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Review Article

Translational Development and Clinical Implementation of Recombinant Immunoglobulin Gamma 1 (IgG1) Monoclonal Antibody Lecanemab in Management of Alzheimer's Disease

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Introduction

Alzheimer's disease (AD) is a permanent and progressive neurodegenerative disorder caused by accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain. The buildup of plaques leads to neuronal death and neurodegeneration. AD is the most common cause of dementia leading to gradual decline in memory and eventual loss of ability to carry out activities of daily living [1]. There are an estimated 55 million people affected worldwide making AD the 7th leading cause of death in the United States [2].

Currently, the gold-standard aim of AD pharmacological therapy focuses on slowing disease progression and providing supportive management rather than addressing the underlying pathophysiology. Developing a novel drug that targets the underlying pathology is important as it can help halt the rate of disease progression further with hopes to ultimately get us one step closer to finding a definitive cure. This has the potential of having a significant impact on not only patients, but also their family and friends.

The pathophysiology behind AD lies in the formation of Ab plaques and neurofibrillary tangles (NFTs). Ab plaques are formed by accumulation of the Ab peptide. Familial AD are caused by mutations in the amyloid precursor protein (APP) gene which leads to increased formation of Ab and makes it more susceptible to clumping. [2] Ab plaques and NFTs are pathognomonic for Alzheimer's disease, hence making them a good therapeutic target. [3]

For the past 20 years, researchers have been trying to make use of the idea of using antibodies to clear amyloid-beta (Ab) from the brain. However, no significant results were able to be achieved. Recent studies performed using the drug lecanemab (BAN2401) has shown promising results.

Lecanemab is a recombinant humanized version of immunoglobulin gamma 1 (IgG1) monoclonal antibody. It works by selectively binding to amyloid-beta fibrils. [3] This decreases the number of Ab plaques, likelihood of clumping and inhibits its deposition in the brain. This directly targets the underlying pathophysiology of Alzheimer's disease.

[3] There is new found evidence revealing that the solubility and amount of Ab may indicate the severity of the disease and clinical status. Thereby, targeting the build-up of plaques would be of significant clinical benefit. [4, 5]

Pre-clinical studies:

In its preclinical development stage, mAb158, a mouse monoclonal antibody was used and tested on transgenic mice for a total duration of 4 months. This antibody is highly selective for protofibrils, hence, has an affinity for large soluble Ab protofibrils. The increased affinity to Ab plaques makes this drug extremely effective as decreased plaque load improves disease burden as this appears to be linked to the amount of accumulation of Ab in the brain. [4]

In mice with amyloid plaque present at time of mAb158 administration, there was a decrease in protofibril levels and no change in the insoluble Ab. On the other hand, mice which received treatment before the development of plaques had decreased levels of Ab protofibril and amyloid deposition inhibited. [6]

In a separate study performed on mouse neuron-glial co-cultures, it was found that mAb158 protected neurons from apoptosis caused by Ab accumulation by working against build-up of Ab protofibril. This suggests that astrocytes might play a key role in anti-Ab immunotherapy. [5, 7]

Drug development and clinical trials

The BAN2401 clinical trial was a phase 1 study that consisted of 80 participants with mild to moderate AD. This was a 2 year double-blinded randomized control trial that ran from 2010 to 2012. The primary outcome was to assess the safety and tolerability of lecanemab at single and multiple doses for 4 months. It was found that lecanemab was well tolerated at the doses given. The pharmacokinetic results obtained served as a useful guide for designing phase II trials. [8]

Following completion of phase 1 trials, phase 2 trials commenced in 2014. This was a multicentered 18-month long randomized controlled trial that assessed the effect of five different intravenous doses of lecanemab. A total of 856 participants with early AD were included. Participants were randomized into the lecanemab group (n=609) or placebo group (n=245). [5] The primary outcome measure was assessed using the Alzheimer's Disease Composite Score (ADCOMS), to determine the dose that attained 90% of maximum effect of treatment at 12 months (ED90). [8] Other endpoints used were the Clinical Dementia Rating-Sum-of-Boxes (CDR-SB) score and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14). This study found no significant difference between the two groups in terms of primary endpoint.

However, at 18 months, it was found that lecanemab exhibited a decrease in brain amyloid with a delay in clinical deterioration. The dose of 10mg/kg twice monthly was the ED90, leading to a reduction of brain amyloid by up to 93%. It was concluded that clinical efficacy was consistent and robust across endpoints used. The results obtained from data collected for 18 months in the trial were used in the designing of a phase 3 trial to further evaluate the efficacy and safety of this intervention. [8] Some of the adverse effects noted from this study include ARIA-E; a temporary inflammatory reaction detected on MRI which usually occurs in the first 3 months of starting immunotherapy and infusion related reactions. [8]

Clarity AD is a phase 3 clinical trial which started in March 2019 and is set to run until 2027. It is a multicenter double-blinded randomized controlled trial with a total of 1795 participants across 250 sites. Patients were placed into 2 groups with one receiving 10 mg/kg of lecanemab every 2 weeks and another given placebo for a duration of 18 months. [5, 10] The inclusion criteria involves patients between 50 and 90 years with proven amyloid on positron emission tomography (PET) scans or cerebrospinal fluid (CSF) samples. Primary endpoint was to determine whether there was a difference from baseline in CDR and CDR-SB score at 18 months. Secondary endpoints include amyloid burden on PET scan and ADCOMS. [5] It was found that although the drug decreased the build-up of amyloid fibrils in about 65% in early AD and delayed the decline of cognition and function in 27% measured using CDR-SB, there were adverse events noted. Hence, trials with longer duration are needed to further assess the safety and effectiveness of this drug. [10] Common adverse events experienced by participants included infusion-related reactions in 1.2%, amyloid-related imaging abnormalities (ARIA) in 0.8% and atrial fibrillation in 0.7%. Patients experiencing infusion related reactions will have symptoms like nausea, vomiting and flu-like symptoms. Patients with ARIA will present with symptoms such as headache, dizziness and seizures. [5, 10]

Lecanemab, with the brand name of leqembi, was approved by FDA on 6th January 2023 for use in early or preclinical Alzheimer's disease as a means of delaying cognitive and functional decline. [5] This drug was approved via the accelerated approval pathway where drugs which are designed for use in severe conditions have a proven effect on the surrogate endpoint in trials, hence likely to bring about medical benefits. [1] From the Phase 2 and 3 trials, results showed that lecanemab has a definite effect in reducing Ab protofibrils build up in a dose and time dependent manner and ultimately slowing down disease progression, hence, supporting the approval of this drug. [1, 3] This drug is delivered via intravenous route and is indicated in patients with mild cognitive impairment or dementia. [1]

Lecanemab is currently only used in AD with the recommendation of commencing the treatment before symptom onset. In order to achieve this, it would be ideal if an antecedent diagnostic test could be established to aid early detection of AD. A recent study commenced in November 2021 is looking into combining lecanemab with the anti-tau antibody E2814 for use in people with familial AD mutations. This trial involves 168 people and is a multicentered, randomized controlled trial running until 2027. [7] If this is proved to be a success, lecanemab will likely be approved for use in familial AD in addition to current use in early AD.

A phase I study looking at subcutaneous administration of lecanemab was started in September 2021 involving 60 participants of good health. It is a randomized study with a parallel-group to evaluate the bioavailability of one subcutaneous dose of lecanemab and its half-life. They were given a single injection of 700 mg subcutaneously on the abdomen. [5] The study concluded in January 2022 and is still awaiting publication.

A similar study began in September 2022 looking into bioequivalence of one subcutaneous dose of lecanemab. This study is an open-label, parallel-group involving 160 people with an aim to finish by February 2023. No papers have been published yet.

[5] These studies will contribute hugely to clinical management of patients with AD as patients can be easily educated with subcutaneous injection compared to IV administration. This will reduce the burden on the healthcare system by reducing dependency on hospital facilities. It is also less time consuming and encourages patient involvement.

Leqembi has not reached T4 yet as it is still new to the market and has not made its way fully into clinical practice. However, from current trials, this drug has shown tremendous potential in changing management of early onset Alzheimer's disease.

Clinical implementation

Lecanemab has only just arrived in the market 3 months ago in the United States after FDA approval. At present, Leqembi is priced at $26,500 per year in the US and it is unclear whether Medicare will cover part of the cost. This might make the drug unaffordable for many. [11] This is another factor to consider regarding global access of medication for patients.

Eisai and Biogen had filed for approval in the european market, however, it had been rejected by the European Medicines Agency (EMA). It could potentially be approved by March 2024. In the future, after the approval of leqembi in Europe, challenges such as pricing and reimbursement by governments could be extremely problematic with regards to access and availability. [11]

Apart from the financial intricacies, clinical practice will also pose a challenge as clinicians will be required to select a patient cohort based on imaging and biomarkers present. Ability to monitor the effects of leqembi and decision to complete treatment are still not fully established. [11] Monitoring patients for side effects could also be challenging and time consuming.

In conclusion, following the failure of previous trials of monoclonal antibodies targeting AD, it will definitely be interesting to follow the outcome of leqembi being approved in Europe and determine how this would impact AD clinical care and development of drug resistance.

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