

Bapineuzumab, an Investigational Agent For Alzheimer's Disease

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, characterized by a gradual decline in cognitive functioning and memory.¹ Approximately 5.4 million Americans are affected by this illness. Thirteen percent of persons 65 years of age and older have AD, with 1,275 new cases per 100,000 patients (65 years of age and older) reported annually.² Advanced age is found to be the greatest risk factor for AD, although baseline mild cognitive impairment, previous head trauma, family history, and genetics also play a role.¹ The genetic factor, apolipoprotein E-ε4 (*APOE* ε4) genotype in particular, has been linked to late-onset AD. Inheriting a single ε4 allele increases the risk of late-onset AD by a factor of 4, whereas inheriting two alleles increase the risk by a factor of 19.²⁻⁴

The etiologic mechanism of AD is unknown; however, several postulated theories involve the formation and accumulation of amyloid beta (Aβ) peptides in the cerebral vasculature. These peptides influence many of the abnormalities that result in the cognitive decline observed in patients with AD. Amyloid beta peptides are neurotoxic and drive the aggregation of cytotoxic tau proteins, also known as neurofibrillary tangles. Impaired cholinergic transmission (resulting from amyloid beta peptides) further fuels tau

protein formation. Mitochondrial functioning also becomes impaired as a result of amyloid beta peptides and yields reactive oxidative species that mediate vascular inflammation and injury. The degree of amyloid beta plaque accumulation correlates with severity of disease.¹

To date, no definitive diagnosis of AD can be made unless a direct examination of brain tissue on biopsy or autopsy is performed. Thus, a clinical diagnosis of the diseases involves identifying a decline in cognitive functioning and an accompanying decline in the ability to perform independent activities or activities of daily living (ADL). Several tools are used to detect changes in cognition among AD patients. The most commonly used tool to quantify cognitive changes is the Mini-Mental State Exam (MMSE). Current guidelines recommend reassessing cognition in these patients every 6 months or at any time an abrupt change in cognition occurs.⁵

No FDA-approved agents are available that stop or slow of the progression of AD (e.g., deterioration of brain cells). Therapy recommendations include one of the four FDA-approved cholinesterase inhibitors:⁵

- donepezil (Aricept, Eisai/Pfizer)
- galantamine (Razadyne, Ortho-McNeil/Janssen)
- rivastigmine (Exelon, Novartis)
- memantine (Namenda, Forest), the N-methyl-D-aspartate (NMDA) antagonist.

Cholinesterase inhibitors work through similar mechanisms via acetylcholinesterase inhibition. These agents are most commonly associated with gastrointestinal (GI) symptoms and anticholinergic effects. Memantine reduces glutaminergic transmission at NMDA receptors and may be used alone or adjunctively with cholinesterase inhibitors to treat symptoms of AD.⁶ All of the cholinesterase inhibitors are indicated for mild-to-moderate AD, but only donepezil and memantine are also indicated for moderate-to-severe AD.^{7,8}

In clinical trials, these agents have shown a small but statistically significant improvement in cognitive symptoms, behavior, and the ability to perform ADL, compared with baseline measures. However, neither agent has proved to be disease-modifying. Vitamin E and *Ginkgo biloba* have also been evaluated for the treatment of cognitive symptoms in AD patients, but sufficient data are currently lacking to support their use for the treatment of AD.⁵

Strategies to develop disease-modifying therapies for AD have been explored with the goal of reducing the formation of cerebral amyloid beta plaques via passive and active administration of anti-amyloid beta antibodies. The first immunomodulator studied was terbinafil (AN-1792, Elan/Wyeth), an aggregated, full-length, synthetic human amyloid beta₁₋₄₂ peptide that targeted amyloid beta formation. Phase 2 trials were interrupted because of a 6% incidence of meningoencephalitis and neurological sequelae observed in patients being treated with AN-1792.⁹

A newer agent, bapineuzumab (AAB-001, Pfizer/Elan), was studied in phase 3 trials for its potential efficacy in reducing the formation of amyloid beta plaques and slowing disease progression.¹⁰⁻¹²

PHARMACOLOGY AND MECHANISM OF ACTION¹¹⁻¹³

Studies investigating AN-1792 noted substantial antibody response elicited toward the N-terminal residues on amyloid beta peptides. Bapineuzumab is a humanized monoclonal antibody that specifically targets these N-terminal residues of amyloid beta peptides. Mouse models have revealed that specifically targeting N-terminal residues of amyloid beta plaques with a monoclonal antibody may lead to a decrease in neurotoxicity, cytotoxicity, and fibrillogenesis without the neurological sequelae seen with AN-1792 immunotherapy. Bapineuzumab was developed in response to this finding, with the goal of reducing plaque formation and improving cognitive symptoms without neurological sequelae.

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PHARMACOKINETICS¹³

Bapineuzumab is administered intravenously and reaches peak concentration in 1 to 2 hours when given in doses of 0.5 mg/kg, 1.5 mg/kg, and 5 mg/kg. Peak concentrations and area-under-the-curve (AUC) analyses have indicated increasing concentrations with each of the doses, with a time to peak concentration of 1 to 2 hours after infusion. The volume of distribution and clearance were highest in the 0.5-mg/kg dose when compared with the 1.5- and 5 mg/kg dose groups. Its elimination half-life ranges from 21 to 26 days (dependent on dose), and is thus administered every 13 weeks.

CLINICAL TRIALS¹³⁻¹⁸

Randomized controlled trials evaluating the clinical efficacy of bapineuzumab and one randomized-controlled trial evaluating amyloid beta peptide clearance have been published.

Phase 1¹³

The phase 1 trial was a multicenter, randomized, third-party unblinded, placebo-controlled single ascending-dose study of mild-to-moderate AD in patients 50 to 85 years of age. MMSE scores ranged from 14 to 26 (with 30 being the maximum score). This study evaluated the safety, tolerability, and pharmacokinetics of bapineuzumab.

Thirty patients were randomly assigned to receive placebo or escalating doses of intravenous (IV) bapineuzumab 0.5 mg/kg, 1.5 mg/kg, or 5 mg/kg every 10 weeks for a period of up to 2 years. Dose escalation was terminated at 5 mg/kg because the patients were experiencing increased rates of vasogenic edema. Pharmacokinetic analyses indicated a mean half-life of 23.7 days and a time to peak concentration of 1 to 2 hours after the infusion. Exploratory analyses revealed an MMSE increase from baseline at all time points for the 0.5-mg/kg treatment group and at all time points, except month 6, for the 1.5-mg/kg group. MMSE scores decreased from baseline at all time points for those receiving 5 mg/kg and at all time points, except month 6, for the placebo group.

Results of the primary endpoint analysis revealed that 93% of patients had reported at least one adverse event. This trial established the safety of bapineuzumab at doses of 0.5 mg/kg and 1.5 mg/kg

and provided an optimal dosing regimen every 13 weeks, given the long half-life of this agent.

Phase 2¹⁴

A multicenter, randomized, double-blinded, placebo-controlled, multiple ascending-dose study was conducted to evaluate bapineuzumab in 234 patients 50 to 85 years of age with mild-to-moderate AD. MMSE scores ranged from 16 to 26. Cognitive changes were observed from baseline, measured by several cognitive assessment scales, in patients receiving IV bapineuzumab 0.15 mg/kg, 0.5 mg/kg, 1 mg/kg, and 2 mg/kg every 13 weeks for a total of six infusions.

Results of the co-primary endpoint efficacy analysis revealed no difference for any dose cohort between bapineuzumab and placebo in reducing scores in the Assessment Scale-Cognitive (ADAS-Cog) and the Disability Assessment for Dementia (DAD). However, exploratory analyses revealed a treatment difference in non-*APOE* $\epsilon 4$ carriers receiving bapineuzumab. As a result, phase 3 trials were undertaken to further evaluate efficacy and to determine whether treatment benefits existed for patients with the *APOE* $\epsilon 4$ genotype versus patients without the *APOE* $\epsilon 4$ genotype.

Phase 2a¹⁵

A second phase 2 multicenter, placebo-controlled, double-blind, ascending-dose study was conducted in 28 patients 50 to 80 years of age who received IV bapineuzumab 0.5 mg/kg, 1 mg/kg, or 2 mg/kg or placebo. Patients received up to six infusions 13 weeks apart and underwent positron emission tomography (PET) scans at baseline and at weeks 20, 45, and 78 in order to determine the retention ratio of Pittsburgh compound B (¹¹C-PiB), which is thought to reflect the clearance of amyloid beta peptides, in predefined cortical areas of the brain. Even though bapineuzumab patients experienced reduced cortical ¹¹C-PiB retention from baseline, increased retention was observed in the placebo group.

The clinical impact of this phase 2 study was unclear. Further investigation is required for possible translation into clinical benefit.

Phase 3¹⁶⁻¹⁸

Treatment response in patients with the

APOE $\epsilon 4$ genotype versus patients without the *APOE* $\epsilon 4$ genotype, was assessed in two phase 3, multicenter, randomized, double-blind, placebo-controlled studies, which reached completion in April and June 2012. The first study, enrolling 1,331 patients, compared 0.5 mg/kg and 1 mg/kg of bapineuzumab versus placebo. The second study, enrolling 1,121 patients with the *APOE* $\epsilon 4$ genotype, compared responses to bapineuzumab 0.5 mg/kg versus placebo after six infusions given 13 weeks apart.

Co-primary endpoints for each trial were the changes in ADAS-Cog and DAD scores from baseline. Secondary endpoints included brain amyloid burden on PiB-PET, cerebrospinal fluid (CSF) phospho-tau, and MRI brain volume.

Neither study found any statistically significant differences in the co-primary efficacy endpoints of ADAS-Cog and DAD scores versus placebo in *APOE* $\epsilon 4$ carriers and non-carriers. However, a secondary endpoint analysis revealed a reduction in amyloid plaques on PET imaging in *APOE* $\epsilon 4$ carriers in mild-AD patients.

Similar results were also reported by a pooled analysis of the two trials in both co-primary and secondary endpoints. In addition, significant decreases in CSF phospho-tau concentrations in the analysis of *APOE* $\epsilon 4$ carriers and non-carriers receiving 1 mg/kg, subgroup analysis of patients with mild and moderate AD. Pooled analyses also revealed a decline in MRI brain volume.

Based on the lack of clinical efficacy in ADAS-Cog and DAD scores in these two studies, phase 3 trials investigating the long-term efficacy and tolerability of bapineuzumab over a 4-year period were halted.

ADVERSE DRUG REACTIONS¹³⁻¹⁸

Phase 1¹³

Most patients reported at least one adverse drug event with bapineuzumab during phase 1 and phase 2 trials (93% and 94%, respectively). In phase 1, the most frequently reported adverse events were back pain (20%), accidental injury (17%), asthenia (13%), headache (13%), and infection (13%); however, these events were mild to moderate in nature and were considered to be unrelated to treatment. High signal intensity on fluid-attenuated inversion recovery (FLAIR) sequences that were not noted at baseline and consistent with vasogenic edema was

present on magnetic resonance imaging (MRI) scans in three patients receiving the 5-mg/kg dose. Two of three patients were asymptomatic; the third patient experienced transient confusion, reflected by a decline in MMSE scores 4 weeks following treatment. Cognitive status returned to baseline by week 16. One patient who received bapineuzumab died as a result of respiratory failure 7 months after treatment with the 1.5-mg/kg dose, but the investigator considered the death to be unrelated to the study drug.¹¹

Phase 2¹⁴

Adverse events that were reported as being greater than 5% (and two-fold higher than placebo) in this study included back pain, anxiety, vasogenic edema, paranoia, vomiting, hypertension, weight loss, skin laceration, gait disturbance, and muscle spasm. Vasogenic edema was the only event noted to be dose-related; it was detected on MRI in 12 patients (9.7%), but it was not detected in any patients receiving placebo. Ten of the 12 cases of vasogenic edema were detected in APOE ε4 carriers, and incidence rates increased as bapineuzumab doses were escalated. Half of these patients were symptomatic, with most patients commonly reporting headache, confusion, vomiting, and gait disturbances. Symptoms resolved in the majority of patients after bapineuzumab was discontinued.¹²

Phase 2a¹⁵

Adverse events were reported in 19 of 20 bapineuzumab-treated patients and in all eight placebo-treated patients. The events most commonly reported (in 10% or more of bapineuzumab patients) were headache, fatigue, nasopharyngitis, diarrhea, urinary tract infections, falls, abrasions, and muscle spasms.

Most adverse events were generally mild to moderate and transient; however, serious events were reported in four bapineuzumab-treated patients and in three placebo-treated patients, with no relation to dose. Two patients in the 2-mg/kg bapineuzumab group experienced cerebral vasogenic edema, as identified on MRI scans, and were found to be APOE ε4 carriers. Both patients were asymptomatic and developed vasogenic edema after the first bapineuzumab dose. The edema resolved after treatment was discontinued.

Phase 3¹⁶⁻¹⁸

Phase 3 studies reported a higher rate of vasogenic edema in both the APOE ε4 carriers and the non-carriers. Treatment-emergent vasogenic edema was observed in 15.1% of the APOE ε4 carriers receiving bapineuzumab versus 0.2% of patients receiving placebo. Of the non-carriers, 4.2%, 9.4%, and 0.2% of patients in the 0.5-mg/kg, 1-mg/kg, and placebo groups, respectively, were affected.

Of the APOE ε4 carriers and non-carriers found to have vasogenic edema, 2.4% and 1.5% reported symptoms. Other adverse events such as syncope, dehydration, and pneumonia occurred at similar rates between patients receiving bapineuzumab versus placebo in both APOE ε4 carriers and non-carriers.

DRUG INTERACTIONS¹³⁻¹⁸

No interactions have been reported.

CONTRAINDICATIONS, PRECAUTIONS, AND WARNINGS¹³⁻¹⁸

Data are limited regarding the use of bapineuzumab.

DOSAGE AND ADMINISTRATION¹³⁻¹⁸

The dosing ranges in phase 2 and 3 trials were 0.5 to 2 mg/kg as continuous IV infusions, 13 weeks apart for up to six doses.

CONCLUSION

Bapineuzumab failed to demonstrate significant therapeutic efficacy in clinical trials. Based on the recent findings of the phase 3 trials and previous literature, there does not seem to be a clinical benefit to bapineuzumab therapy in AD. Future investigation of the clinical correlation between biomarker reduction, therapeutic efficacy, and safety may be warranted for both APOE ε4 carriers and non-carriers.

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