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RESEARCH HIGHLIGHT

Early Intervention in Alzheimer's Disease: How Early is Early Enough?

Dong-Yu Fan[1,2] · Yan-Jiang Wang[1,2]

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In 1906, Dr. Alois Alzheimer reported a case of dementia and thought it was a new type of disease. Later, Dr. Emil Kraepelin named it Alzheimer's disease (AD). One hundred years later, AD has become the most common type of dementia affecting the elderly population and a heavy health burden. However, the pathogenesis of the disease remains unclear, and no disease-modifying therapies are available to prevent, halt, or even slow the progression of the disease [1].

Dr. Alzheimer first observed the presence of intracellular neurofibrillary tangles and extracellular plaques in the brain of the first AD patient. The plaques were identified as being composed of the fibrous β-amyloid peptide (Aβ) [2] and named senile plaques, which are considered to be the only specific pathological hallmark of AD. The pathology of senile plaques has become the gold standard for diagnosing AD. Accordingly, the amyloid cascade hypothesis, in which Aβ accumulates in the brain and drives neurodegeneration and cognitive impairment, was proposed to explain the pathogenesis of AD [3]. A large body of evidence indicates that Aβ accumulation in the brain due to Aβ overproduction and/or clearance disorders is the cause of AD, so Aβ-lowering is considered to be the most promising therapeutic strategy. At present, drug research for AD is mainly focused on two approaches: one is to reduce Aβ production by inhibiting key enzymes, including beta-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) and gamma-secretase, which cleave the APP to generate Aβ, and the other is to clear Aβ from the brain with various antibodies against Aβ.

During the past two decades, several enzyme inhibitors and antibodies have been tested in patients with mild-to-moderate AD [4]. Unfortunately, none of them had therapeutic effects. From these failures, a consensus was reached that the mild-to-moderate stage of dementia is too late for the drug to reverse or halt the progression of the disease. In this regard, new criteria were proposed (National Institute on Aging/Alzheimer's Association 2011) to achieve early diagnosis allowing early intervention. In addition, much hope has been placed on interventions for patients who are at prodromal and preclinical stages.

Unfortunately, two phase III clinical trials with prodromal or preclinical patients have recently been declared to fail. The tested drugs were verubecestat [5] and atabecestat [6], both of which are BACE1 inhibitors that were expected to reduce Aβ generation at the early stage of AD. Egan *et al*. presented the results of a phase III trial in AD patients at the prodromal stage using verubecestat for 104 weeks [5]. The results were unexpected: although the levels of both amyloid deposition in the brain and Aβ in the cerebrospinal fluid decreased, cognitive function and the results of structural brain imaging became worse with verubecestat than with placebo. Henley *et al*. reported the preliminary results of a trial using atabecestat in patients in the preclinical stage of AD who were cognitively unimpaired with an elevated deposition of amyloid in the brain [6]. That is, the patients were at an even earlier stage than prodromal AD. However, patients taking the drug had worse cognitive function than those taking the placebo. These two studies were the first wave of attempts at

✉ Yan-Jiang Wang
yanjiang_wang@tmmu.edu.cn

[1] Department of Neurology and Center for Clinical Neuroscience, Daping Hospital, Third Military Medical University, Chongqing 400042, China

[2] Chongqing Key Laboratory of Aging and Brain Diseases, Chongqing 400042, China

intervention at an early stage of the disease, but the results were disappointing.

The reasons for the failure of these two early intervention trials need to be addressed. This may have been because the medication was not administered early enough, and if so, how early is early enough to achieve therapeutic benefits? We believe that these two trials did not provide a clear answer to the question of whether early intervention is effective. The main reason is that the intervention in these trials was not actually early. Here, we must distinguish between the concepts of the early phase of biology and the early phase of clinical manifestations. The accumulation of Aβ begins 15–20 years before the onset of dementia and reaches a plateau in the prodromal stage, and there is a long period of time with the activation of secondary pathological events that forms its own vicious circle. Therefore, when patients have prodromal clinical manifestations, they are actually in the decompensation phase, that is, in the advanced stages of the disease. Even in the preclinical phase with evident brain Aβ deposition, the pathophysiological mechanisms have already been initiated, and they become complicated, making it difficult to achieve therapeutic effects by solely interfering with Aβ at this stage. Therefore, the period in which the intervention can be truly effective may be earlier, that is, the initial stage of brain Aβ accumulation without activation of secondary pathological events such as tau hyperphosphorylation and neuroinflammation. This requires more effective methods of early detection, the identification of high-risk individuals earlier, and the use of drugs to prevent Aβ production and accumulation from the very beginning of the disease.

Another striking result of these two trials was that the use of BACE1 inhibitors caused a decline in cognitive function in the preclinical and prodromal patients, while not having this effect in mild-to-moderate AD patients in previous clinical trials. This was exactly the opposite of what was expected. The researchers were unsure why BACE1 inhibitors would cause more harm earlier than later in the disease. Our view is that the deterioration of cognition was not caused by the decrease in Aβ but by the side-effects of BACE1 inhibition. It may be that the adverse effects of the BACE1 inhibitors masked their protective effects. Current research shows that BACE1 has a particular physiological function in addition to being responsible for the proteolytic processing of APP. BACE1 is required for myelination and the correct bundling of axons by Schwann cells and is thus directly involved in myelination of the peripheral nervous system during early postnatal development [7]. Several animal experiments have shown that BACE1-knockout mice exhibit a variety of abnormal physiological conditions, such as decreased myelination of neurons, spontaneous epilepsy and an abnormal EEG, memory function defects, axonal growth abnormalities, and other abnormal phenotypes. Therefore, when the dose of the inhibitor is high, the physiological function of BACE1 is severely inhibited, which can mask its protective effects.

On the one hand, as discussed in Egan's report, it is possible that BACE1 inhibitors have a greater effect on relatively normal synaptic function in prodromal patients, so they may be more sensitive to the effects of substantial BACE1 inhibition [5]. This is consistent with the animal experiments noted above, so researchers believe that lowering the dose of BACE1 inhibitors may reduce the adverse effects while inhibiting Aβ generation. In addition, suppressing BACE1 has been reported to promote an alternate cleavage pathway, in which η-secretase snips APP to create a synaptotoxic Aη fragment [8], and it has been suggested that inhibition of BACE1 leads to the accumulation of this fragment, which damages the synapses, so it could be that inhibiting the cleavage of APP itself causes problems. The third reason may be the inhibition of BACE2, as most existing inhibitors act on both BACE1 and BACE2. BACE2 levels are usually low in the brain, and BACE2 is thought to be unrelated to amyloid pathogenesis and therefore unlikely to be the culprit. However, current research has revealed little about BACE2 function, and this possibility should not be ruled out.

A safer method is needed to reduce the adverse effects. It may be a better choice to reduce the dose of BACE1. The rate of Aβ deposition in the brain is 30 ng/h, accounting for 5% of the total normal Aβ production (580 ng/h) [9]. Therefore, a first approximation would be that a 5%–10% lowering of production over the 20-year window would abrogate the effect of this degree of clearance failure. Higher levels of inhibition would be required over shorter time intervals closer to the onset of prodromal AD. The other direction is to develop more precise drugs that specifically target Aβ generation by BACE1.

Given the fact that none of the anti-Aβ clinical trials has succeeded so far, an important concern is whether Aβ is the cause of AD or whether it is a suitable therapeutic target. Mounting evidence from human studies supports causative or pivotal roles of Aβ in AD pathogenesis, such as: (1) overproduction of Aβ in the brain due to mutations of APP or presenilin genes, and an additional copy of the APP gene in Down syndrome clearly causes AD [10]; (2) reduction of Aβ generation due to a mutation of the APP gene, which inhibits the cleavage of APP by BACE1, significantly reduces AD occurrence in the Icelandic population [11]; and (3) increase of Aβ in the brain precedes other AD abnormalities including tau hyperphosphorylation, brain atrophy, and cognitive decline in longitudinal studies [12]. Several reasons can explain the failures of current Aβ-targeting trials, including the possibility that interventions

are given too late, a low capacity for Aβ reduction, and the adverse effects of tested drugs. Therefore, the failure of the above clinical trials cannot be used as evidence to deny the Aβ-lowering strategy, and this is not the time to abandon Aβ cascade hypothesis.

In future studies, lowering Aβ remains the cornerstone of AD prevention and treatment. We need more accurate early diagnostic methods to identify patients at the early biological stage of the disease for early intervention. Moreover, the future direction of AD interventions should aim at tertiary prevention strategies [13]. At the early stage of the disease, an Aβ-lowering intervention alone may have a preventive effect; after neurodegenerative and other pathological events have been initiated, comprehensive interventions are required.

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