BACE Inhibitors and Tau Protein Targeting Drugs in Prevention of Alzheimer's Disease

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Jonathan Orf¹ and Scot Walker²

Abstract

Alzheimer's disease (AD) is a common disease in the United States with almost 10% of people older than 65 suffering from the disease. A few drugs provide some improvement in mental function in mild-to-moderate disease, but no treatments are available to prevent the development of AD. Two new classes of drugs being investigated for the treatment or prevention of AD include drugs to decrease beta amyloid accumulation and Tau protein aggregation inhibitors. After disappointing results for treatment of AD, both classes are being tested in prevention trials.

Keywords

investigational drugs, formulary management/P&T, neurology

Epidemiology

Alzheimer's disease (AD) is the sixth leading cause of death in the United States.¹ Almost 10% of people aged 65 or older suffer from AD; they are not the only ones suffering. Caregivers to people with the disease provided 18.2 billion hours of unpaid service in 2016 alone. Predictions estimate that in 2017, AD and other forms of dementia will cost the United States up to \$259 billion, making it the disease with the highest cost.²

Current Treatment

Currently, no treatment is available to prevent the development of AD. Instead, there are a few treatment options to help reduce symptoms in patients with mild-to-moderate forms of AD. Symptoms associated with disease progression include loss of memory, loss of cognitive function, and loss of judgment or the ability to solve problems. Cholinesterase inhibitors including donepezil, galantamine, and rivastigmine help by inhibiting the breakdown of acetylcholine at the synaptic cleft in turn increasing neuronal function and reducing symptoms. Memantine, an N-methyl-D-aspartate (NMDA) antagonist, has also been shown to improve mental status scores with minimal risk of side effects in patients with moderate-to-severe AD.³

New Treatment Options

A definitive pathophysiology on the development of AD has not been determined. One theory is that AD is due to the

buildup of beta amyloid plaques on the neuronal surfaces in the brain.⁴ Others feel the disease is a result of the entanglement of neurons caused by the degeneration and destruction of Tau proteins.⁵ However, both groups can agree that both beta amyloid and Tau protein play a key role in AD development and progression.

Beta Amyloid Plaques

Beta Secretase (BACE) inhibitors (Table 1) are drugs that have been in development over the past few years. These drugs target the enzyme Beta-secretase, which is responsible for one of the 2 important cleavage steps in the formation of amyloid- β peptides.⁶ The accumulation of these amyloid- β peptides is what researchers have theorized to be one of the essential causes for the development of AD.⁵ Unfortunately, recent Phase III studies, such as a late-phase verubecestat study, have not shown a benefit to patients with established mild-to-moderate AD. Results such as these are forcing drug companies to look into new target areas for the disease. However, a few BACE inhibitors still have ongoing trials in early AD. Researchers are hoping that by catching the buildup of beta amyloid early, they will stop the progression

¹St. Louis College of Pharmacy, MO, USA

²Prescribe Right, LLC, Wildwood, MO, USA

Corresponding Author:

Scot Walker, Chief Executive Officer, Prescribe Right, LLC,
1602 Westglen Farms Dr, Wildwood, MO 63011, USA.
Email: scot.walker@prescriberight.com

Table 1. Beta Amyloid Plaque Reduction.

	Sponsor	Route	Comments
Verubecestat	Merck & Co	Oral	A BACE inhibitor. The Phase II/III trial was terminated in February 2017 in patients with mild-to-moderate AD after an external data review committee determined the drug had no chance of positive outcomes. A 1500-patient, Phase III trial in patients with early AD is expected to be completed in 2019.
Aducanumab	Biogen Inc	IV infusion	A monoclonal antibody that binds to beta amyloid. Phase I data have shown a reduction in amyloid plaque. Two Phase III trials will examine use of the drug in patients with early disease.
Lanabecestat (AZD3293)	AstraZeneca and Eli Lilly & Co	Oral	A BACE inhibitor. A Phase I trial demonstrated a reduction in amyloid beta proteins with lanabecestat. Two Phase III trials are currently active and are evaluating efficacy in patients with mild AD. Both trials are expected to be completed in 2019.
Crenezumab	F. Hoffmann-La Roche AG	IV infusion	A monoclonal antibody that binds to beta amyloid. The drug failed to slow a decline in cognition in 2 Phase II trials in mild-to-moderate AD patients with a dose of 15 mg/kg. A Phase Ib trial found no safety issues with doses up to 120 mg/kg, so 2 Phase III trials are underway in patients with early AD using a dose of 60 mg/kg. Results from one of the trials are expected in 2020.
Gantenerumab	F. Hoffmann-La Roche AG	Subcutaneous injection	A monoclonal antibody that binds to beta amyloid. A Phase III trial of presymptomatic AD was stopped early when gantenerumab failed to improve cognition. Two Phase III trials are underway in patients with early or mild AD using a higher dose of gantenerumab.
Elenbecestat	Eisai Co, Ltd, and Biogen Inc	Oral	Elenbecestat, a BACE inhibitor, decreased beta amyloid plaque in a Phase II trial. A 1330-patient Phase III trial began in late 2016 in patients with early AD and is expected to be completed in 2020.

Source. Information adapted from the Prescribe Right Pharmaceutical Pipeline Tracker database.⁷

Note. IV = intravenous; AD = Alzheimer's disease; BACE = Beta Secretase.

Table 2. Tau Protein Targeting Drugs.

	Sponsor	Comments
LMTX	TauRx Therapeutics Ltd	LMTX is a small-molecule Tau aggregation inhibitor. LMTX failed to demonstrate a cognitive improvement over placebo in 2 Phase III trials. The drug is now being tested in a new trial in Alzheimer's patients who are not receiving cholinesterase inhibitors or memantine.
AADvac1	Axon Neuroscience SE	AADvac1 is active immunotherapy targeting Tau protein. In a 12-week, Phase I trial, AADvac1 induced an immunological response to pathological Tau proteins. No safety issues occurred during the trial and cognition remained stable. Axon has completed enrollment in a 24-month, Phase II trial, that is testing AADvac1 long-term safety and efficacy in patients with mild AD. The trial is expected to be completed in 2019.
ABBV-8E12	AbbVie, C2N Diagnostics, LLC	ABBV-8E12 is passive monoclonal antibody targeting Tau protein. In a Phase I trial, ABBV-8E12 was well tolerated with no major safety issues detected. A 180-patient, 96-week, Phase II trial in 400 patients with mild AD diagnosed is currently active with a primary outcome of decrease in the Clinical Dementia Rating and adverse effects. The trial is expected to be completed in 2020.

Source. Information adapted from the Prescribe Right Pharmaceutical Pipeline Tracker database.⁷

Note. LMTX = leuco-methylthionium-bis(hydromethanesulfonate); AD = Alzheimer's disease, ADAS-Cog II = Alzheimer's Disease Assessment Scale; ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change Scale

of the disease. Researchers have also been testing antibodies that bind to beta amyloid proteins (Table 1) as another way to reduce accumulation.

Tau Protein Targeting Drugs

Because of disappointments with BACE inhibitors, Tau protein targeting drugs (Table 2) are becoming the new hope to finally

solve AD. Tau protein is a protein responsible for maintaining the structure of neurons by supporting microtubules.⁵ In AD, the Tau protein becomes hyperphosphorylated and begins to form tangles.⁵ These tangles can cause the neurons to lose their ability to communicate and to receive nutrients causing the neuron to decay and degenerate.⁵ This loss of neuron function is what many believe to be one of the leading causes of AD. Leuco-methylthionium-bis(hydromethanesulfonate)

(LMTX), the most advanced of the Tau protein targeting drugs, had disappointing results in 2 Phase III trials in mild-to-moderate AD. Like the BACE Inhibitors, Tau protein targeting drugs are now being tested in early disease.

Authors' Note

Information is summarized from selected materials; additional information may be available from other sources. Due to the preapproval nature of the information, non-peer-reviewed data may be utilized. The information provided is meant to provide a way to assess the development status of a new drug and should not be used in making patient care decisions.

Declaration of Conflicting Interests

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