (ARIA) which can cause brain swelling or bleeding into the brain in people at risk. Amyloid is a structural component of blood vessels, thus anti-amyloid-beta antibodies can cause unexpected bleeding. Clinical trials have shown that certain genetic mutations or variants may have an impact on the efficacy and safety of anti-amyloid beta antibodies. APOE4 homozygotes show poor efficacy and higher ARIA risk. This makes them a group with a particularly high unmet treatment need, giving them up to a 15-fold increased risk of developing AD over the general population.

Monoclonal antibodies mark the start of a new era in AD therapy. Their modest efficacy suggests beta-amyloid is only part of the disease's pathology. As a heterogeneous condition, AD may benefit from a precision medicine approach, tailoring therapies to specific patient groups and combining diverse drug targets. A deeper understanding of the biology underlying AD heterogeneity and the physiological role of amyloid could drive the development of more effective and safer future treatments.