Alzheimer's & Dementia: Translational Research & Clinical Interventions 3 (2017) 622-635

Featured Article

A randomized, exploratory molecular imaging study targeting amyloid β with a novel 8-OH quinoline in Alzheimer's disease: The PBT2-204 IMAGINE study

Victor L. Villemagne[a,b], Christopher C. Rowe[a,b], Kevin J. Barnham[b], Robert Cherny[b,c], Michael Woodward[d], Svetlana Bozinosvski[a], Olivier Salvado[e], Pierrick Bourgeat[e], Keyla Perez[b], Christopher Fowler[b], Alan Rembach[b,1], Paul Maruff[b,f], Craig Ritchie[g], Rudy Tanzi[h], Colin L. Masters[b,*]

[a]*Department of Molecular Imaging and Therapy (Research), Austin Health, Melbourne, Victoria, Australia*
[b]*The Florey Institute, The University of Melbourne, Melbourne, Victoria, Australia*
[c]*Prana Biotechnology, Melbourne, Victoria, Australia*
[d]*Medical and Cognitive Research Unit, Aged Care and Residential Services, Austin Health, Melbourne, Victoria, Australia*
[e]*Health and Biosecurity, CSIRO, Brisbane, Queensland, Australia*
[f]*Cogstate Ltd, Melbourne, Victoria, Australia*
[g]*Psychiatry, University of Edinburgh, Edinburgh, Scotland, UK*
[h]*Genetics and Aging Research Unit, Massachusetts General Hospital, Boston, MA, USA*

Abstract

Introduction: We are developing a second generation 8-OH quinoline (2-(dimethylamino) methyl-5, 7-dichloro-8-hydroxyquinoline [PBT2, Prana Biotechnology]) for targeting amyloid β (Aβ) in Alzheimer's disease (AD). In an earlier phase IIa, 3 month trial, PBT2 lowered cerebrospinal fluid Aβ by 13% and improved cognition (executive function) in a dose-related fashion in early AD. We, therefore, sought to learn whether PBT2 could alter the Aβ-PET signal in subjects with prodromal or mild AD, in an exploratory randomized study over a 12-month phase in a double-blind and a 12-month open label extension phase trial design.

Methods: For inclusion, the usual clinical criteria for prodromal or probable AD, Mini–Mental State Examination ≥20, and global Pittsburgh compound B (PiB)-PET standardized uptake volume ratio (SUVR) >1.7 were used. As this was an exploratory study, we included contemporaneous matched control data from the Australian Imaging Biomarker and Lifestyle Study (AIBL). Other measures included fluorodeoxyglucose-positron emission tomography, magnetic resonance imaging volumetrics, blood Aβ biomarkers, and cognition and function.

Results: Forty subjects completed the first 12-month double-blind phase (placebo = 15, PBT2 = 25), and 27 subjects completed the 12-month open label extension phase (placebo = 11, PBT2 = 16). Overall, PTB2 250 mg/day was safe and well tolerated. The mean PiB-PET SUVR at baseline was 2.51 ± 0.59. After adjusting for baseline SUVR, in the double-blind phase, the placebo group showed a nonsignificant decline in PiB-PET SUVR, whereas the PBT2 group declined significantly (P = .048). Subjects who did not enter or complete the extension study had a signifi-

Conflict of interest declaration: K.J.B. is a paid consultant and R.C. was a part-time employee of Prana Biotechnology. C.R. was, at the time, a retained consultant with Prana Biotechnology Ltd as part of their standing scientific advisory group and performed the duties of the medical monitor during the course of the study. R.T. is a paid consultant and shareholder in Prana Biotechnology Ltd. R.T. had no input into the drafting or review of any portion of the manuscript other than those portions pertaining to study concept and design and consultation on biochemistry, and no input into the analysis of the data from other portions. C.L.M. was a Founding Director and shareholder of Prana Biotechnology but has no current appointment with the company.

[1]Deceased.

*Corresponding author. Tel.: +61 3 9035 6575; Fax: +61 9035 8768.
E-mail address: c.masters@florey.edu.au

https://doi.org/10.1016/j.trci.2017.10.001

cantly higher 12-month Aβ-PET SUVR (2.68 ± 0.55) compared with those who completed (2.29 ± 0.48). Both groups differed significantly from the rate of change over 12 months in the AIBL control group. In the open label 12-month extension study, the PiB-SUVR stabilized. There were no significant differences between PBT2 and controls in fluorodeoxyglucose-positron emission tomography, magnetic resonance imaging volumetrics, blood Aβ biomarkers, or cognition/function over the course of the double-blind phase.

Discussion: There was no significant difference between PBT2 and controls at 12 months, likely due to the large individual variances over a relatively small number of subjects. PBT2 was associated with a significant 3% PiB-PET SUVR decline in the double-blind phase and a stabilization of SUVR in the open-label phase. From this exploratory study, we have learned that the entry criterion of SUVR should have been set at ≥ 1.5 and <2.0, where we know from the AIBL study that subjects in this band are accumulating Aβ in a linear fashion and that subjects who withdrew from this type of study have much higher SUVRs, which if not taken into account, could distort the final results. Because of large individual variations in SUVR, future studies of PBT2 will require larger numbers of subjects ($n > 90$ per arm) over a longer period (18 months or more). Further evaluation of higher doses of PBT2 in earlier stages of AD is warranted.

Trial Registration: ACTRN 12611001008910 and ACTRN 12613000777796.

Keywords: Randomised control trial; Alzheimer's disease; Aβ-amyloid PET molecular imaging; Novel 8-OH quinoline; Clinical trial design; Biomarkers for Alzheimer's disease

1. Background

The advent of a biomarker definition of sporadic Alzheimer's disease (AD) now allows determination of the efficacy of therapeutic interventions using the two validated biomarkers of amyloid β (Aβ): Aβ-PET and cerebrospinal fluid (CSF)-Aβ [1–3]. An abnormally high cortical signal from Aβ-PET reflects the amount of Aβ-amyloid closely associated with an insoluble pool in plaques and perivascular Aβ deposits [4,5], whereas a decreasing CSF-Aβ level may reflect the interstitial diffusible pool of Aβ which feeds irreversibly the more insoluble fibrillary Aβ-amyloid plaque pool [6].

Despite the differing origins of these Aβ-biomarker signals, they are closely interrelated with similar predictive utility for diagnostic classification and progression of cognitive impairment [7,8]. Longitudinal cohort studies demonstrate that the Aβ burden as measured by PET increases linearly at about 3% per year in the preclinical and prodromal stages of AD, which then slows after the full clinical syndrome of AD has developed [9,10]. Similarly, CSF-Aβ levels decline over time during the evolution of AD [11].

We have been developing a second generation 8-OH quinoline (2-(dimethylamino) methyl-5, 7-dichloro-8-hydroxyquinoline [PBT2, Prana Biotechnology]) for targeting Aβ in AD. Originally developed as a metal-protein attenuating compound [12,13], more recent results indicate that PBT2 can stabilize a non-toxic oligomeric (dimeric) conformer of Aβ [14]. In a phase IIa, 3-month trial, ($n = 74$) in mild/moderate AD, PBT2 lowered CSF Aβ by 13% and improved cognition (executive function) in a dose-related fashion [15]. We, therefore, sought to learn whether changes in the Aβ-PET signal could be detected after PBT2 administration in an exploratory study in a small number of subjects ($n = 40$; 15 placebo and 25 active) with prodromal or mild AD, over a 12-month phase in a placebo controlled double-blind study with a 12-month open label extension phase (the IMAGINE Study; Australian New Zealand Clinical Trials Registry Trial identifiers ACTRN 12611001008910 and ACTRN 12613000777796).

2. Methods

2.1. Study design and participants

The exploratory PBT2-204 IMAGINE study was a 12-month randomized, double-blind, placebo-controlled phase with an extension for another 12 months as an open-label phase. The primary objectives were to assess safety and tolerability of PBT2, and its effect on Aβ amyloid accumulation over these two 1-year intervals in subjects with prodromal or mild AD. The study was conducted at five sites in Melbourne from February 2012 through December 2014.

Eligible subjects were ≥55 years of age, met the criteria for prodromal or probable AD [16,17], a Mini–Mental State Examination (MMSE) score ≥ 20, a score on the Hachinski Ischemic scale of four or lower, and a global Pittsburgh compound B (PiB)-PET standardized uptake volume ratio (SUVR) > 1.7. Concurrent use of standard anti-acetylcholinesterase inhibitor AD medications was permitted.