Alzhemed: A Potential Treatment for Alzheimer's Disease

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Abstract: As a potential disease-modifying treatment for AD, Alzhemed (tramiprosate) is a compound that binds to soluble amyloid-beta peptide (Aβ) and inhibits the formation of neurotoxic aggregates that lead to amyloid plaque deposition in the brain. The safety, tolerability, and pharmacodynamic effects of Alzhemed were assessed in a double-blind study in which 58 individuals with mild-to-moderate AD (MMSE 13-25) were randomized to receive placebo or Alzhemed 50, 100 or 150 mg BID for 3 months. At the end of the double-blind phase, 42 of these subjects entered a 36-month open-label (OL) phase in which they received Alzhemed 150 mg BID. Assessments included plasma and cerebrospinal fluid (CSF) Alzhemed concentrations, CSF levels of Aβ, as well as cognitive (Alzheimer’s Disease Assessment Scale-cognitive subscale, Mini-Mental State Examination) and clinical performance (Clinical Dementia Rating scale, Sum-of-Boxes) measures. Alzhemed was safe and well tolerated, crossed the blood-brain barrier, and dose-dependently reduced CSF Aβ42 levels after 3 months of treatment. Mild AD subjects (MMSE 19-25 at entry) displayed greater reduction of CSF Aβ42 levels than moderate AD participants (MMSE 13-18 at entry). There was no effect of Alzhemed on the cognitive or clinical measures after 3 months of treatment. The OL follow-up suggested a stabilization of cognitive function especially in mild AD subjects over the 36-month study period. Alzhemed thus appears to be well tolerated with long-term exposure and reduces CSF Aβ42 levels in mild-to-moderate AD subjects. These findings will be discussed in the context of two large-scale randomized, double-blind, placebo-controlled Phase III clinical trials that are currently being conducted to test the long-term safety and efficacy of Alzhemed.

INTRODUCTION

Alzheimer’s disease (AD), among the most important health care problems worldwide, is a progressive neurodegenerative disorder causing decline in memory, learning and other aspects of cognitive function associated with impaired activities of daily living, frequent behavioral complications, and eventually death. AD is now a treatable condition. Elucidation of the central role of cholinergic dysfunction in the symptoms of the disease led to the development of cholinergic therapies, specifically the acetylcholinesterase inhibitors, for AD treatment [1]. These drugs partially compensate for the cholinergic deficiency by slowing acetylcholine clearance from the synapse via inhibition of the primary clearance enzyme. Treatment with cholinesterase inhibitors donepezil, rivastigmine and galantamine results in modest improvement on cognitive symptoms evident in the first few months of treatment, as well as stabilization of daily function and behavior.

Current AD treatment options also include memantine. Memantine acts on glutamate neurotransmission; it is a moderate affinity antagonist at the NMDA receptor. While it was hoped that NMDA inhibition might reduce excitotoxic neuronal damage and thus slow disease progression, clinical study results suggest symptomatic improvement without clear evidence of altered rate of decline. The apparent absence of disease modification may be explained the high drug concentrations necessary to provide neuroprotection [2]. Memantine treatment appears to be particularly useful in moderate to severe AD, either as monotherapy [3] or in combination with a cholinesterase inhibitor [4].

These symptomatic AD treatments, all developed within the past 15 years, provide modest but clinically meaningful benefits to people with AD and their caregivers. But there is no definitive evidence that any of these drugs alters the underlying disease process, or significantly slows the relentless progression of dementia. This remains the major goal of current drug development efforts in AD research.

AMYLOID HYPOTHESIS

As noted above, the current treatments target neurotransmission, and thus modulate cognitive function without addressing the initiating events in the neurodegenerative cascade. But steady progress in identifying the pivotal events in that cascade presents clear targets for disease-modifying therapy.

The two principal pathological lesions in the AD brain are the extracellular amyloid plaque and the intracellular neurofibrillary tangle. The primary constituent of the amyloid plaque is the Aβ peptide, a fragment derived by two sequential cleavages from a parent protein, the amyloid precursor protein (APP). The Aβ peptides aggregate into oligomers and amyloid fibrils, and ultimately deposit as amyloid plaques. Neurofibrillary tangles consist primarily of hyperphosphorylated tau protein. Tau is an essential micro-
tubule stabilizing protein; hyperphosphorylation is associated with conformational change, fibrillization and loss of function. Both amyloid and tau cascades have been viewed as plausible therapeutic target systems for disease modifying AD treatments [5].

However, compelling evidence suggests that it is the amyloid cascade that is pivotal in driving the neurodegenerative process [6]. Most convincing is the genetic evidence. Each of the three genes that, when mutated, can cause familial autosomal dominant AD (FAD), are directly involved in the cleavage of APP to release the Aβ peptide; these genes code APP itself (the mutations increase susceptibility to secretase cleavage at the β or γ sites at either end of the Aβ sequence), and presenilins 1 and 2 (components of the γ secretase complex, that when mutated increase γ secretase cleavage). This means that the cause of FAD must be related to APP cleavage with generation of Aβ. Since FAD and sporadic AD differ only in age of onset and inheritance, it follows that APP cleavage must be pivotal in sporadic AD as well (though in sporadic AD there are no pathogenic mutations; rather, insufficiently characterized processes presumably related to aging must increase Aβ generation).

The mechanism by which APP cleavage to release Aβ initiates the neurodegenerative cascade is less clear. The amyloid plaques may contribute, as suggested by the characteristic neuritic changes surrounding plaques. But there is growing evidence that Aβ is damaging in its diffusible monomeric and oligomeric forms (Klein, 2006). It has long been known that Aβ is highly toxic to neurons in culture; recent studies using transgenic mouse models show that oligomeric Aβ is implicated in synaptic dysfunction [7] and tau hyperphosphorylation [8].

It is thus clear that the amyloid pathway is pivotal in AD, and offers primary targets for disease modifying drug development [9]. But whether the specific goal of treatment should be reduction of plaque density, or reduction of diffusible forms of Aβ, or even protection of neurons against damage caused by either or both, remains uncertain.

ANTI-AMYLOID DRUG DEVELOPMENT

In theory, the first step in the amyloid cascade, APP cleavage, is optimal for drug intervention. But there have been some practical obstacles to this approach. An inhibitor of the β-secretase would be a promising candidate, as this enzyme is required for Aβ generation, though inessential for life [10, 11]. But development of a specific and drug-like β-secretase inhibitor has proven to be technically difficult [9]. Inhibitors of the γ-secretase complex have been identified, but γ-secretase activity is essential, and toxicity has been an issue with some drug candidates. A subset of non-steroidal anti-inflammatory drugs show γ-secretase modulating activity with reduction in amyloid accumulation in transgenic mice [12], though tolerable doses may be insufficient for brain amyloid reduction; R-flurbiprofen, an NSAID enantiomer that is tolerated at relatively high doses (because it lacks the cyclooxygenase inhibition of the L-form), is currently being tested in a Phase III AD trial [13].

It is also feasible to reduce amyloid accumulation by increasing clearance of amyloid by enhancing phagocytosis or transport to the periphery. The interrupted active amyloid vaccination program, while unsuccessful (because of a serious adverse effect, encephalitis, in some subjects), demonstrated the promise of this approach [14]. The vaccine apparently induced clearance of amyloid plaques by augmenting phagocytosis, with cognitive benefit. At present, a number of companies and investigators are pursuing passive immunization programs aiming to augment phagocytosis, or alternatively promote clearance by sequestering Aβ peptides in the periphery [15, 16].

Reducing aggregation of amyloid and fibrillogenesis may increase clearance of insoluble amyloid from brain. There are several approaches to reducing aggregation. Since heavy metals promote the aggregation process, chelating agents may increase clearance; this has been demonstrated with the zinc and copper binding compound clioquinol [17, 18]. Derivatives of β-sheet binding dyes have also been considered candidate anti-aggregation compounds [19].

THE ALZHEMED PROGRAM

The strategy that led to the development of Alzhemed (tramiprosate) focused on the role of proteoglycans in the amyloid aggregation and fibrillogenesis process [20, 21]. The polyanionic glycosaminoglycan (GAG) chains of tissue proteoglycans bind to amyloid peptides promoting aggregation in brain. Small sulfated or sulfonated molecules were developed to interfere with this binding and slow the process of fibrillogenesis. One such low molecular weight molecule, Alzhemed, proved to be a potent inhibitor of aggregation and fibrillogenesis in vitro, and also inhibited the neurotoxicity of amyloid peptides [20, 21].

A study in an APP transgenic mouse model confirmed the impact of systemic Alzhemed treatment on amyloid accumulation in brain [20]. Treatment of 9 week old TgCRND8 mice for 8 weeks reduced the area occupied by amyloid plaques in brain by 29%. There was a reduction of similar magnitude in brain levels of both soluble and insoluble amyloid peptides.

While there continues to be debate regarding the relative contribution of fibrillar amyloid versus other forms of the peptide to neurodegeneration, increasing evidence points to the importance of diffusible oligomeric forms. For example, treatment of transgenic mice with anti-amyloid antibodies produces a rapid improvement in memory prior to any change in amyloid plaque burden [22]; this suggests that the interaction of the antibodies with diffusible rather than plaque-bound amyloid peptide improves function. It has been confirmed that oligomeric Aβ peptides inhibit long term potentiation in brain slices, a model for synaptic information storage. The rapid cognitive improvement reported with treatment of AD with pooled human immunoglobulin (which contains natural anti-amyloid antibodies) [23] may be mediated by an immediate impact on diffusible Aβ.

The growing acceptance of the importance of oligomeric Aβ in the pathophysiology of Alzheimer’s disease provides a strong rationale for targeting non-fibrillar Aβ with anti-amyloid interventions against AD. There is even concern that drugs or antibodies that interact with fibrillar deposits may increase levels of diffusible Aβ, aggravating cognitive
dysfunction. It is notable that, in contrast to the amyloid vaccine, Alzhemed specifically targets diffusible Aβ; there is no interaction between the drug and fibrillar deposits [20].

Preclinical studies of Alzhemed support its potential as a drug candidate [20]. Genotoxicity studies including AMES testing, the mammalian cell cytogenetic test and the mouse micronucleus test have been negative. hERG testing did not suggest any adverse effect on cardiac conduction. Long term oral toxicity studies in rats and dogs demonstrate safety over a wide dosing range, with only mild gastrointestinal symptoms at high doses. Studies with systemically-administered 14C labeled drug demonstrated brain penetration. The half life of the drug after oral administration was about 3 hours in plasma and at least 16 hours in brain.

CLINICAL DEVELOPMENT OF ALZHEMED

A series of Phase I studies in both young and elderly adults explored the safety and tolerability of Alzhemed in humans (unpublished data provided by Neurochem, Inc.). Single (up to 200mg orally) and repeated doses (up to 200mg, bid orally) were safe and generally well tolerated; treatment with higher doses was limited by gastrointestinal side effects, specifically nausea and vomiting. The time to reach peak plasma level was 5 hours, with estimated terminal plasma half life in the range of 1.5 to 5 hours.

A randomized double-blind placebo-controlled Phase II study was conducted at six U.S. centers; the aims were to assess safety, tolerability, pharmacokinetics and pharmacodynamic effects. The mechanism of action of the drug indicates that the impact on disease will be slowed progression with long-term treatment rather than symptomatic improvement; since no measurable decline in the placebo group is expected in 12 weeks, no effect of treatment on cognitive or clinical measures at 12 weeks was anticipated.

A total of 58 individuals with mild to moderate AD were randomly assigned to one of four treatment groups: placebo, or Alzhemed 50mg bid, 100mg bid or 150mg bid orally. Eligible subjects had MMSE scores ranging from 13 to 25 (stratified into two groups, mild [19-25] and moderate [13-18]), and could be taking stable doses of cholinesterase inhibitors. Study medication was administered for 12 weeks. Outcome measures included clinical and laboratory examinations, and cognitive (Mini Mental State Examination, or MMSE [24] and the cognitive subscale of the Alzheimer’s Disease Assessment Scale, or ADAScog [25]) and clinical (Clinical Dementia Rating Sum of Boxes, or CDR-SB [26]) assessments. Lumbar punctures were performed before and after the 12 week course of treatment, for measurement of drug and biomarker levels.

The results of this Phase II trial indicated that treatment with Alzhemed at these doses was safe. There was a dose-dependent occurrence of gastrointestinal symptoms, particularly transient nausea and vomiting. There were no serious adverse events related to treatment, and no adverse effects on vital signs, laboratory studies or electrocardiograms. As expected, there was no decline in cognitive or clinical measures in the placebo group during the 12 week blinded phase, and no difference on these measures between groups.

Analysis of plasma drug levels indicated that the time to maximum level was between 4.5 and 6 hours after dosing; the elimination half-life was approximately 2-2.5 hours. There was no evidence of plasma accumulation with repeated dosing. Measurement of Alzhemed levels in CSF confirmed penetration into the central nervous system; CSF levels were measurable in 21/36 actively treated subjects, with concentrations ranging from 2.6 to 7.3 ng/ml.

Of particular interest, a regression analysis performed on Aβ CSF concentration changes as a function of Alzhemed dosage level revealed a significant linear relation (\(\rho = 0.041\)) between decrease in Aβ42 concentration and dose of Alzhemed administered after three months of treatment. The magnitude of the change in CSF Aβ42 in these two groups was greater for the mild subgroup (32% decline) than the moderate subgroup (14% decline). In general, CSF Aβ42 levels reflect diffusible levels of the peptide in brain [27-29]; though amyloid plaque load influences CSF Aβ42 levels, since plaque levels presumable remain stable over 12 weeks, change in CSF level should be an accurate indicator of change in diffusible Aβ levels. Thus, the CSF Aβ results suggest that Alzhemed has the anticipated pharmacodynamic impact in individuals with AD.

Subjects in the Phase II study were invited to participate in an open-label extension trial; 42 individuals elected to participate. In the extension, subjects were treated with Alzhemed 150mg po bid, and were followed with cognitive and clinical assessments at 3 month intervals for up to 36 months. In the absence of a concurrent control group, the open-label extension assessment data must be interpreted with caution. However, the rate of decline, particularly in the mild group, appeared to be slow in comparison to expectations based on published data [30] (Figs. 1 and 2). The open label experience confirmed the long term tolerability of Alzhemed in individuals with AD.

These encouraging results led to the launch of a large Phase III pivotal trial in the U.S. and Canada, followed by a similar trial in Europe. The Phase III trial design reflects the expected clinical response: slowing of decline in relatively mildly impaired individuals. Eligible subjects in the North American trial are on stable symptomatic treatment (cholinesterase inhibitors, with or without memantine), and have an MMSE score between 16 and 26. To allow sufficient time for the cognitive and clinical trajectories for the active and placebo groups to separate, the treatment period is 18 months. Standard cognitive (ADAScog, MMSE), behavioral (Neuropsychiatric Inventory, or NPI [31]) and functional (Disability Assessment for Dementia, or DAD [32]) measures are used. To explore the effect of treatment on amyloid and the neurodegenerative process, lumbar punctures for CSF Aβ and tau determination, and structural MRI scans for hippocampal, entorhinal cortex and whole brain volumes, are obtained in subsets of study participants.

The U.S./Canada Phase III trial was launched in mid-2004, and was fully enrolled with over 1000 subjects in less than one year. The European study started in the fall of 2005, with enrollment still in progress.

The primary purpose of these pivotal trials is to establish the clinical efficacy of Alzhemed using standard cognitive
and clinical assessment tools, and to establish the safety and tolerability of the medication in a large study population. Disease-modification will be assessed by examining Alzheimer’s effect on hippocampal entorhinal cortex, and whole brain atrophy rate, as indicated by structural MRI scanning at Baseline and following 18 months of treatment. The analysis of the pattern of effect on cognitive and clinical assessment scores may also support disease modification. Specifically, absence of a short term treatment effect (eg, at 6 months), with increasing treatment group separation at 12 and 18 months (ie, a change in the slope of decline), would be suggestive of disease-modification. Ancillary data will be used to confirm the pharmacodynamic effect (reduction in soluble amyloid peptide in brain, as reflected by levels in cerebrospinal fluid).
FIBRILLEX: VALIDATION OF ANTI-AMYLOID STRATEGY

The concept that systemic treatment with an anti-amyloid drug shown pre-clinically to prevent fibril formation and deposition in tissues leads to clinical benefits has now been tested in a multicenter trial. In amyloid A (AA) amyloidosis, the amyloidogenic peptide is derived from serum amyloid associated protein, or SAA. SAA is an acute phase protein, elevated in many chronic inflammatory conditions including rheumatoid arthritis, familial Mediterranean fever and tuberculosi. As in any amyloid related disease, the pathogenic protein adopts a highly aggregable β-sheet conformation, with resultant deposition in tissue. In AA amyloidosis, the kidney is a primary site of the deposition, leading to proteinuria and renal insufficiency.

Fibrillex is an anti-amyloid drug, like Alzhemed, that has been shown to inhibit amyloid deposition in a mouse model of AA amyloidosis. To study its clinical efficacy, the trial enrolled 183 individuals with AA amyloidosis and renal involvement, and followed renal function and other clinical endpoints during 24 months of treatment. Treatment with Fibrillex resulted in preservation of renal function as measured by creatinine clearance and need for dialysis. The Fibrillex trial provides some support to this strategy, and suggests that the brain-penetrating, anti-amyloid drug Alzhemed may reduce amyloid-mediated damage in the AD brain.

CONCLUSION

The leading hypothesis regarding the pathophysiology of AD suggests that the amyloid peptide is the most promising target for disease-modifying interventions. Alzhemed is a small molecule that binds soluble Ab peptide and prevents amyloid formation and deposition, and inhibits Ab-induced neurotoxicity. The drug penetrates the blood-brain barrier, and is safe and tolerable in humans. Phase II testing has confirmed an anti-amyloid pharmacodynamic effect, as demonstrated by a reduction of CSF Ab42 in Alzhemed treated patients. Two pivotal phase III trials will now determine the efficacy of Alzhemed in slowing progression of AD. If the anti-amyloid activity of Alzhemed does indeed significantly slow disease progression, it will represent a major advance in AD therapeutics.

REFERENCES


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