Alzheimer's & Dementia: Translational Research & Clinical Interventions 2 (2016) 169-176

Alzheimer's & Dementia

Featured Article

First-in-human, double-blind, placebo-controlled, single-dose escalation study of aducanumab (BIIB037) in mild-to-moderate Alzheimer's disease

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Abstract

Introduction: Aducanumab (BIIB037), a human monoclonal antibody selective for aggregated forms of amyloid beta, is being investigated as a disease-modifying treatment for Alzheimer's disease (AD).

Methods: This randomized, double-blind, placebo-controlled single ascending-dose study investigated the safety, tolerability, and pharmacokinetics (PK) of aducanumab in patients with mild-to-moderate AD. Eligible patients were sequentially randomized 6:2 to aducanumab (0.3, 1, 3, 10, 20, 30, and 60 mg/kg) or placebo.

Results: The primary outcome was safety and tolerability. Doses ≤30 mg/kg were generally well tolerated with no severe or serious adverse events (SAEs). All three patients who received 60 mg/kg aducanumab developed SAEs of symptomatic amyloid-related imaging abnormalities, which completely resolved by weeks 8–15. Aducanumab C_{max}, AUC_{0-last}, and AUC_{inf} increased in a dose-proportional manner.

Discussion: In this single-dose study, aducanumab demonstrated an acceptable safety and tolerability profile and linear PK at doses ≤30 mg/kg (clinicaltrials.gov NCT01397539).

Keywords: Alzheimer's disease; Monoclonal antibody; Clinical trial; Pharmacokinetics; Adverse events

1. Introduction

Alzheimer's disease (AD) is characterized by progressive memory loss and decline in cognitive function and accounts for 50%–75% of dementia cases [1]. Pathologically, AD is defined by the presence in the brain of extracellular neuritic plaques containing aggregated amyloid beta (Aβ) peptide and intraneuronal neurofibrillary tangles containing phosphorylated tau proteins.

The "amyloid cascade hypothesis" proposes that the accumulation of Aβ, resulting from an imbalance between Aβ production and clearance in the brain, is the main driver of AD pathogenesis [2,3]. Aβ, a peptide generated by sequential enzymatic cleavage of the amyloid precursor protein (APP), exists in several isoforms, including Aβ40 and Aβ42. These monomeric peptides have a tendency to aggregate into higher molecular weight oligomers, which may transit into insoluble fibrils that deposit in the brain as amyloid plaques [4]. The deposition of Aβ plaques occurs long before any clinical symptoms and as many as 20 years before the onset of dementia [5,6]. Evidence suggests that both soluble oligomers and amyloid plaques are neurotoxic [7–10], and clearance of amyloid plaques can

Conflicts of interest: L.W., A.M., and J.O. are employees of Biogen and may hold stocks/stock options in Biogen. J.F., H.S., K.L., and J.S. are former employees of Biogen. Current affiliations are J.F., retired; K.L., Dedham High School, Dedham, MA, USA; and J.S., F. Hoffmann-La Roche Ltd., Basel, Switzerland.

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http://dx.doi.org/10.1016/j.trci.2016.06.002

lead to normalization of calcium homeostasis, neuronal activity, and reduction of oxidative stress in the brain of an animal model of AD [11–14].

Currently approved therapies for AD provide only modest symptomatic benefit and do not attenuate the course of the disease (are not disease modifying). The screening of libraries of human memory B cells for reactivity against aggregated Aβ led to the molecular cloning, sequencing, and recombinant expression of aducanumab (BIIB037), a human anti-Aβ monoclonal antibody that selectively targets aggregated forms of Aβ, including soluble oligomers and insoluble fibrils. Preclinical studies in Tg2576 mice showed brain penetration and target engagement of aducanumab, leading to a reduction of brain amyloid burden [15]. Aducanumab is currently being investigated as a disease-modifying treatment for AD.

The objectives of the present study (clinicaltrials.gov NCT01397539) were to investigate the safety, tolerability, and pharmacokinetics (PK) of aducanumab after single ascending-dose administration in patients with mild-to-moderate AD. This was the first study of aducanumab in humans.

2. Methods

2.1. Study design

This was a single-dose-escalation, randomized, double-blind, placebo-controlled Phase 1 multicenter study (clinicaltrials.gov NCT01397539). Eligibility criteria included: age 55 to 85 years; and a clinical diagnosis consistent with (1) probable AD according to National Institute of Neurological and Communicative Disease and Stroke and Alzheimer's Disease and Related Disorders Association criteria [16] and (2) dementia of Alzheimer's type according to *Diagnostic and Statistical Manual of Mental Disorders–Text Revision* criteria [17]; and a Mini-Mental State Examination (MMSE) score of 14–26.

Patients were scheduled to be enrolled into seven sequential cohorts of eight patients each randomized 6:2 to receive aducanumab (0.3, 1, 3, 10, 20, 30, and 60 mg/kg) or matching placebo. For the last cohort, a ratio of *APOE* ε4 carriers to noncarriers of at least 1:1 was planned but was not achieved due to early termination of that cohort after five patients had been enrolled (three for 60 mg/kg and two for placebo). Patients received a single dose, administered by intravenous (IV) infusion after dilution into saline, on day 1 at the study clinic. Randomization was performed by a centralized Interactive Voice and Web Response System. A dose of 0.3 mg/kg was predicted to provide a mean aducanumab exposure (area under the serum concentration—time profile from time 0 extrapolated to infinite time [AUC_{inf}]) in humans of up to approximately 1000 μg•h/mL. This predicted human exposure calculation assumed human clearance of approximately 7 mL/day/kg (based on allometric scaling and considering human clearance values reported for similar compounds). A dose of 60 mg/kg was predicted to provide a mean exposure that would not exceed the mean exposure in Tg2576 mice given 500 mg/kg (402,000 μg•h/mL). Tg2576 mice are a commercially available animal model of AD that, with aging, accumulate amyloid in the central nervous system and are considered the most relevant pharmacologic species to evaluate the toxicity profile of aducanumab. Before escalation to the next dose level, the Data Safety Review Committee reviewed unblinded safety data for all patients in the current cohort through 21 days after dosing and before escalation to the highest dose for all patients from all previous cohorts through 11 weeks after dosing. Patients were followed-up for 24 weeks after dosing.

The primary objective of this study was to assess the safety and tolerability of a range of aducanumab doses administered as single IV infusions in patients with AD. Secondary objectives were to assess the PK and to evaluate the immunogenicity of aducanumab after single-dose administration. Exploratory objectives were to assess the effects of aducanumab on potential plasma biomarkers and on cognition.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation and Good Clinical Practice guidelines, and ethics committee approval was obtained at each participating site. All patients provided written informed consent.

2.2. Study assessments

Vital signs, physical and neurologic examinations, clinical chemistry and hematology, and urinalysis were assessed during inpatient observation and at eight follow-up visits on days 3 and 4 and weeks 1, 2, 3, 6, 11, and 24 after dosing. Electrocardiograms (12-lead paper ECGs) were performed during inpatient observation and at weeks 1 and 24 after dosing. Continuous cardiac monitoring using Holter monitoring was performed during the study treatment infusion and for 12 hours after the end of the infusion. ECGs were read by the investigator and reported as normal, abnormal-no adverse event (AE), or abnormal-AE. All AEs and serious AEs (SAEs) were monitored and recorded continuously throughout the study.

Magnetic resonance imaging (MRI) scans (including T1, T2, fluid-attenuated inversion recovery, and gradient echo) taken at screening and at weeks 3, 11, and 24 were evaluated by each site's local radiologist and by a central reader (Bioclinica Inc.), who performed blinded assessment of all MRIs for ARIA-edema/effusion (ARIA-E) and/or ARIA-microhemorrhage/hemosiderosis (ARIA-H). Radiographic evidence of ARIA-E was followed with serial MRI until resolution. Radiographic evidence of incident hemorrhage(s) was followed-up with MRI within approximately 2 weeks of observation to assess stability.

Samples were collected at pre-infusion, ≤10 minutes, 0.5, 1, 2, 4, 8, 12, 24, 48, and 72 hours, and weeks 1, 2, 3, 6, 11, and 24 after dosing, with periodic biomarker sampling.