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Monoclonal antibodies treatment for Alzheimer's dementia – a literature review

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ABSTRACT

Alzheimer's disease (AD), recognized by the World Health Organisation (WHO) as one of the leading causes of death and disability among older people globally, is the most common form of dementia. The accumulation of amyloid plaques and neurofibrillary tangles in the brain leads to synaptic and neuronal loss, causing cognitive impairment and functional decline. Current treatment options, such as cholinesterase inhibitors and NMDA receptor antagonists, provide partial symptomatic relief but do not alter disease progression. Monoclonal antibodies targeting amyloid-β (Aβ) have emerged as potential disease-modifying therapies by promoting the clearance of Aβ plaques. This paper reviews recent scientific literature and ongoing clinical trials related to monoclonal antibody treatments for AD. Aducanumab, Bapineuzumab, Gantenerumab, Lecanemab, and Solanezumab are among the most discussed monoclonal antibodies. Aducanumab, which has received accelerated approval from the FDA, demonstrates efficacy in reducing Aβ plaques but has generated controversy due to differing opinions among regulatory agencies. Adverse reactions, particularly amyloid-related imaging abnormalities (ARIA), are associated with monoclonal antibody treatment. However, more extensive trials are required to establish their long-term safety and efficacy. Overall, monoclonal antibodies represent a potential breakthrough in AD treatment, although their use outside the US remains uncertain. Ongoing research and clinical trials are essential for further understanding and validating the efficacy and safety of these novel therapies.

Keywords: Alzheimer's disease, dementia, death, synaptic and neuronal loss, Monoclonal antibodies, disease-modifying therapies, treatment

INTRODUCTION

Alzheimer's Disease (AD) is the most common cause of dementia, being recognized by the World Health Organization (WHO) as one of the main leading causes of death and one of the major causes of disability and dependency among older people globally, also demanding an enormous amount of direct and indirect expenses. Both men and women are affected, but women experience a higher disability-adjusted life year and mortality [1]. AD is a chronic and progressive disease that resides in global cognitive impairment that impacts all daily living activities, causing substantial functional impairment [2,3]. AD's most common clinical feature is episodic memory impairment. As the neurocognitive impairment progresses, cognitive difficulties become more profound and widespread and interfere with everyday activities. Death is on average 8.5 years from presentation [2].

The cardinal features of AD pathology are the amyloid plaques and neurofibrillary tangles formed by intracellular accumulation of hyperphosphorylated tau protein. The final consequence of the pathological pathway is neurodegeneration, with synaptic and neuronal loss that leads to atrophy. Because of the disease's complexity, several hypotheses were elaborated over time to explain AD and, therefore, find a better treatment approach. Among them, the amyloid hypothesis suggests that the accumulation of pathological amyloid-β (Aβ) forms the amyloid plaques, produced by the cleavage of amyloid precursor protein (APP) by β- and γ-secretase enzymes in the brain is responsible for the imbalance between Aβ production and Aβ clearance and, therefore, responsible for the clinical picture [2-4].

Treatment options include both pharmacological and non-pharmacological approaches. The key factor includes the importance of a correct diagnosis in the

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early stages of the disease when therapeutic management can benefit the patient. Optimal treatment needs to be tailored to the individual patient and their specific circumstances and adapted to the stage of the disease [2]. Pharmacological treatments currently approved for AD include Acetyl-cholinesterase inhibitors (AChEIs) (donepezil, galantamine and rivastigmine) that enhance the acetylcholine availability by inhibiting its breakdown in the synapse and memantine, a low-affinity N-methyl-D-aspartate receptor antagonist, that aims to reduce L-glutamate excitatory neurotoxicity [2]. Unfortunately, cholinesterase inhibitors and NMDA receptor antagonists, the current pharmacological resources, represent an incomplete solution for neurocognitive impairment, that target only the result of the neurodegenerative process, therefore determining only partial symptomatic relief and being unable to alter AD progression. [4].

Despite advances in neuroimaging and biological studies, our global understanding of AD remains limited. However, new pharmacological options using monoclonal antibodies targeting Aβ offer hope for this incapacitating neurocognitive disease. Growing evidence suggests that removing the Aβ plaques can slow its progression [3]. Immunotherapeutic approaches are now promoting the clearance of amyloid plaques from the cerebral tissue either in an active way (by injecting Aβ antigens) or in a passive way (by intravenously injecting anti-Aβ antibodies). Antibodies bind to the soluble Aβ peptides in the periphery and form an immune complex that can be removed from the circulation, reducing the level of Aβ implicated in forming the amyloid plaques. Because the efficacy of this mechanism is based on the availability of circulating Aβ, this treatment can be beneficial only during the mild and moderate forms of AD. In severe forms, little to no improvement may occur due to the presence of massive plaques already formed within the nervous system [5,6].

OBJECTIVE

The purpose of this paper is to review available recent scientific papers that approach this subject and provide an overview of the latest treatment options. Despite the controversial nature of this emerging field, the potential for this new opportunity to enhance the overall quality of life in patients with AD and delay the progression of symptoms has generated significant interest among the scientific community worldwide.

METHODS

To realize this paper, we used PubMed and Google Scholar databases to perform a search using the keywords “Alzheimer’s Disease” and “Monoclonal Antibody Treatment”. We then selected the articles that reviewed the new treatment opportunities in this field.

Additionally, we were interested in exploring ongoing clinical trials, so we performed a search using the same keywords on the clinicaltrials.gov platform. This led to a total of 23 studies, of which 11 were completed, three were terminated, five were still recruiting, one was suspended. Three studies were excluded from as they did not pertain to our subject of interest, leaving us with a final total of 20 relevant results.

RESULTS

Disease-modifying therapies that can alter the underlining pathophysiology of AD represent a significant advancement in pharmacology and have the potential to greatly improve patient outcomes. Monoclonal antibodies targeting the soluble Aβ have shown promising results in controlling the Aβ balance and slowing the progression of AD. Recently, various series of Aβ antibodies have been proposed as new therapies, although there remains controversy surrounding their efficacy [7]. Aducanumab, Bapineuzumab, Gantenerumab, Lecanemab, and Solanezumab are among the most widely discussed Aβ antibodies [5,8].

The continuous ageing of the general population increases the incidence and prevalence of patients diagnosed with AD [1]. Because of the crucial functional impact that the disease carries and of the insufficient pharmacological resources available at this point, the FDA made several accelerated approval procedures. The new treatment options represented by monoclonal antibodies may be a response to the severe impairment that AD carries but seeing that the trials were incomplete, those new molecules gather a lot of uncertainty from specialists. Outside of the US, there are no approvals for administering antibodies as treatment for AD, which raises a sceptical attitude among healthcare professionals [9-11].

The main adverse reaction cited in the literature is the appearance of amyloid-related imaging abnormalities (ARIA). Although generally asymptomatic and only detectable via MRI, ARIA can sometimes result in severe, life-threatening reactions such as cerebral oedema or hemorrhage. In most cases, the adverse effects are milder, such as headache, confusion, dizziness, visual disturbances, and seizures [7].

Aducanumab is a monoclonal antibody classified as a human immunoglobulin gamma 1 (IgG1) that can cross the blood-brain barrier and selectively target and bind to the soluble oligomers and insoluble fibril conformations of Aβ plaques in the central nervous system. This action mechanism reduces the amount of Aβ plaques, resulting in an improvement

in AD symptomatology [11]. The Food and Drug Administration (FDA) offered accelerated approval for Aducanumab in 2021 for mild cognitive impairment and mild dementia. It is currently one of the few monoclonal antibody treatments for whom there are still ongoing clinical trials [12]. The controversy surrounding it is driven mainly by the dismissed approval by other societies that regulate drugs and other available pharmacological options outside of the US, such as Japan's Minister of Health or the European Medicines Agency [8,13]. Aducanumab can be administered monthly intravenously, and the most common adverse reaction cited in literature is ARIA (oedema being the most common, in approximately 35% of patients, microhemorrhages in 19% and superficial siderosis in 15%). Among other adverse reactions are noted headache (21%), fall (15%), diarrhoea (9%), confusion/delirium/mental disorientation (8%), and hypersensitivity and immunogenicity in less than 1% of the cases. Because of the relatively high risk of important adverse reactions, close neuroimaging follow-up is required, with brain scans after 6 and 12 months to monitor for brain swelling and bleeding. No contraindications have yet been reported [10,14]. Although aducanumab is not yet approved outside of the US and because of the skepticism the new molecule still carries as a result of the fast acceptance procedure, the increased amount of data currently being collected offers new perspectives of the innovative treatment and gives hope for a better outcome for patients with AD [5,9,11].

Bapineuzumab is a humanized form of monoclonal antibody 3D6, which targets the N-terminal region of Aβ, also being an IgG1. Randomized control studies that evaluate its clinical efficacy have been published, along with one randomized-controlled trial, in which bapineuzumab failed to demonstrate significant therapeutic efficacy in AD. Further investigation of the clinical correlation between biomarker reduction, safety and therapeutic efficacy must be conducted both for APOE ε4 carriers and non-carriers. One of the most frequent adverse reactions was vasogenic oedema (observed in approximately 15% of the APOE ε4 carriers and 2.4% in non-carriers) [15-17]. Because of the negative results regarding its impact on AD, bapineuzumab is not one of the monoclonal antibodies that receive attention as a possible future treatment. However, there is valuable information that these studies have offered to further research in this area [18].

Gantenerumab, after over two decades of development in the context of scientific discoveries in the field of AD, represents one of the studied molecules for AD. It is a monoclonal antibody that can also be administered subcutaneously [19]. The mechanism of action is through glial recruitment and phagocytosis of the Aβ plaque, resulting in a dose-dependent reduction in the burden at cerebral level of amyloid accumulation. Although there were discouraging results in a phase 3 study that was carried out on patients with prodromal AD because of a lack of efficiency of treatment compared with placebo, there were still a diminution of Aβ plaques. There results may suggest that despite a reduction in the amyloid levels at the minimum concentration of the drug, higher doses may be needed to achieve a clinically efficient response [20,21].

There were two complete phase 3 studies regarding solanezumab for patients diagnosed with mild to moderate AD that did not significantly reduce the decline in cognition or function as measured by ADAS-cog14 at 80 weeks as primary outcome. There were no significantly different severe adverse reactions between the drug and placebo, administered intravenously. There are several possible explications why the antibody treatment did not work: solanezumab reduced the peripheral amyloid but this did not result in a clinically significant impact, the dose of solanezumab administered may have been insufficient to produce meaningful effects, or the pathological changes in mild to moderate AD may not be amenable to treatment with a drug that is targeting Aβ [6,22].

Lecanemab, also a humanized IgG1 monoclonal antibody, that binds with high affinity to Aβ soluble protofibrils, is one of the new molecules introduced as a therapy that targets the accumulation of insoluble amyloid plaques. It was recently approved by FDA, by accelerated approval procedure, for treatment of AD in patients with documented elevated Aβ, being administered intravenously [23]. The results that are presented with lecanemab are promising as in a study that enrolled over 1500 individuals, it reduced markers of amyloid in early AD and results in a moderately less decline in measures of cognition and function, compared with placebo after 18 months, but not absolved of adverse reactions. Longer and more extensive trials are necessaire to make stronger statements regarding this new treatment [24].

Regarding patients with early AD, donanemab results in better composite score for cognition and for the ability to perform activities of daily living that placebo, although results for secondary outcomes were mixed. Accelerated approval was rejected in 2023 and longer and larger trials are necessary to study its efficacy and safety [25,26].

Among the clinical trials that are registered on the platform ClinicalTrials.gov, we arranged the results in Table 1 [27]. All the clinical trials were with the primary purpose of treatment, the study type was interventional (clinical trial). Almost all were randomized, with two exceptions that were non-randomized. Among those that were terminated, the study

for LY2062430 (solanezumab) was due to insufficient scientific evidence that solanezumab would likely demonstrate a meaningful benefit to participants with prodromal AD as defined by study protocol, the one for Gantenerumab terminated due to safety and efficacy. The one about Gantenerumab that was suspended because there was little to no statistical difference, giving overall disappointing results [28].

TABLE 1. Studies from ClinicalTrials.gov

Drug	Recruitment Status	Estimated Enrolments (participants)	Intervention model	Masking	Allocation	Study start date	Study completion date (estimated)	Phase
LY2062430 (solanezumab)	Completed	1000	Parallel Assignment	Quadruple	R	May-09	Apr-12	3
IBC-Ab002	Recruiting	40	Sequential Assignment	Quadruple	R	Feb-23	Dec-24	1
JNJ-63733657	Recruiting	480	Parallel Assignment	Triple	R	Jan-21	Nov-25	2
LY2062430 (solanezumab)	Terminated	26	Parallel Assignment	Triple	R	Jun-16	May-17	3
Pepinemab	Recruiting	40	Parallel Assignment	Quadruple	R	Jul-21	Jul-21	1 and 2
TB006	Recruiting	48	Sequential Assignment	Triple	R	Jun-21	Jan-23	1
Bapineuzumab	Completed	1121	Parallel Assignment	Quadruple	R	Dec-07	Apr-12	3
LY2062430 (solanezumab)	Completed	1040	Parallel Assignment	Quadruple	R	May-09	Jun-12	3
Bapineuzumab	Completed	1331	Parallel Assignment	Quadruple	R	Dec-07	Jun-12	3
Bapineuzumab	Terminated	194	Parallel Assignment	None (Open Label)	NR	Dec-06	Sep-12	2
PF-04360365	Completed	37	Parallel Assignment	Triple	R	Mar-07	Sep-09	1
MEDI1814	Completed	77	Parallel Assignment	Triple	R	Feb-14	Sep-16	1
Gantenerumab	Terminated	1379	Single Group Assignment	None (Open Label)	NR	Feb-21	Mar-23	3
Crenezumab	Completed	77	Parallel Assignment	Double	R	Feb-15	Mar-19	1
MABT5102A	Completed	448	Parallel Assignment	Double	R	Apr-11	Feb-14	2
MABT5102A	Completed	91	Parallel Assignment	Double	R	Aug-11	Apr-14	2
Gantenerumab and Solanezumab	Completed	194	Parallel Assignment	Quadruple	R	Dec-12	Mar-20	2 and 3
Gantenerumab, Solanezumab, E2814, Lecanemab	Recruiting	490	Parallel Assignment	Quadruple	R	Dec-12	Oct-27	2 and 3
Gantenerumab	Suspended	220	Parallel Assignment	Quadruple	R	Dec-22	Mar-34	2 and 3
Gantenerumab	Completed	28	Parallel Assignment	Double	R	Jun-12	Jun-14	1

Double - Participant, Investigator / Triple - Participant, Care Provider, Investigator / Quadruple - Participant, Care Provider, Investigator, Outcomes Assessor / R- randomized, NR – non-randomized

DISCUSSION

The rising interest for finding a new treatment for AD is reflected in a wide number of clinical studies that assess the potential benefit of monoclonal antibody treatment. Although there are still many steps to be followed before releasing a complete molecule that addresses all the clinical aspects, this new approach is getting more and more attention and some promising results are published. At this moment, there is no biological treatment approved for AD in Europe and most of them are studied in United States under the jurisdiction of the FDA. However, the adverse reaction profile shows some worrying results like ARIA, which can be potentially deadly if not managed immediately and correctly, a fact that has been raising suspicion among clinicians.

Nevertheless, the rising incidence and prevalence of AD that impact the quality of life demand new treatment approaches that require an intermediate period before perfecting any new molecules.

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