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Successes and Failures for Drugs in Late-Stage Development for Alzheimer's Disease

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Abstract

To date, symptomatic medications prevail as the mainstay of treatment options for Alzheimer's disease (AD). There have been tremendous investments made to increase the numbers of drugs approved and the targets engaged, in an effort to alter the disease course or pathophysiology of AD. Unfortunately, almost all studies have not met expectations and no new drug (beyond medical foods) has been approved for the treatment of AD in the last decade. This review is a comparison of novel AD therapies in the late phases of clinical testing with recent high-profile clinical failures and agents in development with relatively unexplored mechanisms of action, with a focus on their potential as therapeutic agents and their proposed advantages over the treatments currently in use.

Introduction

Alzheimer's disease is a neurodegenerative disorder responsible for a significant and growing population of patients suffering from dementia, with a projected prevalence in the United States alone of 13.2 million patients by 2050 (1). In postmortem assessment of Alzheimer's-afflicted brains, neuropathological hallmarks of the disease include aggregation of beta amyloid in plaques and highly phosphorylated tau proteins in neurofibrillary tangles (2). Prior to end-stage illness, patients with Alzheimer's disease experience variable symptomatic trajectories with a common element of progressive cognitive decline over a period of years. Dementia is the most prevalent symptom but often patients also experience changes in mood, increases in aggression, agitation, and psychosis, depleted physical ability and reduction in lifespan. Alzheimer's disease is especially costly for the caregivers responsible for helping patients manage their disease, and as the number of people afflicted continues to increase in coming years, pressures on the support systems for these patients will also increase.

Current FDA-approved and European Medicines Agency (EMA)-approved treatments for Alzheimer's disease are limited to cholinesterase inhibitors (ChEIs) for patients with mild to moderate disease, (with the exception of donepezil, which is also approved for moderate to severe disease), and the N-methyl-D-aspartate (NMDA) receptor partial antagonist

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memantine approved for use in moderate to severe AD, in addition to being under investigation for efficacy in a wide variety of other neurological conditions including but not limited to autism, Tourette Syndrome, neuropathic pain and non-AD types of dementia (3). These types of therapies have been shown to improve symptoms and may decrease the rate of cognitive decline, but there are currently no FDA-approved therapeutic approaches that either arrest decline or reverse neuronal damage caused by the disease. Additionally, while the EMA has similar standards for efficacy and safety as the FDA (4), its approval speed is generally slower in terms of both initial and final reviews for new drug therapies. This means that internationally, the best options for patients with Alzheimer's disease are what amount to temporary symptomatic reductions rather than anything approaching effective amelioration of AD pathology. There are at present several encouraging experimental therapy options in varying stages of clinical development, many of which are immunotherapies targeting amyloid beta designed to enhance and facilitate amyloid beta (AB) clearance from the brain (5), but there have also been significant high profile failures of drugs in late stage clinical trials that could potentially alter the future landscape of novel treatment through their inefficacy. While treatments currently under investigation are valuable in that they stand to improve the dearth of disease-altering pharmacological therapeutic options, failures are worth taking note of for their potential to change the way drug efficacy, disease models, treatment administration and patient populations are accounted for in new development. The purpose of this paper is to detail recent therapeutic failures juxtaposed with treatment options that still exhibit potential as well as novel pathological models to exploit for benefit in the future, and to examine the commonalities of failed trials and their potential repercussions on studies in the future.

Data and analysis in this review are derived from Pubmed and clinicaltrials.gov searches, review of abstracts and presentations at the Alzheimer's Association International Conference (AAIC), Clinical Trials on Alzheimer's Disease (CTAD), American Neurological Association (ANA) and American Academy of Neurology (AAN) meetings. The criteria searched included being listed as a phase II or III study in AD, with keywords including flurbiprofen (tarenflurbil), tramiprosate, latredipine, semagecestat, IVIg, Cerebrolysin, EGb 761, DHA, and late stage failure with final searches conducted in March 2013.

Currently Active Late-Stage Trials

Cerebrolysin

Pharmacological Properties—Cerebrolysin is a peptide-based neurotrophic and neuroprotective agent. The drug is created through a standardized enzymatic breakdown of purified brain proteins and is comprised of free amino acids. Cerebrolysin is currently approved for use in 44 countries as a treatment for dementia and stroke and is in Phase III trials in multiple countries in Europe (6) Cerebrolysin is analogous to brain-derived neurotrophic factors in that they act in both the central and peripheral nervous systems to increase growth of new neurons and support existing ones and are thought to protect against amyloid beta toxicity (6). Its pleiotropic effects include neuroplasticity as well as

neuroprotection (6). Its therapeutic possibilities increase when combined with cholinesterase inhibitors to relieve symptomatic effects as well as potentially impact disease course.

Therapeutic Efficacy and Tolerability—While Cerebrolysin is approved for use in Austria, China, Germany, Russia and South Korea, the FDA has yet to approve it for use in the United States. A 2011 study published in the European Journal of Neurology seeking to establish efficacy and safety of Cerebrolysin in moderate to moderately severe Alzheimer's disease concluded with positive results. Patients with AD in the trial received 100 ml intravenous infusions of Cerebrolysin (10 ml diluted in saline, N=32; 30 ml diluted in saline, n=34; 60 ml diluted in saline, N=35) or a 100 ml saline infusion for placebo control (n=32) (6). Primary efficacy criteria included the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog+) and the Clinician Interview Based Impression of Severity (CIBIC+) in a 24-week post-baseline assessment (6). At 24 weeks, all three dose level cohorts showed significantly improved global clinical function, with specific benefits varying with dosage level; improvements in cognition were seen with the 10 ml dose arm, improvements in initiation of activities of daily living were seen in the 30 ml arm, and improvement in neuropsychiatric symptoms were seen in the 60 ml arm (6). There was no significant change for scores in Mini Mental State Examination (MMSE) and Trail-making test secondary parameters. The authors indicated that larger trials are necessary to confirm benefit in more advanced cases of AD.

In this assessment 133 patients with an MMSE of <20 were evaluated for safety. There were no adverse events related to differences in dosage each cohort received. 56.3% of patients in the 10 ml cohort experienced at least one adverse event (AE), as well as did 47.1% of patients in the 30 ml cohort, 62.9% of patients in the 60 ml cohort, and 62.5% of the patients taking the placebo. AEs with the most common incidence rate (>10%) in the 10 ml group were depression, urinary tract infection and fever, with each affecting 12.5%; 20.0% in the 60 ml group and 25.0% in the placebo group also experienced urinary tract infections (6). No serious adverse events were related to the study drug. No safety issues related to Cerebrolysin were indicated by the study's conclusion. As a result of the relative success of this trial, Ever Neuro Pharma GmbH is moving forward with a phase 4 study to compare the efficacy of Cerebrolysin to that of donepezil (NCT01822951) set to begin September 2013 (7).

Masitinib

As a tyrosine kinase inhibitor, masitinib is thought to ameliorate AD symptoms by inhibiting the survival, migration and activity of mast cells and thereby reducing neuroinflammation. In a Phase II, randomized, placebo-controlled study to determine if receiving masitinib in addition to a cholinesterase inhibitor in doses of 3 or 6 mg/kg/day twice daily for 24 weeks showed improvement of ADAS-Cog scores from baseline, it was determined that rates of clinically significant cognitive decline were considerably lower with masitinib adjunct treatment compared to placebo (7). The mean treatment effect in terms of change in ADAS-Cog was 6.8 and 7.6 at weeks 12 and 24 respectively (7). Masitinib shows potential as an additional therapy option in conjunction with typical treatment. The effect of mast cells in AD pathology are not well understood; pursuing treatment options that manipulate mast cell

production in response to amyloid beta presence could provide a novel symptomatic treatment for AD even if it is ineffective in terms of altering causal factors of AD.

TRx 0237

Pharmacological Properties—TRx0237 is a tau protein inhibitor that is currently enrolling in Phase III trials for safety and efficacy in the United States, Europe and Asia. TRx0237 is a modified version of Rember, an earlier compound TauRx Therapeutics tested in relation to the treatment of Alzheimer's disease (8). The newer version of the drug is a stabilized and reduced form of methylthionine which is thought to target tau tangles and tau protein precursors as well as early-stage tau oligomers, dissolving them and slowing or halting their harmful effects on cognition (8).

Therapeutic Efficacy and Tolerability—To date, no data regarding the Phase I and Phase II trials of TRx0237 have been published. The rationale given by TauRX Therapeutics is that Phase II data tends to not be meaningful in terms of ultimate outcome of the clinical process, and that the data regarding safety and efficacy has been presented to regulating authorities in the United States, Europe and Asia has engendered enough confidence to secure a Phase III trial as well as almost entirely private funding for the study (8). TRx0237 is currently recruiting for a double blind, placebo controlled, parallel group safety and efficacy studies in patients with mild and mild-to-moderate AD (identifier number NCT01689246). The primary endpoints of change from baseline of ADAS-cog scores and safety parameter changes. Secondary endpoints are changes in activities of daily living and change in baseline of MMSE scores. Two experimental arms will be receiving 150 mg/day and 250 mg/day respectively.

Negative Late-Stage Trials

Bapineuzumab

Pharmacological Properties—Bapineuzumab is a humanized monoclonal antibody active in the nervous system designed to limit amyloid beta aggregation in the brain through binding and removal, ameliorating the damage accumulated amyloid beta does to neurons. Bapineuzumab operates through targeting the N-terminus and amino acid sequences 1-5 of amyloid plaques as opposed to soluble amyloid beta or amyloid beta monomers (9). Anti-amyloid beta passive immunotherapy approaches have been shown to be effective with regard to preventing amyloid beta accumulation in the brains of AD model transgenic mice and has been shown to reverse cognitive decline in transgenic mice. In human trials, patients vaccinated with amyloid beta peptide who produced anti-amyloid beta antibodies exhibited a significantly protracted pace of cognitive decline compared to unvaccinated counterparts. Bapineuzumab is the first monoclonal antibody to demonstrably reduce total tau and statistically significantly reduce phosphorylated tau in the cerebrospinal fluid of patients compared to placebo, potentially indicating an impact on the neurodegenerative biomarkers downstream of amyloid beta. When combined with lowered brain amyloid density there is the indication that decreased phosphorylated tau pathology is linked to amyloid beta plaque pathology, although it is presently unclear how.

Therapeutic Efficacy and Tolerability—In an 18 month phase II double-blind, placebo-controlled multiple ascending dose trial to assess safety, tolerability and efficacy in patients with mild to moderate Alzheimer's disease, the results were generally positive. 243 patients were randomized to receive one of four dosing levels of bapineuzumab (0.15 mg/kg [n=31], 0.5 mg/kg [n=33], 1.0 mg/kg [n=30] or 2.0 mg/kg [n=30]) or placebo [n=110] through intravenous infusion every 13 weeks and then assessed at efficacy endpoints of change from baseline in Assessment Scale-Cognitive Subscale (ADAS-cog), Disability Assessment Scale for Dementia (DAD) the Neuropsychological Test Battery (NTB), the Clinical Dementia Rating Sum of Boxes (CDR-SB) and in total brain volume as measured by magnetic resonance imaging (MRI) (9). In ApoE4 carriers, no significant differences from baseline occurred at the end of the study for any of the metrics used.

However, in prespecified analyses, Apo E4 non-carrier subjects showed significant positive effect from bapineuzumab with regards to the ADAS-Cog, NTB and CDR-SB. Additionally MRI analysis of participating patients indicated that cortical Pittsburgh compound B (PiB) retention was reduced as a result of bapineuzumab administration. In a study where patients were assigned to bapineuzumab (n=20) or a placebo (n=8) there was an estimated mean 11C-PiB retention ratio change of -0.09 (95% CI -0.16 to -0.02; p=0.014) from baseline to week 78 in the experimental group compared to the ratio change of 0.15 (95% CI 0.02 to 0.28; p=0.022) (9). Additionally, the 11C-PiB retention ratio change between the two groups was an estimated mean difference of -.24.

Treatment with bapineuzumab has been linked to reports of Amyloid-related imaging abnormalities (ARIA) including vasogenic edema, sulcal effusions (ARIA-E), microhaemorrhages and hemosiderin deposits (ARIA-H). In order to evaluate associated risk factors during bapineuzumab treatment, 210 patients from two Phase II trials and one open-label study were included in a risk analysis (9). 36 (17%) of patients experiences ARIA-E during bapineuzumab treatment; of these, 78% remained asymptomatic while 8 reported adverse events of headache, confusion, and neuropsychiatric and gastrointestinal symptoms (9). 17 (47%) of the patients with ARIA-E also experienced ARIA-H. ARIA-E frequency increased in ApoE4 carriers and with dose escalation of bapineuzumab (9).

The only dose-related adverse effect in the Phase II trial was also the most severe of the side effects reported during the study; 12 patients experienced temporary vasogenic edema. 10 of these patients were ApoE4 carriers and two were non-carriers. As a result the Phase III study is not evaluating the largest (2.0mg/kg) dose level, to be replaced with a 1.0mg/kg dosage (9).

The Phase III trial of efficacy of intravenous bapineuzumab in mild-to-moderate Alzheimer's patients who are carriers of ApoE4 did not meet either primary endpoint; there was no significant change in cognitive or functional performance. Additionally, the second phase III trial involving ApoE4 non-carriers failed to separate from placebo on any measure of cognition (10). Currently Bapineuzumab is in Phase II, randomized, double blind, placebo-controlled, multicenter study to determine safety and pharmacokinetics of subcutaneous administration in subjects with mild to moderate AD. Results are expected in 2014 (11).

Dimebon (latrepirdine)

A Phase III multinational trial for Dimebon, an inhibitor of cholinesterase and NMDA receptors potentially operating through apoptosis, was initiated after Phase II studies showed positive clinical efficacy in addressing cognitive and behavioral decline. The mechanism of action of latrepirdine has been speculated upon including being a weak cholinesterase inhibitor and NMDA antagonist. In a phase III study of dimebon as monotherapy to treat AD or in combination with memantine, the experimental cohort saw no statistically significant difference in cognitive function compared to the control cohort when assessed through ADAS-Cog and CIBIC-plus measures (12).

Solanezumab

Pharmacological Properties—Solanezumab is a humanized monoclonal antibody against amyloid beta. Its binding is specific to the central region of soluble monomeric amyloid beta, potentially allowing peptides in the brain to be drawn out through the blood and disposed of in the periphery. In Phase II trials solanezumab was shown to increase amyloid beta 42 concentrations in plasma and cerebrospinal fluid, indicating that aggregated plaques were potentially flowing out of the brain into the periphery. Following assay analysis to determine that the primary endpoint of monoclonal antibodies binding to their target was met, solanezumab advanced to phase III study (13).

Therapeutic Efficacy and Tolerability—The actual therapeutic benefit on cognition for solanezumab has not been established. In a 21-day Phase II trial with 19 participants being administered single dose infusions of solanezumab ranging from .5 to 10 mg/kg, there was no evidence of any adverse effects with the exception of chills during intravenous administration, but also no evidence of any cognitive efficacy (14). Additionally no data available regarding whether or not the amyloid beta plaques that had potentially been dissolved into plasma were excreted or degraded any more effectively than those still bound in the brain. Eli Lilly announced in September 2012 that neither cognitive nor functional endpoints were met in a series of Phase III, double blind, placebo-controlled trials. However, in pooled analyses, when the mild subjects were analysed in a pre-specified pooled analysis of the combined studies, solanezumab treatment was associated with a 35% reduction in the rate of decline compared to placebo (14). In December 2012, Eli Lilly announced the launch in 2013 of a new large-scale Phase III clinical trial testing solanezumab in populations with mild Alzheimer's disease in light of the drug's apparent success with the mild disease subgroup in the more general Phase III trials concluded in 2012; results are expected within three years.

Intravenous Immunoglobulin (IVIg)

Pharmacological Properties—IVIg is an intravenous infusion of naturally produced anti-amyloid antibodies that could potentially effect concentrations of CNS and peripheral amyloid beta and improve cognitive function. It has been shown that passive immunotherapy of amyloid beta antibodies can reduce cognitive decline and decrease amyloid plaque disposition in the brain (15). IVIg is procured from the blood plasma of healthy human donors. It has been used safely as therapeutic intervention in hundreds of

thousands of patients since the first discoveries of its clinical benefits more than 30 years ago and is already an FDA-approved treatment for a wide variety of immunodeficiencies in adults and children, including but not limited to Guillian-Barré syndrome, lupus erythematosus, Kawasaki disease, autoimmune hemolytic anaemia, immune thrombocytopenia, and paediatric HIV (15). Additionally, there are dozens of off-label uses for IVIg, including treatment of chronic lymphocytic leukaemia, multiple myeloma, muscular dystrophy and multiple sclerosis.

IVIg was proposed as a treatment in the category of immunotherapy. IVIg has been shown to contain natural anti-amyloid beta antibodies making it viable for development as a potential novel protein therapeutic in the treatment of Alzheimer's disease. Corroborating results have been produced indicating IVIg's ability to decrease cerebrospinal A-beta and increase MMSE scores by 2.5 points after 6 months of treatment (15). IVIg is administered as plasma protein replacement therapy to improve antibody production in immune-compromised patients, or in the case of Alzheimer's disease patients to provide passive antibodies against amyloid beta proteins determined to occur naturally in IVIg proteins (15). Though both passive and active immunotherapeutic strategies have proven effective in animal models, the exact mechanisms for efficacious use of antibodies in combatting amyloid beta are not completely clear (15).

Hypotheses for mechanisms of action include microglial mediated phagocytosis, peripheral sink, and inhibition of fibrillogenesis and cytotoxic amyloid beta species. Transgenic models show microglial phagocytosis is initiated following the passive administration of antibodies, wherein antibodies entering the CNS to bind to amyloid beta fibrils recruits microglia to phagocytose the compound through immunoglobulin G Fc receptor ligation and ultimately clear amyloid beta out of the CNS, though non-Fc mechanisms such as scavenger receptors have been implicated in other studies (16). The peripheral sink hypothesis operates on the necessity of maintaining equilibrium between CNS and peripheral plasma concentrations of amyloid beta. Sequestering plasma amyloid beta through administration of antibodies evokes a transportation of amyloid beta out of the brain to maintain equilibrium, therefore decreasing CNS amyloid load. Inhibition of fibrillogenesis and cytotoxic amyloid beta species could result in disaggregation of amyloid beta plaques through binding the N-terminus of amyloid beta, binding existing fibrils and preventing in vitro aggregation of new ones (16). These mechanisms could each operate individually or in concert for novel treatment of Alzheimer's disease or prevention thereof.

Therapeutic Efficacy and Tolerability—Results of the phase I trial for safety and preliminary efficacy indicated that of the 7 patients who participated in 6 months of therapy, all 7 experienced a cessation in cognitive decline and 6 of the 7 experienced improved cognitive functioning from baseline as evaluated by the ADAS-Cog, with a mean improvement of 3.7 +/- 2.9 points (16). Total amyloid beta in cerebrospinal fluid was reduced by 17.3-43.5 percent. Phase II results presented at AAIC in July 2012 indicated that IVIg has the potential to reduce both brain atrophy and cognitive decline (16). In a 3-year extension study of the Phase II IVIg trial, 16 originally enrolled subjects completed 36 months of treatment with IVIg in doses of 400mg/kg every two weeks (16). Participants in the experimental arm for the full 36 months showed no decline with regards to comparison

at baseline of scores on the ADAS-Cog, Clinical Global Impression of Change (CGIC), Modified Mini Mental State (3MS), Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL), Neuropsychiatric Inventory (NPI,) or quality of life (QOL) at the three-year mark (16). Additionally, participants originally in the placebo arm that switched to IVIg treatment (n=5) experienced less rapid decline following IVIg administration compared to typical decline on placebo (16).

Because this therapy is derived from donated blood it carries a risk of disease transmission but there have been no reported cases of diseases transmitted through IVIg in the last decade. Minor and infrequent side effects include chills immediately following administration and the potential for allergic reactions or possible risk for heart, lung or kidney adverse events. Recently, the primary result of the GAP trial of 400mg/kg of IVIG every 2 weeks for 18months was reported as not beneficial in mild to moderate AD. Subanalyses reported modest beneficial effects in the moderate subjects. The second study has been suspended pending further analysis.

Semagacestat and Avagecestat

Gamma secretase inhibitors (GSIs) were developed because they were able to block gamma secretase, one of the two enzymes that cleave APP to produce A β . GSIs were orally available with good CNS penetration and blood brain barrier permeability. Clinical experimentation of semagacestat was halted in phase III in 2010 after the experimental drug arm exhibited worse performance than the placebo arm in terms of endpoint benchmarks of activities of daily living and cognitive assessment during interim analysis (17). Safety concerns were emerging within the experimental cohort at an excessive rate. These included but were not limited to increased incidence of neoplasms, particularly skin cancer, which might reflect the impact on notch receptors. Earlier, the phase II trial had shown target engagement by lowering cerebrospinal fluid and plasma amyloid beta (A β 42) reliably in the 10 week study. Another GSI, avagecestat, did not move into phase III but the results on phase II have not been reported.

Flurbiprofen (Tarenflurbil)

Development of flurbiprofen, a gamma secretase modulator, was discontinued after it was determined that its proposed mechanism of action of anti-inflammatory activity was ineffective at proposed therapeutic concentrations possibly because it did not cross the blood brain barrier (18). In phase II studies, the primary endpoint on cognition was not met but post hoc assessment suggested a positive signal in mildest subjects receiving the highest dose. The phase III study administered high doses of the study drug to mild AD subjects (MMSE 20-26) to potentially exploit the advantage of a higher dose for early-stage patients. The treatment group failed to separate from placebo (18). Further development for AD has been discontinued.

Tramiprosate

An A aggregation inhibitor operating through the inhibition of glycosaminoglycans (GAGs), tramiprosate was initially proposed to prevent amyloid beta disposition in the brain by preventing protein aggregation. Phase II showed a modest signal of efficacy but these

findings were not recapitulated in phase III. Study of tramiprosate was discontinued due to failure to induce any cognitive improvement as well as causing moderately severe gastrointestinal side effects (19,20).

EGb 761

EGb 761 is an extract of Ginkgo biloba marketed in France for patients with mild AD and other memory disorders and approved in Europe, Asia and Latin America for treatment of cognitive disorders and mental function impairment. Currently it is in phase 3 development in Germany for the treatment of AD. The utility of Ginkgo biloba as an herbal cognitive therapy is dubious. In a 2008 study to determine whether G. biloba slows the rates of global or domain-specific cognitive decline in older adults, it was determined that there is no difference in slowing cognitive decline between G. biloba and placebo (21). In a randomized, double-blind, placebo-controlled clinical trial of 3,069 participants over 6 years, patients received either a twice daily dose of 120-mg extract of G. biloba, (n=1545) or identical placebo (n=1524) (21). Measures of outcome included rates of change for MMSE scores, change in ADAS-Cog scores, and in assessment of z-scores of individual tests regarding memory, attention, visual-spatial construction, language, and executive functions. Despite wide-spread marketing campaigns related to the ability of G. biloba to enhance or improve memory, the study concluded that G. biloba had no effect on either subtle preclinical cognitive changes associated with dementia or the cognitive changes associated with typical aging (21). These results are supported by previous findings of G. biloba's failure to affect cognition in any meaningful way; this therapeutic technique does not hold much promise in terms of experimental value.

Emerging Therapies

Docosahexanoic Acid

Docosahexanoic acid (DHA) is a long-chain polyunsaturated fatty acid found abundantly in the brain. Animal studies demonstrated a link between oral intake of DHA and reduction of brain pathology similar to that of Alzheimer's in humans. In a 2010 randomized, double-blind, placebo-controlled trial of DHA supplementation in patients with mild to moderate stage AD, it was determined that DHA provided no benefit compared to placebo in terms of slowing the rate of cognitive decline and functional decline for mild to moderate disease (22). Of 295 individuals who completed the trial while taking the supplement or placebo (n=171 and n=124 respectively), there was no change in ADAS-cog score between groups. The rate of brain atrophy was not affected by DHA (22). There was a mean brain volume decline of 24.7 cm for the DHA treatment group compared to a decline of 24.0 cm for placebo patients (22). Though severe patients were not treated, the potential for DHA to be a beneficial therapy continues to be investigated in different populations.

INM 176

Among novel therapeutic options with realistic potential for further development is INM 176, an extract of Angelica gigas. INM 176 is widely available as a dietary supplement and is completed Phase III trials for efficacy in 2011, the results of which have yet to be released. Traditionally, A. gigas has been used in Eastern herbal medicine for its sedative

effects and to treat anaemia, but it also shows promise for its anti-amnestic effects. In 2012 animal trials, scopolamine was used to induce memory impairments in mice. The effect of INM 176 was measured using passive avoidance, Morris water maze tasks, and levels of acetylcholinesterase activity as well as cholinergic neural loss (23). Even a single administration of INM 176 was shown to significantly decrease memory impairment in water maze tasks and counteract the memory impairment induced by presence of amyloid beta (1-42) protein. The therapy also reduced astrocyte activation in the hippocampus (23). These results warrant further investigation into development of INM 176 as a symptomatic treatment option.

ELND005

ELND005 is a stereoisomer of inositol found naturally occurring in some varieties of plants. Phase II trials of ELND005 required modification mid-trial after 5% of all high dose (1000 and 2000 mg twice daily) patients died while undergoing treatment (24), and others experienced high rates of adverse events (though Elan hasn't released specifics about what those adverse events are). Though lower doses were approved for safety, the approved dose of 250 mg twice daily did not achieve co-primary outcome measures of improved neuropsychological test battery or ADCS-ADL scores (24). This dose was sufficient to achieve cerebrospinal fluid drug levels associated with therapeutic results in animal models, so potentially effects on clinical endpoints could be enhanced in the future with continued study. In addition to effects on traditional Alzheimer's symptoms, ELND005 is also under investigation as of fall 2012 for treatment of aggression and agitation in Alzheimer's patients.

SKPC-B70M

SKPC-B70M is an extract of oleanolic-glycoside saponins from *Pulsatilla koreana* responsible for protecting A β (1-42) induced toxicity in SK-N-SH cells. In animal trials it was shown that in scopolamine-induced memory deficient rats, SKPC-B70M both improved memory function and reduced A β levels and plaque deposition in the brain (25). In Tg2576 AD model mice, insoluble and soluble A β levels were reduced by 66% and 79% respectively between 11 and 16 months of age, suggesting that SKPC-B70M can attenuate AD-like symptoms in Tg2576 model mice. Western blot analysis showed altered expressions for a variety of cellular factors including up-regulation of transthyretin, phospho-ERK, and phospho-CREB, suppression of neuronal toxicity induced by peroxide, and reduction of malondialdehyde and 4-hydroxy-2-nonenal in the hippocampus. The encouraging animal model results and the variety of potential positive effects makes SKPC-B70M an adequate candidate for further development as a treatment option (25).

RAGE inhibitors

The receptor for advanced glycation endproducts (RAGE) has been implicated in AD pathology though its role as a binding site for amyloid beta, the overproduction of which is linked to neuronal loss and dementia (26). RAGE is part of an immunoglobulin supergene family member expressed in a multitude of cell types in both the brain and periphery, including the cells of the neurovascular compartment (27, 28). RAGE has been hypothesized to contribute to AD pathology in a variety of methods, including promoting vascular

leakage, promoting influx of peripheral amyloid beta, and mediating AB-induced oxidative stress and neural death (29). TTP488 (TransTech Pharma, Inc.), an orally active, centrally acting antagonist of RAGE-RAGE ligand interaction, has been shown to significantly decrease the amyloid burden in the brains of transgenic mice (30, 31, 32). Additionally TTP488 has been associated with behavioral improvements such as reduction of distance traveled in the Morris water maze test, and with improvements in terms of normalizing electrophysiological recordings from hippocampal slices of treated mice (33). Following successful phase I development, a primary phase II/III study met the futility endpoint (34); the results are expected to be reported in the immediate future.

BACE inhibitors

Amyloidogenesis, the process by which amyloid beta (A β) is produced, results from the consecutive endoproteolysis of amyloid precursor protein (APP) by β - and γ -secretases. The amyloidogenic pathway is the preferred pathway in neurons and blood platelets while the non-amyloidogenic pathway is preferred in most other cells (35, 36, 37), though brain inflammation may result in glial cells synthesizing A β (38, 39), as well as BACE1 (40). Furthermore, these processing mechanisms provide several potential therapeutic targets to prevent the accumulation of A β to pathological levels, such as inhibition of BACE1 activity. Several BACE inhibitors are in phase II trials including LY2811376 and MK-8931 and are expected to move into phase III.

Insulin

The relationship between insulin dysregulation and the occurrence of AD pathology combined with the recent successful completion of a phase II study to determine the effects intranasal insulin has on mild memory loss makes it a strong candidate for early intervention therapy. In secondary analyses, the two treatment groups to receive doses of insulin had significantly less cognitive decline over the treatment period than the placebo group. Additionally, the treatment groups experienced less hypometabolism in the bilateral frontal, right temporal, bilateral occipital, and right precuneus during the treatment period. The effects of insulin dysregulation on disease onset deserve more attention, as does the potential for insulin to keep memory loss at bay in mild-stage patients as well as therapeutic potential for other populations (41).

Ganteneurumab

Ganteneurumab is another monoclonal antibody that has entered in phase 2/3 clinical trials in the treatment of mild to moderate AD. It is the first fully human anti-A monoclonal antibody (42). It binds most strongly to aggregated forms and has been shown to reduce plaque. It has been shown to reduce cerebral amyloid 15-35 percent (43).

Discussion

These successes and failures have led to debate about the potential gaps in our understanding of the pathogenesis of Alzheimer's disease and potential pitfalls in the choice of therapeutic targets, development of drug candidates, and design of clinical trials. Many clinical and experimental studies are ongoing, but we need to acknowledge that a single cure

for Alzheimer's disease is unlikely to be found and that the approach to drug development for this disorder needs to be reconsidered (44). 2012 was a watershed year for Alzheimer's therapeutics insofar as it continued the spate of failures in late phase studies. Symptomatic treatments that are currently available can be realistically described as modest in benefit at best in terms of the actual, long-term benefits they provide patients and their families. The recent failures of solanezumab and bapineuzumab mark five large-scale, failed Phase III drugs that had shown promise in phase II. Though solanezumab is being tested further in late stage trials for subcutaneous administration and in mild disease populations respectively, there is a reasonable chance these studies could yield disappointing results.

There is also the possibility that the disease is too entrenched to alter at the stages currently deemed to be the clinical priority. Potentially, amyloid might simply be the wrong target. Nevertheless, amyloid based immunotherapies continue with gantanezumab and crenazumab in phase II studies.. Regardless of IVIg's success or failure in terms of improving cognition, in general the link between the amyloid pathology and clinical progression has not been well established. In fact, there is no evidence from clinical pathological or natural history studies that amyloid loads and clinical measures correlate, a finding that is reinforced by the recent results of bapineuzumab and solanezumab. That might be one reason that amyloid base approaches have not yielded success or that they are being deployed too late.

Compared to amyloid-based therapy courses, many approaches related to other pathways are still in their infancy in terms of clinical development. Attentions should be turned to developing strategies targeting non-amyloid approaches such as those targeting tau, insulin, deep brain stimulation (DBS), and transcranial magnetic stimulation (TMS). Therapies targeting the tau protein are promising for the breadth of approaches being developed. While there is currently no mutation of the tau protein associated directly with Alzheimer's disease, tau dysfunction has been identified as responsible for a variety of neurodegenerative disorders all characterized by tau deposits. Additionally, more than 20 individual protein kinases, including glycogen synthase kinase 3 beta (GSK3beta), cyclin-dependent kinase 5 (cdk5) and microtubule-affinity-regulating-kinase (MARK), can effectively phosphorylate the tau protein. While this poses the problem of needing to narrow the field to determine which most contribute to hyperphosphorylation pathology, the opportunity exists to target kinases as a way of reducing protein aggregation (45).

DBS and TMS have been used to diagnose and treat a variety of psychiatric and neurological disorders and are just recently gaining traction for AD application. DBS has been shown in the past year to increase brain cell glucose metabolism, a corollary to neuronal activity, by 20% among 6 patients being treated with brain pacemakers after one year on a phase I study for safety (the primary outcome of which was met). In addition to reversing the decline of glucose metabolism typical for AD, the tentative success of this therapy option also gives credence to insulin as a treatment option to be hopeful about (46).

A loss of metabolic ability prior to the onset of cognitive decline presents an intriguing path forward for research opportunities for an AD treatment. This is being explored through device (TMS and DBS) as well as through insulin as well as through medical foods.

Conclusions

In conclusion, in addition to the need for exploration into novel disease mechanisms not necessarily related to amyloid pathology, the pattern of success in middle-stage clinical trials with failure in phase III studies should be considered when approaching treatment. Overall the field needs to be more circumspect and better informed. First, we need to consider that amyloid and many other treatments are being deployed too late. Second, animal models are largely misleading giving a false positive signal because animals have limited genetic makeups and very controlled environments. In contrast, humans are heterogeneous genetically, ethnically, temporally (age), and medically. The heterogeneity might confound or offset the effects of drugs that worked in animal models. Third, phase II studies have been largely misinformative. Many have little signal clinical, or post hoc or on biomarker without a robust clinical signal. Fourth, trial designs currently are blunt instruments. Cognitive measures are too reductionistic to measure the complexities of disease when most pathological changes have not been correlated or do not correlate with cognitive changes. Fifth, treatment will inevitably involve hitting multiple targets instead of a single target but multi-target studies have not been conducted to date (above and beyond inclusion of symptomatic drugs)..

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