

Efficacy and safety profiles of monoclonal antibodies used in the therapy of Alzheimer's disease

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Abstract

Introduction: Advances in molecular biology and biotechnology in recent decades have led to creation of new therapeutic strategies for Alzheimer's disease (AD) patients. Among the emerging therapeutic approaches, monoclonal antibodies are attracting particular attention due to their ability to modulate the accumulation of amyloid plaques and tau protein in the brain, thus proposing promising pathogenetic approach. Aim: to summarize efficacy, side effects and mortality rates of monoclonal antibodies based on the results of clinical trials in comparison with conventional therapy.

Methods: All registered clinical studies related to AD treatment using monoclonal antibodies were found in ClinicalTrials.gov database. The information on adverse effects was obtained from the articles related to the third phase clinical studies, with total 21 articles included in the analysis. Data on conventional therapy were retrieved from clinical guidelines related to AD treatment.

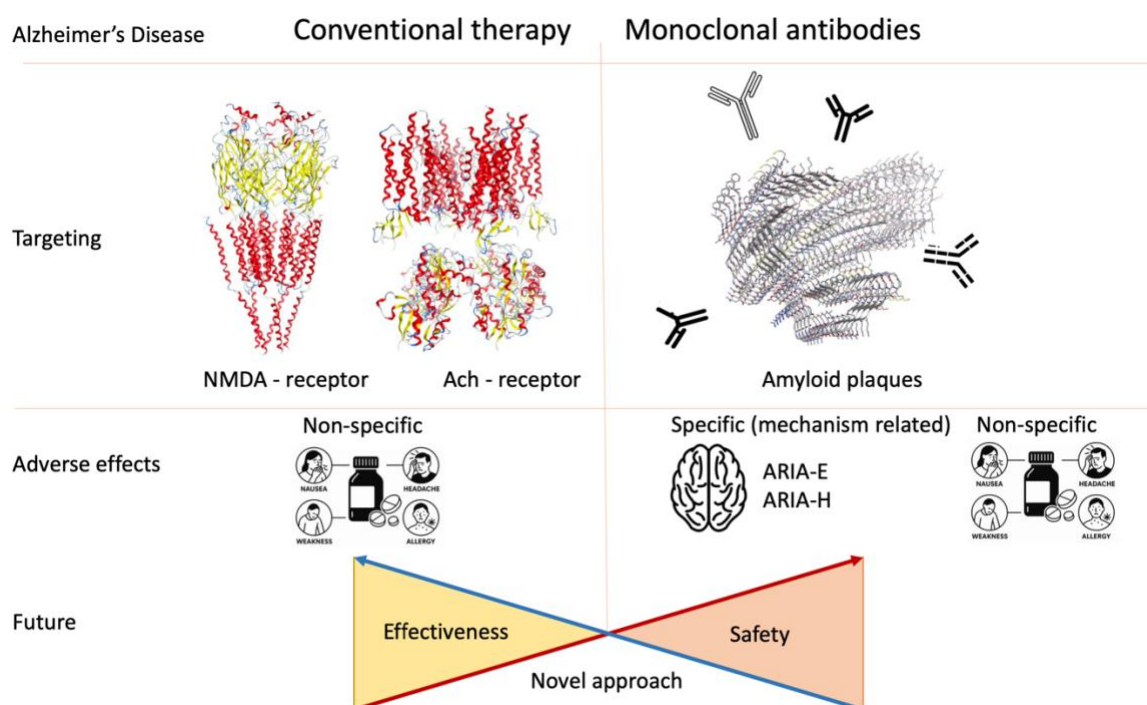
Results: We found that the number of significant side effects and mortality varies significantly for different monoclonal antibodies. For the most part, side effects are not specific to the drugs used, and therefore it is not possible to assess the direct effect of the drug on the development of certain adverse events, as well as to adequately compare the safety of different drugs, due to different mechanisms of action and recommended doses. Magnetic resonance imaging with estimation of amyloid-related imaging abnormalities changes is the most promising method for antibodies comparison, but this approach still lacks correlation with clinical course. Also, it is recommended to separately consider the side effects associated with infusion.

Conclusion: The use of pathogenetic antibody therapy will improve the quality of AD treatment in the future. However, up to date, there are no unified protocols for estimation of drug effectiveness and its comparison. Evaluation of side effects and determination of antibody-specific side effects is necessary to improve the safety of treatment of patients with AD.



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Graphical Abstract



Keywords

Alzheimer's disease, therapy of Alzheimer's disease, efficacy, safety, monoclonal antibodies, ARIA-H, ARIA-E

Introduction

Alzheimer's disease (AD) is the subject of intensive scientific research due to its complex pathophysiology, varied clinical presentation and large number of diagnostic biomarkers. Advances in molecular biology and biotechnology in recent decades have led to significant changes in the diagnosis and treatment of AD patients. Among the emerging therapeutic approaches, monoclonal antibodies are attracting particular attention due to their ability to modulate the accumulation of amyloid plaques and tau protein in the brain.

Most of the developed monoclonal antibodies target aggregated forms of β -amyloid peptide ($A\beta$), particularly $A\beta$ fibrils, which constitute the structural core of amyloid plaques. New types of antibodies that target specific $A\beta$ conformations persisting at the early stages of amyloid plaque formation are currently being developed. These conformations are not yet detectable by neuroimaging methods (Perneczky et al. 2024).

Despite the large number of patients and variety of studies conducted, unified clinical guidelines for AD therapy are not currently available, except for recommendations developed by the Alzheimer's Association. Nowadays only a limited number of drugs are prescribed as part of disease-modifying therapy. It is well established that early diagnosis and treatment initiation significantly improve quality of life in this patient group. However, the complexity of diagnosis as well as absence of florid early symptoms often result in the development of "resistant" and irreversible forms of the disease characterized by significant cognitive decline.

The current standard for AD diagnosis includes a neuropsychological assessment using scales to evaluate the severity of cognitive impairment, as well as positron emission tomography (PET) scans using 18F-florbetaben, 18F-flutemetamol and 18F-fluorodeoxyglucose. The use of these scales has not been standardized for a long time, which complicates comparisons between different studies and hinders the development of a unified approach to AD diagnosis and treatment. The most commonly used tools nowadays include:

1. The Global Deterioration Scale for assessment of primary degenerative dementia (Reisberg et al. 1982);
2. The FDA (The Food and Drug Administration) guidance classification for conducting clinical trials in the early stages of AD FDA (2024) Early Alzheimer's Disease: Developing Drugs for Treatment.);
3. Recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for AD (Sperling et al. 2011);
4. All scales used to assess cognitive function, daily activities, behavioral responses, and quality of life (Robert et al. 2010);
5. ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive Subscale) (Rosen et al. 1984).

To evaluate the effectiveness of various therapeutic strategies, it became necessary to classify patients by the severity of cognitive impairment and by the severity of disease progression. Thus, the ADAS-Cog developed by the Alzheimer's Association in 2018 includes six stages of AD progression (Rosen et al. 1984).

The first stage (asymptomatic) is characterized by the absence of clinical symptoms and deviation of cognitive tests results; AD can only be identified through biomarkers. At the second stage (transitional), mild minimal cognitive changes that do not affect daily functioning are detected. Cognitive decline is observed over a period of 1–3 years and persists for at least six months. At the third stage (mild), cognitive changes are noticeable to external observers and can be identified using cognitive tests. Complex activities take more time to complete. The fourth stage is dementia with mild functional impairment, when the patient requires assistance with household tasks. The fifth stage is dementia with moderate functional impairment. Patient requires help with routine daily activities. At the sixth stage (dementia with severe functional impairment), progressive cognitive and functional decline with complete dependence for basic daily care is observed.

The most recently revised criteria for the diagnosis and staging of AD were published on June 27, 2024, by the working group of the Alzheimer's Association (USA). In that revision, it was suggested to add a zero stage of disease progression, at which any symptoms of detectable pathological changes in the brain are not presented (Jack et al. 2024).

Methods

For the analysis of the frequency of adverse events of monoclonal antibodies, all studies registered in the ClinicalTrials.gov database were selected. In the next step, only phase III clinical trials with published results were included. The selected protocols are presented in Table 1. Serious adverse events with a frequency of more than 5% were assessed.

Table 1. Phase 3 clinical studies with posted results available on ClinicalTrials.gov

Drug	Phase 3 study (study start and study completion date)
Aducanumab	• NCT04241068 (02.03.2020 - 22.07.2024) • NCT02484547 (15.09.2015 - 05.08.2019) • NCT02477800 (13.08.2015 - 08.08.2019) • NCT05310071 (02.06.2022 - 12.08.2024) • NCT05108922 (16.11.2021 - 19.09.2023)
Donanemab	• NCT05108922 (16.11.2021 - 19.09.2023) • NCT04437511 (19.06.2020 - 08.2025)
Gantenerumab	• NCT04374253 (26.01.2021 - 06.03.2023) • NCT06424236 (03.06.2020 - 13.11.2023) • NCT04339413 (22.05.2020 - 04.01.2023) • NCT03443973 (22.08.2018 - 28.11.2022) • NCT03444870 (06.06.2018 - 17.02.2023) • NCT05256134 (19.04.2022 - 13.03.2023) • NCT02051608 (27.03.2014 - 16.04.2021) • NCT01224106 (30.11.2010 - 10.09.2020) • NCT04623242 (12.2012 - 06.03.2020)
Solanezumab	• NCT02760602 (06.2016 - 05.2017) • NCT01127633 (12.2010 - 02.2017) • NCT01900665 (07.2013 - 02.2017) • NCT02008357 (28.02.2014 - 08.06.2023) • NCT04623242 (12.2012 - 06.03.2020)
Crenezumab	• NCT03491150 (11.04.2018 - 31.05.2019) • NCT03114657 (29.03.2017 - 11.06.2019) • NCT02670083 (22.03.2016 - 31.05.2019)

The search of AD grading and treatment strategies was performed using the open databases of national AD societies. To date there are no national guidelines (Russian, European, USA), thus we reviewed international AD societies including (Alzheimer's Association; Alzheimer's Disease Association; Alzheimers.gov; Alzheimer's Society; Alzheimer's Foundation of America; Alzheimer Society of Canada; Dementia Singapore; ADAKC (Alzheimer's Disease Association of Kern County); ARDCI (Alzheimer's and Related Disorders Society of India); Alzheimer's Association Australia; Federation of Brazilian Alzheimer's Associations (Febraz)). In this regard, we retrieved and analyzed all existing guidelines – European Federation for Neurological Societies (EFNS), The National Institute on Aging and the Alzheimer's Association (NIA-AA).

Results

Conventional therapy of Alzheimer's disease

At present, the majority of international clinical associations still maintain the position that acetylcholinesterase inhibitors ([donepezil](#), [galantamine](#), and [rivastigmine](#)) and [memantine](#) (NMDA receptor antagonist) play the main role in the treatment of AD (Varadharajan et al. 2023; NHS 2025; Alzheimer's Society 2025). According to the clinical guidelines issued by NICE (National Institute for Health and Care Excellence, UK), the first line treatment for mild to moderate stages of AD is a monotherapy of [donepezil](#), [galantamine](#), and [rivastigmine](#). [Memantine](#) monotherapy is recommended as a treatment option for the severe form of AD, in cases of intolerance to acetylcholinesterase inhibitors or when there are contraindications to their use. Additionally, [memantine](#) is considered as an adjunct to acetylcholinesterase inhibitors in moderate and severe stages of the disease (NICE guideline 2018).

Acetylcholinesterase inhibitors may be used at all stages of AD progression. [Memantine](#), either as monotherapy or in combination with acetylcholinesterase inhibitors, is used in moderate and severe stages. [Donepezil](#) is initiated at a dose of 5 mg per day, which may be increased to 10 mg per day after four weeks of treatment, in case the drug is well tolerated. The initial dose of [rivastigmine](#) is 1.5 mg twice a day with incremental increases every two weeks: first to 3 mg twice a day and then up to a maximum of 6 mg twice a day. [Galantamine](#) is initiated at 4 mg twice a day and is titrated every 4 weeks: first to 8 mg twice a day, and then up to 12 mg twice a day. [Memantine](#) is administered at 5 mg twice a day, with weekly increases of 5 mg to reach a maximum dose of 10 mg twice a day. It has been shown that the incidence of side effects with transdermal [rivastigmine](#) is lower than with oral administration.

Some studies have shown that cholinesterase inhibitors retain their efficacy over a long term (up to one year). The benefit of long-term use of acetylcholinesterase inhibitors is supported by the evidence of cognitive and overall functional decline after drug discontinuation. Patients who begin treatment with these medications require re-evaluation after 4–6 weeks to identify side effects and adjust the dose if necessary. If a patient does not tolerate one acetylcholinesterase inhibitor, and there is no improvement with dose reduction or slower titration, a switch to another cholinesterase inhibitor is possible. High-dose prolonged-release [donepezil](#) (11.5 mg and 23 mg) is used for moderate and severe AD after three months of treatment at a dose of 10 mg and stabilization of the patient's condition (Shaji et al. 2018).

Despite the widespread use of these medications, they are disease-modifying rather than pathogenic therapy agents. Thus, these medications are prescribed for long-term use after a confirmed diagnosis of AD. Prolonged administration is often associated with the development of dose-dependent side effects. The conducted research has shown that [donepezil](#) at doses of 5 mg and 10 mg, as well as [galantamine](#), has a positive effect on cognitive function. However, the use of [donepezil](#) at 10 mg and [galantamine](#) at doses from 16 to 24 mg is likely associated with a higher incidence of side effects. [Donepezil](#) at 10 mg demonstrates greater efficacy on cognitive function, but is also associated with a higher rate of adverse effects (Battle et al. 2021, Rozankovic et al. 2021).

In symptomatic treatment of moderate to severe AD, [memantine](#) is primarily used. In addition, [rivastigmine](#), [donepezil](#), and a combination drug containing both [memantine](#) and [donepezil](#) have been approved by the FDA for the treatment of moderate and severe stages. [Donepezil](#) and [galantamine](#) are also used in mild AD to prevent the breakdown of acetylcholine in the brain (Alzheimer's Association 2025; National Institute on Aging 2025).

Adverse effects of conventional therapy

The most common adverse effects of [rivastigmine](#) include nausea, vomiting, dyspeptic disorders, headache, and dizziness (>10%). For [galantamine](#), the most frequently reported side effects are nausea, vomiting, diarrhea, and weight loss (>10%). In addition to the aforementioned side

effects, **donepezil** is also associated with sleep disturbances and infectious complications (>10%). **Memantine** is associated with the following adverse effects: dizziness, confusion, unsteadiness, hypertension, headache, and dyspnea (>10%) (Drugs.com and Register of Medicines of Russia – **rivastigmine**, **galantamine**, **memantine**).

The combination of **memantine** and an acetylcholinesterase inhibitor is also used in the treatment of AD pathology. For example, Namzaric (**memantine/donepezil**), containing a fixed dose of **memantine** 10 mg, and a varying dose of the acetylcholinesterase inhibitor (7, 14, 21, and 28 mg). Its most common side effects (>10%) are nausea, diarrhea, sleep disturbances, and infectious complications. Less frequently observed adverse reactions to **donepezil** include headache, vomiting, seizures, anorexia, hypertension, hallucinations, and syncope.

The American Academy of Neurology issued guidelines for managing patients with cognitive impairment in 2001 (Update in 2018) (Petersen et al. 2018), and no subsequent editions have been published since. The most recent reference to AD appears in a publication discussing the appropriateness of **aducanumab** as a treatment option for this condition, further highlighting the potential of monoclonal antibody-based therapy (Knopman et al. 2001, Day et al. 2022). The adverse effects of disease-modifying therapy can be classified as mild, whereas their efficiency remains unsatisfactory due to the inability to restore lost functions.

Pathogenetic therapy of Alzheimer's disease

The existing drugs to treat AD are aimed at alleviating symptoms but do not affect the underlying cause of the disease. Some evidence suggests that the elimination of A β slows disease progression. Currently, five drugs are in the late phase of clinical trials: **aducanumab**, **donanemab**, **gantenerumab**, **crenezumab**, and solanezumab. All of these are IgG1 monoclonal antibodies targeting aggregated forms of A β (Söderberg et al. 2023).

As of 2022, **aducanumab** was the only FDA-approved drug that affects the pathogenesis of A β plaque formation. **Aducanumab** selectively binds A β aggregates in both the oligomeric and fibrillar states, rather than A β monomers, which distinguishes it from other drugs in this group. It reduces the formation of A β oligomers, thus interrupting A β aggregation (Haddad et al. 2022).

Donanemab is a humanized IgG1 antibody which binds to the insoluble, modified, N-terminal truncated form of A β . By binding to modified A β plaques, **donanemab** boosts their removal through microglial phagocytosis, in which brain immune cells engulf and destroy the plaques (Alawode et al. 2021, Rashad et al. 2023).

Gantenerumab, a human IgG1, targets both the N-terminal (3–11) and mid-domain (18–27) regions of the A β peptide. **Gantenerumab** interrupts the growth of aggregation of A β forms and activates microglial phagocytosis (Bohrmann et al. 2012, Klein et al. 2019). **Gantenerumab** was also found to have an effect on other mechanisms of AD pathogenesis: a dose- and time-dependent decrease in cerebrospinal fluid tau protein levels, a decrease in phosphorylated tau (p-tau), a decrease in the level of the synaptic biomarker neurogranin (Ostrowitzki et al. 2017, Salloway et al. 2021), and a decrease in the level of neurofilament light chain (NfL) (Salloway et al. 2021).

Solanezumab is the humanized monoclonal IgG1 antibody. Solanezumab was developed to target the mid-domain of soluble monomeric A β . In phase 3 trials, solanezumab did not meet primary clinical endpoints (Honig et al. 2018). **Crenezumab**, an IgG4 monoclonal antibody that binds to both monomeric and oligomeric forms of A β , was studied in phase 3 with similar results (Cummings et al. 2018, Guthrie et al. 2020). Clinical trial results of solanezumab and **crenezumab** showed no effect or limited clinical effect. While **crenezumab**'s precise therapeutic mechanism in AD is unknown, it shares high structural similarity with the A β -targeting antibody solanezumab. **Crenezumab** was engineered for improved A β clearance combined with attenuated microglial effector function. This design aims to stimulate A β phagocytosis without triggering excessive inflammatory cytokine release, reducing the risk of side effects such as vasogenic edema (Plotkin and Cashman 2020).

It is currently not possible to standardize the comparison of the aforementioned monoclonal antibodies due to the lack of universal criteria for evaluating their efficacy and safety. For example, these monoclonal antibodies differ in their A β targets: A β oligomers for **aducanumab**, protofibrils for lecanemab, pyroglutamate A β for **donanemab**.

Administration

All listed anti-A β monoclonal antibodies for AD (**aducanumab**, **donanemab**, **gantenerumab**, **crenezumab**, solanezumab) require parenteral administration, primarily via intravenous infusion due to their protein nature and poor oral bioavailability. **Aducanumab**, **donanemab**, **crenezumab**, and solanezumab are administered only via slow intravenous infusion (typically over 1 hour or more) at specified intervals (e.g., monthly) in clinical trials and real-world use (for approved

agents). **Gantenerumab** was investigated using both intravenous and subcutaneous routes of administration. The subcutaneous route explored as a potentially more convenient option for patients. Importantly, **donanemab** is approved with a treatment discontinuation protocol upon achieving a predefined level of amyloid plaque clearance, distinguishing it from the lifelong administration typical of the other agents (Cummings et al. 2023).

Efficacy evaluation

Most studies have compared monoclonal antibodies to placebo rather than other drugs. While comparative studies of monoclonal antibodies against placebo remain predominant, emerging head-to-head trials are now directly evaluating these therapeutics against one another. The efficacy of anti-A β monoclonal antibodies has been evaluated through large Phase III trials, revealing significant heterogeneity in clinical outcomes despite shared A β -target mechanisms. This divergence underscores complexities in translating clearance of A β into cognitive preservation and highlights critical limitations of current strategies of therapy. All five mAbs demonstrate robust amyloid plaque reduction (e.g., -59.1 centiloids with **donanemab**, -70% with high-dose **aducanumab**). However, clinically meaningful cognitive benefits are inconsistently observed. In terms of efficacy based on the Mini-Mental State Examination and the cognitive subscale of the Alzheimer's Disease Assessment Scale, all active drugs performed significantly better than placebo (Cummings 2025).

Aducanumab (EMERGE/ENGAGE trials): Mixed results. EMERGE showed a 22% slowing of cognitive decline (CDR-SB*; $p=0.01$) at a high dose, while ENGAGE failed its primary endpoint. Post-hoc analyses suggested benefits in early-stage patients with longer exposure.

Donanemab (TRAILBLAZER-2): Slowed decline by *35%* on iADRS** ($p<0.001$) and *36%* on CDR-SB ($p<0.001$) at 18 months. Notably, 47% of early-stage participants showed no cognitive decline at 1 year.

Gantenerumab (GRADUATE I/II): Failed primary endpoints (CDR-SB, ADAS-Cog13). Despite 25% amyloid reduction, cognitive decline slowed by only *4%* (statistically insignificant).

Solanezumab & Crenezumab: No significant cognitive benefits across multiple trials (EXPEDITION, CREAD), despite amyloid reduction.

While **donanemab** demonstrates the most convincing efficacy to date, its benefits remain incremental. **Aducanumab**'s approval remains controversial due to inconsistent trial data. **Gantenerumab**, **crenezumab**, and **solanezumab** underscore the limitations of monotherapy A β targeting (Budd Haeberlein et al. 2022, Ostrowitzki et al. 2022, Bateman et al. 2023, Jack et al. 2023, Sims et al. 2023, Sperling et al. 2023).

In the phase 3 TRAILBLAZER-ALZ-4 trial, an open-label design was employed to assess differential amyloid plaque clearance efficacy between **donanemab** and **aducanumab** in early symptomatic AD patients. For example, when comparing the effects of **aducanumab** and **donanemab** on amyloid plaques, published data showed that at 6, 12, and 18 months after treatment, amyloid plaques clearance was achieved in 37.9%, 70.0%, and 76.8% of participants treated with **donanemab**, compared with 1.6%, 24.6%, and 43.1% of participants treated with **aducanumab**, respectively ($P < 0.001$). ARIA was observed in 23.9% and 34.8% of **donanemab**- and **aducanumab**-treated participants (Salloway et al. 2025).

At this stage, a unified comparison of the mentioned monoclonal antibodies is quite difficult due to the absence of universal criteria for evaluating their efficacy and safety.

Adverse effects

Infusion reactions

Infusion reactions associated with anti-A β monoclonal antibodies (**aducanumab**, **donanemab**, **gantenerumab**, **crenezumab**, **solanezumab**) are a common side effect of anti-A β monoclonal antibodies used for AD treatment. They are predominantly mild to moderate in severity. They typically occur during or shortly after infusion and are more frequent with initial doses. Common symptoms include: flu-like symptoms (fever, chills), headache, nausea, fatigue, hypertension or hypotension, dizziness.

Infusion reactions to anti-A β monoclonal antibodies represent a significant clinical concern because they may limit treatment tolerability and necessitate additional medical intervention. Their occurrence can lead to infusion interruptions, treatment delays and patient refusal to continue therapy. Thus, despite being manageable, infusion reactions remain a key factor impacting treatment safety and adherence to treatment (Cáceres et al. 2019, Malik and Ghatol 2023, Cummings 2025).

Main side effects

Side effects recorded during phase 3 trials can be found on ClinicalTrials.gov (study references can be found in Table 1). The vast majority of side effects are not specific to the drug molecular mechanisms. All adverse effects were divided in two main groups including serious adverse events (causing life-threatening conditions, resulting death, hospitalization, or disability) and non-serious (any unfavorable or unintended medical occurrence experienced by a participant that does not meet the criteria for a serious adverse event). Thus, the number and structure of effects were recorded for each clinical trial for the intervention and placebo group. Number of serious effects varied from study to study without significant difference with placebo group, thus underlining difficulties in delaminating drug-specific events. Number of non-serious adverse events was observed more than in 50% of patients in placebo and administration group.

The only formalized criteria for serious adverse monitoring created – amyloid-related imaging abnormalities (ARIA). ARIA, specifically ARIA-A (referring to edema/effusion) and ARIA-E (hemorrhage/hemosiderin deposits) – have become critical biomarkers in AD research, particularly in the context of anti-amyloid immunotherapy. These radiological findings are closely tied to treatments like with [aducanumab](#) and lecanemab, which target amyloid plaques in the brain but come with potential side effects that require careful monitoring. ARIA-E typically manifests as temporary brain swelling or fluid buildup visible on MRI scans, often triggered by the inflammatory response following amyloid clearance. While many patients remain asymptomatic, some may experience headaches, confusion, or dizziness, prompting clinicians to adjust or pause treatment in severe cases. On the other hand, ARIA-H encompasses small brain bleeds and iron deposits, which tend to be more permanent and are linked to underlying vascular fragility, especially in patients with cerebral amyloid angiopathy (Hampel et al. 2023).

The emergence of these biomarkers has reshaped clinical protocols, making regular MRI surveillance a mandatory part of therapy for patients receiving these groundbreaking but complex treatments. They also serve as important screening tools – individuals with significant pre-existing vascular amyloid deposits might be deemed unsuitable candidates due to heightened risks. Interestingly, the severity of ARIA often correlates with factors like drug dosage and genetic predisposition, particularly the presence of the APOE4 allele, adding another layer of personalization to Alzheimer's management strategies.

Ultimately, while ARIA presents challenges in balancing therapeutic benefits against potential harm, its study has been invaluable. It not only refines safety measures but also deepens our understanding of how amyloid removal interacts with the brain's delicate vascular system. As research progresses, these insights could pave the way for safer, more effective interventions in the fight against AD (Sperling et al. 2011, Sevigny et al. 2016).

Visualization finding associated with vascular integrity disruptions detected by PET were most frequently identified with [aducanumab](#), and least frequently with lecanemab. However, as some AD patients have contraindications to MRI, it is impossible to study antibody safety thoroughly. Since these reactions can only be detected by brain MRI, patients unable to undergo this examination cannot be safely treated with antibodies. Thus, infusion tolerability and ARIA can be considered as a safety criteria (Cummings et al. 2022, 2023, 2024, Perneczky et al. 2023).

The therapeutic effect of immunotherapy was also assessed using various scales applied to AD patients. The study below included 33 randomized controlled trials with a total of 21,087 patients, involving eight different monoclonal antibodies. Based on changes in Mini-Mental State Examination (MMSE) and Clinical Dementia Rating scale Sum of Boxes (CDR-SB), [aducanumab](#) (87.01% and 99.37%, respectively) was most likely to achieve the best therapeutic effect. [Donanemab](#) (88.50% and 99.00%, respectively) showed the best results in comparison with other drugs on the cognitive subscale (ADAS-cog) and standardized uptake value ratio from PET (PET-SUVr). Based on the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL), lecanemab (87.24%) may be the most promising agent. "When analyzing the incidence of adverse events (subjects with any treatment-related adverse event), [gantenerumab](#) (89.12%) had the lowest potential for adverse effects, while lecanemab (0.79%) may have caused more adverse events. Solanezumab (95.75% and 80.38%, respectively) had the lowest rate of amyloid-related imaging abnormalities characterized by edema and effusion (ARIA-E) and cerebral microhemorrhages (ARIA-H) among all immunotherapeutic drugs included in the analysis" (Qiao et al. 2024). The occurrence of ARIA-E/H changes are presented in Tables 2 and 3.

Table 2. Incidence of ARIA-H (serious adverse effects)

Drug	ClinicalTrials.gov ID	ARIA-H						
Aducanumab	NCT04241068	3/1696 (0.18%)						
	NCT02484547	0/547 (0.00%)	4/544 (0.74%)	2/547 (0.37%)	0/131 (0.00%)	0/132 (0.00%)	0/251 (0.00%)	0/257 (0.00%)
	NCT02477800	0/540 (0.00%)	0/549 (0.00%)	2/558 (0.36%)	1/150 (0.67%)	1/152 (0.66%)	0/299 (0.00%)	0/251 (0.00%)
	NCT05310071	0/343 (0.00%)	2/681 (0.29%)					
	NCT05108922	17/69 (24.64%)†	13/71 (18.31%)†					
Donanemab	NCT05108922	17/69 (24.64%)†	13/71 (18.31%)†					
	NCT04437511	4/853 (0.47%)	0/874 (0.00%)					
Gantenerumab	NCT04374253	1/14 (7.14%)†	21/691 (3.04%)†	0/29 (0.00%)†	7/647 (1.08%)†			
	NCT06424236	2/18 (11.11%)†	5/27 (18.52%)†	0/28 (0.00%)†				
	NCT04339413	N/a	N/a					
	NCT03443973	2/474 (0.42%)†	33/501 (6.59%)†	0/13 (0.00%)†	0/14 (0.00%)†			
	NCT03444870	0/481 (0.00%)	2/503 (0.40%)	0/33 (0.00%)	0/35 (0.00%)	0/9 (0.00%)	0/20 (0.00%)	
	NCT05256134	N/a	N/a					
	NCT02051608	0/195 (0.00%)	2/192 (1.04%)	0/117 (0.00%)	1/108 (0.93%)			
	NCT01224106	31/266 (11.65%)†	58/271 (21.40%)†	36/260 (13.85%)†	7/49 (14.29%)†	17/105 (16.19%)†		
	NCT04623242	N/a	N/a	N/a	N/a	N/a		
Solanezumab	NCT02760602	N/a	N/a					
	NCT01127633	N/a	N/a					
	NCT01900665	N/a	N/a	N/a	N/a			
	NCT02008357	N/a	N/a	N/a	N/a			
	NCT04623242	N/a	N/a	N/a	N/a	N/a		
Crenezumab	NCT03491150	N/a	N/a					
	NCT03114657	N/a	N/a					
	NCT02670083	N/a	N/a					

Note: † – ARIA-H was presented in “not serious” adverse events.

Table 3. Incidence of ARIA-E (serious adverse effects)

Drug	ClinicalTrials.gov ID	ARIA-E						
Aducanumab	NCT04241068	9/1696 (0.53%)						
	NCT02484547	1/547 (0.18%)	5/544 (0.92%)	8/547 (1.46%)	0/131 (0.00%)	1/132 (0.76%)	0/251 (0.00%)	0/257 (0.00%)
	NCT02477800	0/540 (0.00%)	2/549 (0.36%)	7/558 (1.25%)	2/150 (1.33%)	2/152 (1.32%)	0/299 (0.00%)	0/251 (0.00%)
	NCT05310071	0/343 (0.00%)	7/681 (1.03%)					
	NCT05108922	23/69 (33.33%)†	17/71 (23.94%)†					
Donanemab	NCT05108922	23/69 (33.33%)†	17/71 (23.94%)†					
	NCT04437511	13/853 (1.52%)	0/874 (0.00%)					
Gantenerumab	NCT04374253	5/14 (35.71%)†	67/691 (9.70%)†	3/29 (10.34%)†	16/647 (2.47%)†			
	NCT06424236	7/18 (38.89%)†	6/27 (22.22%)†	5/28 (17.86%)†				
	NCT04339413	N/a	N/a					
	NCT03443973	12/474 (2.53%)†	114/501 (22.75%)†	0/13 (0.00%)†	1/14 (7.14%)†			
	NCT03444870	0/481 (0.00%)	7/503 (1.39%)	0/33 (0.00%)	0/35 (0.00%)	0/9 (0.00%)	0/20 (0.00%)	
	NCT05256134	N/a	N/a					
	NCT02051608	2/195 (1.03%)	2/192 (1.04%)	2/117 (1.71%)	2/108 (1.85%)			
	NCT01224106	0/266 (0.00%)‡	0/271 (0.00%)‡	0/260 (0.00%)‡	0/49 (0.00%)‡	2/105 (1.90%)‡		
	NCT04623242	N/a	N/a	N/a	N/a	N/a		
Solanezumab	NCT02760602	N/a	N/a					
	NCT01127633	N/a	N/a					
	NCT01900665	N/a	N/a	N/a	N/a			
	NCT02008357	N/a	N/a	N/a	N/a			
	NCT04623242	N/a	N/a	N/a	N/a	N/a		
Crenezumab	NCT03491150	N/a	N/a					
	NCT03114657	N/a	N/a					
	NCT02670083	N/a	N/a					

Note: † – ARIA-E was presented in “not serious” adverse events; ‡ – ARIA-E was presented in serious and not serious adverse events.

Taking into account the difficulties in delimiting the side effects between placebo and nocebo groups and direct comparison of safety profiles between groups, currently it is not possible to identify the most safe monoclonal antibody drug because of several reasons: differences in target mechanisms among drugs; varying adverse infusion reactions depending on dosage; the choice of monoclonal antibody depending on disease stage; the use of different, non-standardized scales to assess therapy outcomes; and the influence of comorbid conditions and concurrently taken medications on the effect of immunotherapy.

Mortality

For **aducanumab**, 64 deaths were reported. Thus, the overall mortality rate was 0.82%. During the placebo-controlled period of the study, five deaths occurred in the placebo group (mortality rate of 0.35%), three deaths were registered in the low-dose group, and eight deaths were recorded in the high-dose group (mortality rate of 0.72%). In the second part of the study, deaths were reported in all groups of participants (4 – in group who continued receiving low doses of **aducanumab**, 2 – in group who continued receiving high doses, 1 – in group who started receiving low doses later and 1 – in group who started receiving high doses later). According to the existing literature, fatalities during **aducanumab** administration were not treatment-related (Budd Haeberlein et al. 2022, Rahman et al. 2023).

For **donanemab**, 26 deaths were reported, resulting in an overall mortality rate of 1.45%. In the **donanemab**-treated group, 16 deaths were registered (mortality rate of 1.73%). In the placebo group, 10 deaths were noted (mortality rate of 1.14%). According to the study authors, three deaths in the **donanemab** group and one death in the placebo group were assessed as treatment-related. The researchers correlate these fatalities to pronounced amyloid-related imaging abnormalities (in one case – ARIA-E, in one case – ARIA-H, and in one case – pre-existing imaging abnormalities associated with hemosiderin deposition) (Sims et al. 2023).

For **gantenerumab**, 82 deaths were registered (overall mortality rate of 1.49%). The global literature does not provide specific data on the causes of death among patients receiving **gantenerumab**; however, it is well established that using **gantenerumab** increases the risk of ARIA-H and ARIA-E (Ostrowitzki et al. 2017, Menegaz de Almeida et al. 2024).

For **solanezumab**, 26 deaths were reported (overall mortality rate of 1.16%). Among patients receiving placebo, 12 deaths occurred (1.10%), and among those receiving the drug – 13 death was reported (1.27%). According to the global literature, fatalities in **solanezumab** trials were not treatment-related (Doody et al. 2014).

Phase III clinical trials of **crenezumab** were presented in three studies: CREAD, CREAD OLE and CREAD2. During the CREAD study, the overall mortality rate was 1.61%, including 13 fatal outcomes. In the placebo group, 5 deaths were recorded (1.23%), and in the treatment group – 8 deaths were reported (1.98%). In the CREAD2 study, the overall mortality rate was 0.75%, with 6 deaths recorded. All 6 deaths occurred in the placebo group (1.51%); no deaths were reported in the treatment group. In the CREAD OLE study, there were no deaths reported. According to the researchers, mortality was not drug-related (Ostrowitzki et al. 2022).

Mortality rate for phase 3 studies is listed in Table 4.

Discussion

The safety profile of anti-A β monoclonal antibodies – including **aducanumab**, **donanemab**, **gantenerumab**, **solanezumab**, and **crenezumab** – has emerged as a pivotal consideration in the therapeutic management of AD, particularly regarding their association with ARIA. These biologic agents represent a paradigm shift in targeting the A β pathology central to AD pathogenesis, yet their clinical application is complicated by significant safety considerations that warrant thorough examination. The controversial FDA approval of **aducanumab** in 2021 (FDA (ADUHELM™ (aducanumab-avwa) injection) highlighted the substantial risk of ARIA, with phase III clinical trials demonstrating ARIA-E (edema) incidence rates approaching 35% and ARIA-H (microhemorrhages) occurring in approximately 20% of treated participants, with particularly elevated risk among APOE ϵ 4 allele carriers (Sperling et al. 2011, Sevigny et al. 2016). The clinical manifestation of these adverse events exhibits considerable variability, ranging from asymptomatic radiographic findings detectable only through neuroimaging to severe neurological symptoms necessitating treatment cessation. This safety profile has precipitated stringent monitoring protocols incorporating serial MRI surveillance, which introduces substantial practical and economic challenges to widespread clinical implementation.

The development of **donanemab** has introduced a novel therapeutic approach characterized by finite-duration treatment contingent upon amyloid plaque clearance. While this strategy may theoretically attenuate long-term ARIA risk, clinical trial data continue to demonstrate significant ARIA incidence, suggesting that the rapidity of amyloid clearance itself may constitute an independent risk factor for these adverse events. In contrast, **gantenerumab**'s subcutaneous administration route appears to facilitate more gradual amyloid removal, potentially accounting for its comparatively lower ARIA incidence rates observed in clinical trials (Ostrowitzki et al. 2017). These differential safety profiles underscore the critical importance of pharmacokinetic and pharmacodynamic considerations in therapeutic

Table 4. All-cause mortality in phase 3 studies of monoclonal antibodies

Drug	ClinicalTrials.gov ID	Mortality						
Aducanumab	NCT04241068	37/1696 (2.18%)						
	NCT02484547	5/547 (0.91%)	0/544 (0.00%)	6/547 (1.10%)	0/131 (0.00%)	0/132 (0.00%)	3/251 (1.20%)	0/257 (0.00%)
	NCT02477800	0/540 (0.00%)	3/549 (0.55%)	2/558 (0.36%)	1/150 (0.67%)	1/152 (0.66%)	1/299 (0.33%)	2/251 (0.80%)
	NCT05310071	0/343 (0.00%)	3/681 (0.44%)					
	NCT05108922	0/69 (0.00%)	0/71 (0.00%)					
Donanemab	NCT05108922	0/69 (0.00%)	0/71 (0.00%)					
	NCT04437511	16/853 (1.88%)	10/874 (1.14%)					
Gantenerumab	NCT04374253	0/14 (0.00%)	5/691 (0.72%)	2/29 (6.90%)	4/647 (0.62%)			
	NCT06424236	0/18 (0.00%)	0/27 (0.00%)	0/28 (0.00%)				
	NCT04339413	2/59 (3.39%)	0/56 (0.00%)					
	NCT03443973	5/477 (1.05%)	7/498 (1.41%)	0/13 (0.00%)	0/14 (0.00%)			
	NCT03444870	11/481 (2.29%)	3/503 (0.60%)	0/33 (0.00%)	0/35 (0.00%)	1/9 (11.11%)	0/20 (0.00%)	
	NCT05256134	0/12 (0.00%)	0/13 (0.00%)					
	NCT02051608	11/195 (5.64%)	8/192 (4.17%)	5/117 (4.27%)	5/108 (4.63%)			
	NCT01224106	6/266 (2.26%)	0/271 (0.00%)	2/260 (0.77%)	1/49 (2.04%)	3/105 (2.86%)		
	NCT04623242	0/52 (0.00%)	0/52 (0.00%)	0/89 (0.00%)	1/69 (1.45%)	0/0		
Solanezumab	NCT02760602	0/13 (0.00%)	0/13 (0.00%)					
	NCT01127633	N/a	N/a					
	NCT01900665	N/a	N/a	N/a	N/a			
	NCT02008357	6/572 (1.05%)	7/591 (1.18%)	7/383 (1.83%)	5/401 (1.25%)			
	NCT04623242	0/52 (0.00%)	0/52 (0.00%)	0/89 (0.00%)	1/69 (1.45%)	0/0		
Crenezumab	NCT03491150	0/76 (0.00%)	0/73 (0.00%)					
	NCT03114657	6/398 (1.51%)	0/404 (0.00%)					
	NCT02670083	5/405 (1.23%)	8/404 (1.98%)					

development. The cases of solanezumab and [crenezumab](#) present an instructive counterpoint, wherein favorable safety profiles were offset by insufficient clinical efficacy (Doody et al. 2014, Salloway et al. 2018), highlighting the complex risk-benefit calculus inherent to amyloid-targeting therapies.

The APOE ε4 genotype has emerged as a critical determinant of ARIA susceptibility, with homozygous carriers demonstrating particularly elevated risk (Foley and Wilcock 2024). This genetic association raises important ethical and practical considerations regarding pre-treatment genotyping and risk stratification. Current surveillance protocols employing frequent MRI monitoring present substantial economic and logistical burdens, prompting ongoing debate regarding the optimal balance between safety vigilance and therapeutic accessibility.

Currently, the therapeutic use of monoclonal antibodies for AD remains a novel approach. Consequently, its comparative efficacy and safety profile relative to conventional therapy require thorough investigation in controlled clinical trials. A significant factor in the treatment decision is the disease stage, as therapy at early stages in patients who are carriers of the APOE ϵ 4 allele is associated with a risk of serious adverse events. The potential for combination therapy using monoclonal antibodies alongside standard medications also remains unexplored. Thus, the clinical efficacy of this approach necessitates further in-depth study. Besides the promising preliminary results of monoclonal antibodies, fundamental research aimed at discovering novel targets of AD therapy lacking specific adverse effects continues. Recent studies revealed that the adverse effects induced by anti-A β antibodies may be associated with the distribution of A β and its precursor protein on cell surfaces (including endothelial cells of cerebral blood vessels) and their involvement in normal physiological processes of the body (Boche et al. 2008, Masters and Selkoe 2012). Furthermore, the ability of IgG to cross the blood-brain barrier is relatively low in both mice and humans, amounting to only 0.1–0.2% of the plasma IgG concentration (Finke and Banks 2017). A potential solution to this issue could be the development of truncated antibody variants, including bispecific antibodies (Janowicz et al. 2019, Rofo et al. 2022). However, from a therapeutic perspective, a more critical factor may be the reduced half-life of such shortened antibody forms (Shimizu et al. 2000).

With aging, humans exhibit an increased proportion of A β molecules with isomerized Asp7 (isoD7-A β), the most prevalent A β isoform in senile plaques (Kozin et al. 2018, Gnoth et al. 2020). It has been demonstrated that isoD7-A β induces pathological processes characteristic of AD (Kozin et al. 2013, Mitkevich et al. 2013, 2023, Zatsepina et al. 2018). Based on this, it can be hypothesized that therapeutics neutralizing the pathological activity of isoD7-A β without directly affecting the native form of A β could significantly slow or even reverse the progression of AD without inducing severe side effects. To date, one murine monoclonal antibody targeting isoD7-A β has been developed (Gnoth et al. 2020). Administration of this monoclonal antibody in a mouse model of AD (Forner et al. 2021) proved effective and, unlike other anti-A β antibodies, did not cause massive release of A β into the bloodstream (Gnoth et al. 2020). It can be speculated that antibodies targeting isoD7-A β may prevent the formation of pathogenic A β oligomers that drive disease progression while exhibiting a reduced potential to trigger neuroinflammation. However, no such therapeutic antibody has yet been developed for human use.

The present study has several limitations resulting in its inability to provide clinical recommendations on improvement of AD treatment regimen, due to lack of clinical data. Future therapeutic strategies may benefit from combinatorial approaches incorporating both amyloid-targeting antibodies and neuroprotective agents to optimize both efficacy and safety. Collectively, the clinical experience with these monoclonal antibodies underscores both the promise and challenges of amyloid-targeting therapies, with their safety profiles continuing to influence both clinical practice and future therapeutic development in Alzheimer's disease.

Conclusion

The clinical translation of anti-A β monoclonal antibodies – a groundbreaking class of therapeutics targeting a core pathological hallmark of Alzheimer's disease – is severely limited by the prevalent risk of ARIA. The incidence and severity of ARIA, which is strongly potentiated by the APOE ϵ 4 genotype, necessitate rigorous and costly monitoring protocols, creating substantial practical and economic barriers to implementation. The divergent profiles of agents like [aducanumab](#), [donanemab](#), and [gantenerumab](#) illustrate that the risk of ARIA is intricately linked to the pharmacodynamic properties of each antibody, particularly the potency and rapidity of amyloid plaque clearance. This creates a complex risk-benefit calculus, further complicated by the historical precedent where safer antibodies like solanezumab lacked efficacy. Therefore, the future of this therapeutic class hinges on several critical factors: refining patient stratification through genetic screening, optimizing dosing regimens to mitigate ARIA risk, and establishing clearer long-term risk-benefit profiles through continued controlled clinical trials. Ultimately, realizing the potential of these novel biologics will require balancing ambitious therapeutic goals with diligent and manageable safety surveillance.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

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Data availability

All of the data that support the findings of this study are available in the main text.

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