TECHBRIEF

HORIZON SCANNING REPORT

DONANEMAB IN EARLY ALZHEIMER'S DISEASE

Report No: 008/2023

MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

"DOKUMEN TERHAD"

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EXECUTIVE SUMMARY

Alzheimer's disease (AD) is a progressive neurodegenerative disorder causing cognitive decline and functional impairment. Donanemab is an immunoglobulin G1 monoclonal antibody directed against insoluble, modified, N-terminal truncated form of β-amyloid present only in brain amyloid plaques. Donanemab binds to the N-terminal truncated form of β-amyloid and aids plaque removal through microglial-mediated phagocytosis. The initial clinical trials of donanemab have shown promising results in improving cognitive and functional outcomes. Reductions in amyloid-beta plaque burden have been observed, suggesting potential disease-modifying effects. However, further research is still needed to observe the safety and economic impact on the patients.

Keywords: Donanemab, LY3002813, Alzheimer's disease, amyloid-plaques, cognitive decline, functional impairment

INTRODUCTION

Worldwide, around 55 million people suffer from dementia, with over 60% living in low- and middle-income countries.[1] This figure is predicted to rise to 78 million in 2030 and 139 million in 2050, as the proportion of older people in the population increases in almost every country.[1]

In Malaysia, the prevalence of dementia is 8.5% among older adults aged 60 and above.[2] Listed as one of the leading causes of death in 2020, curbing AD is not only a burden to the public health system but also brings perpetual stress to the family members who often undertake the primary caregiving role.[2] According to the Alzheimer's Disease Foundation Malaysia data in 2016, it is predicted that currently there are about 50,000 people in Malaysia

with this disease.[3] The estimated number of older people with this disease worldwide is expected to double for every 20 years.[3] As derived from the Malaysian National Health and Morbidity Survey 2018: Elderly Health, the overall prevalence of probable dementia was 8.5% (95% CI 6.97 to 10.22).[4] The prevalence was found to be higher among females, those with no formal education and those in rural areas in Malaysia.[5]

Alzheimer's disease is the commonest type of dementia (60 - 70%), and patients often present initially with gradual episodic memory impairment.[6] Alzheimer disease occurs on a continuum, progressing from asymptomatic preclinical AD, to mild cognitive impairment, and to mild, moderate, and severe AD.[6] In early-onset of AD (less than 65 years old), patients may present with behavioural (frontal), visual (posterior cortical atrophy) or language (logopenic) variants with relatively well-preserved memory until the later stages of the disease.[7]

Overall, the total estimated annual worldwide cost of AD and other dementias is over USD 1.3 trillion and is projected to increase to USD 2.8 trillion by 2030.[8] About two-thirds of this total cost comes from indirect costs and the rest from direct costs.[9] With the prevalence of dementia increasing dramatically, the healthcare costs of dementia and its subtypes such as AD would soon surpass almost all other medical expenses.[9]

THE TECHNOLOGY

Donanemab (LY3002813) is an experimental antibody treatment for Alzheimer's disease (AD) that targets brain amyloid plaque.[10] It is an amyloid-targeting therapy that specifically targets the N-terminal pyroglutamate Aβ epitope that is only present in mature brain amyloid plaques.[10] It was developed to remove existing amyloid plaques through microglial-mediated clearance and attacks the soluble and insoluble plaque buildup, slowing down the progression of the disease.[10] It was dosed at 700 mg monthly for the first three months, then 1,400 mg for up to 18 months in the recent phase III clinical trials.[11]

Donanemab was developed by the company Eli Lilly and Co and had been awarded with U.S. Food and Drug Administration (FDA) Breakthrough Therapy designation in June 2021.[12] In January 2022, FDA halted the accelerated approval for donanemab until further phase III results obtained.[13]

There are multiple ongoing and planned trials of donanemab including TRAILBLAZER-ALZ 3, which is focused on preventing symptomatic Alzheimer's disease in participants with preclinical AD; TRAILBLAZER-ALZ 5, a registration trial for early symptomatic AD currently

enrolling in China; and TRAILBLAZER-ALZ 6, which is focused on expanding our understanding of amyloid-related imaging abnormalities (ARIA) through novel MRI sequences, blood-based biomarkers and different dosing regimens of donanemab.[14]

PATIENT GROUP AND INDICATION

Donanemab is indicated for the individuals with Alzheimer's disease in the early stage. It may have an effect on disease pathology by reducing the amyloid-beta (Aβ) and to slow down the progression of the disease.

Alzheimer's disease is the commonest type of dementia (60 - 70%), and patients often present initially with gradual episodic memory impairment.[6] Alzheimer disease occurs on a continuum, progressing from asymptomatic preclinical AD, to mild cognitive impairment due to AD, and to mild, moderate, and severe AD.[6] In early-onset of AD (less than 65 years old), patients may present with behavioral (frontal), visual (posterior cortical atrophy) or language variants with relatively well-preserved memory until the later stages of the disease.[7]

The pathogenesis of Alzheimer's disease is closely related to the processing of the amyloid precursor protein (APP), which results in the synthesis of various amyloid-beta (A) peptides.[15] They are found as insoluble aggregates in senile plaques, the histopathological hallmark of the disease.[15] In particular, the concentration of Aβ1–42 in the CSF undergoes a characteristic drop during disease progression, which is interpreted as the consequence of the ongoing parenchymal Aβ deposition in senile plaques.[15]

CURRENT PRACTICE

Management of AD patients is complex as the development of psychiatric and behavioural disturbances upon pharmacological treatment might overlap with the symptoms of cognitive decline.[16] The diagnosis of dementia should be based on detailed history and physical examination, and supported by cognitive, functional and behavioral evaluation.[16] There are no disease-modifying therapies accessible at this time but the medications aimed at managing symptoms (cognitive and behavioural), improve independence and preserve function.[17]

According to the Malaysian Clinical Practice Guidelines on the Management of Dementia, to improve cognitive function in mild to moderate dementia, cognitive stimulation therapy and physical activity should be offered as a non-pharmacological intervention.[16]

Meanwhile, for the pharmacological treatment, the guidelines recommended several drugs that can help to manage the symptoms.[16] Donepezil should be offered in AD of all severity while rivastigmine and galantamine are options of drugs in mild to moderate AD.[16] Memantine may be considered in moderate to severe AD as monotherapy or in combination with acetylcholinesterase inhibitors (AChEI).[16]

In the management of dementia, caregivers should be actively involved and supported. Advanced care planning should be considered in the management of dementia once the diagnosis is established.[16]

EFFICACY AND SAFETY

Based on the systematic search up to 1st August 2023, there were 13 articles retrieved from the scientific databases (Medline, PubMed), the general search engines [Google Scholar] and from the references of retrieved articles. The 13 retrieved evidence included one systematic review, five randomised controlled trials (RCTs) that evaluated the safety and effectiveness of donanemab, one cost-effectiveness study and six brief commentary report on donanemab. A systematic review, five RCTs and a cost-effectiveness study were included in this review.

In a systematic review of donanemab which included a total of 396 Alzheimer's disease patients across four studies, patients received either donanemab or a placebo (228 and 168 participants, respectively).[18] The trial included both either randomised or non-randomised trial. Adult patients with Alzheimer's disease being intervened with donanemab compared to placebo or standard of care in the clinical trial setting were included.[18] The outcomes comprised of measures of brain amyloid plaque levels and tests, including the ADAS-Cog13 (the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale), ADAS-Cog14 (the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale), ADCS-iADL (the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory), ADCS-MCI-ADL-24 (Alzheimer's Disease Cooperative Study–Activities of Daily Living–Mild Cognitive Impairment 24-item version), CDR-SB: (Clinical Dementia Rating Scale–Sum of Boxes), MMSE (Mini-Mental State Examination), and the NTB (Neuropsychological Test Battery).[18]

There was a favourable reduction in amyloid plaque levels which depended on baseline amyloid levels such that patients with lower amyloid plaque levels were found to have complete amyloid clearance.[18] Other favourable outcomes were a reduction in the accumulation of overall tau levels and relatively lower functional/cognitive decline with

donanemab which can be seen in the study conducted by Lowe et al. [10,18]. Two patients in the single-dose cohorts (one patient in the 20 mg/kg and one patient in the 40 mg/kg) and nine patients in the multiple-dose cohorts (two in the 10 mg/kg Q2weekly, two in the 10 mg/kg Q4 weekly, and five in the 20 mg/kg Q4 weekly) had a complete amyloid clearance status of below 24.2 centiloids.[10] The Aβ-plaque reduction was found to be dependent upon baseline levels, such that lower baseline levels had complete amyloid clearance (<24.1 Centiloids).[18] However, other findings were insignificant, including the fact that the difference between the Donanemab/placebo group has changed from baseline at week 76 was −0.36 for CDR scores, −1.86 for ADAS-Cog13 scores, 1.21 for ADCS-iADL scores, 0.64 for the MMSE score as reported in the secondary outcome analysis of TRAILBLAZER-ALZ.

There was a slowing of overall tau levels accumulation as well as relatively reduced functional and cognitive decline noted on the Integrated Alzheimer's Disease Rating Scale (IADS) by 32% in the Donanemab arm.[18] Study by Shcherbinin et al found a significant association between percentage of amyloid reduction and changes on the IADS only in apolipoprotein E (APOE) ε4 carriers.[11]

In the TRAILBLAZER-ALZ-2 phase III trials, there were 1736 participants with early symptomatic Alzheimer disease and amyloid and tau pathology included in the trials and 860 were assigned to receive donanemab and 876 were assigned to receive placebo.[19] This trial was a 76-week, phase 3, randomised, double-blind, parallel, multicenter, placebo-controlled trial with participants screened at 277 sites in eight countries.[19] The primary outcomes were the possible scores on the iADRS range from 0 to 144 (lower scores indicate greater impairment), and the meaningful with inpatient change (MWPC) which is a change of 5 points for those with Alzheimer disease with MCI and 9 points for those with Alzheimer disease with mild dementia.[19] Prespecified secondary outcomes included changes from baseline to 76 weeks by sum of boxes of the Clinical Dementia Rating Scale (CDR-SB), the ADAS-Cog13, the ADCS-iADL, and MMSE in the low/medium tau or combined population.[19] Amyloid plaque reduction at 76 weeks, percentage of participants reaching amyloid clearance (<24.1 Centiloids measured by amyloid PET9,29) at 24 weeks and 76 weeks, tau PET1 (frontal cortical regions) change, volumetric MRI (vMRI; whole brain, hippocampus, and ventricles) change, and adverse events were additional secondary outcomes.[19]

The least-squares mean (LSM) change in iADRS score at 76 weeks was −6.02 (95%CI, −7.01 to −5.03) in the donanemab group and −9.27 (95%CI, −10.23 to −8.31) in the placebo group (difference, 3.25 [95%CI, 1.88-4.62]; P < .001) in the low/medium tau population and −10.2 (95%CI, −11.22 to −9.16) with donanemab and −13.1 (95%CI, −14.10 to −12.13) with placebo (difference, 2.92 [95%CI, 1.51-4.33]; P < .001) in the combined population.

Representing a 22.3%(95%CI, 11.38%-33.15%) slowing of disease progression. [19]. The secondary outcomes of CDR-SB, ADASCog13, and ADCS-iADL scores with donanemab treatment resulted in clinically meaningful benefit (considered to be >20% slowing of clinical progression 39-41) on the iADRS and CDR-SB scales for both the low/medium tau and combined populations.[19] The amyloid clearance was reached in 29.7% (95% CI,26.56%-33.04%) of participants at 24 weeks and 76.4% (95% CI, 72.87%-79.57%) at 76 weeks of donanemab-treated participants compared with 0.2% (95% CI, 0.07%-0.90%) at 24 weeks and 0.3% (95% CI, 0.08%-1.05%) at 76 weeks of placebo-treated participants.[19]

The systematic review by Rashad et al showed that the safety of Donanemab was established with key adverse events related to Amyloid-Related Imaging Abnormalities (ARIA), ranging between 26.1 and 30.5% across the trials.[18] The incidence of ARIA was consistent with the TRAILBLAZER-ALZ Phase III study. The amyloid-related imaging abnormalities of oedema or effusion occurred in 205 participants (24.0%; 52 symptomatic) in the donanemab group and 18 (2.1%; symptomatic during study) in the placebo group and infusion-related reactions occurred in 74 participants (8.7%) with donanemab and 4 (0.5%) with placebo.[19] Three deaths in the donanemab group and 1 in the placebo group were considered treatment related.[19]

ESTIMATED COST

The cost of donanemab is not yet established, and there is no official price available.

In a cost-effectiveness study with decision analytic modeling based on clinical trial data of Donanemab and Aducanumab, it was estimated that neither Aducanumab nor Donanemab was cost-effective at their expected prices of more than $25 000 (RM116 912.50; 1USD:RM4.68) per year.[20] Aducanumab became cost-effective when priced below $3000 (RM14 029.50; 1USD:RM4.68) per year, whereas owing to its possibly greater efficacy (based on phase 2 trial data) and limited-duration dosing, Donanemab was cost-effective when priced around $20 000 (RM93 530; 1USD:RM4.68) per year.[20]

POTENTIAL IMPACT

Overall, the evidence suggests that donanemab is a promising treatment for AD, with a significant reduction in amyloid plaques and improvement in cognitive and functional outcomes, although further studies are needed to establish its safety and efficacy.

A full economic evaluation will be needed to determine the cost-effectiveness and affordability of incorporating donanemab into the current treatment strategies.

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Disclosure: The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

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