# INNOVATIVE THERAPIES IN ALZHEIMER'S DISEASE

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## I. INTRODUCTION

Alzheimer's disease predominantly affects patients over the age of 65 with progressive loss of memory and their own independence[2]. It is recognized by the World Health Organization (WHO) as a major health-care problem. There are currently no disease-modifying therapies despite advances in understanding the pathogenesis of the disease[1].

In this chapter we will address the definition of the disease, its pathogenesis, and current and future therapeutic strategies.

## II. EPIDEMIOLOGY

Dementia is characterized by an acquired loss of cognitive function and is not a physiological condition related to advancing age. According to one estimate, 44 million people are thought to be affected by Alzheimer's disease. The cost of treating these patients is around USD 600 million[2]. In England constitutes a primary cause of death, accounting for 11.6% of all deaths recorded in the year 2015[3]. Recent studies indicate that the incidence of this condition is decreasing due to a better cardiovascular risk management[4-5]. In the coming years it is expected a higher prevalence of disease in individuals from lower economic classes with cardiovascular comorbidities[2]. Alzheimer's disease is the prevalent cause of dementia, accounting for 50-75% of cases, and its prevalence increases greatly at ages over 65[2].

## III. AETIOLOGY

Most cases of Alzheimer's disease are sporadic, but there are cases related to mutations in 3 genes, amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2), which cause a rare (<0.5%) form of familial Alzheimer's disease (fAD). Symptoms develop early in familial forms, around age from 30to 50[6].Alzheimer's disease developing in elderly is due to an interplay of genetic and environmental factors. Seventy percent of the risk of Alzheimer's disease is due to genetic factors. The APOE gene is the single biggest risk for sporadic AD. It has three variants, e2, e3 and e4. E4 heterozygotes have an odds ratio (OR) of developing AD of 3, rising to 12 in homozygotes, compared to non-e4 carriers[7]. Twenty risk factor genes have been identified. These genes are implicated in inflammation, cholesterol metabolism and endosomal vesicle recycling pathways[8]. In particular, microglial activation in response to amyloid deposition is considered to play a key role in the pathogenesis of AD[9].

 

Epidemiological studies show a protective factor against Alzheimer's disease of physical activity, while hypertension and diabetes increase this risk[10]. Obesity has long been considered a risk factor, but not anymore[11].

## IV. PATHOLOGY

The main feature of Alzheimer's disease are amyloid plaques and neurofibrillary tangles (NFTs).

These alterations produce neurodegeneration with loss of neurocytes, leading to macroscopic atrophy.

Mixed forms of dementia develop particularly in older patients and include vascular disease and Lewy bodies[13]. Lewy bodies can be also found in familiar forms[14].

Amyloid plaques develop as a result of altered metabolism of the APP protein, which at some point in life onward, for unknown reasons, is metabolized poorly. Neurofibrillary tangles are primarily composed of paired helical filaments consisting of hyperphosphorylated tau. Tau pathology typically begins in the allocortex of the medial temporal lobe before spreading to the associative isocortex. Primary sensory, motor and visual areas tend to be relatively spared. Neurocyte loss parallels tangle formation, and the severity of Alzheimer's disease correlates better with NFT pathology[12], whilst beta-amyloid pathology reaches a plateau early in the symptomatic phase of the disease[15].

## V. PATHOGENESIS

The amyloid hypothesis suggests that the pathogenesis of Alzheimer's disease is related to the accumulation of pathological forms produced by sequential cleavage of the APP protein, driven through an imbalance between the production and its clearance. The formation of NFTs is consequent to this imbalance and it leads to dysfunction and neurodegeneration, mediated via inflammation [19]. In support of this theory, it has been observed that in familial forms all mutations are linked in the generation or processing of pathological amyloid[20].

A few evidence suggest that the innate immune system may play a critical role in the pathogenesis of Alzheimer's disease. Clinical studies using PET ligands which bind to activated microglia provide further in vivo evidence for a role of neuroinflammation in AD[21-22]. Whether the role of neuroinflammation is protective or harmful, or both, remains to be clarified.

## VI. CLINICAL FEATURES

The most common presentation of AD is of an elderly individual that develops progressive problems centred on episodic memory. As the condition progresses, cognitive difficulties become more profound and widespread and interfere with activities of daily living; at this stage a patient can be diagnosed with AD dementia. Progressing with the disease, patients become increasingly dependent on the caregiver, and at the last stage may

 

experience behavioral changes, hallucinations, and seizures. Death manifest on average 8.5 years from presentation[23].

## VII. TREATMENT

Disease-modifying treatments are not yet available. Therapies focus on limiting symptoms.

Acetyl-cholinesterase inhibitors (AChEIs) (donepezil, galantamine and rivastigmine) are used as symptomatic treatment, increasing acetylcholine availability by inhibiting its breakdown in the synapse. The common cholinergic side effects are leg cramps and gastrointestinal upset, but they are usually well tolerated, especially when the drugs are introduced at low dose and titrated slowly. AChEIs have proven beneficial effects in mild to severe AD, with most evidence at the mild to moderate stage[24]. There are fewer data on measures of behavioural disturbance and activities of daily living, but some evidence of benefit. In all domains, however, the benefit observed in clinical trials is modest at best. There is no evidence that one drug in the class is more efficacious than another[24]. The DOMINO-AD study demonstrated that withdrawal of donepezil in moderate to severe AD increases the risk of admission to nursing homes. Therefore, the authors suggest continuing the therapy even if there is no clear benefit[25]. Memantine is an alternative symptomatic treatment, indicated for severe AD. Memantine, a low affinity N-methyl- D-aspartate receptor antagonist, aims to reduce L-glutamate excitatory neurotoxicity without interfering with its physiological actions. Side effects include constipation and headache. Memantine has been shown to have a small but clinically appreciable benefit on cognition and functional decline in patients with moderate to severe AD, with some evidence that it reduces the likelihood of patients developing agitation[26]. Acetylcholinesterase inhibitors can be administered in combination with memantine[27].

In the later stages of the disease, patients develop agitation, aggression, and psychosis. Atypical antipsychotics are usually favoured over typical agents but, regardless of drug, benefits are moderate[28], and no treatments are licensed for behavioural symptoms in dementia. Serious adverse events include chest infection, stroke and death. Consequently, antipsychotics should be avoided if possible and limited to those with neuropsychiatric symptoms, particularly psychosis, that are severe, debilitating or pose safety risks[28]; ongoing use needs regular review. Where required, the best evidence is for low dose risperidone[29]. Non-pharmacological approaches are preferred and include communication skills training, music therapy and person-centred care training which have some evidence of benefit[30].

## VIII. MONOCLONAL ANTIBODIES

The amyloid hypothesis postulates that neurodegeneration is caused primarily by beta-amyloid-related toxicity[31]. Evidence suggest that targeting amyloid beta could benefit patients with Alzheimer's disease. So far, many attempts at therapeutically targeting Aβ have not been successful[33–36]. One possible explanation could be the inability of the antibodies to adequately engage their target or the proper target in the brain.

Screening human memory B cell libraries that were reactive against amyloid beta led to the sequencing of aducanumab (BIIB037), a human monoclonal antibody that selectively

 

reacts with Aβ aggregates, including soluble oligomers and insoluble fibrils. In preclinical studies, an analogue of aducanumab is capable of crossing the blood–brain barrier, engaging its target, and clearing Aβ from plaque-bearing transgenic mouse brains. These results prompted the start of clinical trials on humans[37].

1. **Aducanumab:** Aducanumab is a human monoclonal antibody, IgG1, directed against agglomerated forms of beta-amyloid. It received its first approval in the US for the treatment of Alzheimer's disease on June 7, 2021. This indication is approved under accelerated approval and is subject to verification of clinical benefit in one or more confirmatory studies. According to FDA prescribing information, treatment should be initiated in patients with mild cognitive impairment or mild dementia, the population in which treatment was initiated in clinical trials. There are no safety or efficacy data on initiating treatment in earlier or later stages of the disease than those studied.

   The recommended dosage of aducanumab is 10 mg/kg and is administered intravenously in about 1 hour every 4 weeks and at least 21 days after the previous administration.

   In the phase III registrational studies EMERGE (NCT02484547) and ENGAGE (NCT02477800) in patients with early Alzheimer's disease (mild cognitive impairment), aducanumab reduced β-amyloid plaque levels in a dose and time-dependent manner. In both studies, EMERGE and ENGAGE, both high-dose and low-dose aducanumab significantly ($p < 0.0001$) reduced β-amyloid plaque levels in the brain at weeks 26 and 78. In both phase III studies, the primary endpoint was the change from baseline in Clinical Dementia Rating-Sum of Boxes(CDR-SB) scores. This endpoint was not met in the ENGAGE study. This caused both studies to be stopped in March 2019.The most observed adverse events were Amyloid-Related Imaging Abnormalities (ARIA) with cerebral microhaemorrhages, or hemosiderosis (ARIA-E and ARIA-H). The pathological significance of these alterations is not yet clear; however, it is good to keep in mind, considering that these are elderly patients[38].

2. **Lecanemab:** Lecanemab is a humanized gamma immunoglobulin 1 (IgG1) directed against aggregated forms of β-amyloid. It received initial approval on January 6, 2023 in the United States under the accelerated approval pathway.

   According to prescribing information, treatment should be initiated in patients with mild cognitive impairment or mild dementia at the disease stage and a confirmed presence of β-amyloid pathology. There are no data on the efficacy or safety of initiating treatment in earlier or later stages of the disease than those studied.

   Accelerated U.S. approval is based on the reduction in β-amyloid plaques observed in patients who received lecanemab as part of a completed multinational, double-blind phase II study (NCT01767311), with an open-label extension phase still ongoing. Continued approval for this indication may be subject to verification of clinical benefit in a confirmatory study.

 

The recommended dose of lecanemab is 10 mg/kg administered intravenously for approximately 1 hour every 2 weeks. The presence of β-amyloid must be confirmed before starting lecanemab therapy.

In the multinational phase II study (NCT01767311) of patients with early Alzheimer's disease, lecanemab 10 mg/kg infused every 2 weeks significantly reduced β-amyloid plaque levels in the brain at months 12 and 18 compared with placebo (nominal $p < 0.001$).

In a substudy of the phase III study, Clarity AD (NCT03887455), it was found that 18 months of lecanemab therapy was associated with a statistically significant ($p < 0.00001$) reduction in amyloid plaque (key secondary endpoint) compared with placebo. This reduction resulted in an amyloid level below the threshold for amyloid positivity, at which individuals are considered to have elevated amyloid brain levels.

The primary endpoint as measured by the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score at 18 months was achieved. This benefit was seen as early as month 6 and was maintained at each subsequent time point until month 18.

In terms of secondary endpoints, significant differences were found between groups in favor of lecanemab 10 mg/kg, every 2 weeks, on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog14), the Alzheimer's Disease Composite Score (ADCOMS) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL).

In the phase II study (NCT01767311), patients received lecanemab or placebo. Lecanemab 10 mg/kg every 2 weeks did not meet the study's primary endpoint (defined as a change from baseline at 12 months on ADCOMS).However, 18-month analyses of the primary and secondary endpoints, which assessed clinical decline, found that therapy with lecanemab 10 mg/kg every 2 weeks was associated with reductions in ADCOMS, CDR-SB and ADAS-Cog14.

The most frequently reported adverse events were: infusion-related reactions, Amyloid-Related Imaging Abnormalities (ARIA) with cerebral microhemorrhages, cerebral macrohemorrhages or superficial siderosis (e.g., ARIA-H); ARIA-E; headache; and falls.

Most of the infusion-related reactions were mild to moderate (96%) and occurred with the first dose (75%).

Two extension studies of Clarity AD (NCT03887455) and the phase II study (NCT01767311) are ongoing.

In addition, recruitment is ongoing for the phase II/III DIAN-TU-001 study (Tau NexGen; NCT05269394), for individuals with a genetic mutation causing Alzheimer's disease, and the phase III AHEAD 3-45 study (NCT04468659), for patients with preclinical Alzheimer's disease and high amyloid and those with early preclinical Alzheimer's disease and intermediate amyloid[42].

 

## IX. CONCLUSIONS

The use of monoclonal antibodies directed against beta-amyloid has been a highly promising strategy that, however, has failed to translate into clinical efficacy. Experimental data indicate molecular efficacy with controversial data regarding clinical symptomatology. In addition, very high direct and indirect costs are expected. The therapy involves expensive examinations, such as MRI, to prevent the most associated side effects, i.e., ARIA-E and ARIA-H. Such side effects are still understudied in terms of their actual severity. We must wait for the efficacy and safety results of the clinical trials still ongoing to determine whether these innovative therapies will be viable.

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