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Review Article

REMTERNETUG: AN INVESTIGATIONAL MONOCLONAL ANTIBODY AGAINST B-AMYLOID FOR THE TREATMENT OF ALZHEIMER'S DISEASE (AD)

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ABSTRACT

In today's aging world, Alzheimer's disease (AD) is a leading cause of dementia and a major chronic illness among the elderly, affecting 55 million people. The World Health Organization (WHO) has identified AD as a top public health priority. Unfortunately, there are currently no definitive cures for this condition. Treatment strategies primarily focus on alleviating symptoms, such as acetylcholinesterase inhibitors (AChEI) and the N-Methyl-D-aspartate (NMDA) antagonist Memantine. The most effective approaches for managing the disease at present appear to involve a combination of medication and non-medication-based therapies aimed at stimulating cognitive reserve. Over the past two decades, several drugs have been discovered that target the established biological indicators of AD, including the build-up of β-amyloid aggregates and the accumulation of hyperphosphorylated tau protein within cells. The amyloid cascade hypothesis is a useful framework for developing therapies for Alzheimer's disease (AD). Experimental treatments have targeted amyloid b1-42 (Aβ) due to its neurotoxic effects and potential adverse effects on the brain, detectable through positron emission tomography (PET). Recent trials support the clinical efficacy of third-generation anti-amyloid immunotherapies in reducing brain Aβ burden and preventing cognitive decline. This has led to the recent FDA approval of aducanumab and lecanemab under an accelerated approval pathway. In this overview, we aimed to assess the safety and effectiveness of Remternetug in treating AD. Remternetug is an enhanced version of donanemab that also targets N-terminal pyroglutamated Aβ. The initial findings show promise for the development of an effective novel drug. However, more phase III studies are needed to provide sufficient clinical evidence for its effectiveness. Current evidence is limited to phase I and II studies and has yet to prove its worth in a larger population.

Keywords: Alzheimer's disease (AD), Monoclonal antibody, Remternetug, β-amyloid, Drug development, Evidences

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INTRODUCTION

Dementia refers to a significant decline in cognitive abilities that impacts daily activities. Alzheimer's disease (AD) is the most common type of dementia in those aged 65 and older, making up at least two-thirds of cases. It is a neurodegenerative condition characterized by gradual cognitive decline. While AD itself is not a direct cause of death, it increases the risk of complications that can ultimately lead to death [1, 2]. In 2022, Alzheimer's disease ranked seventh among causes of death in the U. S., according to the CDC, while COVID-19 was fourth. Prior to the pandemic, Alzheimer's was the sixth leading cause of death after stroke [1, 3, 4]. Currently, there are approximately 50 million Alzheimer's disease (AD) patients worldwide, and this number is expected to double every 5 years, reaching 152 million by 2050. The burden of AD affects individuals, their families, and the economy, with estimated global costs of US$1 trillion annually. At present, there is no cure for Alzheimer's disease; however, there are treatments that can only alleviate symptoms [5]. Alzheimer's disease (AD) poses a significant public health challenge, with just two types of approved medications available: cholinesterase inhibitors and NMDA antagonists. These medications focus solely on alleviating symptoms without offering a cure. Recent clinical trials in AD have seen few successes, with suggested pathways for effective treatments including abnormal tau protein metabolism, β-amyloid accumulation, inflammatory responses, as well as cholinergic and free radical damage [1, 6-9]. This review aims to summarize the current evidence from both preclinical and clinical studies to evaluate the drug's safety and efficacy in humans, which will inform further studies and potential approval.

Alzheimer's disease (AD) typically appears after age 65, known as late-onset AD (LOAD). Early-onset AD (EOAD), occurring before age 65, is rarer, affecting about 5% of patients. EOAD often presents atypical symptoms, resulting in a delayed diagnosis and a more aggressive progression of the disease [10]. Alzheimer's disease (AD) is a complex condition influenced by factors like age, genetics, head injuries, vascular diseases, infections, and environment. The exact cause of the pathological changes in AD remains unknown [11]. Alzheimer's disease (AD) is marked by two types of neuropathological changes: positive lesions, which include neurofibrillary tangles, amyloid plaques, and other deposits, and negative lesions, characterized by significant neural, neuropil, and synaptic atrophy. Additional factors like neuroinflammation, oxidative stress, and cholinergic neuron injury also contribute to neurodegeneration in AD [5, 12-14].

Method

This narrative review examines the literature on remternetug, an anti-amyloid monoclonal antibody (mAb). We found insufficient information on preclinical studies despite extensive research. To identify relevant studies, we searched for terms related to "transgenic" and non-clinical assessments. Data for Phase I, II, and III clinical trials were obtained from ClinicalTrials.gov, along with a review of primary publications on key clinical and biomarker outcomes. We also gathered secondary literature to enhance primary findings, ensuring these sources provided new information rather than just re-analyses or interpretations.

Mechanism of action

Remternetug (LY3372993), is an investigational monoclonal antibody. It is IgG1 humanized antibody specifically designed to target the N3pGlu peptide of the amyloid beta A4 precursor protein (APP) Aβ42. It is an N3pG-Aβ mAb, which means it targets a pyroglutamate modification found on the third amino acid of the amyloid-beta peptide, a feature exclusive to amyloid plaques in the brain. It recognizes a pyroglutamated form of Aβ aggregated in amyloid plaques [15, 16].

Clinical trial

A phase I clinical trial (NCT03720548) with 36 healthy participants evaluated the safety and tolerability of remternetug. The trial included single-and multiple-dose, dose-escalation regimens over 6 mo, with a 1-year extension. Participants received monthly doses of

250, 700, 1400, or 2800 mg by intravenous infusion and were compared with a placebo. Results showed a dose-dependent decrease in Aβ plaque, with participants receiving the 2800 mg dose dropping below 24 centiloids within 3 mo. Safety data related to ARIA-E and ARIA-H were blinded, so comparisons between remternetug and placebo cannot be assessed [17].

In a phase 1 trial (NCT04451408), which included 224 individuals, researchers studied the safety and tolerability of remternetug in two parts. Part A consisted of non-Japanese participants with Alzheimer's disease (AD), while Part B involved healthy first-generation Japanese individuals. Remternetug was administered as either single or multiple doses over a period of approximately 61 w. The primary outcome measure was the number of participants experiencing serious adverse events. Secondary outcomes included pharmacokinetics (PK): Area Under the Concentration Versus Time Curve of LY3372993 after a single dose, maximum observed concentration (Cmax) of LY3372993 at steady state after multiple doses, and pharmacodynamics-specifically, the change from baseline in amyloid load. Although recruitment for the study has concluded, the results have not yet been published. New interim data from a phase 1 multiple ascending dose (MAD) study involving patients with mild cognitive impairment or mild to moderate dementia due to Alzheimer's disease indicated that treatment with remternetug, an investigational agent developed by Eli Lilly, resulted in rapid and significant reduction of amyloid plaques [18].

A phase III study, known as trailrunner-ALZ 1, is currently ongoing with 600 participants who have early symptomatic Alzheimer's disease (AD). This study began in 2022, and while recruitment is complete, the study itself is still in progress. Eligible participants exhibit a gradual and progressive decline in cognitive function, have a Mini-Mental State Examination (MMSE) score between 20 and 28, show plasma p-tau levels consistent with the presence of amyloid beta (Aβ), and have a positive amyloid PET scan. Initially, all 600 participants were enrolled in a double-blind treatment phase. During this period, they received either remternetug or a placebo, administered via subcutaneous injection or intravenous infusion. After the main study period of 52 w, participants could continue for an additional 52 w in an extension phase. Those who initially received remternetug were then switched to placebo and vice versa, ensuring that all participants would eventually receive remternetug if they completed the study. Additionally, an extra 640 participants with early Alzheimer's disease were enrolled in a safety cohort addendum. In this cohort, participants received open-label remternetug via subcutaneous injection or intravenous infusion, but they will not be eligible for the extension period. The primary goal of the study was to measure the percentage of participants who achieve Aβ plaque clearance on PET scans. Secondary objectives include assessing changes in Aβ plaque levels from baseline, determining the time required to achieve Aβ plaque clearance, measuring the trough serum concentration of the drug, and monitoring the number of participants who develop treatment-emergent anti-drug antibodies [19]. The study is still continuing and will be completed in 2026.

Future directions

The development of new anti-amyloid monoclonal antibodies (mAbs) is a major focus in drug development for Alzheimer's disease. These agents are designed to improve efficacy, safety, and convenience. Current research is exploring subcutaneous (SC) administration, which could eliminate the need for intravenous infusions. This approach would make home treatment more accessible for many patients, particularly those living far from infusion centers. [20] More research is needed to evaluate the long-term safety and effectiveness of Remternetug, as well as to identify biomarkers for treatment response and the best patient populations for this therapy. Combining Remternetug with other treatments targeting different aspects of Alzheimer's disease (AD) may enhance its effectiveness. Monoclonal antibodies (mAbs) have emerged as the first disease-modifying therapies for AD, representing a significant advancement in treatment. They show that reducing Aβ plaques can slow disease progression, shifting the focus from temporary symptom relief to Aβ reduction alongside symptomatic treatments like cholinesterase inhibitors and memantine. The introduction of mAbs requires healthcare systems to adapt, emphasizing early diagnosis, Aβ evaluations via PET scans or lumbar punctures, infusion centers for treatment, and monitoring for amyloid-related imaging abnormalities (ARIA) through multiple MRI scans. Overall, mAbs are backed by extensive research into Aβ's role in AD progression [21].

CONCLUSION

The first disease-modifying treatments (DMTs) for Alzheimer's disease are anti-amyloid monoclonal antibodies (mAbs), with three drugs—aducanumab, lecanemab, and donanemab—approved by the US FDA. These mAbs have shown effectiveness in reducing amyloid-beta (Aβ) plaques and slowing cognitive decline. Clinical trials provide valuable insights into Aβ targeting, drug administration, and the relationship between Aβ plaques and cognitive function. Remternetug, an advanced version of donanemab that targets N-terminal pyroglutamated Aβ, represents a promising development. Ongoing clinical trials are essential to determine its role in the landscape of Alzheimer's therapies and improve outcomes for patients.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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