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Are antibodies directed against amyloid- β (A β) oligomers the last call for the A β hypothesis of Alzheimer's disease?

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“The multiple failures of previous anti-A β drugs may suggest that in the AD brain, the accumulation of A β could be secondary to an unknown initial disrupting event.”

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Alzheimer's disease (AD) is a devastating and incurable age-related neurodegenerative disorder with a long presymptomatic period. The accumulation of the amyloid- β (A β) peptide in the brain is believed to be the initial event of the AD process and starts 15–20 years before clinical symptoms occur. During the last 20 years, several compounds were designed to decrease the levels of monomeric, oligomeric, aggregates and A β plaques. Drugs have been developed and shown to decrease the A β production, antagonize A β aggregation or increase A β brain clearance. Unfortunately, all these drugs, including A β aggregation inhibitors (tramiprosate, scyllo-inositol, PBT2), A β antigens (AN-1792, vanutide, AD02, CAD-106), anti-A β monoclonal antibodies (ponezumab, bapineuzumab, solanezumab, gantenerumab and crenezumab), anti-A β polyclonal antibody (immunoglobulins), γ -secretase inhibitors (begacestat, semagacestat and avagacestat), γ -secretase modulators (tarenflurbil), β -site amyloid precursor protein cleaving enzyme (BACE) inhibitors (LY2811376, LY2886721, AZD3839, verubecestat, atabecestat and lanabecestat), have failed in clinical trials involving mild-to-moderate AD patients or subjects with mild cognitive impairment (MCI) and biomarker evidence of brain amyloid deposition (prodromal AD). Surprisingly, some drugs (tarenflurbil, scyllo-inositol, semagacestat, avagacestat, AD02, CAD-106 and verubecestat) caused worsening of the cognitive or clinical condition of the patients compared with those treated with placebo.

Recent failures of anti-A β drugs for treating AD

Recently, there were three major clinical failures of three BACE inhibitors in patients with mild-to-moderate AD and with prodromal AD. The three drugs were lanabecestat (AZD3293, LY3314814) [1], atabecestat (JNJ-54861911) [2] and verubecestat (MK-8931) [3,4]. The discontinuation of the trials with atabecestat was due to observations of serious elevations in liver enzymes. Conversely, the interruptions of the verubecestat and lanabecestat trials were apparently due to lack of efficacy. The concerning safety profile of atabecestat and verubecestat could be molecule specific, but these data should nevertheless be kept in mind in the evaluation of other trials of BACE inhibitors (elenbecestat, CNP520) that are presently ongoing in subjects at early stages of AD.

Another group of extensively studied anti-A β drugs are anti-A β monoclonal antibodies [5]. Several anti-A β monoclonal antibodies were developed and most of them were found not effective in mild-to-moderate AD patients. Some of them (solanezumab, gantenerumab, crenezumab and aducanumab) are now being developed in subjects during early phases of AD or in subjects at preclinical stage of familial AD or even in asymptomatic subjects at high risk of developing AD. Solanezumab was tested in a large Phase III trial (EXPEDITION3) involving 2129 subjects with mild AD or prodromal AD with very modest cognitive or clinical efficacy [6]. A Phase II/III study (SCarlet RoAD) of gantenerumab in 797 prodromal AD patients was prematurely halted for futility [7]. More recently, drugs are being tested in cognitively normal subjects at risk of developing AD (biomarker evidence of brain A β deposition, *APOE* ϵ 4 genotype or family history of AD). This approach has inherent risk of exposing cognitively healthy individuals to potential drug toxicity (as the recent interrupted trial on atabecestat has indicated) and requires long-term, expensive studies with high drop-out rate and consequent biases in interpretation.

The updated version of the A β cascade hypothesis of AD affirms that the major pathogenic species of A β are represented by oligomers. There are numerous types of A β oligomers including small oligomers (dimers, trimers), middle size oligomers (9mers, 12mers, A β *52, A β -derived diffusible ligands [ADDLs]) and high molecular oligomers (protofibrils), and it is unknown if one or more specific oligomeric species are pathogenic in AD. When fibrils are solubilized by immunotherapy, they may produce oligomers. A β oligomers are in equilibrium with A β monomers on one side, and with A β fibrils and plaques on the other side. It is reasonable to imagine that an immunotherapy that efficiently clears A β monomers or A β fibrils will also alter, in the long-term, the equilibrium between the different A β species, including A β oligomers. Scyllo-inositol (ELND005) was shown to neutralize toxic effects of A β oligomers, including amelioration of oligomer-induced synaptic loss, long-term potentiation (LTP) inhibition, and memory deficits [8]. Solanezumab acts by stabilizing A β monomers and may prevent the formation of neurotoxic A β oligomers [9]. Crenezumab (MABT5102A, RG7412) has been shown to bind A β monomers, oligomers and fibrils with an equally high affinity. Gantenerumab shows 20-fold higher affinities for A β oligomers than A β monomers [10]. Intravenous human immunoglobulins (IvIg) contain several types of A β antibodies, including those recognizing A β oligomers and fibrils. IvIg antibodies have been shown to interfere with the oligomerization and fibrillization of A β protect neurons against A β -mediated toxicity, and promote A β clearance from the brain. Unfortunately, all these immunological approaches which interfere directly or indirectly with A β oligomers have not shown clinical efficacy in AD patients.

New potent anti-oligomeric A β antibodies against AD

Recently, some hopes were raised by two potent anti-A β oligomers monoclonal antibodies that have shown encouraging signals of efficacy. Aducanumab (BIIB037) is a recombinant human IgG1 antibody in development for the treatment of prodromal AD. Aducanumab binds to soluble A β aggregates and insoluble fibrils with >10,000-fold selectivity over monomers. Aducanumab emerged from a large screen of B-cell clones obtained from healthy, aged donors who were cognitively normal. It recognizes N-terminal residues 3-7 of the A β sequence [11]. A 12-month Phase Ib study evaluated the safety and tolerability of intravenous doses in 165 prodromal-to-mild AD patients positive on ¹⁸F-florbetapir positron emission tomography (PET) amyloid scan [12]. 40 patients discontinued treatment (24%), mostly due to severe adverse events (SAEs) (20 patients) and withdrawal of consent (14 patients). Treatment discontinuations for SAEs were 10, 10, 6, 10 and 31% in the placebo, 1, 3, 6 and 10 mg/kg groups, respectively. Amyloid-related imaging abnormalities -vasogenic oedema (ARIA-E) occurred in 3–31% of aducanumab recipients in a dose-dependent manner. ARIA-E was commoner in *APOE* ϵ 4 carriers, reaching 55% at the highest dose. The occurrence of ARIA may have contributed to unblinding of the study. Aducanumab dose-dependently and time-dependently decreased brain amyloid burden at 12 months. At 52 weeks, there was less decline in both Mini Mental State Examination and Clinical Dementia Rating scale-Sum of Boxes (CDR-SB) scores, two tools exploring global cognition, in aducanumab-treated subjects compared with placebo-treated patients. The effect of the 10 mg/kg dose reached statistical significance on both variables, although no *p* value adjustments were made for multiple comparisons. These data are encouraging because it is the first time that a lowering effect on A β brain load by an anti-A β therapy was coupled with a positive effect on cognition and clinical global status with dose-dependent trends. However, there was an imbalance in the proportion of mild AD drop-outs in the 10 mg/kg compared with placebo groups (53 vs 29%) that may have contributed to this apparent effect. After study completion, a further arm was added comprising 31 *APOE*- ϵ 4 carriers titrating from 1 mg/kg up to 10 mg/kg; in this group ARIA-E occurrence was 35%. About 80% of patients completing the double-blind phase entered a long-term open extension period, with everyone receiving aducanumab.

More recently, positive results were announced for BAN2401 (mAb158) a monoclonal antibody that selectively binds soluble A β protofibrils [13], in an 18-month, Phase IIb study in 856 subjects with prodromal AD or mild AD that tested five dose regimens of the drug (2.5 mg/kg every 2 weeks, 5 mg/kg once monthly, 5 mg/kg biweekly, 10 mg/kg monthly or 10 mg/kg biweekly) versus placebo [14]. A Bayesian adaptive design approach was adopted so that patients were randomized into treatment arms with a higher likelihood of efficacy after interim assessments of the data. This resulted in 247 patients in the placebo arm, 52 in the 2.5 mg/kg bi-weekly arm, 51 in the 5 mg/kg monthly arm, 92 treated with 5 mg/kg bi-weekly, 253 in the 10 mg/kg monthly arm and 161 in the 10 mg/kg bi-weekly arm. At 18 months, the reduction of accumulated amyloid plaques (PET) in the brain was statistically significant at all doses. At the highest dose of 10 mg/kg bi-weekly, there was a mean plaque reduction from 74.5 at baseline to 5.5 at 18 months as assessed by the Centiloid scale. In addition, at 18 months there was a dose-dependent slowing in cognitive (Alzheimer's disease composite score or ADCOMS) decline from baseline. At the highest dose of 10 mg/kg bi-weekly, the reduction was 30% versus placebo ($p = 0.034$). Also, the highest BAN2401 dose slowed clinical decline by 47% compared with placebo at 18 months, according to the Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog; $p = 0.017$). However, the slowing in cognitive decline from baseline as assessed by CDR-SB was not statistically significant. Dose-dependent increases in A β levels were observed in cerebrospinal fluid ($p < 0.0001$ at the highest dose at 18 months), and there was a statistically significant reduction in total τ levels against placebo in both of the 10 mg/kg dose regimens ($p < 0.05$). The treatment-related adverse event rate was 26.5% for the placebo arm, 53.4% for the 10 mg/kg monthly treatment arm and 47.2% for the 10 mg/kg bi-weekly treatment arm. ARIA-E did not occur in more than 10% of patients in any of the treatment arms but was 14.6% in the APOE $\epsilon 4$ carriers of the 10 mg/kg bi-weekly group. Concerns around safety related to ARIA led regulators to limit number of APOE $\epsilon 4$ carriers in the high-dose group (30%), a percentage substantially lower than the placebo arm and other dose groups (from 70 to 91%). This unbalance may have impacted the rates of cognitive decline between the various arms and contributed to the appearance of benefit of the 10 mg/kg bi-weekly group compared with placebo.

Conclusion

The multiple failures of previous anti-A β drugs may suggest that in the AD brain, the accumulation of A β could be secondary to an unknown initial disrupting event. The increase in brain A β concentrations could be a reactive compensatory response of neurons damaged by unknown causes. Current clinical studies on aducanumab and BAN2401 in subjects with prodromal AD and of other monoclonal antibodies and BACE inhibitors in presymptomatic subjects with early onset familial autosomal dominant AD will answer to this difficult question.

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