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POTENTIAL OF MONOCLONAL ANTIBODY (mAb) AS ALTERNATIVE TREATMENT OF ALZHEIMER: A SYTEMATIC SCOPING REVIEW

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A B S T R A C T

Alzheimer's disease (AD) is a global problem that is expected to increase along with the increasing rate of population aging. Monoclonal antibodies (mAb) are considered capable of overcoming the accumulation of amyloid-β plaques; pathological signs of AD. This study aims to explore the potential of mAbs as alternative pharmacological therapies for the elderly with AD. This study uses a scoping review design based on the PAGER framework. The results of the study were identified based on the PRISMA-ScR protocol and criticized using the JBI Critical Appraisal Checklist. Article searches were conducted through 3 databases including EBSCO-Host Academic Science Complete, PubMed, and ScienceDirect, and 3 online resources including Sage Journals, Taylor Francis, and Google Scholar. Inclusion criteria were full English text, primary research articles, and published between 2018-2022. A total of 8 articles were included in the review. Most of the evidence shows 6 mAbs have potential to reduce amyloid-β accumulation in AD patients. Alternative therapy with monoclonal antibodies has side effects that represent a major problem in the high incidence of vasogenic cerebral edema and micro cerebral hemorrhage or Amyloid Related Imaging Abnormalities (ARIA). Plasma tau has the potential to strengthen the clinical diagnosis of AD. The use of mAbs as AD immunotherapy can reduce amyloid-β with side effects that are monitored continuously. Differences in mAb examination results can be influenced by less accurate clinical diagnostic accuracy.

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1. INTRODUCTION

Globally, the pace of population aging is accelerating. The United Nations Population Division has projected the world's population of people aged 60 years will increase 21% in 2050 (Divo et al., 2014). This is because life expectancy has increased to over 60 years of age. Therefore, demographic changes are a big challenge to providing a good service and treatment of health problems for the elderly.

As the aging population grows, age-related health problems such as dementia will increase during the aging process. Dementia is one of the early signs of Alzheimer's disease. The results of a study by Suriastini et al., (2020) show that 20.1% of elderly people in Indonesia have dementia. The Alzheimer's Association reports that more than 6 million Americans have Alzheimer's (Alzeimer Association, 2022). Seventy-two percent of them are over 75 years old and an estimated 6.2 million sufferers are elderly over 65 years.

Alzheimer's Disease (AD) is a disease manifested by the presence of amyloid plaques and neurofibrillary tangles (NFTs) in the intracellular brain consisting of abnormal amyloid-β (Aβ) and tau protein. Abnormal accumulation of Aβ is a major pathogenic event that triggers complex cascades and leads to tau pathology, neurodegeneration, and cognitive decline (Selkoe & Hardy, 2016). Elderly with AD not only experience cognitive decline, but also memory loss or forgetfulness to the point where it is difficult to carry out daily activities (National Institute of Aging, 2019). Therefore, medical therapy is needed that can support the implementation of the daily activities of AD patients to maintain physical and cognitive abilities so that they have a prosperous life which is the goal of long-term care (Masciadri et al., 2019).

Effective Alzheimer's treatment continues to be developed by scientists. Currently, the existing treatments are only symptomatic, that is, reducing the symptoms of the disease by acting on various levels of the neuropathological process which can improve the quality of life of the patient. However, none of them is completely capable of slowing down the rapid and fatal progression of the disease (Chiang & Koo, 2014; Folch et al., 2018). Therefore, seeing the current scientific and clinical advances, most of the development of AD therapy has begun to be directed at drugs that target Aβ and tau which are the main compounds that cause AD (Congdon et al., 2019; Plotkin & Cashman, 2020).

Among the many approaches to anti-Aβ therapy, the most widely developed is passive immunotherapy through the administration of monoclonal antibodies (mAb). Monoclonal antibodies are antibodies made by identical immune cells which are all clones of unique stem cells (Plotkin & Cashman, 2020; van Dyck, 2018). The use of monoclonal antibodies has been widely considered as a candidate for the therapy of choice against Aβ due to its good mechanistic selectivity and tolerance (Panza et al., 2019). Several studies have found a positive correlation between mAbs and Alzheimer's disease (Prins & Scheltens, 2013; Quinteros et al., 2017). These findings prove that mAbs can selectively target amyloid plaques, which can damage synapses in the brain in AD patients. Monoclonal antibodies have monovalent affinity because they bind to the same epitope and have been assigned to multiple epitopes, especially on Aβ species (Avgerinos et al., 2021; Brännström et al., 2014; Prins & Scheltens, 2013). Several mAb therapies that have

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been developed include aducanumab, crenezumab, and solanezumab. Furthermore, experimental studies, several randomized controlled trials, and several systematic reviews are still underway to discover the mechanism, efficacy, and safety of mAb for treating AD.

Considering the widespread use of mAb therapy in society after the issuance of a marketing authorization and mass production by the U.S. Food and Drugs Administration (FDA), it is important to identify various types of therapies that have been developed as an effort to anticipate side effects of treatment especially for patients that using these therapies. In addition, to our knowledge, there has been no review study that specifically discusses clinical outcome and adverse event risk in elderly patients. The elderly requires certain considerations that are different from adults in general specifically in the aspect of treatment. Through this review study, the contribution to nursing care, especially to reduce the burden of care and improve the quality of life of elderly AD patients related to the risk of adverse events, can be conveyed. Therefore, this literature study aims to explore the potential of monoclonal antibodies as alternative pharmacological therapies for elderly patients with Alzheimer's disease.

2. METHODS

Design Study

This study used a scoping review design and was conducted following the Bradbury-Jones PAGER framework (Pattern-Progress-Gaps-Evidence for Research-Practice recommendations). This framework was considered to provide a consistent approach to analyzing and reporting the results of various studies related to the research topic. Selected Reporting Items for Systematic Reviews and Meta-Analysis for Scoping Reviews (PRISMA-ScR) were used to systematically identify relevant study results. The scoping review methodology is suitable for this subject because it allows comprehensive recent studies on the use of monoclonal antibodies for diagnosis and treatment among elderly patients with Alzheimer's Disease (AD) (Bradbury-Jones et al., 2021).

Eligibility Criteria

We identified elderly or older persons as the population (P), monoclonal antibodies as the concept (C), and Alzheimer's disease as the context (C). Through this PCC framework, all primary studies addressing the use of monoclonal antibodies for diagnosing and treating Alzheimer's in the elderly population were included. Subsequent articles were selected based on predetermined criteria. The articles included in this review must be full-text primary research articles written in English and published within the last 5 years (2018 – 2022). Secondary studies, animal model studies, opinions, and editorials that did not report on the use of monoclonal antibodies were not included in this review.

Information Sources

A systematic search was conducted in mid-February 2022 through 3 databases, EBSCO-Host Academic Science Complete, PubMed, and ScienceDirect, and 3 online resources, including Sage Journals, Taylor Francis, and Google Scholar.

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Searching Strategy

The initial search was carried out by identifying studies based on 3 main keywords retrieved from PCC's Framework, namely "Elderly", "Monoclonal Antibody", and "Alzheimer's Disease". Synonyms for each keyword are used to get all possible relevant articles. Boolean operators "AND" and "OR" are used in the search process to expand the article's findings through various forms of words. The keywords used in the article searching process include: "elderly", "elderly population", "elderly", "monoclonal antibody", "anti-amyloid-beta", "Alzheimer's disease*", and "Dementia*".

Article Screening

All authors consisting of 4 members independently completed the study selection process following the PRISMA Flow Diagram (figure 1): (1) identifying duplicates; (2) screening of titles and abstracts; and (3) checking full-text availability; and (4) filtering full text based on the inclusion and exclusion criteria. All articles are filtered and selected manually by the author using a reference manager application. The further final determination was made through discussion of full-text articles content with all authors.

Data Extraction and Critical Appraisal

The methodological validity of the study was evaluated using the Joanna Briggs Institute (JBI) instrument to obtain the highest article quality with minimal bias. Studies were selected based on the results of a quality assessment with criteria for an assessment score above 60% of the overall JBI checklist format. All authors used the JBI critical assessment checklist for RCTs and cohort studies to assess and report the risk of bias. The results of the quality assessment were then discussed between the respective authors as a basis for determining which studies were finally included. Author, country, study design, model, and effectiveness were the extraction data of interest. All research data were manually extracted from the study result using the tabulation method.

3. RESULT

Description of Study Findings

The initial search identified 8.989 studies from the databases. The authors screened 40 full-text articles and excluded 1.874 studies that did not meet the inclusion criteria. As a result, the authors included 8 studies in this scoping review. Figure 1 depicts the number of studies retrieved using the PRISMA flow chart diagram.

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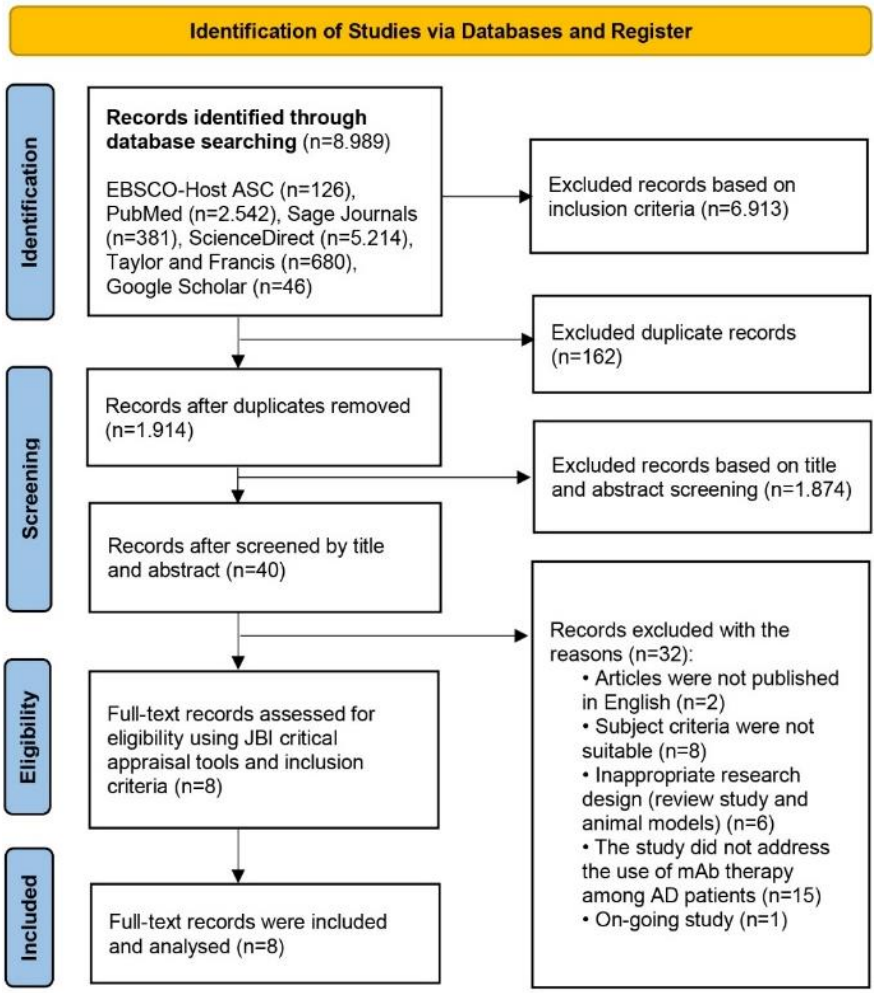

Figure 1. PRISMA Flow Diagram

Study Characteristics

All articles identified in this review are experimental studies with Randomized Control Trial (RCT) design (n = 8) of the use of monoclonal antibodies as an alternative treatment in elderly patients with Alzheimer's. The majority of these studies were conducted in the United State of America (USA) (n= 7) and some of the other studies were identified as multicenter studies conducted in multiple countries including Switzerland (n=1), Japan (n=1), Spain (n=1), France (n=1), and Canada (n = 1) with a total number of study participants amounting to 3,408 elderly people aged around 50-80 years. The study follow-up period ranged from 4 months to 5 years (Table 1.).

Table 1. Studies Characteristics

Author, Published Year	Research Method	Country	Age (Years old)	Participant	Follow-up Period	Critical Appraisal
(Yang et al., 2019)	*RCT*	USA	50-80	104 subjects with Alzheimer Disease	68 weeks	11/13 (84,6%)
(Klein et al., 2019)	*RCT*	Switzerland	50-90	379 subjects with Alzheimer Disease	2 years	13/13 (100%)

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(Schwarz et al., 2019)	*RCT (Phase III trials)*	USA	55-90	2.129 subjects who had symptoms similar with Alzheimer Disease	80 weeks	13/13 (100%)
(Lowe et al., 2021a)	*RCT (Phase III)*	USA and Japan	50	61 subjects who diagnosed positive Alzheimer's amyloid plaques with cognitive impairment and mild to moderate Alzheimer's dementia	5 years	11/13 (84,6%)
(Salloway, Honigberg, et al., 2018)	*RCT (Phase II study)*	USA, Spain, France	50-80	91 subjects with mild to moderate Alzheimer Disease	69 weeks	11/13 (84,6%)
(Dyck et al., 2021)	*RCT (Phase 3 trial)*	USA	50-90	1795 participants with either mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease– related dementia	18 months	11/13 (84,6%)
(Budd Haeberlein et al., 2022)	*RCT (Phase 3 trial)*	USA	50-85	3285 participants with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia,	78 weeks	13/13 (100%)
(Shcherbinin et al., 2022)	*RCT*	USA & Canada	60-85	272 participants with gradual and progressive change in memory function for 6 months or more, early symptomatic Alzheimer disease	76 weeks	11/13 (84,6%)

Risk of Bias

According to the risk of bias assessment, the overall quality of studies had low risk of bias. The several studies had a low risk of bias reporting follow-up studies with the lowest score was >84,6% (Table 1).

Result Finding

Research data from each article was extracted based on the PAGER Framework consisting of Patterns, Advances, Gaps, Evidence for practice, and Research recommendations as shown in table 2.

Table 2. Data Extraction Results based on PAGER Framework

Study	Pattern	Advances	Gaps	Evidence for Practice	Research Recommendations
(Yang et al., 2019)	Effect of crenezumab on decreasing levels of amyloid-β oligomers in CSF	Crenezumab can reduce the levels of amyloid-β oligomers present in the CSF	There is no evidence showing that anti-amyloid-β antibodies can reduce levels of amyloid-β oligomers in humans.	Amyloid-β oligomers in CSF can be a new bio-pharmacodynamic marker for use in trials of anti-amyloid-β agents.	The current findings recommend the use of a high-sensitivity oligomer selective immunoassay in clinical trials of other anti-amyloid-β agents.
(Klein et al., 2019)	Effect of gantenerumab administration on reducing amyloid-β plaque levels in moderate AD patients	PET analysis results show that gantenerumab doses up to 1200 mg can reduce strong amyloid-β plaques within 2 years	There is limited evidence regarding the long-term safety of and pharmaco-dynamic effects of gantenerumab titrated to the maximum dose.	Gantenerumab has been shown to be able to reduce amyloid-β plaque which is the main pathological feature of AD.	Further investigation is needed to prove the clinical efficacy of gantenerumab through phase III clinical trials (still ongoing).

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(Schwarz et al., 2019)	Effect of solanezumab administration on localized brain atrophy in moderate AD patients	Changes in brain volumetric size after administration of solanezumab therapy were not shown to be statistically significant during the 80-week trial	There is not enough evidence to see how the effect of giving solanezumab on slowing brain atrophy widely	Changes in brain volume and their relationship with cognitive status are consistent with the results of previous studies	Further investigation into a wider range of brain structures is needed to examine the effects of solanezumab treatment in AD patients
(Lowe et al., 2021a)	Effect of single and multiple doses of Donanemab on amyloid plaque burden in the brain	There was a change in Positron Emission Tomography amyloid at single and double doses of Donanemab which continued for up to 72 weeks.	There is limited evidence regarding the different dosing regimens of Donanemab on immunogenicity, potential immune problems, and reduction of amyloid plaques	Donanemab rapidly reduced amyloid plaques and was well tolerated by ARIA-E and cerebral microhemorrhage as a side effect which resolved after discontinuation of treatment.	Studies related to the use of Donanemab need to be discussed more fully in larger clinical studies
(Salloway, Honigberg, et al., 2018)	Effect of Crenezumab on cognitive changes in Alzheimer's patients	Amyloid plaque accumulation was not significant at high IV doses. There were no significant results on ADAS-Cog12 and CDR-SB.	There is limited evidence for the use of the subcortical white matter reference area in the assessment of SUVR and other DA biomarkers	There is potential involvement of the amyloid-β target with Crenezumab as well as the possibility of slower accumulation of amyloid plaques.	It is possible to administer an escalating Crenezumab dosing regimen in early AD patients to improve clinical outcomes without compro-mising patient safety.
(Dyck et al., 2021)	Effect of Lecanemab on cognitive and function changes in alzheimer's patient	Lecanemab has high selectivity for soluble aggregated species of Aβ and it is considered to target the most toxic pathologic amyloid species. The incidence of ARIA, including symptomatic ARIA, was numerically lower	There is limited data because it included for only 18 months of treatment; an open-label extension study is ongoing.	Lecanemab reduced brain amyloid level in early Alzheimer's disease and resulted in moderately less decline on clinical measures of cognition and function	Longer trials are warranted to determine the efficacy and safety of lecanemab in early Alzheimer's disease

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Table 2. Data Extraction Results based on PAGER Framework (*Continue*)

Study	Pattern	Advances	Gaps	Evidence for Practice	Research Recommendations
(Budd Haeberlein et al., 2022)	Efficacy and safety of aducanumab in patients with early AD	Aβ accumulation triggers downstream tau pathology and subsequent clinical decline and that targeting aggregated Aβ in the brain via aducanumab treatment could result in clinical benefit.	the CSF and tau PET biomarker substudies had relatively small sample sizes from a nonrandom subset of trial participants (i.e., those who chose to opt in to each substudy) and the populations in these studies lack diversity, including racial/ethnic diversity, patients with co-morbid conditions, and those on some concomitant medications.	Aducanumab Aducanumab statistically significant slowing of clinical decline, supporting the possibility that removal of Aβ from the. It affects both an upstream biomarker of AD (Aβ plaque) as well as an intermediate biomarker of AD (soluble p-tau).	Clinical efficacy of aducanumab should be further evaluated in a forthcoming clinical trial
(Shcherbinin et al., 2022)	Effect of Donanemab on inducing amyloid & tau levels, and clinical decline after treatment	The donanemab-induced slowing of tau was more pronounced in those with complete amyloid clearance and in brain regions identified later in the pathologic sequence	There is limited evidence regarding the trial population has less racial and ethnic diversity compared with the target population; therefore, any differences in response to treatment are not reflected	Donanemab was associated with lower amyloid at baseline and slower disease progression at 76 weeks as determined by tau accumulation and clinical decline.	Further trials and planned analyses is needed to to ascertain whether these findings are robust and also data from other trials will be important to confirm revealed trends

4. DISCUSSION

Until now, the available AD modification therapy options have not been able to provide a cure but are only able to offer mild symptoms with minimal neuropathological effects (Wang et al., 2016; World Health Organization, 2018). Monoclonal antibodies were then developed as immunotherapy that can slow or delay the process of Alzheimer's disease by reducing the progressive accumulation of amyloid-β peptide (Panza et al., 2019). Accumulation of amyloid-β peptide is believed to be a major pathological sign of AD leading to synaptic dysfunction, and neurodegeneration which ends in the appearance of AD symptoms (Salloway, Marshall, et al., 2018; Selkoe & Hardy, 2016). Although the results of previously reported clinical trials were quite varied, anti-amyloid-β immunotherapy was relatively well tolerated and has the potential to improve cognitive function if vasogenic cerebral edema (ARIA) can be reduced (Penninkilampi et al., 2017).

During the last two decades, the development of aducanumab as a monoclonal antibody-based therapy for Alzheimer's has become a new hope for treating AD (Rahman et al., 2023). Since then, several experimental studies and clinical trials have been conducted to analyze the effectiveness and safety of this drug and several other drugs have been developed and clinical trials have been carried out. Our results study shows there is 6 types of anti-amyloid-β immunotherapy given intravenously (IV) or subcutaneously (SC) were used in clinical trials of patients with mild

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to moderate AD (Table 2.). The therapeutic effects of these mAbs on AD are through targeting and reducing the accumulation of soluble and insoluble aggregated amyloid-beta (Aβ) that can potentially interfere with brain pathological processes in Alzheimer's, such as aducanumab targeting Aβ oligomers (ABO) and plaques, crenezumab targeting ABO, gantenerumab targeting Aβ fibrils, lecanemab tatgeting Aβ protofibrils, and solanezumab targeting Aβ monomers (Shi et al., 2022).

Several study demonstrated the potential of monoclonal antibodies to improve clinical outcomes and biomarker responses of Alzheimer's. Lecanemab has high selectivity for soluble Aβ-aggregated species and is therefore thought to be able to target the most toxic pathological amyloid species (Dyck et al., 2021). Based on the results of these clinical trials, the US FDA granted accelerated approval of lecanemab to treat AD in January 2023. As for another type of mab, use of donanemab can result in rapid, potent, and sustained reduction of amyloid for up to 72 weeks (Lowe et al., 2021b). A decrease in cerebral amyloid plaques has also been reported with other anti-amyloid monoclonal antibodies, such as gantenerumab, lecanemab, and aducanumab. In addition, gantenerumab and crenezumab have the potential to significantly reduce amyloid-β plaques that oAβ levels (Klein et al., 2019; Salloway, Honigberg, et al., 2018; Yang et al., 2019). Solanezumab, was reported to have a good safety profile during the phase II trial (Farlow et al., 2012). However, (Schwarz et al., 2019) shows that there was no statistically significant effect on cognitive decline after treatment in patient with mild AD. In addition, among all mAbs that have been developed and undertaken in clinical trial so far, aducanumab was found to be the most effective mAb treatment and has been approved by the FDA on June 7, 2021 (Tampi et al., 2021). Aducanumab has been shown to have a clear therapeutic effect by binds to Aβ plaques and ABO and stimulates microglia to reducing brain Aβ (Budd Haeberlein et al., 2022).

Moreover, differences doses of anti-amyloid-β are known to affect the reduction of the number of amyloid-β plaques in AD patients. IV administration of a double dose of donamemab (40 mg/kg) has been shown to reduce amyloid plaques quickly, strongly, and sustainably with a decrease of more than 50 Centiloids in 24 weeks (Lowe et al., 2021b). In addition, high doses of gantenerumab (up to 1200 mg) are known to have a strong amyloid-β plaque reduction effect over a longer time span of 2 years (Klein et al., 2019). Although the study conducted by Salloway, Honigberg, et al., (2018) reported a non-significant effect of using crenezumab (15 mg/kg & 300mg) on the accumulation of amyloid-β plaques, using higher doses of crenezumab in subsequent clinical trials may be possible to obtain greater clinical benefits. Similar results also occurred in the administration of solanezumab (400 mg) which also found that there was no statistically significant effect on changes in brain volumetric and cognitive function in mild AD patients (Schwarz et al., 2019). This was due to the limited sample size and no testing of doses >15 mg/kg which could limit the accuracy of the study results. Therefore, the use of higher doses of immunotherapy has the potential to improve clinical efficacy and effectively reduce amyloid-β accumulation.

Alternative monoclonal antibody treatment in the elderly with Alzheimer's has side effects that require multidisciplinary training. Several studies seriously detract from the safety aspect or

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the risk of side effects arising from the administration of immunotherapy. Our results study showed the main problems of treatments with these mAbs is the high incidence of developing vasogenic cerebral edema and cerebral micro-hemorrhages or named as amyloid-related imaging abnormalities (ARIA), and specifically ARIA-E (vasogenic edema) and ARIA-H (micro-hemorrhage). Events of ARIA-E occurs in aducanumab, lecanemab and donanemab group. In lecanemab, ARIA-E were mostly mild to moderate and mostly asymptomatic during the first 3 months of the treatment (Dyck et al., 2021). It is also similar to other clinical studies in aducanumab that most ARIA-E events occurred in the early stages of the treatment period and were reduced during subsequent treatment (Budd Haeberlein et al., 2022). Furthermore, the side effect ARIA-E that occurs in AD patients with donanemab administration can still be tolerated and healed after treatment recovery (Lowe et al., 2021a; Shcherbinin et al., 2022). In addition, ARIA-H occurs in a small number of study samples after administration of monoclonal antibodies of the type donanemab and crenezumab. However, this can still be tolerated, and the patient can continue to study treatment (Lowe et al., 2021a; Salloway, Honigberg, et al., 2018; Yang et al., 2019). ARIA side effects and erythema at the injection site were also identified in AD patients treated with gantenerumab and were well tolerated (Klein et al., 2019). Based on these side effects, no significant problems were found in AD patients with this type of mAb immunotherapy and they were able to be overcome. Nonetheless, continuous clinical training is also necessary to avoid unwanted conditions. Therefore, the role of the nurse as a holistic nursing care provider is needed to pay attention to the needs of patients during Alzheimer's care or treatment. In the care of patients with Alzheimer’s, it is among the responsibilities of the nurse to regulate the environment and relationships to preserve patient’s functionality and stability, to compensate for the losses associated with the disease, and to provide therapeutic environments that help maintain their privacy and quality of life. The holistic care delivered by nurses has been reported to maintain the well-being and quality of life of people with alzhaimer’s. It also help patient to recognize the cognitive change process and corporate care with other chronic diseases (Gibson et al., 2021). The successful treatment of Alzheimer's patients must also be supported by quality health services. Treatment and care are available for Alzheimer's patients and need to be appropriately managed through service management so that health workers can provide optimal care for patients in treatment planning and determining strategies to achieve the best nursing care (Ayatulloh et al., 2021).

Despite the advantages of monoclonal antibody treatment, there were only five treatments for neurocognitive symptoms in AD approved by the US FDA, namely three cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and one N-methylD-aspartate receptor antagonist (memantine) as well as a combination of donepezil and rivastigmine (Huang et al., 2020). The comparisons between long-term treatment with acetylcholinesterase inhibitor (AChEI) therapy and mAbs is a topic that has been studied extensively by researchers. The potential of the mAb aducanumab to reduce Aβ plaques prompted many experts to investigate this treatment. However, the risks of aducanumab which are judged to be greater than the benefits are still being questioned by the FDA (Food and Drug Administration) (Chin et al., 2022). In

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addition, the use of this treatment is also known to be more cost-effective when compared to mAb treatment. So more research is needed regarding the use of mAbs as a treatment for Alzheimer's.

However, the authors admit there are some limitations in this scoping review. First, we were only taking English-language studies. Second, all the studies were conducted in developed countries and were limited to certain countries. Therefore, its clinical applications in other parts of the world, especially in rural or urban areas are still unknown.

5. CONCLUSION

The development of monoclonal antibodies has created a new approach to treating Alzheimer's disease. Monoclonal antibodies that have been designed as AD immunotherapy have been shown to reduce amyloid-β plaques in the brain and potentially improve cognitive function in Alzheimer's patients. In addition, their ability to identify disease-causing target antigens with high specificity also makes monoclonal antibodies a promising biomarker for more efficiently diagnosing Alzheimer's disease at the earliest preclinical stage.

The use of higher doses of immunotherapy is recommended in subsequent clinical trials while still paying attention to patient safety aspects, especially anticipating the occurrence of Amyloid Related Imaging Abnormalities (ARIA.) Further research is also needed to ensure the sensitivity and specificity of monoclonal antibody biomarkers used to detect pathological agents of Alzheimer's disease.

6. ACKNOWLEDGEMENT

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7. CONFLICT OF INTEREST

The authors have no conflicts of interest to declare

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