American Journal of Alzheimer's Disease & Other Dementias®
27(5) 296-300

DOI: 10.1177/1533317512452034
http://aja.sagepub.com
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Disease Modifying Drugs Targeting β-Amyloid

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Abstract

At this time there are no effective methods to alter the disease course in Alzheimer's disease. All FDA approved interventions are for symptomatic relief only. However, it is an exciting time as many agents in development have theorhetical potential to impact the disease course. This review discusses some of the agents that have been in clinical trials, particularly those that affect amyloid processing. Some agents have failed while others still provide hope. Since amyloid is the peptide most closely linked to disease pathogenesis, it is possible that some of the anti-amyloid agents will impact the disease progression in a meaningful way.

Keywords

Alzheimer's disease, Amyloid-β, disease-modifying, intervention, pharmacological

Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive learning impairment and memory loss, eventually resulting in global cognitive decline. One of the hallmarks of AD is the presence of a high density of senile plaques in the hippocampus and cerebral cortex. The main component of the senile plaque is the peptide, amyloid-beta (Aβ). Abnormal processing and/or accumulation of Aβ disrupts metabolic processes within the neuron leading to neuronal (and synaptic) dysfunction and ultimately neurodegeneration. Amyloid-β is toxic to neurons, and the deposition of Aβ and subsequent formation of senile plaques are considered to be the primary pathological hallmark of AD.[1] In the initial stages, accumulation of aggregated oligomeric Aβ species can interfere with neuronal and synaptic function without affecting neuronal viability. Alzheimer's disease is frequently preceded by a prodromal mild cognitive impairment stage. Half of these individuals progress to AD within 4 years.[2] Most individuals with mild cognitive impairment have early AD pathology in their brains, including numerous Aβ plaques, which is a long process with a potential duration of 20 years or even longer, for people who survive into the final substages of the disease process.[3] Since neurons are postmitotic, strategies for intervention would optimally normalize the pathogenic AD cascades before (irreversible) neuronal loss occurs. Administering the treatment in the early stages of AD is likely to be important for effectiveness of these Aβ-directed therapies.

The key step regulating Aβ generation is the sequential proteolytic processing of amyloid precursor protein (APP) by β-secretase (BACE) and γ-secretase proteases. When the alpha-secretase pathway is used for APP processing instead, no Aβ is produced. Presenilins 1 and 2, the catalytic components of γ-secretase, are essential for Aβ generation, age-dependent Aβ accumulation, and inflammatory responses during progression of the disease.[4]

Although AD is the leading cause of dementia in the elderly individuals, there is no disease-modifying therapy yet available. Currently approved treatments include cholinesterase inhibitors and the *N*-methyl-D-aspartate receptor antagonist memantine hydrochloride. In this review article, we focused on interventions that decrease Aβ. Currently developing therapies include β-secretase inhibitors, γ-secretase inhibitors, glucagon-like peptide 1, bapineuzumab, statins, ibuprofen, and methylene blue.

γ-Secretase Inhibitors

The key step regulating Aβ generation is avoiding the sequential proteolytic processing of the APP by β-secretase and then γ-secretase proteases. Therefore, modulation of these secretases using inhibitors has been suggested as potential therapeutic strategy to reduce Aβ-induced pathology and associated clinical symptoms in AD.[4] Inhibition of γ-secretase may be more likely to cause side effects because genetic knockout

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animal models of presenilin 1 and 2, the catalytic subunits of γ-secretase, lead to embryonic lethality due to failure in the activation of notch, which is essential for development and differentiation.[5] Thus, a key question in the development of γ-secretase inhibitors for preventing Aβ production is whether undesired mechanism-based side effects will result from inhibition of cleavage of additional substrates and, if so, whether a suitable window exists to reduce brain Aβ.[6]

In 2008, a phase 2 clinical trial to evaluate the safety, tolerability, and Aβ response to a γ-secretase inhibitor (LY450139) in AD lead to unwanted adverse events in the category of "skin and subcutaneous tissue" problems. These problems reached statistical significance. In this category, there were 3 possible "drug-related" rashes and 3 reports of hair color change (lightening) in the treatment groups, with none in the placebo group. LY450139 was generally well tolerated at doses of up to 140 mg/d for 14 weeks, with several findings indicating the need for close clinical monitoring in future studies. Decreases in plasma Aβ concentrations were consistent with inhibition of γ-secretase.[7]

In 2010, Samson et al reported that the phase III trial of the γ-secretase inhibitor semagacestat was halted after the cognitive symptoms of patients who received the drug worsened more than those who received placebo. There were more skin cancers associated with semagacestat. The IDENTITY (International Alzheimer's Dementia by Evaluating Treatment of Amyloidal Pathology) and IDENTITY-2 trials involved more than 2600 patients with mild-to-moderate AD, from 31 countries. They were treated for 21 months. The company is collecting safety data, including cognitive scores, in an effort to answer a number of questions and to determine whether differences between treated and untreated patients continue after treatment is discontinued.[8]

New compounds and molecules have been found under the name of γ-secretase modulators. Some nonsteroidal anti-inflammatory drugs (NSAIDs) and other small organic molecules modulate γ secretase, shifting its cleavage activity from longer to shorter β-amyloid species without affecting the notch cleavage.[9] Acute administration of GSM-10h to rats causes a dose-dependent decrease in the level of Aβ42 in plasma, cerebrospinal fluid (CSF), and brain, with no deleterious effect on notch processing.[10] Notch cleavage properties of γ-secretase inhibitors cause their toxic effects. γ-Secretase modulators may be effective in AD without showing as serious side effects.

β-Secretase Inhibitors

Initial studies in animal models with deletion of the β-secretase gene resulted in only minor phenotypic changes in mice, suggesting that a partial reduction in Aβ generation by β-secretase inhibitors maybe safe in clinical treatments.[11] Since then, significant research effort has been directed toward the development of inhibitor drugs against β-secretase as potential preventive strategies or early intervention agents against AD.[12]

In 2010, Chang et al provide the first direct experimental evidence that the treatment of Tg2576 transgenic mice with an inhibitor of β-secretase (GRL-8234) rescued age-related cognitive decline. They also demonstrated that the injected GRL-8234 decreased soluble Aβ in the brain of Tg2576 mice. The rescue of cognition, which was observed only after long-term inhibitor treatment, was associated with a decrease in brain Aβ plaque load. Treatments of shorter periods or starting treatment at a later age (18 months) failed to show cognitive rescue in animals. The presence of cognitive rescue in young (but not older) mice suggests that β-secretase inhibitors may have the best chance of success at an early stage of disease pathogenesis. However, they observed a reduction in Aβ plaque load in older mice treated with this β-secretase inhibitor, suggesting possible utility in the treatment of patients with later-stage AD.[13]

Beta-site amyloid precursor protein cleaving enzyme (BACE-1) is involved in the processing of APP. Since BACE-1 was reported as the β-secretase in AD over 10 years ago, encouraging progress[14] has been made toward understanding the cellular functions of BACE-1. The BACE-1 cleaves the APP leading to the production of 2 peptide fragments, Aβ40 and Aβ42. Inhibition of BACE-1 is expected to stop amyloid plaque formation, and it has emerged as an interesting and attractive therapeutic target for AD.[15]

Isoliquiritigenin from glycyrrhiza uralensis, a series of hydroxychalcones, were synthesized and evaluated for their in vitro inhibitory activities of BACE-1.[16] TAK-070 is a non-peptidic compound that also inhibits BACE-1. This agent has been shown to lower the levels of soluble Aβ, increases neurotrophic APP, inhibits cerebral deposition of insoluble Aβ, and it rescues behavioral deficits in vivo in a transgenic mouse model of AD. Notably, the partial inhibition of soluble Aβ resulted in a reduction in Aβ deposition after 6 months of treatment. TAK-070 appears to be pharmacologically effective and safe, avoiding the potential adverse events due to complete inhibition of BACE-1. The use of this agent in clinical trials as a disease-modifying treatment is under consideration. Animal model studies are ongoing.[17]

Anomalies in the behavior and biochemistry of BACE(−/−) mice have pointed to the role this enzyme plays in the processing of neuregulin and of the voltage-gated sodium channel β-subunit.[18] The BACE-1 cleaves and activates neuregulin 1 and is thus directly involved in myelination of the peripheral nervous system during early postnatal development.[19] The potential effect of neuregulin 1 in schizophrenia is also under investigation.

Bapineuzumab

In 2003, initial clinical studies of active immunization with synthetic full-length Aβ peptide (AN1792) were discontinued after reports of meningoencephalitis in 6% of patients. This complication resulted in cognitive or neurologic damage in some.[20] Subsequent epitope mapping indicated that antibody responses to AN1792 were almost exclusively directed toward the N-terminal residues.[21] Various studies in mouse models have demonstrated that immunotherapy with

antibodies targeted to the N-terminus of Aβ, which does not contain T-cell-activating epitopes, inhibits neurotoxicity and fibrillogenesis.[22]

Evidence for the efficacy of N-terminal antibodies, combined with the desire to avoid harmful T-cell effects, led to clinical trials using monoclonal antibodies targeting Aβ. Bapineuzumab (AAB-001) is a fully humanized monoclonal antibody that is specific to the N-terminal region of Aβ. Black et al noted magnetic resonance imaging (MRI) abnormalities on fluid-attenuated inversion recovery (FLAIR) sequences in a phase one trial. Repeat MRI scans performed over the subsequent weeks showed that the observed MRI FLAIR changes generally resolve. Other studies confirm the presence of vasogenic edema, likely due to of altered vascular permeability induced by the interaction of bapineuzumab with Aβ in blood vessel walls. Microhemorrhage is also associated with the emergence of vasogenic edema. Fortunately, most cases of vasogenic edema and microhemorrhage are asymptomatic. Preliminary evidence suggests that Mini-Mental State Examination scores improved at the lower doses of bapineuzumab compared with placebo but not with the highest dose (5 mg/kg). Higher doses are also associated with MRI FLAIR abnormalities.[23] However, the primary efficacy outcomes in phase 2 trials were not significant. Potential treatment differences in the exploratory analyses supported further investigation of bapineuzumab in phase 3 trials with special attention to apolipoprotein E (APOE) ε4 carrier status. Exploratory analyses showed potential treatment differences in cognitive and functional end points in study "completers" especially in APOE ε4 noncarriers. Reversible vasogenic edema, detected on brain MRI in 12/124 bapineuzumab-treated patients, was more frequent in higher dose groups and APOE ε4 carriers.[24] Phase 3 clinical trials are currently ongoing with monitoring participants of differing APOE genotypes for vasogenic edema as well as efficacy. Subcutaneous and intravenous forms of the treatment are under investigation.

Glucagon-Like Peptide

Type 2 diabetes has been identified as a risk factor for AD. Both AD and diabetes share several clinical and biochemical features, particularly important among these is an impaired insulin signaling.[25] Among numerous deficits in the AD brain, insulin receptors are reported to be desensitized, and this condition has been termed type 3 diabetes.[26] It is thought that an effective treatment strategy against Type 2 diabetes may have potential value in AD.

Li et al demonstrated that Glucagon-like peptide (GLP)-1 receptor stimulation reduces Aβ accumulation and neurotoxicity in both cellular and animal models of AD.[27] Other studies demonstrate that GLP-1 reduces APP levels and is neuroprotective in neuronal cultures, lowering brain Aβ levels in wild-type mice.[28] These findings provide preclinical support for translational studies in human participants with diabetes and/or early AD.[27]

Statins

Epidemiological studies indicate that intake of statins is associated with a reduced risk of developing AD. In a retrospective study,[29] Haag et al found an association between the use of statins and a lowered risk of AD compared with those who never used cholesterol-lowering drugs. The protective effect was independent of the lipophilicity of statins. However, there are also reports of statin agents worsening cognition, so caution must be used when assessing the usefulness of these agents.

One possible mechanism by which statins may exert a beneficial effect is described by Tamboli et al. Here, statins strongly enhanced the degradation of extracellular Aβ by stimulation of insulin-degrading enzyme release from microglia. Statin treatment of mice enhanced the levels of insulin-degrading enzyme in the blood serum, while insulin-degrading enzyme levels in the cell pellets was decreased, also indicating a selective stimulation of insulin-degrading enzyme secretion in peripheral cells. Levels of soluble Aβ were found to be increased in the brains of microglia-depleted mice, indicating a role of this cell type in the metabolism of extracellular Aβ.[30] However, increased cholesterol levels correlate with increased AD risk, so it is difficult to determine whether these results are due to the statins or to an improved lipid profile.

Lipid-lowering agents may have differential associations with AD. The Lipitor's Effect in Alzheimer's Dementia study was a randomized controlled trial evaluating the efficacy and safety of atorvastatin in patients with mild-to-moderate AD. They found no significant differences in the cognition or global function compared with placebo. Atorvastatin 80 mg/d was not associated with significant clinical benefit over 72 weeks.[31] Cholesterol Lowering Agent to Slow Progression of AD is a phase 3 research study to investigate the safety and effectiveness of simvastatin to slow the progression of AD. The study design is randomized, double-blind, placebo-controlled, parallel group design with equal randomization to drug and placebo. Further studies are clearly needed to fully address the risks and benefits of statin therapy in AD.[32]

NSAIDs

In 2008, Vlad et al found that the long-term use of NSAIDs is protective against AD. This was a retrospective human epidemiological study. Findings were clearest for ibuprofen.[33]

Prophylactic treatment of young 3×Tg-AD mice with ibuprofen is associated with a reduction in intraneuronal oligomeric Aβ and improved cognitive performance. In addition to improved cognition, prophylactic treatment of 3×Tg-AD mice is also associated with fewer hyperphosphorylated tau immunoreactive hippocampal neurons.[34] In 2010, Wilkinson et al[35] reported that ibuprofen acts in an enantiomer-specific manner to inhibit nicotinamide adenine dinucleotide phosphate oxidase activation and reactive oxygen species production. This is associated with a dramatic reduction in oxidative damage and Aβ deposition in a murine model of AD. However, the existing data from mouse models suggest that ibuprofen acts

through multiple independent pathways to affect AD-related pathology.

The outcomes of experiments in animal models have not been predictive of the effects of NSAIDs in humans, and it remains unclear how these drugs affect AD risk and pathogenesis.[35] Many studies have been done, or are ongoing, and results from most well-controlled studies have been disappointing. In Alzheimer's Disease Anti-inflammatory prevention trial (ADAPT), it was found that the use of naproxen or celecoxib did not improve cognitive function.[36] Still NSAIDs are potentially promising because of their γ-secretase modulator effects. γ-secretase modulators have been shown to selectively lower Aβ42 production without shutting down key γ-secretase-dependent signaling pathways.[37]

Methylene Blue

The phenothiazine, methylene blue, has been used as an antimalarial agent, a urinary antiseptic and also an agent for methemoglobinemia treatment.[38] It crosses the blood–brain barrier and has high bioavailability in the brain.[39] Medina et al report that this agent decreases soluble Aβ and rescues early learning and memory deficits in the 3xTg-AD mice. Although other pathways may be involved, the mechanism underlying the decrease in Aβ is mediated by an increase in proteasome function. Toward this end, Medina et al show that there is no impact on APP processing, although 2 out of 3 enzymatic activities of the proteasome are increased. Their results are consistent with data from other studies showing that soluble Aβ can be degraded by the proteasome. In this study, they show that 16 weeks of methylene blue administration improved learning and memory deficits in 3xTg-AD mice, consistent with the results of the phase II clinical trial.[40]

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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