Long-Term Care Updates

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What's New with Alzheimer's Disease

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Introduction

Alzheimer's disease (AD) currently affects approximately 6.2 million Americans aged 65 years and older. It is the most common cause of dementia, affecting 36% of Americans older than 85 years of age. AD is a progressive neurological disease that can start many years before symptoms present (i.e., memory loss and cognitive decline). The pathogenesis of AD consists of multiple neurodegenerative pathways such as protein fragment amyloid-beta (Aβ) or plaque accumulation outside neurons in the brain and twisted strands of protein tau or tangles inside neurons. Plaques can interfere with neuron-to-neuron synaptic communication and tangles can block the transport of nutrients and other important molecules. Together, Aβ plaques and tau tangles may trigger microglia, which can induce inflammation associated with abnormalities in glycolysis and particularly, glucose metabolism in the brain. In addition, AD can cause acetylcholine to deplete due to cholinergic neuron involvement. These brain changes can lead to death of neurons and brain tissue damage.[1]

Treatment Guidelines

In the past decade, various organizations published practice recommendations for the treatment of AD. Two drug classes recommended by these guidelines include cholinesterase inhibitors (ChEIs) and n-methyl-d-aspartate (NMDA) receptor antagonists. ChEIs such as donepezil, galantamine, and rivastigmine work by increasing levels of acetylcholine. Memantine, an NMDA receptor antagonist, affects glutamatergic transmission in AD. Over the past years, these agents have been the mainstay to improve symptoms or delay decline. However, neither ChEIs nor memantine directly affect the neurological pathogenesis of AD.[2]

In 2007, the American Psychiatric Association (APA) published their first practice guidelines for the treatment of AD. The organization recommended the use ChEIs for mild to moderate AD and memantine plus donepezil for moderate to severe AD. The American Geriatrics Society published the same guidance in 2009, recommending an initial trial treatment period with those agents of at least three months. In 2008, the American Academy of Family Physicians (AAFP) partnered with the American College of Physicians and recommended only memantine for moderate to severe AD. The AAFP then updated their recommendation for the treatment of moderate to severe AD to consider combination therapy of ChEIs and memantine in 2011. This recommendation was rated with inconsistent or limited-quality patient-oriented evidence.[3]

The most recent guidelines for the treatment of AD to date were published by the APA in 2014. The organization recognized that evidence still supports the use of ChEIs for mild to moderate AD; however, donepezil at higher doses lacks evidence that demonstrates clinically meaningful advantages. The APA notes that higher doses of rivastigmine patches may be associated with a greater benefit. For the treatment of moderate to severe disease, evidence remains to support the individual use of ChEIs and memantine, but with unclear clinical significance for both agents used as combination therapy.[4] Currently, there are no new practice recommendations for the treatment of AD.

FDA Guidance on Clinical Drug Development

There have been numerous disease-modifying investigational drug treatments that have failed phase 3 clinical trials for AD. These drugs include Aβ-targeting agents, B-secretase inhibitors, intravenous immunoglobulin, and other existing agents. These clinical trials studied patients with symptomatic AD, in which researchers have suggested that clinical trials should be conducted in earlier stages of AD.[5-6] In 2018, the FDA published a treatment guidance for the industry for AD drug development. The FDA recognized and suggested that optimal treatment may involve targeting early AD stages that occur before the onset of overt dementia. The purpose of the guidance is to assist drug industries in the clinical development of drugs that target those sporadic stages.[7]

Understanding the Early Stages of AD

In support of clinical drug development for AD treatment, the FDA proposed a four-stage classification to assist clinical trial design and evaluation.

Table 1. FDA Proposed Stages of Early AD.

Stage	Description
Stage 1	**Patients with characteristic pathophysiologic changes of AD but no evidence of clinical impact.** Patients are asymptomatic with no subjective complaint, functional impairment, or detectable abnormalities on sensitive neuropsychological measures.
Stage 2	**Patients with characteristic pathophysiologic changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures, but no functional impairment.** The emergence of subtle functional impairment signals a transition to Stage 3.
Stage 3	**Patients with characteristic pathophysiologic changes of AD, subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment.** The functional impairment in this stage is not severe enough to warrant a diagnosis of overt dementia.
Stage 4	**Patients with overt dementia.** This diagnosis is made as functional impairment that worsens from that seen in stage 3.

The FDA reports that clinical trials in early-stage disease may provide evidence that a targeted drug may alter the course of AD by direct impact on the pathophysiology of AD.

Investigational Drugs and Emerging Clinical Trials

Investigational drugs in previous clinical trials have mostly targeted amyloid plaques; however, repeated failures have led researchers to consider other treatment interventions including β- and gamma-secretase inhibitors to decrease Aβ production and drugs to prevent Aβ aggregation. Although such agents have failed to demonstrate clinical benefit, some investigational drugs may be promising based on updated results. [5-6]

Donanemab

Donanemab is an antibody that targets a modified form of deposited Aβ currently investigated for the treatment of early AD. This drug has completed its phase 2 trial, TRAILBLAZER-ALZ (NCT03367403), in 257 patients with early symptomatic AD who had tau and amyloid deposition on positron-emission tomography (PET). This was a randomized trial where patients in the intervention group (n=131) received intravenous donanemab 700 mg for three doses initially, and then 1400 mg every 4 weeks for up to 72 weeks compared to placebo. The primary outcome of this study was a change from baseline in the Integrated Alzheimer's Disease Rating Scale (iADRS) score which ranged from 0 to 144. Lower scores on this scale indicate greater cognitive and functional impairment. Patients who received donanemab had a significantly smaller decrease in iADRS score from baseline at 76 weeks compared to the placebo group (-6.86 versus -10.06 score reduction, respectively; p = 0.04). Researchers have concluded that donanemab has resulted in a better composite score for cognition and functionality of daily living activities than placebo but suggest longer and larger trials to further assess donanemab's efficacy and safety.[6,8]

Aducanumab

Aducanumab is an antiamyloid human monoclonal antibody that binds selectively to aggregated Aβ fibrils and soluble oligomers. Its phase 3, placebo-controlled EMERGE (NCT02484547) and ENGAGE (NCT02477800) trials were discontinued due to a futility analysis that predicted the trials would not meet their primary outcomes. However, after analyzing a larger data set from the EMERGE trial, aducanumab had met the primary endpoint, the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score after 72 weeks of treatment. In the intention-to-treat analysis, patients who received 10 mg/kg of aducanumab (n= 547) demonstrated a 23% less decline in CDR-SB score from baseline which was significantly different than placebo (n=548) at 78 weeks (p=0.01). Secondary outcome results in the same treatment population also demonstrated a lower percent reduction in the following scores which were significant compared to placebo: ADAS-Cog13 (AD Assessment Scale-Cognitive Subscale 13 Items; -27%, p=0.01) and ADCS-ADL-CI (Alzheimer's Disease Cooperative Study-Activities of Daily Living scale; -40%, p = 0.001). Based on these findings, the industry applied for a Biologic License Application (BLA) in July 2020, which was granted priority review by the FDA in August 2020, scheduled for June 7, 2021.[5,9]

Table 2. Investigational drugs for AD treatment.[5,10-17]

Drug	Mechanism	Clinical Trial Information
ALZT-OP1 *Consists of inhaled cromolyn and oral ibuprofen*	Reduce neuroinflammation and promote clearance of Aβ	COGNITE, Phase 3 Trial (NCT02547818) completed November 18, 2020. Results not available.
COR388	Irreversible inhibitor of gingipains	GAIN Phase 2/3 trial (NCT03823404) active, not recruiting. Primary study completion in 2022.
Gantenerumab	Antiamyloid, IgG1 human monoclonal antibody	GRADUATE I & II (NCT03443973 & NCT03444870) Phase 3 Trials currently recruiting: primary study completion in 2022
Lecanemab (BAN2401)	Antiamyloid monoclonal antibody	CLARITY AD (NCT03887455) Phase 3 Trial currently recruiting: primary study completion in 2022
LMTX or Leuco-methylthioninium bis (hydromethanesulphonate) *Prodrug of methylene blue*	2nd generation tau aggregation inhibitor	TRX 005 and TRX 015 phase 3 trials were completed in 2016. High doses (150-250 mg/day) LMTX monotherapy demonstrated greater efficacy than cholinesterase inhibitors ± memantine. LUCIDITY (NCT03446001) is another phase 3 trial to confirm whether low-dose (16 mg/day or 8 mg/day) monotherapy is effective for AD compared to placebo. Primary study completion in 2022.
Masitinib	Selective tyrosine kinase inhibitor	Phase 3 trial (NCT01872598) completed December 2020. Results not available.

Conclusion

AD is a progressive neurodegenerative disorder that can be managed by ChEIs and NMDA receptor antagonists. Limited by their mechanisms of action, donepezil, memantine, and other FDA approved agents recommended by the guidelines only improve symptoms and delay cognitive decline. As addressed by the FDA, the progression of AD can be altered with treatments that target early stages which have encouraged industries to investigate drugs in these patient populations. With donanemab and aducanumab, there is reason to believe new treatments for early AD are on the horizon. However, until clinical trials and analyses are completed, pharmacologic treatment of AD will remain the same.

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