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NEW THERAPEUTIC OPPORTUNITIES IN ALZHEIMER'S DISEASE: THE ROLE OF ANTI-AMYLOID ANTIBODIES: A COMPREHENSIVE REVIEW

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, neuronal loss, and the accumulation of β-amyloid plaques and tau pathology. For many years, pharmacological treatment has been limited to symptomatic therapies, including acetylcholinesterase inhibitors and memantine, which provide only modest clinical benefits without modifying disease progression. The development of anti-amyloid monoclonal antibodies has introduced the first disease-modifying therapeutic approach targeting the underlying pathology of AD. Agents such as aducanumab, lecanemab, and donanemab reduce cerebral amyloid burden through selective targeting of different forms of β-amyloid. Clinical trials, including CLARITY AD and TRAILBLAZER-ALZ 2, have demonstrated that these therapies can slow cognitive decline in patients with early-stage AD, although their efficacy depends on disease stage and patient selection. Despite remaining challenges, including safety concerns and the risk of amyloid-related imaging abnormalities, anti-amyloid therapies represent a major advancement in the treatment of Alzheimer's disease and mark a transition toward disease-modifying strategies.

KEYWORDS

Beta-Amyloid, Alzheimer's Disease, Aducanumab, Lecanemab, Donanemab, Monoclonal Antibodies, Aducanumab, Amyloid Target Therapy

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1. General Information About Alzheimer's Disease

1.1 Epidemiology of Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia, accounting for approximately 60–70% of all dementia cases. As the global population ages, the number of affected individuals continues to rise, making AD one of the greatest challenges facing modern medicine and public health. The risk of developing AD increases with age, with individuals over 65 years representing the largest patient population. The global prevalence of dementia is projected to continue increasing in the coming decades. [9], [10]

1.2 Pathophysiology of Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disorder characterized by neuronal and synaptic loss, particularly in the hippocampus and cerebral cortex. Its main neuropathological features include extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau, accompanied by neuroinflammation and progressive neurodegeneration. [11] Clinically, AD presents gradual impairment of memory, followed by decline in executive function, language, orientation, and daily functioning. Since pathological changes begin years before symptom onset, early biomarker-based diagnosis is essential for identifying at-risk individuals and enabling timely therapeutic intervention. [1,2]

1.3 The Amyloid Hypothesis

The amyloid hypothesis remains the leading explanation for Alzheimer's disease pathogenesis. It suggests that excessive accumulation of β-amyloid (Aβ), particularly Aβ42, initiates a cascade leading to synaptic dysfunction, neuroinflammation, tau pathology, and progressive neuronal loss. Strong genetic evidence, including mutations in the *APP*, *PSEN1*, and *PSEN2* genes, as well as trisomy 21, supports this model. However, the weak correlation between amyloid burden and clinical symptoms, together with the limited success of earlier anti-amyloid therapies, has raised questions about its validity. Nevertheless, the recent clinical benefits of monoclonal antibodies such as lecanemab and donanemab have renewed interest in β-amyloid as a therapeutic target. [3,4]

1.4 Limitations of Conventional Symptomatic Treatment

For over two decades, Alzheimer's disease treatment relied solely on symptomatic therapies, including acetylcholinesterase inhibitors and the NMDA receptor antagonist memantine, which provide modest cognitive benefits without affecting the underlying neurodegenerative process. The limited efficacy of these treatments has driven the development of disease-modifying therapies. Monoclonal antibodies targeting β-amyloid are the first agents shown to slow disease progression in patients with early Alzheimer's disease, marking a new era in AD treatment. [5]

2. Current Therapeutic Approaches

2.1. Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors (AChEIs), including donepezil, rivastigmine, and galantamine, have been the mainstay of Alzheimer's disease treatment for over two decades. By inhibiting acetylcholinesterase, they increase central acetylcholine levels and partially compensate for cholinergic deficits associated with AD. Donepezil selectively inhibits acetylcholinesterase, rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase, and galantamine additionally modulates nicotinic acetylcholine receptors. [6] AChEIs are recommended primarily for mild to moderate AD, while donepezil is also approved for severe disease. Clinical trials have shown modest improvements in cognition, daily functioning, and some neuropsychiatric symptoms; however, these benefits are symptomatic and do not alter the underlying neurodegenerative process. [6,7] Common adverse effects include gastrointestinal symptoms, weight loss, and bradycardia, making cardiovascular assessment and treatment monitoring essential. [6]

2.2. Memantine

Memantine, a non-competitive NMDA receptor antagonist, is another symptomatic treatment for Alzheimer's disease. By reducing pathological glutamate-mediated NMDA receptor activation while preserving normal neurotransmission, it helps limit excitotoxic neuronal damage. [6], [7] It is recommended for patients with moderate to severe AD and has been shown to provide modest improvements in cognition, daily functioning, and behavioral symptoms. However, like acetylcholinesterase inhibitors, memantine does not modify the underlying disease process. It is generally well tolerated, with dizziness, headache, somnolence, constipation, and confusion being the most common adverse effects. Combination therapy with acetylcholinesterase inhibitors may provide greater clinical benefits than either treatment alone in moderate to severe AD. [7], [8]

2.3. Efficacy and Limitations of Current Therapeutic Approaches

Despite the well-established efficacy of both therapeutic classes in alleviating the symptoms of dementia, neither targets the underlying cause of Alzheimer's disease. Both acetylcholinesterase inhibitors and memantine provide symptomatic relief and may delay cognitive decline by several months; however, they do not address the fundamental pathogenic mechanisms responsible for disease progression. Specifically, these agents do not prevent β-amyloid accumulation, tau hyperphosphorylation, or the progressive loss of neurons. Consequently, the underlying neurodegenerative process continues despite ongoing treatment. [6], [7] The limited efficacy of symptomatic therapies has been the primary driving force behind the search for disease-modifying treatments. In recent years, monoclonal antibodies targeting β-amyloid have attracted considerable scientific interest. These agents are the first to demonstrate the ability to slow disease progression, although their clinical benefit has thus far been observed only in patients with early-stage Alzheimer's disease. The introduction of these therapies has marked a major milestone in Alzheimer's disease management, shifting the therapeutic paradigm from exclusively symptomatic treatment toward interventions that target the underlying pathological mechanisms of the disease. [6], [7]

3. Anti-Amyloid Antibodies

3.1. Mechanism of Action

Anti-amyloid antibodies are a new class of disease-modifying therapies for Alzheimer's disease that reduce cerebral amyloid burden by selectively binding different forms of β-amyloid (Aβ) and promoting microglial-mediated plaque clearance. Their targets differ: aducanumab primarily binds fibrillar amyloid, lecanemab targets soluble Aβ protofibrils, and donanemab recognizes pyroglutamate-modified Aβ in mature plaques. [12], [13], [14] Clinical trials have shown that amyloid reduction is associated with slower cognitive decline in early Alzheimer's disease. In the CLARITY AD trial, lecanemab significantly reduced amyloid burden and slowed disease progression compared with placebo, while also improving plasma biomarkers, including p-tau181 and the Aβ42/Aβ40 ratio. [13]

3.2. Patient Selection

Anti-amyloid antibodies are indicated for patients with early Alzheimer's disease, including mild cognitive impairment due to AD and mild dementia. Treatment requires confirmation of cerebral amyloid pathology using validated biomarkers and a baseline brain MRI to assess the risk of amyloid-related imaging abnormalities (ARIA). Particular caution is needed in APOE ε4 carriers, who have a higher risk of ARIA and other treatment-related adverse events. [13], [15], [16]

3.3. Biomarkers

The introduction of anti-amyloid therapies has substantially increased the clinical importance of biomarkers in both the diagnosis of Alzheimer's disease and patient selection for treatment. Currently, the gold standard for confirming cerebral β-amyloid deposition consists of amyloid positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) analysis. In CSF, the characteristic biomarker profile of Alzheimer's disease includes decreased concentrations of Aβ42 or a reduced Aβ42/Aβ40 ratio, accompanied by increased levels of total tau (t-tau) and phosphorylated tau (p-tau181 or p-tau217). These biomarkers reflect both amyloid accumulation and the extent of neuronal injury, making them valuable

4. Overview of the Major Anti-Amyloid Therapies

4.1. Aducanumab (Aduhelm): History and Controversies

Aducanumab was the first monoclonal antibody developed to target β-amyloid and the first disease-modifying therapy for Alzheimer's disease to receive approval from the U.S. Food and Drug Administration (FDA), which granted accelerated approval in 2021. Aducanumab is a fully human IgG1 monoclonal antibody that exhibits high affinity for aggregated forms of β-amyloid present within amyloid plaques. Its mechanism of action involves activation of microglia, promoting the phagocytic clearance of amyloid deposits from the brain, an effect that has been confirmed by studies using amyloid positron emission tomography (PET). [17], [18] The approval of aducanumab was, however, highly controversial. The FDA's decision was based primarily on the drug's ability to reduce cerebral amyloid burden, despite inconclusive evidence regarding its clinical efficacy. Two pivotal phase III clinical trials yielded conflicting results. In one study, patients receiving the highest dose of aducanumab exhibited a modest slowing of cognitive decline, whereas the second trial failed to demonstrate a significant clinical benefit. These inconsistent findings sparked considerable debate regarding the drug's true therapeutic value and the appropriateness of its regulatory approval. Furthermore, treatment with aducanumab was associated with a substantial incidence of adverse events, particularly amyloid-related imaging abnormalities (ARIA), including cerebral edema (ARIA-E) and cerebral microhemorrhages (ARIA-H). These complications occurred more frequently in carriers of the APOE ε4 allele. As a result, the clinical adoption of aducanumab has remained limited, and the drug did not receive marketing authorization in Europe. [18], [19]

4.2. Lecanemab (Leqembi): Results of the CLARITY AD Trial

Lecanemab is a humanized IgG1 monoclonal antibody that selectively binds soluble β-amyloid protofibrils, which are considered among the most neurotoxic forms of the peptide. By targeting these aggregates, lecanemab promotes the clearance of amyloid plaques and reduces further amyloid accumulation, thereby influencing the underlying neurodegenerative process. The efficacy of lecanemab was primarily evaluated in the multicenter, randomized, placebo-controlled phase III CLARITY AD trial, which enrolled nearly 1,800 patients with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's dementia and confirmed cerebral amyloid pathology. After 18 months of treatment, lecanemab significantly slowed cognitive and functional decline compared with placebo. The primary endpoint, assessed using the Clinical Dementia Rating–Sum of Boxes (CDR-SB) scale, demonstrated an approximately 27% reduction in the rate of clinical progression in the lecanemab-treated group. In addition, amyloid PET imaging revealed a marked reduction in cerebral amyloid burden, accompanied by favorable changes in cerebrospinal fluid and plasma biomarkers. The most frequently reported adverse events were amyloid-related imaging abnormalities, including vasogenic edema (ARIA-E) and cerebral microhemorrhages (ARIA-H), most of which were asymptomatic. The risk of ARIA was higher among carriers of the APOE ε4 allele; therefore, genetic testing before treatment initiation and regular brain magnetic resonance imaging (MRI) during therapy are recommended. The findings of the CLARITY AD trial represent the first compelling evidence that reducing cerebral β-amyloid burden can translate into a measurable slowing of clinical disease progression in Alzheimer's disease, although the magnitude of the clinical benefit remains modest. [20]

4.3. Donanemab (Kisunla): Results of the TRAILBLAZER-ALZ 2 Trial

Donanemab is a monoclonal antibody directed against the pyroglutamate-modified form of β-amyloid (N3pG), which is found predominantly in mature amyloid plaques. Unlike lecanemab, donanemab exhibits high affinity for established amyloid deposits, enabling their rapid clearance from the brain.The efficacy of donanemab was evaluated in the phase III TRAILBLAZER-ALZ 2 trial, which enrolled more than 1,700 patients with early symptomatic Alzheimer's disease. Treatment with donanemab significantly slowed cognitive and functional decline compared with placebo. The greatest clinical benefit was observed in patients with a lower baseline burden of tau pathology, suggesting that the therapy is most effective when initiated during the earliest stages of the disease. Donanemab also produced a marked reduction in cerebral amyloid burden. In a substantial proportion of patients, amyloid PET imaging demonstrated sufficient amyloid clearance to reach amyloid-negative status, allowing treatment to be discontinued after achieving the predefined biological target. The safety profile of donanemab was broadly consistent with that of other anti-amyloid antibodies. The most common adverse events were amyloid-related imaging abnormalities, including vasogenic edema (ARIA-E) and cerebral microhemorrhages (ARIA-H), necessitating regular monitoring with brain magnetic resonance imaging (MRI). Despite these safety concerns, the results of the TRAILBLAZER-ALZ 2 trial established donanemab as another effective disease-modifying therapy for patients with early Alzheimer's disease. [21], [22]

4.4. Other Anti-Amyloid Antibodies Under Investigation

In addition to the currently approved therapies, several other anti-amyloid monoclonal antibodies have been evaluated in clinical trials. One of the most extensively studied agents is gantenerumab, a fully human monoclonal antibody that selectively binds fibrillar forms of β-amyloid. Although gantenerumab effectively reduced cerebral amyloid burden, phase III clinical trials failed to demonstrate a significant slowing of cognitive decline. Consequently, its clinical development for the treatment of Alzheimer's disease was discontinued. [23] Similarly, solanezumab, a monoclonal antibody directed primarily against soluble β-amyloid monomers, failed to demonstrate the anticipated clinical efficacy despite exhibiting a favorable safety profile. [24] Current research has focused on next-generation anti-amyloid antibodies, including remternetug and trontinemab, which are designed to achieve more efficient amyloid clearance while minimizing treatment-related adverse effects. Ongoing clinical trials are evaluating whether these agents can provide greater clinical benefit than currently available therapies and whether they may be effective when administered at even earlier stages of Alzheimer's disease. The outcomes of these studies have the potential to substantially influence the future standard of care for Alzheimer's disease. [25]

5. Efficacy of Anti-Amyloid Antibody Therapy

5.1. Effects on the Rate of Cognitive Decline

The goal of anti-amyloid antibody therapy is to slow Alzheimer's disease progression, with the greatest benefit seen in patients with early symptomatic disease, including mild cognitive impairment and mild dementia due to AD. In the CLARITY AD trial, lecanemab reduced clinical progression by 27% over 18 months and improved multiple cognitive outcomes. [26] Similarly, the TRAILBLAZER-ALZ 2 trial showed that donanemab slowed disease progression, particularly in patients with lower baseline tau pathology, highlighting the importance of early treatment. [21] In contrast, the clinical benefit of aducanumab remains uncertain because of conflicting phase III trial results. [18], [27]

5.2. Impact on Quality of Life

Current evidence suggests that anti-amyloid antibodies may help preserve patients' independence for a longer period by slowing the decline in cognitive function and the ability to perform activities of daily living. Clinical trials have demonstrated favorable effects on scores obtained using the Alzheimer's Disease Cooperative Study–Activities of Daily Living for Mild Cognitive Impairment (ADCS-MCI-ADL) scale. However, the overall clinical benefits observed to date have been modest. Further studies are needed to evaluate the long-term impact of anti-amyloid therapy on patients' quality of life, functional independence, and caregiver burden. [28]

5.3. Effects on Biomarkers

The most pronounced effect of anti-amyloid antibody therapy is observed in Alzheimer's disease biomarkers. Treatment results in a substantial reduction in cerebral β-amyloid burden, as demonstrated by amyloid PET imaging. Furthermore, reductions in phosphorylated tau levels (p-tau181 and p-tau217) have been observed, suggesting that these therapies may influence downstream neurodegenerative processes. Despite the marked improvement in biomarker profiles, these changes do not always translate into proportionally large clinical benefits. This discrepancy highlights the complexity of Alzheimer's disease pathophysiology and suggests that amyloid reduction alone may not fully determine the clinical outcome of therapy. [26], [21]

6. Safety of Anti-Amyloid Antibody Therapy

6.1. ARIA-E and ARIA-H

The most common adverse event associated with anti-amyloid antibody therapy is amyloid-related imaging abnormalities (ARIA). Two main types of ARIA are recognized: ARIA-E and ARIA-H. ARIA-E refers to vasogenic edema or sulcal effusions, whereas ARIA-H includes cerebral microhemorrhages and superficial siderosis. Most ARIA cases are asymptomatic and are detected incidentally during routine magnetic resonance imaging (MRI) monitoring. However, some patients may develop clinical manifestations, including headache, altered mental status, dizziness, or seizures. The risk of ARIA appears to decrease with continued treatment over time. [29], [30], [31]

6.2. Intracerebral Hemorrhages

During treatment with anti-amyloid antibodies, cerebral microhemorrhages may occur, and, less frequently, more severe intracerebral hemorrhagic events. The risk of these complications is increased in patients with cerebral amyloid angiopathy and in those receiving anticoagulant therapy. For this reason, careful patient selection is essential before initiating treatment. In individuals requiring long-term anticoagulation, anti-amyloid antibody therapy is often not recommended due to the increased risk of hemorrhagic complications. [30], [31]

6.3. MRI Monitoring

Magnetic resonance imaging (MRI) has become an essential component of both patient selection and monitoring during anti-amyloid antibody therapy. A baseline MRI scan is recommended before treatment initiation, followed by regular surveillance imaging during therapy, particularly prior to the 5th, 7th, and 14th infusions. The primary purpose of MRI monitoring is the early detection of ARIA-related changes, allowing timely clinical management, including temporary interruption of therapy when necessary to reduce the risk of serious complications. [30], [29]

6.4. Contraindications

Patients with significant cerebrovascular abnormalities, extensive cerebral microhemorrhages, a history of major intracerebral hemorrhage, or contraindications to magnetic resonance imaging (MRI) are generally not considered eligible for anti-amyloid antibody therapy. Caution is also required in patients receiving anticoagulant therapy or those with suspected cerebral amyloid angiopathy, as these conditions are associated with an increased risk of hemorrhagic complications. [30], [31]

6.5. Role of the APOE ε4 Genotype

The presence of the APOE ε4 allele, particularly in the homozygous state, is associated with an increased risk of developing amyloid-related imaging abnormalities (ARIA) during anti-amyloid antibody therapy. In the CLARITY AD trial, the incidence of ARIA was highest among APOE ε4 homozygous carriers. Therefore, genetic testing is recommended before initiating therapy, along with a thorough discussion with the patient regarding the potential benefits and risks associated with treatment. APOE genotyping enables more individualized risk assessment and facilitates appropriate planning of treatment monitoring strategies. [30]

7. Controversies

7.1. Cost of Therapy

One of the major controversies surrounding anti-amyloid antibody therapy is the high cost of treatment. The overall financial burden includes not only the cost of the drug itself but also the expenses associated with diagnostic procedures required for treatment eligibility and ongoing patient monitoring, including costly investigations such as regular magnetic resonance imaging (MRI) scans. Current economic analyses suggest that, at the present treatment costs, the cost-effectiveness ratio in relation to the achieved clinical benefits remains a subject of ongoing debate. [32]

7.2. Accessibility of Therapy

Access to anti-amyloid therapy remains limited due to the requirement for confirmation of cerebral amyloid pathology, the need for regular magnetic resonance imaging (MRI) monitoring, and the necessity of treatment administration in specialized clinical centers. As a result, only a proportion of patients meet the eligibility criteria and can receive these therapies. [32], [33]

7.3. Patient Selection Criteria

Only patients with early-stage Alzheimer's disease and confirmed cerebral amyloid pathology are currently eligible for anti-amyloid therapy. In addition, treatment decisions must consider the risk of adverse events, the presence of comorbidities, and neuroimaging findings, which significantly narrows the group of potential candidates for treatment. [32]

7.4. Are the Clinical Benefits Sufficiently Significant?

The greatest controversy surrounding anti-amyloid therapies concerns the assessment of their real-world clinical benefits. Although clinical trials have demonstrated statistically significant slowing of cognitive decline and effective reduction of cerebral β-amyloid burden, some researchers emphasize that the observed clinical effect remains modest and may not reach the threshold of meaningful improvement from the patient's perspective. Therefore, ongoing debate continues regarding whether the clinical benefits of these therapies justify their substantial costs, potential risks, and treatment burden. [32], [34]

8. Conclusions

Alzheimer's disease remains one of the greatest challenges in modern neurology due to its continuously increasing prevalence and limited therapeutic options. Currently available treatments do not modify the underlying neurodegenerative process and provide only symptomatic benefits. The introduction of next-generation therapies, including lecanemab and donanemab, represents the first attempt to target the underlying pathology of Alzheimer's disease by reducing β-amyloid burden and slowing cognitive decline in patients with early-stage disease. Despite the promising results of clinical trials, anti-amyloid therapies are associated with several important limitations. The clinical benefits achieved to date are modest, treatment requires careful patient selection, regular monitoring with magnetic resonance imaging (MRI), and consideration of potential adverse events, particularly amyloid-related imaging abnormalities (ARIA). Additional challenges include the high cost of therapy and limited accessibility for eligible patients. Nevertheless, current evidence indicates that anti-amyloid antibodies may represent the first step toward disease-modifying treatment for Alzheimer's disease. Further development of therapeutic strategies, refinement of patient selection methods, and identification of novel biomarkers may contribute to improving treatment efficacy and reducing the incidence of adverse effects in the future.

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