REVIEW

Disease-modifying drugs in Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is an age-dependent neurodegenerative disorder and the most common cause of dementia. The early stages of AD are characterized by short-term memory loss. Once the disease progresses, patients experience difficulties in sense of direction, oral communication, calculation, ability to learn, and cognitive thinking. The median duration of the disease is 10 years. The pathology is characterized by deposition of amyloid beta peptide (so-called senile plaques) and tau protein in the form of neurofibrillary tangles. Currently, two classes of drugs are licensed by the European Medicines Agency for the treatment of AD, ie, acetylcholinesterase inhibitors for mild to moderate AD, and memantine, an N-methyl-D-aspartate receptor antagonist, for moderate and severe AD. Treatment with acetylcholinesterase inhibitors or memantine aims at slowing progression and controlling symptoms, whereas drugs under development are intended to modify the pathologic steps leading to AD. Herein, we review the clinical features, pharmacologic properties, and cost-effectiveness of the available acetylcholinesterase inhibitors and memantine, and focus on disease-modifying drugs aiming to interfere with the amyloid beta peptide, including vaccination, passive immunization, and tau deposition.

Keywords: Alzheimer's disease, acetylcholinesterase inhibitors, memantine, disease-modifying drugs, diagnosis, treatment

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the most prevalent cause of dementia with ageing. The prevalence of AD increases with age, from 5% of people affected after 65 years of age to about 30% in people aged 85 years or older.

In the majority of cases, AD develops as a result of multiple factors, with increasing age bringing the greatest risk; nevertheless, up to 3%–5% of cases are linked to genetic causes. Mutations in genes encoding for amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) account for about 5% of cases, and are characterized by an early onset (before 65 years of age). Comorbidities and lifestyle are also contributing factors. In this regard, several studies have been designed to determine the role of diet in contributing to the risk of AD. The Washington Heights-Inwood Columbia Aging Project provides the first evidence of a beneficial effect of the Mediterranean diet on the risk of AD. However, the exact magnitude of such risk factors is still unknown. Histopathologically, the typical hallmarks of the disease include deposition of amyloid beta (Aβ) peptide in so-called senile plaques and accumulation of tau protein in cells, leading to neurofibrillary tangles and pyramidal cell loss.

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Cholinergic hypothesis and current treatments

In the past few decades, treatment for AD has largely involved replacement of neurotransmitters known to be lacking in AD, mostly based on the "cholinergic hypothesis" of AD.[1–3] This hypothesis states that a deficit in central cholinergic transmission caused by degeneration of the basal forebrain nuclei is an important pathologic and neurochemical feature of AD. A progressive loss of nicotinic receptors over the course of the disease has also been described,[4] and there is evidence of a role for these receptors in memory and cognition deficits.[5]

Different strategies have been investigated to improve cholinergic neurotransmission, including increasing acetylcholine synthesis, augmentation of presynaptic acetylcholine release, stimulation of cholinergic postsynaptic muscarinic and nicotinic receptors, and reduction of acetylcholine synaptic degradation with cholinesterase inhibitors. The current data do not support the use of precursors of acetylcholine, presynaptic releasing agents, or muscarinic agonists because of a lack of efficacy and unacceptable side effects.[6]

Acetylcholinesterase inhibitors act by restricting the ability of the cholinesterase enzyme to break down acetylcholine, thus increasing the concentration and duration of acetylcholine at sites of neurotransmission. So far, three acetylcholinesterase inhibitors are approved for the treatment of patients with mild-to-moderately severe AD, ie, donepezil, rivastigmine, and galantamine.

Donepezil is a reversible, specific acetylcholinesterase inhibitor. It is easily absorbed by the body and can be taken once a day, initially at 5 mg and then, after 4 weeks of use, titrated up to 10 mg per day. It was approved for the treatment of mild-to-moderate AD in 1996.

Acetylcholinesterase inhibitors are associated with a range of side effects as a result of cholinergic stimulation in different areas of the brain and the periphery. Possible side effects include nausea, vomiting, diarrhea, and sleep disturbances, associated with cholinergic activity in the cortex, caudate nucleus, brainstem, and medulla, respectively, and muscle cramps, weakness, bradycardia (particularly in people with sick sinus syndrome or other supraventricular cardiac conduction conditions), and urinary incontinence, associated with peripheral cholinergic activity.[7]

There is evidence that donepezil is effective in improving and maintaining global outcomes in the short to medium term (12–24 weeks),[8] and is supported by a large open-label trial that investigated the efficacy of donepezil in a routine setting in clinical practice.[9] A meta-analysis showed that improvements in Mini-Mental State Examination score are maintained at 52 weeks with donepezil 10 mg/day compared with placebo.[10] In the AD2000, a clinical trial of 565 community residents, improvements in Mini-Mental State Examination score were maintained beyond 52 weeks with donepezil 5 or 10 mg/day.[11] However, despite the effects of donepezil on major symptoms of AD, its impact on patient quality of life has not been consistently demonstrated, perhaps reflecting the difficulty of assessing this aspect in the AD patient population.[8]

Rivastigmine tartrate is an acetylcholinesterase inhibitor and also a butyrylcholinesterase inhibitor. Owing to its short half-life (1.5 hours), it has to be taken twice a day. Doses start at 3 mg per day and increase gradually to between 6 mg and 12 mg per day. Rivastigmine can be taken orally or by a transdermal patch, with doses of either 4.6 mg or 9.5 mg per 24 hours. Care should be exercised in patients with renal disease (due to its elimination pattern), mild or moderate liver disease (mainly metabolized by the liver), sick sinus syndrome, conduction abnormalities, gastric or duodenal ulcers, or a history of asthma or obstructive pulmonary disease. The main side effects are nausea and vomiting. However, these events can be minimized using slow dose escalation, with small dose graduations and administration with food.[7]

A Cochrane review by Birks et al considering nine trials with a total of 4,775 participants concluded that rivastigmine gives benefit to people with mild-to-moderate AD when compared with placebo at 26 weeks.[12] Indeed, the rivastigmine 9.6 mg transdermal patch demonstrates the same efficacy but fewer side effects than capsules. The main adverse effects are gastrointestinal (nausea and vomiting), usually occurring during the titration phase.[12]

Rivastigmine preferentially inhibits the G1 isoform of cholinesterase, which is predominantly located in the cortex, hippocampus, and neuritic plaques, while donepezil and galantamine are not selective for any cholinesterase isoforms and have wide cholinergic activity both centrally and peripherally. The cholinergic activity of rivastigmine, in contrast with donepezil and galantamine, is apparently more targeted at clinically relevant brain sites.[7]

Two head-to-head studies comparing donepezil with high-dose and low-dose rivastigmine showed that results for rivastigmine on functional and global outcomes were significantly better than those for donepezil.[13,14] Bullock conducted another head-to-head study comparing donepezil with rivastigmine, and found a similar decline in cognitive, behavioral, and functional domains in the two groups of patients at 2 years of follow-up.[15]

Galantamine was originally made from snowdrop and narcissus bulbs, but is now produced synthetically. It is a reversible acetylcholinesterase inhibitor with a half-life of about 7 hours, indicating that it should be taken twice a day at the recommended dose of 16–24 mg each time. An alternative version is taken once a day at doses of 8, 16, or 24 mg. The side effects of galantamine are similar to those of the other acetylcholinesterase inhibitors, and are mainly gastrointestinal (abdominal pain, diarrhea, nausea, and vomiting), although bradycardia and dizziness have been also reported.

Several randomized controlled trials (RCTs) have compared the clinical efficacy of galantamine versus placebo. The benefit appears to vary depending on the dose, with greater benefits on cognition found with 16 and 32 mg/day after 21–26 weeks of treatment.[16] With regard to functional ability, a number of RCTs have analyzed the effectiveness of galantamine versus placebo; the outcome measures considered were the Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory and the Disability Assessment of Dementia scale. All studies found that participants receiving galantamine (16 mg/day, 24 mg/day, and/or 32 mg/day) experienced a significantly smaller deterioration on galantamine compared with placebo.[16]

Ancori-Israel et al compared the effects of galantamine 16 mg with those of donepezil 10 mg on patients' and caregivers' sleep patterns. Their study was suggestive of small benefits resulting from galantamine treatment; however, the results were not statistically significant.[17]

Memantine

Memantine is approved for the treatment of moderate-to-severe AD, as measured by a Mini-Mental State Examination score ≤20. It is a voltage-dependent, moderate-affinity, noncompetitive N-methyl-aspartate receptor antagonist, and is taken orally twice a day. The starting dose is 10 mg/day and can be increased to a maximum daily dose of 20 mg/day. Caution should be used when prescribing memantine for people with renal failure or epilepsy; it is also contraindicated for people with severe renal impairment. Side effects may include dizziness, confusion, headache, and incontinence.

An RCT evaluating the efficacy of memantine monotherapy demonstrated a beneficial effect on cognition at 12 weeks but not at 24–36 weeks.[16] A recent meta-analysis[18] confirmed a small but significant benefit of memantine combination therapy on cognitive, global, and behavior measures, but not on function/activities of daily living. In 2012, a post-marketing surveillance study demonstrated that patients on a stable dosage of memantine are more likely to improve in affect, physical behavior, and psychosis domains than those on a modified dosage of memantine (defined as dose change or withdrawal during the study period). The size effect was modest, with behavioral improvement reported in only 24%–30% of patients. Moreover, the study population might not have been representative of the AD population, because patients with clinical relevant comorbidity or taking other central nervous system drugs were excluded.[19]

In 2008, Qaseem et al[20] developed a guideline to assist clinicians in the treatment decision, and made the following recommendations:

- clinicians should base the decision to initiate a trial of therapy with a cholinesterase inhibitor or memantine on individualized assessment (Grade: weak recommendation, moderate quality evidence)
- clinicians should base the choice of pharmacologic agent on tolerability, adverse effect profile, ease of use, and cost of medication; the evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia (Grade: weak recommendation, low quality evidence)
- there is an urgent need for further research on the clinical effectiveness of pharmacologic management of dementia.

Cholinergic drugs under development or in clinical trials
Latrepirdine

Latrepirdine is an oral compound previously approved in Russia as a nonselective antihistamine but was withdrawn from the market after the development of more selective drugs. In two studies, there was improvement over 6 months in all endpoints (cognitive, global, daily functional behavior), with continuing improvement in cognition and daily function at 12 months. However, in the Phase III trial (CONNECTION), latrepirdine failed on primary and secondary endpoints.[21] Two other Phase III studies (CONTACT and COSTELLATION) are in progress.[22]

Huperzine A

Huperzine A is a potent, selective, and well tolerated acetylcholinesterase inhibitor, and is a Lycopodium alkaloid isolated from the Chinese folk medicine *Huperzia serrata* (Qian Ceng Ta). In multiple studies, it has shown a beneficial effect on memory impairment in AβPP/PS1 mice after 8 weeks of administration. Unfortunately, in a recent Phase II trial, huperzine A 200 μg twice daily had no effect

on cognitive function in patients with mild to moderate AD.[23] A Phase III clinical trial evaluating safety and efficacy of sustained-release huperzine A tablets versus placebo in patients with mild-to-moderate AD is ongoing.

Phenserine

Phenserine is a noncompetitive acetylcholinesterase inhibitor that has independent modulatory effects on Aβ generation. A recent study showed a statistically significant benefit on cognition from phenserine 15 mg versus placebo at 12 weeks.[24]

Ladostigil

Ladostigil (TV-3326) is a dual acetylcholine-butyrylcholinesterase and brain-selective monoamine oxidase A and B inhibitor in vivo, and intended for the treatment of dementia comorbid with extrapyramidal disorders and depression. Presently in a Phase IIb clinical study, ladostigil has been previously demonstrated to possess potent antiapoptotic and neuroprotective activity in vitro and in various neurodegenerative rat models.[25]

Amyloid hypothesis

According to the amyloid hypothesis, the deposition of Aβ is a central event in the etiology of AD.[26] Aβ derives from the amyloid precursor protein, which can be processed by two different enzymes, ie, α-secretase and β-secretase.[27] In both cases, the C-terminal fragment undergoes a subsequent additional cleavage event by an enzyme complex called γ-secretase. This second cleavage results in amyloid precursor protein intracellular domain and either the p3 protein in the case of the α-secretase pathway or the Aβ in the case of the β-secretase pathway. Thus, the beta amyloid hypothesis suggests that beta amyloid deposition leads to tau pathology, as well as additional pathogenic mechanisms, such as inflammation and oxidative damage, that result in cell death. Recent evidence suggests that the neurotoxic form of amyloid is soluble oligomers rather than monomers or the fibrillary form found in plaques.[28] New therapeutic strategies aim to interfere with amyloid deposition, either influencing its formation or trying to remove it once deposited in senile plaques, and include mainly vaccination and passive immunization.

β-secretase and γ-secretase inhibitors

β-secretase 1 is an aspartyl protease that shares some features with human immunodeficiency aspartyl proteases. No known mutations in the gene encoding β-secretase have been related to familial AD. Because β-secretase 1 also has other substrates (including neuregulin-1, which is involved in myelination), development of inhibitors may theoretically face problems of toxicity related to nonspecific effects and blood-brain barrier penetration.[24] The thiazolidinediones, rosiglitazone and pioglitazone, have been tested for AD in RCTs, and may in part act as suppressors of β-secretase expression. Rosiglitazone was shown to improve spatial learning and memory ability, and slightly decreased Aβ42 (but not Aβ40) concentrations in the brain, without affecting the amyloid plaque burden in Tg2576 mice. In a Phase II study, after 6 months of treatment with rosiglitazone, patients with mild AD or amnestic mild cognitive impairment showed better delayed recall and selective attention as compared with a placebo group.[29] A subsequent larger Phase III study showed no significant clinical benefit of rosiglitazone, ie, not confirming the preliminary observation made in the Phase II study.[30] MK-8931 is a potent β-secretase 1 inhibitor, and has been shown to reduce Aβ levels in the cerebrospinal fluid and brains of rodents and primates. In Phase I trials, MK-8931 has been generally safe and well tolerated. Two large double-blind, placebo-controlled, Phase II/III RCTs are ongoing in patients with mild-to-moderate AD and prodromal AD.[31,32]

γ-secretase is a protease complex that cleaves proteins at residues within their single membrane spanning domain. The best known substrate of γ-secretase is amyloid precursor protein, cleavage of which produces Aβ. The γ-secretase complex consists of four individual proteins, ie, presenilin, nicastrin, APH-1, and PEN-2.[33] Development of γ-secretase inhibitors as disease-modifying drugs presents problems related to their potential nonspecific effects. This is because γ-secretase is not only responsible for Aβ generation but is also involved in intramembranous cleavage of several proteins (ie, Notch receptor, ErbB4, p75 NTR neurotrophin receptor, N-cadherin, and the sodium channel β4 subunit).[34]

Semagacestat was the first γ-secretase inhibitor to undergo extensive clinical testing and was shown to reduce Aβ concentrations in plasma and Aβ production in the central nervous system.[35] Two large Phase III studies with semagacestat were prematurely stopped because of serious collateral adverse effects, including hematologic, gastrointestinal, and skin toxicity, that have been attributed to inhibition of the Notch signaling pathway. Further, in these studies, no improvement or moderate worsening of cognition was observed, perhaps related to γ-secretase inhibition within the central nervous system.[36]

Notch-sparing γ-secretase inhibitors and/or modulators (agents that shift γ-secretase cleavage activity from longer

to shorter Aβ species without affecting Notch cleavage) are in clinical development. Begacestat, BMS-708163 (avagacestat), and CHF-5074 display 10–100-fold selectivity for amyloid precursor protein over Notch cleavage. Begacestat showed significant reduction in plasma and cerebrospinal fluid levels of Aβ in animal models and a good safety and tolerability profile in Phase I studies. In a Phase I trial, doses of avagacestat >50 mg/day reduced cerebrospinal fluid concentrations of Aβ1–38, Aβ1–40, and Aβ1–42 in a dose-dependent fashion over 28 days of daily dosing without any sign of potential Notch-related dose-limiting toxicity.[37] CHF-5074 showed a good safety and tolerability profile in Phase I clinical trials. Phase II trials are ongoing in patients with mild cognitive impairment (http://www.clinicaltrial.gov).

Vaccination

The concept of immunotherapy for neurodegenerative diseases was introduced by Schenk et al in 1999 when they used an Aβ vaccine to tackle AD.[38] Their vaccine was composed of Aβ itself and the immunologic adjuvant QS21. In mice, it was extremely effective in reducing cerebral Aβ load and ameliorating cognitive performance. In 2001, a multicenter, randomized, placebo-controlled, double-blind, Phase II clinical trial using active immunization with Aβ42 plus an adjuvant was started in 300 patients. Unlike in the preclinical phase, severe adverse events occurred, consisting of aseptic meningoencephalitis in 18 treated patients. Therefore, the trial was halted after 2–3 injections. The final results of the trial were published in 2005.[39]

Double-blind assessment was maintained for 12 months, demonstrating no significant differences in cognition between antibody responders and a placebo group on neuropsychologic assessment. In 2008, a paper was published describing the relationship between Aβ42 immune response, degree of plaque removal, and long-term clinical outcomes.[40] In June 2003, 80 patients (or their caregivers), who had entered Phase I and II of the AN1792 trial, gave their consent for long-term clinical follow-up (maximum 6 years) and post mortem neuropathologic examination. At autopsy, the mean Aβ load was lower in brains from patients who had received immunization than in the placebo cohort. However, despite this observation, no evidence of improved survival or improvement in time to develop severe dementia was observed in these patients. These results suggest that plaque removal is not enough to halt progressive neuronal death, prompting some intriguing challenges to the amyloid hypothesis.

Although severe adverse events occurred in the first AN1792 trial and cognitive results were unclear, immunization was not abandoned. The first second-generation vaccine tested in patients with AD was CAD106 (Novartis, Basel, Switzerland), a vaccine that presents multiple copies of Aβ1–6 peptide derived from the N-terminal B cell epitope of Aβ, and avoids T cell activation. Administration of CAD106 to APP transgenic mice showed a reduction of Aβ deposition in the brain. A double-blind, placebo-controlled, 52-week, Phase I study was carried out in two centers in Sweden,[41] and no cases of clinical or subclinical cases of meningoencephalitis occurred.

Additional vaccines under clinical testing include: ACI-24 (AC Immune, Lausanne, Switzerland), an Aβ1–15 peptide to which two lysines are attached on both ends, embedded in a liposome membrane; Affitope® AD02 (AFFiRiS AG, Vienna, Austria, and licensee GlaxoSmithKline Biologicals SA, Rixensart, Belgium), a six-amino acid peptide vaccine targeting the N-terminus of amyloid-β; Affitope AD03 (AFFiRiS AG and licensee GlaxoSmithKline Biologicals); ACC-001 (vanutide cridificar; Pfizer Inc, Groton, CT, USA); UB-311 (United Biomedical Inc, Hauppauge, NY, USA); and V-950 (Merck and Co, Inc, Whitehouse Station, NJ, USA).[42]

Passive immunization

An alternate solution to avoid undesirable T cell-induced inflammation that can be a source of side effects is to use passive immunization with humanized antibodies. The first antibody tested in a Phase II trial was the humanized monoclonal anti-Aβ antibody bapineuzumab (Wyeth, Madison, NJ, USA, and Élan Corporation, Dublin, Ireland). This 18-month, multidose, one-to-one randomized trial was designed to assess safety, tolerability, and standard efficacy endpoints (ADAS-Cog) of multiple ascending doses of bapineuzumab in patients. On May 2007, Élan Corporation and Wyeth announced their plans to start a Phase III clinical trial of bapineuzumab, based on all the clinical data accumulated from the Phase I and Phase II trials.[43]

Among the analyses carried out, different effects were observed when stratifying patients according to their apolipoprotein E (ApoE) status. It seemed that ApoE noncarriers who received the second to lowest of the four doses six times responded better than the carriers. Therefore, two Phase III studies were started in ApoE4 noncarriers and carriers with mild-to-moderate AD (http://clinicaltrials.gov). Two multicenter, randomized, double-blind, placebo-controlled Phase III studies reached completion in April and

June 2012. The first study compared 0.5 mg/kg and 1 mg/kg of bapineuzumab versus placebo. The second compared responses to bapineuzumab 0.5 mg/kg versus placebo in ApoEε4 carriers. Coprimary endpoints for each trial were the changes in ADAS-Cog and Disability Assessment of Dementia scores from baseline. Secondary endpoints included brain amyloid burden on Pittsburgh compound B-positron emission tomography, cerebrospinal fluid, phospho tau, and brain volume on magnetic resonance imaging. In July 2012, Pfizer (having acquired Wyeth in 2009) reported that the study in ApoE4 carriers did not meet its primary endpoints and announced the discontinuation of the Phase III trials. However, a secondary endpoint analysis revealed a reduction in amyloid plaques on positron emission tomographic imaging in APOE 4 carriers with mild AD.[44]

Solanezumab (LY2062430; Eli Lilly, Indianapolis, IN, USA) is a humanized monoclonal antibody that binds to the central region of β-amyloid. A randomized, double-blind, placebo-controlled, Phase II clinical trial was carried out to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of 12 weekly infusions of solanezumab in patients with mild-to-moderate AD. Clinical laboratory values, cerebrospinal fluid cell counts, and magnetic resonance imaging scans were unchanged by treatment, and no adverse events could be clearly related to administration of the antibody. Two large Phase III trials (EXPEDITION1 and EXPEDITION2) are ongoing, showing that the treatment is effective in mild but not severe AD.[44]

Gantenerumab (R1450; Hoffman-LaRoche, Basel, Switzerland) has been optimized in vitro for binding with subnanomolar affinity to a conformational epitope expressed on Aβ fibrils using HuCAL® phage display technology. In peptide maps, both the N-terminal and central portions of Aβ were recognized by gantenerumab. A large Phase III clinical trial is ongoing.

Passive immunization is considered safer than active immunization, and no cases of encephalitis have been reported thus far. However, passive immunotherapy has its own side effects, most notably microhemorrhages and vasogenic edema. All these antibodies are built on the same immunoglobulin (IgG1) backbone, which is thought to activate microglia. Different from the previously described antibodies, crenezumab (MABT5102A; Genentech Inc, South San Francisco, CA, USA) possesses an IgG4 backbone, which has a milder effect on microglia because it binds more weakly to cell surface immunoglobulin receptors. Nonetheless, it is able to bind all forms of Aβ, including toxic oligomers. The first Alzheimer's Prevention Initiative will study crenezumab in 300 people from a large family in Columbia with a rare genetic mutation that typically triggers AD symptoms around the age of 45 years, and is a collaboration between the National Institutes of Health, Banner's Alzheimer's Institute, and Genentech Inc.

Moreover, another large Phase II/III trial is ongoing to assess the safety, tolerability, and biomarker efficacy of gantenerumab and solanezumab in individuals with autosomal dominant Alzheimer's disease mutation. Additional antibodies are in clinical development, including PF-04360365 (Pfizer), GSK933776A (GlaxoSmithKline), NI-101 (Biogen Idec, Weston, MA, USA), PF-05236812 (Janssen Alzheimer Immunotherapy, South San Francisco, CA, USA, and Pfizer), RN6G (Pfizer), SAR-228810 (Sanofi SA, Paris, France), and BAN-2401 (Eisai Co, Ltd, Tokyo, Japan).[44]

Anti tau strategies

Tau is a cytoplasmic protein that binds to tubulin during its polymerization, thereby stabilizing microtubules. Tau is abnormally phosphorylated in AD, resulting in generation of aggregates (neurofibrillary tangles) toxic to neurons. Tau hyperphosphorylation can be promoted by imbalanced activity of protein kinase. One therapeutic approach is based on inhibitors of tau-phosphorylating kinase (glycogen synthase kinase-3 and p70-S6-kinase). Both lithium and valproate inhibit glycogen synthase kinase-3. A Phase III clinical trial demonstrated that treatment with valproate does not delay emergence of agitation or psychosis or slow cognitive or functional decline in patients with moderate AD.[45] In a recent RCT of 45 patients with amnestic mild cognitive impairment, treatment with lithium was associated with a significant decrease in concentrations of phospho tau in cerebrospinal fluid and better performance on the cognitive subscale of the ADAS-Cog and on attention tasks.[46]

Several glycogen synthase kinase-3 inhibitors are under development. NP-031112 (NP-12) is a thiazolidinedione-derived compound that is able to induce neuroprotection and attenuate the production of proinflammatory cytokines and activation of astrocytes and microglial cells in a rat model of excitotoxicity.[47] This compound has been tested in patients with Alzheimer's disease in a Phase II RCT, but there are no definitive results.[48]

Another approach is based on compounds that inhibit tau aggregation and/or promote aggregate disassembly. Methylthioninium chloride, a reducing agent better known as methylene blue, interferes with tau aggregation by acting on self-aggregating truncated tau fragments.[48] In a placebo-controlled Phase II trial, methylthioninium chloride at 60 mg

was effective in slowing the rate of AD progression by 80% compared with placebo. An open-label Phase II study of methylthioninium chloride 30 mg and 60 mg is ongoing. A new formulation (leuco-methylthioninium), with better bioavailability and tolerability, was designed some years ago, and Phase III RCTs were planned to confirm its safety and clinical efficacy.[48]

Davunetide, an intranasally administered, eight-amino acid peptide fragment, is able to inhibit tau hyperphosphorylation. A Phase II RCT in patients with amnestic mild cognitive impairment demonstrated that it is safe, well tolerated, and has positive effects on cognition.[49]

Nicotinamide is the biologically active form of niacin (vitamin B3), and the precursor of coenzyme NAD+. In mouse models of AD, this compound is able to reduce brain concentrations of a species of phosphorylated tau (Thr231) that inhibits microtubule polymerization.[50] A Phase II study in patients with mild-to-moderate AD has just ended, but no results are available as yet.

Finally, two studies of particular interest are ongoing. The first is a randomized, double-blind, placebo-controlled, parallel-group, 15-month Phase III trial of TRx0237 (TauRx Therapeutics Ltd, Aberdeen, Scotland) in subjects with mild to moderate AD. The second is a Phase I study with BMS-241027 (Bristol-Myers Squibb, New York City, NY, USA), evaluating the safety and pharmacodynamic effects of the drug on tau in cerebrospinal fluid, using functional connectivity magnetic resonance imaging and computerized cognitive tests in subjects with mild AD, following nine weekly intravenous infusions of BMS-241027.

Conclusion

Pharmacologic treatment of AD involves acetylcholinesterase inhibitors and memantine, which provide mainly symptomatic short-term benefits without counteracting the progression of the disease. In the last decade, despite a number of promising disease-modifying compounds having been developed, none has ever succeeded in Phase III trials. Therefore, additional mechanisms at the basis of AD pathogenesis must be better understood; the amyloid hypothesis can explain part of the pathologic processes underlying AD, but Phase III studies of active or passive immunization have failed to demonstrate a cognitive benefit compared with placebo. This suggests that removing senile plaques is necessary, but not sufficient to halt disease progression. Therefore it is of crucial importance to better understand the relationship between tau, Aβ, and other factors when developing novel potentially disease-modifying drugs.

Indeed, all past clinical trials were conducted in patients with mild-to-moderate AD. Disease-modifying drugs might work better in the preclinical stages of the disease, when Aβ and tau burden are not so compromising and patients are still autonomous in daily living tasks. That is why current and future trials will be designed to include patients in the preclinical phase of the disease (prodromal AD), underscoring the need to identify tools for early diagnosis (ie, cerebrospinal fluid or radiologic biomarkers). Last, indicators useful as surrogate biomarkers should be identified in order to: have substitutes for clinical endpoints (at present, represented mainly by neuropsychologic testing); develop tools that are able to predict clinical benefit, or the opposite; and demonstrate whether there are disease-modifying properties.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Bartus RT, Dean RL 3rd, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. *Science*. 1982;217:408–414.
2. Perry EK. The cholinergic hypothesis ten years on. *Br Med Bull*. 1986;42:63–69.
3. Bowen DM, Francis PT, Pangalos MN, Stephens PH, Procter AW. Treatment strategies for Alzheimer's disease. *Lancet*. 1992;339: 132–133.
4. Whitehouse PJ, Martino AM, Antuono PG, et al. Nicotinic acetylcholine binding sites in Alzheimer's disease. *Brain Res*. 1986;371:146–151.
5. Newhouse PA, Potter A, Levin ED. Nicotinic acetylcholine involvement in Alzheimer's and Parkinson's disease: implications for therapeutics. *Drugs Aging*. 1997;11:206–228.
6. Doody RS, Stevens JC, Beck C, et al. Practice parameter: management of dementia (an evidence-based review). *Neurology*. 2001;56: 1154–1166.
7. Inglis F. The tolerability and safety of cholinesterase inhibitors in the treatment of dementia. *Int J Clin Pract Suppl*. 2002;127:45–63.
8. Knowles J. Donepezil in Alzheimer's disease: an evidence-based review of its impact on clinical and economic outcomes. *Core Evid*. 2006;1:195–219.
9. Froelich L, Gertz HJ, Heun R, et al. Donepezil for Alzheimer's disease in clinical practice – the DONALD study. *Dement Geriatr Cogn Disord*. 2004;18:37–43.
10. Birks JS, Harvey R. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev*. 2003;3:CD001190.
11. Courtney C, Farrell D, Gray R, et al. AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet*. 2004;363: 2105–2115.
12. Birks J, Evans JG, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev*. 2009;2:CD001191.
13. Cumbo E. Differential effects or rivastigmine, galantamine and donepezil on behavioral and psychological symptoms in patients with Alzheimer's disease: 18-month, randomized, open-label trial. *Prim Care Community Psychiatr*. 2005;10:95–102.
14. Pattanaprateep O, Phongchareonsuk P, Chaikledkaew U. The cost-effectiveness of donepezil and rivastigmine in the treatment of Alzheimer's disease in Thailand private hospital. *Value Health*. 2005;8:314–815.
15. Bullock R. Treatment of behavioural and psychiatric symptoms in dementia: implications of recent safety warnings. *Curr Med Res Opin*. 2005;21:1–10.

16. Bond M, Rogers G, Peters J, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No 111): a systematic review and economic model. *Health Technol Assess*. 2012;16:1–470.

17. Ancoli-Israel S, Amatniek J, Ascher S, Sadik K, Ramaswamy K. Effects of galantamine versus donepezil on sleep in patients with mild to moderate Alzheimer disease and their caregivers: a double-blind, head-to-head, randomized pilot study. *Alzheimer Dis Assoc Disord*. 2005;19:240–245.

18. Farrimond LE, Roberts E, McShane R. Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. *BMJ Open*. 2012;2:e000917.

19. Clerici F, Vanvacore N, Elia A, et al. Memantine effects on behaviour in moderately severe to severe Alzheimer's disease: a post-marketing surveillance study. *Neurol Sci*. 2012;33:23–31.

20. Qaseem A, Snow V, Cross TJ Jr, et al. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med*. 2008;148:370–378.

21. Jones WR. Dimebon disappointment. *Alzheimers Res Ther*. 2010;2:25.

22. Tayeb HO, Yang HD, Price BH, Tarazi FI. Pharmacotherapies for Alzheimer's disease: beyond cholinesterase inhibitors. *Pharmacol Ther*. 2012;134:8–25.

23. Rafii MS, Walsh S, Little JT, et al. A phase II trial of huperzine A in mild to moderate Alzheimer disease. *Neurology*. 2011;76:1389–1394.

24. Salomone S, Caraci F, Leggio GM, et al. New pharmacological strategies for treatment of Alzheimer's disease: focus on disease-modifying drugs. *Br J Clin Pharmacol*. 2012;73:504–517.

25. Weinreb O, Amit T, Bar-Am O, Youdim MB. Ladostigil: a novel multimodal neuroprotective drug with cholinesterase and brain-selective monoamine oxidase inhibitory activities for Alzheimer's disease treatment. *Curr Drug Targets*. 2012;13:483–494.

26. Hardy J, Akksop D. Amyloid hypothesis deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci*. 1991;12:383–388.

27. Chow VW, Mattsonn MP, Wong PC, Gleichmann M. An overview of APP processing enzymes and products. *Neuromolecular Med*. 2010;12:1–12.

28. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. *Nat Rev Mol Cell Biol*. 2007;8:101–112.

29. Watson GS, Cholerton BA, Reger MA, et al. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry*. 2005;13:950–958.

30. Gold M, Alderton C, Zvartau-Hind M, et al. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. *Dement Geriatr Cogn Disord*. 2010;30:131–146.

31. Merck. An Efficacy and Safety Trial of MK-8931 in Mild to Moderate Alzheimer's Disease (P07738) (EPOCH). In: ClinicalTrials.gov [website on the Internet]. Bethesda, MD: US National Library of Medicine; 2012 [updated November 4, 2013]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01739348?term=MK-8931&rank=2. NLM identifier: NCT01739348. Accessed November 22, 2013.

32. Merck. Efficacy and Safety Trial of MK-8931 in Participants With Prodromal Alzheimer's Disease (MK-8931-019) (APECS). In: ClinicalTrials.gov [website on the Internet]. Bethesda, MD: US National Library of Medicine; 2013 [updated November 19, 2013]. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01953601?term=MK-8931&rank=3. NLM identifier: NCT01953601. Accessed November 22, 2013.

33. Kaether C, Haass C, Steiner H. Assembly, trafficking and function of gamma-secretase. *Neurodegener Dis*. 2006;3:275–283.

34. Tomita T. Secretase inhibitors and modulators for Alzheimer's disease treatment. *Expert Rev Neurother*. 2009;9:661–679.

35. Bateman RJ, Siemers ER, Mawuenyega KG, et al. A gamma-secretase inhibitor decreases amyloid-beta production in the central nervous system. *Ann Neurol*. 2009;66:48–54.

36. Schor NF. What the halted phase III gamma-secretase inhibitor trial may (or may not) be telling us. *Ann Neurol*. 2011;69:237–239.

37. Dockens R, Wang JS, Castaneda L, et al. A placebo-controlled, multiple ascending dose study to evaluate the safety, pharmacokinetics and pharmacodynamics of avagacestat (BMS-708163) in healthy young and elderly subjects. *Clin Pharmacokinet*. 2012;51:681–693.

38. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature*. 1999;400:173–177.

39. Gilman S, Koller M, Black RS. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology*. 2005;64:1553–1562.

40. Holmes C, Boche D, Wilkinson D, et al. Long-term effect of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. *Lancet*. 2008;372:216–223.

41. Winblad B, Andreasen N, Minthon L, et al. Safety, tolerability, and antibody response of active Aβ immunotherapy with CAD106 in patients with Alzheimer's disease: randomised, double-blind, placebo-controlled, first-in-human study. *Lancet Neurol*. 2012;11:597–604.

42. Galimberti D, Ghezzi L, Scarpini E. Immunotherapy against amyloid pathology in Alzheimer's disease. *J Neurol Sci*. 2013;333:50–54.

43. Khorassani F, Hilas O. Bapineuzumab, an investigational agent for Alzheimer's disease. *P T*. 2013;38:89–91.

44. Moreth J, Mavoungou C, Schindowski K. Passive anti-amyloid immunotherapy in Alzheimer's disease: what are the most promising targets? *Immun Ageing*. 2013;10:18.

45. Tariot PN, Schneider LS, Cummings J, et al. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. *Arch Gen Psychiatry*. 2011;68:853–861.

46. Forlenza OV, Diniz BS, Radanovic M, Santos FS, Talib LL, Gattaz WF. Disease-modifying properties of long-term lithium treatment for amnestic mild cognitive impairment: randomised controlled trial. *Br J Psychiatry*. 2011;198:351–356.

47. Luna-Medina R, Cortes-Canteli M, Sanchez-Galiano S, et al. NP031112, a thiadiazolidinone compound, prevents inflammation and neurodegeneration under excitotoxic conditions: potential therapeutic role in brain disorders. *J Neurosci*. 2007;27:5766–5776.

48. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. *Lancet Neurol*. 2010;9:702–716.

49. Morimoto BH, Schmechel D, Hirman J, et al. A phase 2, double-blind, placebo-controlled study to evaluate the safety, tolerability, and effect on cognitive function of AL-108 after 12 weeks of intranasal administration in subjects with mild cognitive impairment. *Dement Geriatr Cogn Disord*. 2013;35:325–336.

50. Green KN, Steffan JS, Martinez-Coria H, et al. Nicotinamide restores cognition in Alzheimer's disease transgenic mice via a mechanism involving sirtuin inhibition and selective reduction of Thr231-phosphotau. *J Neurosci*. 2008;28:11500–11510.