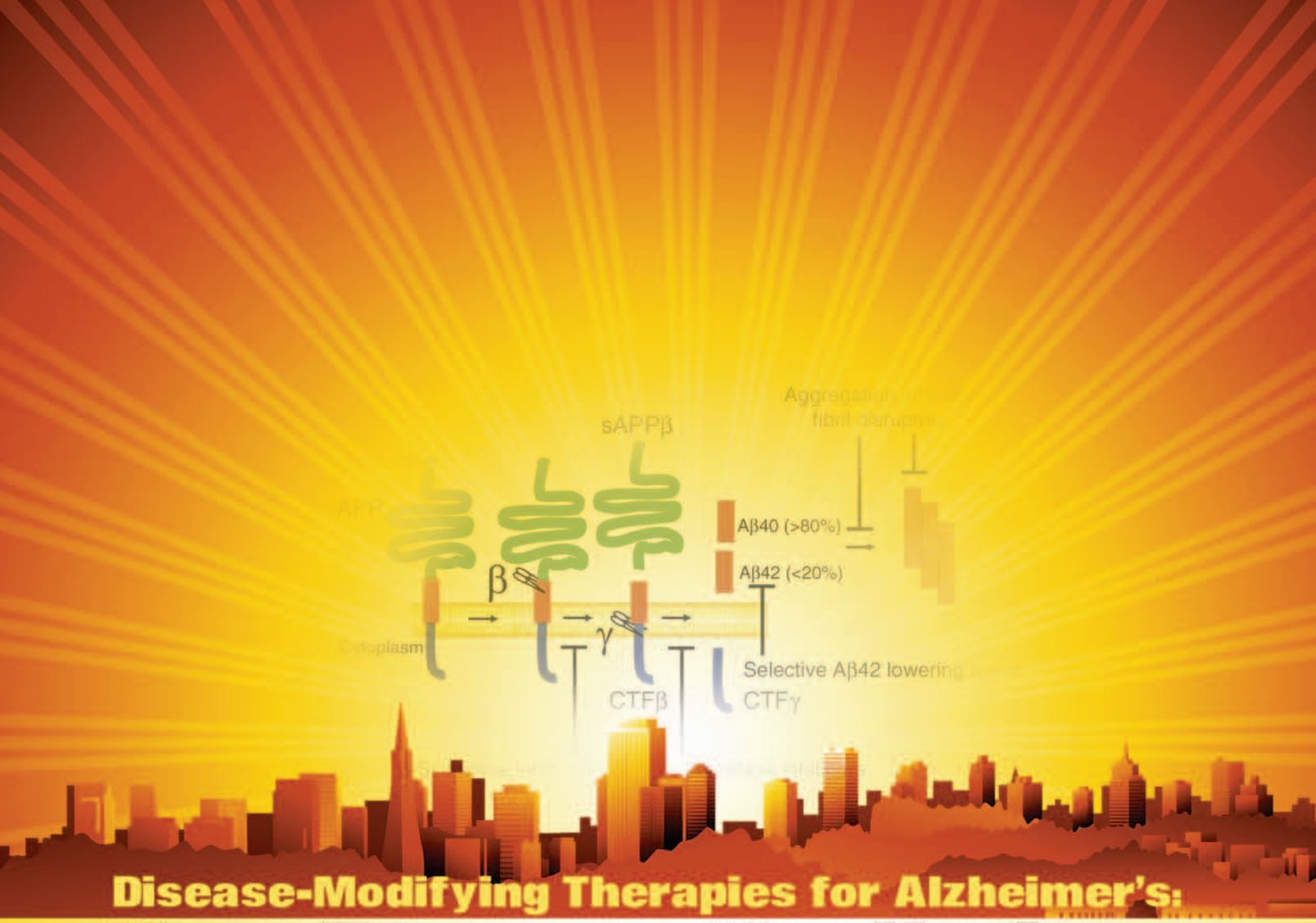


Disease-Modifying Therapies for Alzheimer's:

New Drugs on the Horizon

Anti-amyloid therapy is soon to become a reality. On the eve of its debut, an expert reviews the latest data on several promising agents.

By Daniel D. Christensen, MD

Alzheimer's disease (AD) affects 26.6 million adults worldwide, with nearly five million cases in the United States alone. By mid-century, these numbers are expected to increase by up to 400 percent.[1,2] Contemporary pharmacologic strategies provide treatment for patients with evidence of memory loss, other cognitive deficits, or behavioral disturbance. The cholinesterase inhibitors and memantine are currently available treatments that address cognitive and functional deficits associated with established AD. While these drugs can temporarily reduce symptoms, they do not provide a durable, long-term clinical benefit.[3-4] Indeed, findings from a four-year randomized controlled trial of over 1,000 patients demonstrate that cholinesterase inhibitor therapy was no better than placebo in slowing the progression from mild cognitive impairment to AD.[5]

Clearly, a different approach is needed to stem the growing tide of AD. Rather than wait until memory, cognition and functional deficits are established, future treatment will focus on changing the underlying pathology of AD early in the disease process. The concept of disease-modification is not new. Strategies aimed at altering the course of other pro-

gressive degenerative diseases—rheumatoid arthritis, Parkinson's disease and multiple sclerosis to name a few—are well-known. Disease modification in AD represents a theoretical continuum that ranges from temporary slowing of disease progression to full restoration of cognitive function (Figure 1).

Tremendous resources are being devoted to identifying safe and durable disease-modifying treatments for AD. While the ultimate goal is to fully reverse the effects of AD, ongoing drug development programs seek to find agents that slow or stop cognitive decline early in the course of the disease. In this article, I will review the leading theory of AD pathogenesis and present the current status of anti-amyloid disease-modifying treatments in AD.

Amyloid Hypothesis

The predominant theory explaining the development and pathophysiology of AD is the amyloid hypothesis, which describes a series of events that begins with the processing of amyloid precursor protein (APP) and leads to amyloid plaque accumulation, neurofibrillary tangle formation, neurodegeneration and progressive, irreversible dementia.[6,7] Sequential cleavage of APP first by β-secretase and second by γ-secretase generates beta amyloid (Aβ) peptide fragments of varying length (Figure 2). Aβ40 is the predominant product of APP processing. Aβ42 is a longer fragment that is produced in smaller quantities, but appears to seed plaques and has significantly greater neurotoxic properties. Compared to Aβ40, Aβ42 rapidly aggregates into amyloid, and its production is believed to represent the central pathological event in AD.[7-9]

Amyloid plaques are made up of an insoluble, aggregated core of Aβ that is surrounded by dystrophic axons, dendrites, activated microglia, and reactive astrocytes.[10,11] Aβ also aggregates into neurotoxic soluble oligomers called Aβ-derived diffusible ligands (ADDLs) that may be linked to early cognitive deficits.[12,13] Optimal disease modification would interrupt events, such as Aβ42 production, that occur early in the amyloid cascade and initiate downstream changes. Additional detail on the amyloid hypothesis can be found in a previous article, "From Amyloid to Alzheimer's: The Science Behind the Symptoms," published in Practical Neurology's October 2007 issue and available online at www.avondalemedical.com/archive_PNOctober2007. htm.

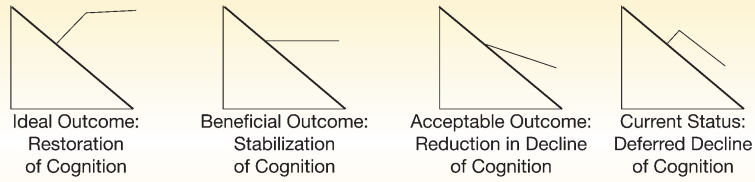


Figure 1. The continuum of disease modification in Alzheimer's disease (reproduced with permission from Cummings JL, Golde TE, Sano M, Tariot PN. Looking to the future of Alzheimer's disease treatments: Anti-amyloid disease-modifying therapies. CNS News. 2007;December:57-66).

Emerging Anti-Amyloid Disease-Modifying Therapies

The sequence of events along the amyloid pathway is very well characterized and provides readily identifiable molecular targets for development of new therapies for AD (Figure 2). Several different classes of anti-amyloid therapies are being studied as potential disease-modifying therapy for AD (Table 1). Promising investigational therapies that target the amyloid pathway are introduced below, and agents that have advanced to late-stage clinical trials are described in more detail.

Immunotherapy. Immunotherapy for AD is a potential new form of anti-amyloid disease-modifying treatment. The mechanism of action for immunotherapy in AD is not known with precision. However, three theories have been suggested: (1) increased amyloid efflux secondary to microglial activation and phagocytosis; (2) increased amyloid clearance from the CNS promoted by antibodies binding to amyloid in the periphery; and (3) disaggregation of amyloid secondary to direct binding of antibodies to Aβ in the CNS.[14,15] Animal studies showing a reduction in amyloid plaque and protection against learning and memory deficits following immunization with Aβ[16,17] formed the basis of a broad clinical trial program of immunotherapy for AD. A large phase II trial of Aβ active immunization was terminated because of meningoencephalitis, possibly caused by an autoimmune response.[18] Phase I testing of other active Aβ immunotherapies is ongoing (Table 1). Transcutaneous administration of β-amyloid is a novel approach, to date tested only in animals, that is designed to minimize neurotoxicity.[19]

Passive immunotherapies, such as humanized monoclonal anti-Aβ antibody (m266, LY-206430; Lilly)[20] and bapineuzumab (AAB-001, Elan/Wyeth) also are in advanced-stage clinical trials (Table 1). Data on the safety of these agents has not yet been reported. Intravenous immunoglobulin (IVIg), which has FDA approval for several diseases, is in Phase II trials in Alzheimer's patients that have shown

increased levels of Aβ in the plasma and decreased levels in the CSF, suggesting clearance of amyloid from the brain.[21,22]

γ-Secretase inhibitors. Inhibition of γ-secretase represents another biological target for anti-amyloid disease-modification, but safety concerns are an issue with this therapeutic class. γ-Secretase is a ubiquitous enzyme with diverse physiological functions in addition to APP processing and Aβ generation. Non-selective inhibition of γ-secretase function affects all substrates of this enzyme, not just APP. The Notch signaling protein is one physiologically important substrate of g-secretase that is involved in lymphopoiesis and differentiation of gastrointestinal cells. Inhibition of γ-secretase therefore could be associated with a broad range of adverse effects.[23,24]

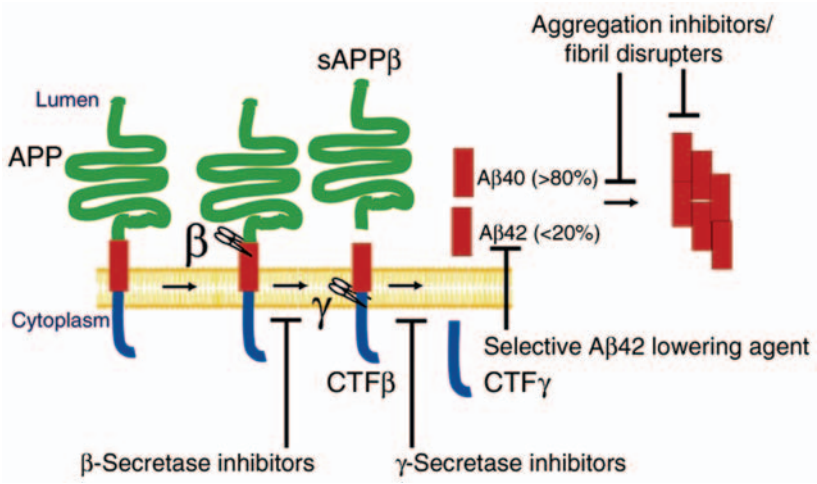


Figure 2. The amyloid pathway in Alzheimer's disease and molecular targets for anti-amyloid disease-modifying therapies. CTF = carboxy-terminal fragment. (Reproduced with permission from Golde. Alzheimer disease therapy: can the amyloid cascade be halted? Journal of Clinical Investigation. 2003;111:11-18. Copyright© 2003).

There are two γ-secretase inhibitors under evaluation in clinical trials. LY-450139 (Lilly), in a six-week Phase II trial of 70 patients with mild to moderate AD, decreased Aβ plasma levels but did not alter cerebrospinal fluid (CSF) levels of Aβ. Changes in cognitive function were not reported. Adverse events included diarrhea, abdominal pain and occult bleeding.[25,26] Phase III studies are ongoing. Results from a Phase I study of another γ-secretase inhibitor, MK-0752 (Merck), have been reported in abstract form. Single oral doses of MK-0752 were well tolerated in healthy young men, and the compound reduced Aβ40 levels in CSF over 24 hours.[27]

Selective Amyloid-Lowering Agents (SALAs). The selective amyloid-lowering agents (SALAs) are a new class of amyloid-based compounds under investigation for AD. Like the γ-secretase inhibitors, the SALAs lower Aβ42 levels by interacting with γ-secretase. However, unlike the γ-secretase inhibitors, which have broad physiologic effects, the SALAs have a focused mechanism of action that selectively lowers Aβ42 levels. Rather than inhibiting γ-secretase, the SALAs modulate γ-secretase without interfering with the other biologically essential functions of the enzyme (*e.g.*, Notch cleavage).[28,29] The selective amyloid-lowering agents reduce Aβ42 production by binding to a different (non-catalytic) site on the enzyme resulting in APP cleavage in a different location (*i.e.*, allosteric modulation) and generating shorter Aβ fragments that appear to be non-toxic.[30-32] Therefore, the safety issues associated with the γ-secretase inhibitors do not appear to be a concern with the SALAs.

Tarenflurbil (Flurizan; Myriad Pharmaceuticals) is the first selective amyloid-lowering agent to reach advanced-stage clinical trials; others are being developed. Other SALAs believed to have advanced to clinical trials are CHF-5022 and CHF-5074 (Chiesi Farmaceutici). Preclinical data demonstrating the anti-amyloid properties of both have been published.[33,34]

Tarenflurbil decreased brain levels of Aβ42[35] and improved spatial learning and memory performance in mouse models of AD.[36] A three-week course of tarenflurbil 200mg, 400mg or 800mg twice daily was as well tolerated as placebo in 48 healthy older volunteers in a Phase I study.[37] In this study, measurement of Aβ42 levels in plasma samples suggested that at the time of peak plasma drug levels, higher drug concentration was related to lower plasma Aβ42 levels.[37]

Evidence for the long-term efficacy and safety of tarenflurbil is provided by the findings of a Phase II study of 210 subjects with mild to moderate AD. In this double-blind trial, patients were randomly assigned to a 12-month course of tarenflurbil 400mg twice daily, 800mg twice daily, or placebo. Patients treated with cholinesterase inhibitors at baseline continued on the same stable doses. Primary efficacy out-

Table 1. Status of Investigational Amyloid-based Disease-Modifying Treatments for Alzheimer's

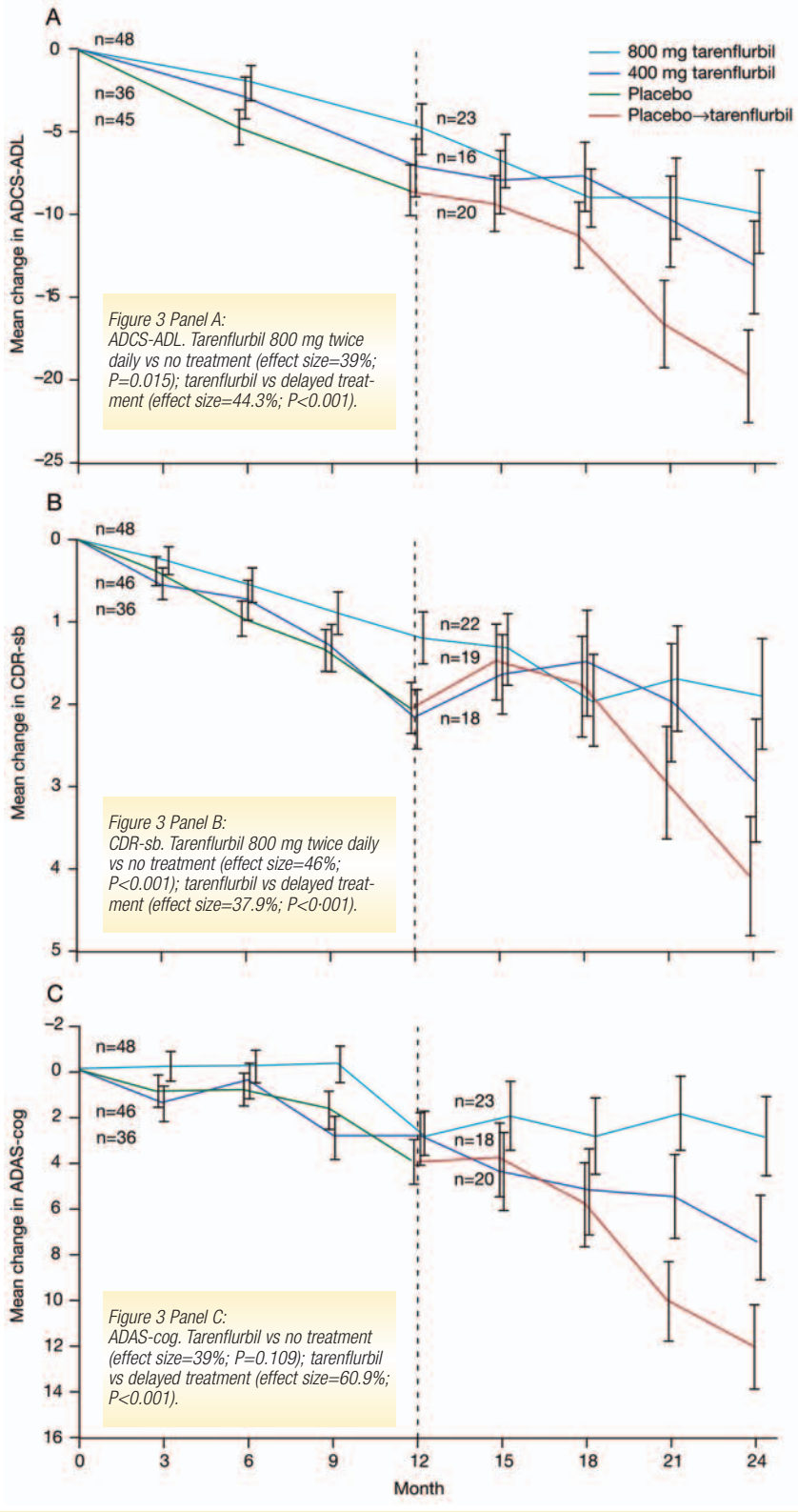
Class	Anti-Amyloid Compound (Sponsor)	Investigation Status
Immunotherapy		
Passive immunization	LY-206430 (humanized version of m266; Lilly)	Phase I
	Bapineuzumab (AAB-001; Elan/Wyeth)	Phase II/III
	Intravenous immunoglobulin (Baxter Bioscience, NIA, ADCS)	Phase II
Active immunization	ACC-001 (Elan/Wyeth)	Phase I
	CAD-106 (Novartis)	Phase I
γ-Secretase inhibitors	LY-450139 (Lilly, ADCS)	Phase III
	MK-0752 (Merck)	Phase I
Selective amyloid-lowering agents (SALAs)	Tarenflurbil (Flurizan; Myriad Pharmaceuticals)	Phase III
	CHF-5022; CHF-5074 (Chiesi Farmaceutici)	Phase II
Anti-aggregation agents	Tramiprosate (Alzhemed; Neurochem)	Phase III (failed; open-label extension phase ongoing)
	Curcumin (John Douglas French Foundation, ISOA)	Phase II
	PBT-2 (Prana Biotechnology)	Phase II
Miscellaneous	Statins (atorvastatin [Lipitor; Pfizer, Inc.], simvastatin [Zocor; Merck, ADCS])	Phase III
	Peroxisome proliferator-activated receptor (PPAR)-gamma agonists (rosiglitazone; Avandia; GlaxoSmithKline, NIA, ADCS)	Phase III

Abbreviations: ISOA = Institute for Study of Aging; ADCS = Alzheimer's Disease Cooperative Study; NIA = National Institute on Aging; NINDS = National Institute of Neurological Disorders and Stroke

comes were the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), and the Clinical Dementia Rating–Sum of Boxes (CDR-sb). Upon completion of the 12-month placebo-controlled period, patients continued to a 12-month follow-on study for a total of 24 months of treatment. Patients who were initially randomized to tarenflurbil continued on the same dose, and patients in the placebo group were re-randomized to tarenflurbil 400mg or 800mg twice daily for the additional 12 months.[38]

During the initial 12-month phase, patients with mild AD in the 800mg twice daily group exhibited a significantly lower rate of decline of activities of daily living (ADCS-ADL) and global function (CDR-sb) compared to placebo. The rate of cognitive decline (ADAS-cog) was slowed compared to placebo, but differences did not reach statistical significance. There were no statistically significant differences in outcome measures for patients with moderate AD. Comparisons during the subsequent follow-on study were made between tarenflurbil 800mg twice daily and placebo in patients with mild AD. Efficacy results for patients with mild AD who were treated with tarenflurbil 800mg twice daily for 24 months were compared to two populations: (1) no active treatment (12 months of placebo) and (2) delayed treatment (12 months of placebo followed by 12 months of tarenflurbil).

Tarenflurbil 800mg twice daily for 24 months resulted in significantly greater reductions in the rate of decline in activities of daily living (ADCS-ADL; effect size=39%; P=0.015) and global function (CDR-sb; effect size=46%; P<0.001) compared to no treatment (Figure 3). Rates of cognitive decline in the tarenflubil group slowed, but were not significantly different than placebo (ADAS-cog; effect size = 39%; P=0.109). Effect size is a measure of the magnitude of treatment effect compared to placebo. When the 24-month course of tarenflurbil was compared to delayed treatment, rates of decline on each of the three primary outcome measures were significantly slower for the group treated with tarenflurbil 800mg twice daily for 24 months compared with



patients taking the placebo for months 0-12 and then tarenflurbil for months 12-24 (P<0.001; Figure 3), which suggests a disease-modifying effect. Treatment with tarenflurbil 800mg twice daily for 24 months was well tolerated compared to placebo.[38]

Tarenflurbil is currently in Phase III testing in two large trials, one of which has been completed. In both, patients with mild AD are randomized to an 18-month course of tarenflurbil 800mg twice daily or placebo. Results of this program are expected in the summer of 2008 and will better delineate the role of tarenflurbil as a potential disease-modifying agent in early AD.

Anti-aggregation agents. Glycosaminoglycans (GAGs) are components of proteoglycans, which are part of the AD amyloid complex. The GAGs promote assembly of soluble Aβ into insoluble amyloid fibrils. Tramiprosate (Alzhemed; Neurochem) is a GAG-mimetic that binds to Aβ, inhibits fibril formation and maintains the random-coil conformation of soluble Aβ. Tramiprosate decreased Aβ42-related neuronal death in cell cultures and reduced amyloid deposition and brain levels of Aβ40 and Aβ42 in a mouse model of AD.[39]

In a Phase II trial of patients with mild to moderate AD, tramiprosate reduced brain levels of Aβ42, but did not improve cognition scores compared to placebo.[40] A large Phase III trial of tramiprosate in Europe was halted in November 2007. The North American Phase III trial failed to differentiate tramiprosate from placebo on primary endpoints at 18 months and was considered a failed trial; however, the open-label extension phase is ongoing.

Three other anti-aggregation agents are currently in clinical trials.

Curcumin is a naturally occurring compound found in the spice turmeric with anti-inflammatory, anti-oxidant and anti-aggregation properties. Curcumin binds Aβ and reduces amyloid plaque burden in mice.[41] Findings from a six-month double-blind, placebo-controlled pilot trial did not show clinical benefit in patients with mild to moderate AD.[42] Phase II studies are ongoing. Metal chelating compounds represent a second class of anti-aggregation agents. Aβ binds copper and zinc, which may enhance amyloid accumulation. Clioquinol is a copper-zinc chelator that reduces Aβ deposition in a mouse model of AD.[43] The clinical trial program for clioquinol has been discontinued. However, a structural analogue, PBT-2 (Prana Biotechnology), is in Phase II testing. The third type of anti-aggregation agents is Colostrinin (ReGen Therapeutics), a proline-rich poly-peptide found in sheep colostrum. Data from a small, open-label study suggest some degree of clinical benefit,[44] and the peptide components of Colostrinin are under investigation as potential pharmaceutical agents. Colostrinin and Alzhemed are said to be under development for release as "nutraceuticals."

Other Amyloid-Based Therapies. Novel uses of drugs traditionally used in therapeutic areas other than AD are being explored as possible anti-amyloid disease-modifying treatments. For example, epidemiologic data suggest that statin therapy may be linked to reduced risk of AD.[45] Statin use was associated with lower burden of amyloid plaques and neurofibrillary tangles at autopsy in one study of 110 cognitively normal older adults.[46] The mechanisms underlying these effects are not known with precision, but one theory is that statins may upregulate α-secretase,[47] which cleaves APP, but does not generate Aβ42. Activation of α-secretase increases Aβ40 and decreases Aβ42 production,[7,48,49] and may serve a protective role in AD. Atorvastatin treatment of patients with mild to moderate AD for one year resulted in modest improvements in cognition and depression scales compared to placebo.[50] Reductions in the rate of cognitive decline were greater for patients with mild AD compared to more advanced disease, which supports the concept of early treatment. In addition, patients with elevated serum cholesterol (>200mg/dl) at baseline exhibited greater cognitive improvement than patients without elevated cholesterol, suggesting a role for cholesterol lowering in patients with mild AD.[51]

Phase III trials of statin therapy in patients with mild to moderate AD are underway.

Insulin resistance, a hallmark feature of type 2 diabetes, is linked to increased risk of AD.[52] The peroxisome proliferator-activated receptor (PPAR)-gamma agonists (*e.g.*, rosiglitazone, pioglitazone and others), which are standard treatment for type 2 diabetes, decrease brain levels of activated microglia, reactive astrocytes, inflammatory markers and Aβ42,[53] and improve spatial learning and memory in animal models of AD.[54] Rosiglitazone treatment in patients with mild to moderate AD produced a modest cognitive benefit which did not reach statistical significance following six months of treatment.[55,56] Phase III trials of rosiglitazone are ongoing.

New Treatment Strategies on the Horizon

Data on the production and accumulation of Aβ42 as pivotal events underlying the pathophysiology of AD plus findings from clinical trials of investigational anti-amyloid disease-modifying treatments are converging to suggest an entirely new treatment paradigm. Current therapies may temporarily reduce cognitive and functional symptoms in patients with established disease. In contrast, treatments of the future are projected to delay, slow or even stop the rate of memory loss and cognitive impairment for patients and will likely be of most benefit in the earliest stages of the disease or even as primary prevention. The rapid pace of clinical testing of anti-amyloid agents offers hope that new drugs will be available in the next few years, possibly as early as 2009.

Bringing a new disease-modifying drug for AD to market is not without significant challenges. Standard short-term randomized, double-blind, placebo-controlled trials are not sufficient to demonstrate disease-modification. Novel trial designs, such as the "natural history staggered start" method, represent one part of the triad of evidence proposed to demonstrate disease modification. The two other components consist of data from validated animal models of AD showing treatment effect and identification of biomarkers able to predict response to treatment.[57]

Physicians, patients and families must understand that disease modification is not a cure. Rather, successful disease-modifying therapy will slow the course of AD and enable patients to enjoy a longer duration of productive, healthy old age. As disease-modifying treatments are approved and become available for clinical use, it is likely that agents from different therapeutic classes will be used in combination to slow the course of AD. For example, a SALA may be administered in combination with Aβ immunotherapy in patients in the earliest stages of mild AD. Symptomatic treatments, like the cholinesterase inhibitors and memantine, would be added later in the course of the disease for patients in more advanced stages of AD. Treatment of AD is entering a new era, and the next several years will surely be a time of hope and encouragement for patients and families.

Physicians, patients and families must understand that disease modification is not a cure. Rather, successful disease-modifying therapy will slow the course of AD and enable patients to enjoy a longer duration of productive, healthy old age.

Conclusions

- Anti-amyloid disease modification appears to be the future of AD treatment.
- Currently available treatments—the cholinesterase inhibitors and memantine—may reduce symptoms of cognitive and functional impairment in patients with established disease, but effects are not durable over time, and the disease progresses unimpeded.
- By slowing or stopping the rate of clinical deterioration, early administration of disease-modifying treatments would alter the course of AD.
- The amyloid hypothesis is the leading pathologic theory of AD. According to the amyloid hypothesis, increased production or decreased clearance of the neurotoxic Aβ42 is the central molecular event initiating AD pathology.
- Ongoing drug development efforts focus on compounds that interrupt events along the amyloid pathway.
- Several different classes of anti-amyloid, disease-modifying treatments are under investigation.
- Tarenflurbil (a selective amyloid-lowering agent), bapineuzumab (a passive form of immunotherapy), LY-450139 (a gamma secretase inhibitor) and atorvastatin (a statin) are the agents that are furthest along in Phase III trials.
- Anti-amyloid disease-modifying therapies, if successful, will change the face of AD. Treatment will be recommended very early in the course of the disease, possibly even presymptomatically, if appropriate patients can be reliably determined from diagnostic biomarkers. The goal of early treatment is to delay symptom emergence and prolong the duration of healthy old age. Symptomatic treatments will likely continue in their current role for those with established disease. **PN**

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Speakers' Bureau Abbott Laboratories; Bayer Healthcare; Bristol-Myers Squibb Company; Eisai Inc.; GlaxoSmithKline; Janssen Pharmaceutica Products; LP; Eli Lilly and Company; Novartis Pharmaceuticals; Pfizer Inc.; Solvay Pharmaceuticals; Upjohn, Inc.; Wyeth-Ayerst Laboratories.

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