New therapeutic opportunities for Alzheimer disease

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Introduction

Alzheimer disease (AD) is the most common cause of dementia worldwide and the total number of patients is increasing [1]. This can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles (NFTs) as a result of accumulation of amyloid-beta peptide in the brain that result in multiple cognitive dysfunctions as well as change in behavioural and emotional control [2]. AD is important public health problem because of high prevalence and subsequent socioeconomic costs. Until 2021, only 4 drugs have been approved for treating AD as three acetylcholinesterase inhibitors (AChEIs) (e.g., donepezil, rivastigmine, and galantamine) and one N-methyl-D-aspartate receptors (NMDAR) [3]. Although significant scientific advances were made in AD research field, current AD drugs are all symptomatic that they just lessen the symptoms of the disease instead of prevent the progression of disease.

Based on the amyloid cascade hypothesis, amyloid-targeted treatment to reduce β-amyloid (Aβ) was expected to inhibit disease progression or delay functional decline, but most clinical trials failed to prove its effectiveness [4]. However, aducanumab, which was recently conditionally approved by the US Food and Drug Administration for the treatment of AD. Although there are many questions to be answered, this would be the landmark for AD drug that attempt to treat a neurodegenerative disease rather than just symptoms. In this review, I would like to discuss the current development status of dementia treatment, its limitations, and the future opportunity.

Keywords: Alzheimer disease; Therapeutics; Amyloid
Emerging anti-amyloid therapies

The monoclonal antibody as passive immunotherapeutic agents were developed after failure of vaccine for AD [17] to reduce effect of Aβ42 in central as well as peripheral region. Although a few clinical trial of anti-amyloid immunotherapy have failed, some is undergoing. Aducanumab is a human anti-amyloid monoclonal antibody of which target is aggregated forms of soluble or insoluble Aβ. In a dose and time dependent manner, aducanumab enters the central nervous system as infusion that is undergoing. Aducanumab is a human anti-amyloid monoclonal antibody that has a higher affinity for Aβ oligomers [18]. Dose-related amyloid-related imaging abnormalities—edema (ARIA-E) are the main safety related finding and more common in Apo-ε4 carriers. The infusion of highest dose of 10 mg/kg was reported the significant decline the progression of cognitive impairment measured by the CDR-sum of boxes [18]. As a result, aducanumab was approved by the FDA for the treatment of AD with the condition that a phase IV trial carefully assess its safety and efficacy in June of 2021. This accelerated approval process for the use toward AD-related mild cognitive impairment (MCI) or mild dementia raised some controversy related to limited evidence of treatment benefit. Recently, appropriate use of aducanumab by expert panel was released (Table 1) [19]. Therefore, patients should meet the clinical criteria for mild AD dementia or MCI due to AD supported by validated cognitive scores. Cholinesterase inhibitors or memantine can be used for these patients.

Amyloid status should be confirmed with an amyloid PET or cerebrospinal fluid (CSF) biomarkers. Apo-E-ε4 genotyping should be discussed with the patient/care giver for the risk of ARIA. A brain magnetic resonance imaging (MRI) should be obtained within 1 year before initiating treatment. Medical, cardiovascular, and psychiatric status should be stable before initiating treatment. Patients who are pregnant, on anticoagulant medications, or have evidence of significant cerebrovascular disease on brain MRI should be excluded from treatment. Patients and care partners should understand the requirements of therapy. Clinicians may need to collaborate with or refer to specialists with expertise in these assessments. This guideline also included dosing and MRI monitoring schedule as monthly infusion for a year [19].

Lecanemab or BAN2401 is IgG1 monoclonal antibody that binds to large soluble Aβ protofibrils selectively. It has showed to increase CSF levels of Aβ, reduce total tau levels and slow cognitive decline, although further validation these findings is necessary [20]. The clinical trials for early AD or preclinical AD looking at efficacy and safety are in progress currently. Donanemab is an immunoglobulin whose molecular target is cerebral amyloid plaque. For early AD subjects, some improvement in composite cognitive scores and activities of daily living score was achieved although asymptomatic ARIA-E were observed in phase 2 trial [21]. A safety and tolerability study showed 40% to 50% amyloid reduction and approximately 90% of participants developed anti-drug antibodies at 3 months after a single intravenous dose [22]. Gantenerumab is another monoclonal antibody that has a higher affinity for Aβ oligomers [23]. At higher doses, there was a reduction of amyloid plaque at two years by PET study [24]. Trials evaluating safety, tolerability, efficacy among early AD subjects or genetic AD are currently ongoing.

The current trends in AD drug research

Development of AD-specific disease modifying therapy is continuing based on pathophysiology. According to Alzheimer’s disease drug development pipeline: 2021’ report by the Alzheimer’s Association, as of January 2021, 152 clinical trials for a total of 126 candidate substances are in progress, and majority of the total drugs (82.5%) are disease-modifying drugs [15]. In terms of drug mechanism, it is expanding its scope to include tau, inflammation, neuroprotection, vascular factors, metabolism, and nerve regeneration as well as beta-amyloid [16].
**Table 1. Appropriate use criteria for aducanumab in clinical practice**

<table>
<thead>
<tr>
<th>Participant feature</th>
<th>Appropriate use in clinical practice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Younger or older patients meeting all other criteria for treatment could be considered candidates for aducanumab</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Clinical criteria for MCI due to AD or mild AD dementia</td>
</tr>
<tr>
<td><strong>Scale score at baseline</strong></td>
<td>MMSE 21–30 or equivalent such as MoCA 17–30</td>
</tr>
<tr>
<td><strong>Amyloid status</strong></td>
<td>Amyloid positive PET (visual read) or CSF findings consistent with AD</td>
</tr>
<tr>
<td><strong>Genetic testing</strong></td>
<td>Genotyping should be discussed with the patient/care partner. ARIA risk should be described, and the patient’s preferences assessed.</td>
</tr>
<tr>
<td><strong>Neurological examination</strong></td>
<td>Non-AD neurological disorders excluded</td>
</tr>
<tr>
<td><strong>Cardiovascular history</strong></td>
<td>Stable cardiovascular conditions required; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td>Stable medical conditions required; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen</td>
</tr>
<tr>
<td><strong>Psychiatric history</strong></td>
<td>Must be stable psychiatrically; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen</td>
</tr>
<tr>
<td><strong>Reproductive status</strong></td>
<td>Female subjects who are pregnant or breast feeding excluded; female subjects who are of childbearing age must be practicing contraception</td>
</tr>
<tr>
<td><strong>Clotting status</strong></td>
<td>Patients on anticoagulants are excluded</td>
</tr>
<tr>
<td><strong>Concomitant medications</strong></td>
<td>Patients can be on standard of care with cholinesterase inhibitors and memantine</td>
</tr>
<tr>
<td><strong>Baseline MRI</strong></td>
<td>Patients should be excluded if there is evidence of acute or subacute hemorrhage, macrohemorrhage, greater than 4 microhemorrhages, cortical infarction (&gt; 1.5 cm), 1 lacunar infarction (&gt; 1.5 cm), &gt; 1 area of superficial siderosis, or diffuse white matter disease</td>
</tr>
<tr>
<td><strong>Care support</strong></td>
<td>May be living independently or with a care partner</td>
</tr>
<tr>
<td><strong>Informed consent</strong></td>
<td>Patient and care partner must understand the nature and requirements of therapy (e.g., monthly infusions to be performed indefinitely) and the expected outcome of therapy (slowing of decline of clinical features)</td>
</tr>
</tbody>
</table>

Cummings et al. J Prev Alzheimers Dis 2021;8:398–410, according to the Creative Commons license [19]. MCI, mild cognitive impairment; AD, Alzheimer disease; MMSE, mini mental state examination; MoCA, montréal cognitive assessment; PET, positron emission tomography; CSF, cerebrospinal fluid; ARIA, amyloid-related imaging abnormalities; MRI, magnetic resonance imaging.

**Controversies in anti-amyloid therapies**

Following accelerated approval of aducanumab, FDA gave “breakthrough therapy designation” on lecanemab and donanemab at June of 2021. This process is a way to accelerate the review and development of drugs underway for life-threatening or serious disease such as AD. This designation is not an indication that the drugs will be finally be affirmed to be safe and effective nor that they will be approved by FDA. Numerous randomized controlled trial studies based on the amyloid cascade reaction hypothesis so far have failed and it is argued that the discrepancy of aducanumab trials between the results of the EMERGE and ENGAGE clinical trials, which were designed with the same subject selection and research method, is derived from statistical error [25]. The difference between the results of the two trials might be derived from the difference in the ApoE-ε4 allele, the method of dose increasing, and the fact that there were relatively many ‘rapid progressors’ among the high-dose patients who participated in the ENGAGE study although the definite standard for ‘rapid progression’ is not established [26]. In clinical trials, post-hoc analysis is not recommended for FDA approval.

Regarding safety, ARIA-E and Amyloid-related imaging abnormalities-haemosiderin (ARIA-H) appear due to damage to the blood-brain barrier in the process of immune-mediated clearance of amyloid accumulated in the brain with anti-amyloid therapy [27]. Aducanumab and gantenerumab occurred in approximately 30%, with ARIA-E occurring more frequently in the high-dose aducanumab group and lecanemab, which has a relatively low affinity for amyloid plaque, occurred in about 10% [27]. ARIA usually appears at the beginning of treatment and is mostly asymptomatic. However, 6% of high-dose treatment patients discontinued treatment due to side effects. Additionally, ARIA showed serious symptoms such as confusion, disorientation, gait disturbance, ataxia, visual impairment, headache, nausea, falls, and blurred vision in about 0.9%. Because of these issues, it is insisted that insurance should not cover aducanumab as a treatment for AD until additional phase III trials prove clinical benefit of high-dose aducanumab in people with mild AD dementia or MCI due to AD [28]. To sum up, the debate on the correlation of reduction of beta amyloid and clinical improvement in AD will continue until a clinical trial for efficacy is over. In addition to it, application of aducanumab to those with AD...
and concomitant condition or those with atypical AD could be the candidate of future studies [29].

**Tau directed therapies**

The shortness of clear efficacy of amyloid-based therapeutics has led researchers to explore other targets [30]. Tau protein is another pathologic hallmark that defines AD. It is a microtubule binding protein which forms NFTs and the accumulation of them have been known to correlate more significantly with severity of cognitive decline than amyloid load. There is evidence that Aβ accumulation exacerbate tau load [31]. Tau protein has been found to mediate some of the toxic effects of Aβ leading to dendritic simplification, synapse loss, and cell death in AD [32]. First approaches for tau directed therapies focused on inhibition of tau aggregation or kinases or stabilization of microtubules. Most of these studies have been stopped due to lack of efficacy or toxicity [33]. Tau immunotherapies are getting research focus currently. Variable targets are made related to tau targeting therapy because post-translational modifications and subsequent tau misfolding and loss of microtubule binding result in elevated levels of tau in the cytosol [32]. For example, the active tau vaccine AADvac1 represented a third of the participants were negative in tau-biomarker while clinical effect was not observed in the ADAMANT phase 2 study [34]. Therapeutic agents targeting tau protein, immunotherapy, tau aggregation inhibitors, and microtubule stabilizing substances are undergoing clinical trials and total of 11 drugs are included as of January of 2021 [15]. Compared to amyloid-related drugs, it is still in the early stages of research.

**Inflammation directed agents**

Lots of evidence has showed the involvement of microglia in AD pathogenesis and it is known to play both neuroprotective and neurotoxic effects [35,36]. Firstly, microglia with dual roles were designated as a pro-inflammatory M1 phenotype and immuno-suppressive M2 phenotype that can be changed under pathological and physiological conditions in the brain [37]. During the pleclinical AD, microglia are activated by pro-inflammatory substances such as Aβ and release inflammatory cytokines, including tumor necrosis factor-α, interleukin (IL)-6, and IL-1β, and reactive oxygen that results in neuronal death and synaptic dysfunction [38]. There are increasing trend in inflammation directed agents that have multiple targets such as microglial activation, stabilization of mast cell, T-cell regulation and reduction of microbiome dystosis [15]. There are 2 phase 3 trials, 12 phase 2 trials and 5 phase 1 trials related inflammation/infection/immunity as of January, 2021.

**Metabolism and bioenergetics**

Metabolic perturbations have been known to be linked to AD both at the cellular level in the brain as well as in the whole body [1]. Type two diabetes increases the risk of AD [39,40] and insulin sensitivity is impaired in the majority of elderly people [41]. Previous studies related to epidemiology, mechanisms of disease and clinical manifestations revealed links between AD and diabetes [2,42–45]. Metabolic pathways leading to energy production are essential for normal neuronal function and the brain of AD was related to decreased glucose metabolism [42]. Although the underlying molecular mechanisms between diabetes and AD are not yet obvious [46], anti-diabetic drugs are reviewed for clinical benefit in AD [47–49]. Additionally, disruption of glucose metabolism and mitochondrial dysfunction are a common feature of both AD and diabetes [50]. Because of the essential role of mitochondria in bioenergetics, targeting the mitochondrial function has emerged as a therapeutic strategy for neurodegenerative diseases such as AD [51–53]. Emerging targets for this area are insulin sensitizer, glucagon-like peptide receptor agonist, mitochondrial enhancers and ketosis-inducing agents. There are 2 phase 3 trials, 4 phase 2 trials and 15 phase 1 trials related metabolism and bioenergetics as of January, 2021 [15].

**Conclusion**

The research experience of monoclonal antibody therapeutics against amyloid beta has led to increasing interest in therapeutic approaches based on disease modifying agents targeting amyloid beta hypothesis in the brain, as well as other targets, such as tau, inflammation and synaptic dysfunction. If there is a lesson learned at a high expense from the failure and success of existing drugs, biological targets must be identified through biomarkers such as PET or CSF in addition to clinical diagnosis when recruiting patients, and drugs required higher doses than initially expected. It can be suggested that patients with mild symptoms had better drug responsiveness, and that a more sensitive cognitive function measurement tool was needed to confirm the effect of the drug. In 2018, the Research Framework, jointly announced by the National Institute of Aging and Alzheimer’s Association, defines AD only with biomarkers [54]. It is expected to play a very important role in confirming the effectiveness of treatment. Biomarkers mainly used include amyloid and tau in CSF, brain MRI, and amyloid
PET, and the use of blood amyloid and tau and tau PET is expected to gradually increase. In fact, the drug development guidelines published in February 2018 by the US FDA emphasize biomarker-based clinical trials in early patients [55]. After decades of development and research of biomarkers in AD, they are having a substantial impact on the development of disease-modifying drugs [54]. Biomarkers were essential to the approval of aducanumab, and are used in other studies for the assessment of treatment efficacy and target engagement and patient selection. Although molecular imaging of beta amyloid and tau were commonly used in clinical trials, the need for high accessibility and reliability for diverse populations was increased a lot this year. Therefore the studies on the use of blood-based biomarkers was validated against molecular imaging that p-tau217 and p-tau181 represented high performance for differentiating AD with other neurodegenerative disease [56,57]. Ultimately, the success of future drug research depends on research innovation that sets the most important targets for the disease process, develops effective drugs for these targets, and conducts rigorous clinical trials. In line with this research trend, AD has been the driving force in the development of new drugs due to the social demand and responsibility due to the limitations of the treatment effect and choice. The recent FDA approval of aducanumab opens a new era in the treatment of AD, bringing interest and hope to patients, families, and healthcare workers facing an aging population. Although there are many controversies to be resolved in the future, the approval of aducanumab will affect and change the approval of future treatments. Physicians must have an ethical responsibility to fully explain to patients and their families not only the effects of drugs, but also aspects of safety or uncertainties. That is to say, clinicians should be well aware of side effect of aducanumab such as ARIA-related symptoms. The debate on whether reduction of Aβ correlates clinical improvement in AD continues and the cost of this medication is high as much as more than 50 thousand dollars annually. On top of that, further studies are needed to assess if aducanumab is appropriate for those with other disease beyond MCI due to AD or AD dementia. Because many questions that should be solved remain, clinicians also need to be well informed about this new drug as upcoming promising therapeutic opportunity.

Notes

Conflicts of Interest
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