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REVIEW ARTICLE

Neuroinflammation and progress in clinical trials for the treatment of Alzheimer's disease and related dementias: An update

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Abstract

According to the latest report in 2024 by the World Health Organization, based on global data from 2021, Alzheimer's disease (AD) and other forms of dementia rank seventh among the leading causes of death worldwide, with an estimated 1.8 million deaths. This alarming number underscores the urgent requirement for effective treatments. AD and other dementias also severely affect the global economy. Unfortunately, no cure has been found, and effective treatments remain limited. Over the past two decades, thousands of disease-modifying drugs have been developed for AD treatment. However, most have failed to progress beyond phase I clinical trials, with only a few reaching phase III. To date, lecanemab (sold under the brand name Leqembi) is the only drug to receive full approval from the United States Food and Drug Administration for slowing AD progression. This drug is specifically designed to target and clear amyloid-beta (Aβ) plaques. Apart from targeting Aβ aggregation and tau tangles, neuroinflammatory regulatory pathways have emerged as promising therapeutic targets. With advancing research, neuroinflammation has been considered one of the core characteristics of AD and the third major pathological hallmark of the disease after Aβ plaques and neurofibrillary tau tangles. In this review, we summarize key research findings in neuroinflammatory regulation of AD and related dementias that are promising for treatments. We also provide an overview of clinical trials targeting the immune system or neuroinflammatory regulatory pathways, analyzing their challenges and potential successes.

Keywords: Alzheimer's disease and related dementias; Immune system dysregulation; Neuroinflammation; Amyloid-beta plaques; Tau tangles; Clinical trials

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease, and it is the most common cause of dementia, with 60 – 80% of cases occurring among elderly

people.[1] Dementia is manifested by a decline in memory, language skills, problem-solving abilities, spatial and temporal awareness, and judgment.[2-6] Over the past three decades, the number of deaths caused by AD and related dementias (RD) has increased from 0.56 million in 1990 to 1.62 million in 2019.[7] A recent report revealed that 6.7 million Americans – equivalent to 1 in 9 individuals aged 65 and older – are affected by AD.[8] AD and RD together are the seventh leading cause of death globally.[7,9-11] These diseases have a direct impact on both global health and the economy. Around 83% of AD caregivers are unpaid family members, friends, or others.[12] If compensated, their collective contribution would amount to approximately 339.5 billion USD, according to the estimated cost of care in 2022. The lifetime care cost for an individual with dementia was estimated to be 392,874 USD in 2022, with unpaid family caregivers shouldering 70% of this burden, including food and medications.[2,13] Over the years, with the increased understanding of the regulatory mechanisms underlying AD pathology, several drugs have been developed and tested in clinical trials. However, finding an effective cure or treatment remains challenging due to the complex pathogenesis of the disease.[14-16] At present, available drugs for AD treatments provide only moderate benefits, primarily by slowing the progression of the disease.

At present, no drug or medication can reverse, halt, or cure AD. The only drug officially approved by the United States Food and Drug Administration (US FDA) is lecanemab, which only moderately slows AD progression by clearing amyloid-beta (Aβ) plaques.[17] Most drug development efforts and clinical trials thus far have primarily focused on clearing Aβ plaques and neurofibrillary tau tangles in the brain. However, there is a growing shift toward targeting the pathological mechanisms responsible for the accumulation of Aβ plaques and neurofibrillary tau tangles, rather than directly targeting them. In addition, several other pathways that link to the disease are now receiving increased attention. Aβ plaques and neurofibrillary tau tangles have long been recognized as hallmark pathological features of AD, and recent research has identified neuroinflammation as the third pathological hallmark. Numerous studies have provided substantial evidence suggesting that inflammatory pathways play a crucial role in the pathogenesis of AD and RD.[18-25] These studies have led to the acknowledgment of neuroinflammation as an important pathological hallmark of AD.

In this review, we aim to highlight the critical role of neuroinflammation in AD and RD, providing a comprehensive summary of immune system dysregulation and its connection to neuroinflammation and AD and RD. Then, we will discuss clinical trials targeting the immune system as a potential therapeutic approach for treating AD patients. Despite the extensive efforts, most drugs have failed in phase 1 clinical trials, with several of them being discontinued in phase II and only a few advancing to phase III trials. We will analyze the reasons behind these failures and discuss promising strategies for achieving success. Over 3,300 clinical trials have been conducted on AD, involving a variety of drug candidates (clinicaltrials.gov),[26,27] but only three drugs have reached the final stages of development. Of these, only lecanemab (Leqembi) has been approved by the US FDA, aducanumab (Aduhelm) is in the approval process, and donanemab is also undergoing US FDA review.[17]

2. Immune system dysregulation and neuroinflammation in AD and RD

2.1. Neuroinflammation as a key factor

Under normal conditions, neuroinflammation plays a crucial role in protecting the brain against the infiltration or infection of pathogens. However, in unfavorable or prolonged circumstances, neuroinflammation can lead to various severe neurological conditions, including AD, Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). These conditions reveal that the pathways linking neuroinflammation to neurodegeneration are distributed across various regions of the central nervous system (CNS).[27] Over the years, a vast number of research has demonstrated the presence of prolonged immune responses in the brains of AD patients. In such a chronic immune response, sustained neuroinflammation becomes detrimental, perpetuating a cycle of neuronal damage and degeneration in the CNS. As research has advanced, neuroinflammation is increasingly recognized as a core contributing factor to the progression of AD and RD. Indeed, neuroinflammation is now considered the third pathological hallmark of AD, alongside Aβ plaques and tau tangles.[28] Importantly, it has been well documented that neuroinflammation exacerbates the severity of the disease by worsening Aβ and tau pathologies.[29,30] This highlights the crucial role neuroinflammation plays in the aggregation of toxic Aβ plaque and tau tangles, leading to disease progression, making neuroinflammation a promising target for the treatment of AD and RD. Moreover, neuroinflammation is not only implicated in AD but has been identified as a key factor in the dysregulation of many neurological diseases, continuously emerging as a potential mediator of cognitive deficits. Therefore, there is an urgent need to explore neuroinflammatory pathways as potential drug targets and advance them through clinical trials to develop effective treatments for AD and RD.

2.2. Chronic neuroinflammation

Chronic neuroinflammation is characterized by excessive activation of glial cells, including microglia and astrocytes. Activated microglia release pro-inflammatory cytokines (such as interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha, and interferon-gamma), chemokines (such as C-X-C motif chemokine ligands and CC chemokine ligands), and reactive oxygen species (such as inducible nitric oxide synthase, superoxide, nitric oxide, and peroxynitrite), all of which, if persistently expressed, contribute to neuronal damage and progressive neurodegeneration, as observed in AD, PD, HD, and MS.[31] Importantly, microglia also express anti-inflammatory markers, such as arginase-1, chitinase-like-3 protein 1, mannose receptor C-type 1, interleukin-10, Fc-gamma receptor I, transforming growth factor-beta 1, and sphingosine kinase 1.[31] Prolonged activation of resident macrophages (such as microglia) and other immune cells in the brain aggravates both Aβ and tau pathology.[28] Similarly, activated astrocytes release pro-inflammatory interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha, and nitric oxide, while they also secrete several beneficial neurotrophic factors and thrombospondins.[31,32] Notably, astrocytes can switch their phenotype and proliferate in response to harmful conditions, leading to the formation of reactive astrocytes, a process known as reactive astrogliosis. Reactive astrogliosis has been observed in various pathological conditions, including intracranial infections, hypoxic-ischemic injury, AD, and epilepsy.[31,32] These findings underscore the profound impact of immune system dysregulation on chronic neuroinflammation in AD and RD, highlighting microglia and astrocyte-mediated neuroinflammation as important therapeutic targets.

Neuroinflammation also increases with aging and neurodegeneration. Age-related changes in neuroinflammation may accelerate the progression of cognitive impairment through glial activation, increased production of pro-inflammatory cytokines, and abnormal neuronal signaling, magnifying deterioration of the CNS microenvironment.[33,34] Apart from AD, dementia is also a clinical symptom in several other neurological diseases associated with neuroinflammation, such as vascular dementia, dementia with Lewy Bodies, frontotemporal dementia, Wernicke–Korsakoff syndrome, PD, ALS, and HD.[35-40] Both innate and adaptive immune system dysregulation are implicated in the pathogenesis of these diseases.[41-47] Microglia, astrocytes, and oligodendrocytes play a major role in innate immune system dysregulation, whereas the involvement of the adaptive immune system is evident from the presence of B and T lymphocytes in the post-mortem AD brain and the cerebrospinal fluid (CSF) of individuals with mild cognitive impairment (MCI) and AD patients.[42,48-52] Moreover, an increased frequency of helper T cells subsets, such as Th17 and Th9 lymphocytes, has been observed in AD patients.[53] These findings have driven the development of drugs targeting neuroinflammatory regulatory pathways as potential treatments to slow, halt, or reverse the progression of AD and RD. A graphical representation of immune system dysregulation in AD and RD, along with possible therapeutic targets, is presented in Figure 1A and B.

At present, several anti-neuroinflammatory drugs are undergoing phase III clinical trials, including hydralazine hydrochloride (ClinicalTrials.gov identifier: NCT04842552), xanomeline–trospium (KarXT, ClinicalTrials.gov identifier: NCT05511363), masitinib (ClinicalTrials.gov identifier: NCT05564169), NE3107 (ClinicalTrials.Gov identifier: NCT04669028), and spironolactone (ClinicalTrials.gov identifier: NCT04522739). In addition, sodium oligomannate capsule (GV-971), an anti-inflammatory drug that inhibits Aβ fibril formation, is also in clinical trials (ClinicalTrials.gov identifier: NCT05181475).

3. Drug candidates in clinical trials, challenges, and current progress for the treatment of AD and RD

3.1. Potential drugs for the treatment of AD and RD

Over the past two decades, several disease-modifying drugs have been developed for the treatment of AD, with approximately 2,700 clinical trials conducted since 2004. However, only a few have shown promising success rates in phase II and III trials.[54] A more recent report showed that over 3,300 clinical trials (clinicaltrials.gov) for AD treatment have been conducted.[26] Despite these efforts, the failure rate remains alarmingly high, estimated at approximately 99%,[54,55] meaning only 1% of drugs progress successfully through clinical trials. The few compounds that have demonstrated potential have primarily been designed for immunotherapy in AD patients. These notable compounds are aducanumab, lecanemab, donanemab, and oligomannate.[17,56-58] Aducanumab (brand name Aduhelm) is a monoclonal antibody designed to bind and eliminate aggregated Aβ plaques. Lecanemab (brand name Leqembi) is designed to reduce Aβ protofibrils in the brain and CSF. Donanemab (brand name Kisunla) is a humanized monoclonal antibody derived from mouse mE8-IgG2a antibody, specifically targeting Aβ (3-42) plaques. Oligomannate (also known as sodium oligomannate or GV-971) is a seaweed-derived oligosaccharide that reduces bacterial metabolite-driven peripheral infiltration of immune cells into the brain while also inhibiting Aβ

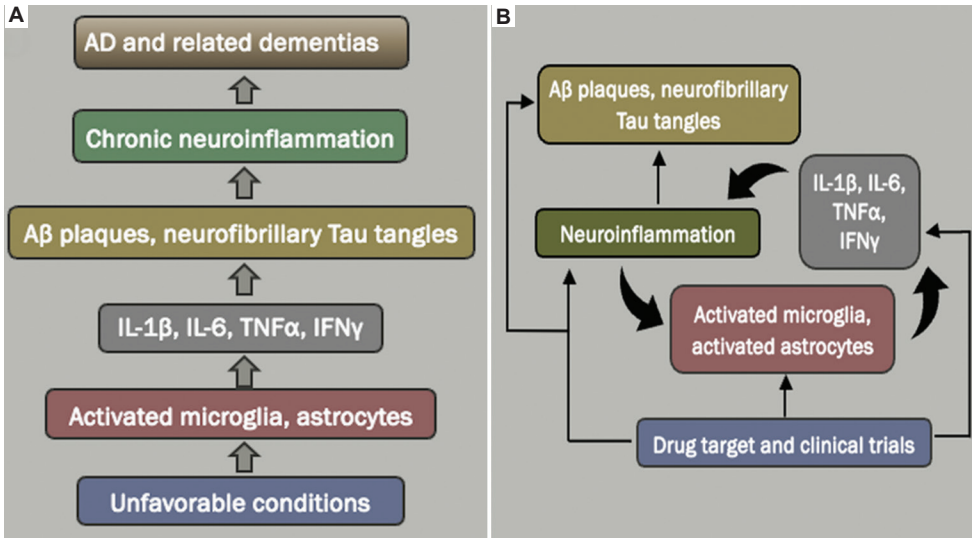

Figure 1. Neuroinflammatory pathways underlying AD and related dementias, and possible target sites for drug development and clinical trials. (A) Graphical representation of immune system dysregulation leading to Alzheimer's disease and related dementias. (B) Potential therapeutic targets. Abbreviations: Aβ: Amyloid-beta; AD: Alzheimer's disease; IFNγ: Interferon-gamma; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; TNFα: Tumor necrosis factor-alpha.

and tau formation. Despite their potential, the long-term effectiveness of these drugs remains uncertain. As of now, only lecanemab has been fully approved by the US FDA for AD treatment on July 6, 2023 (https://www.fda.gov/news-events/press-announcements/fda-converts-novel-alzheimers-disease-treatment-traditional-approval).[17] A summary of promising drugs and their approval status by the US FDA is presented in Table 1.

3.2. Challenges in clinical trials

Most of the currently designed drugs for AD target Aβ pathology, aiming to reduce Aβ production, inhibit Aβ plaque formation, promote Aβ plaque clearance, or develop Aβ vaccines.[6,57,59,60] Other drug targets have also been explored for various objectives, including mitigating tau pathology,[61] reducing inflammation,[28] lowering cholesterol accumulation,[62,63] improving brain energy utilization,[64-67] decreasing vascular burden,[68] enhancing neuroprotectant and antioxidant processes,[69-71] increasing neural growth and regeneration,[72,73] and restoring hormonal balance.[74] Among the 2,695 clinical trials for AD (data available at clinicaltrials.gov), when categorized as disease-modifying versus symptomatic, the failure rates are concerning: 41% failed in phase III, while 59% failed in phase II. Of these, 64% were disease-modifying agents, whereas 36% were symptomatic agents.[54]

Several clinical trials have targeted various drug mechanisms, including beta-secretase 1 (BACE1) inhibition, γ-secretase inhibition, γ-Secretase modulation, apolipoprotein E (ApoE) inhibition, Aβ production inhibition, Aβ aggregation inhibition, Aβ dissociation, synaptic modulation, Aβ toxicity modulation, filament modulation, glutaminyl cyclase inhibition, active immunization, passive immunization, receptor for advanced glycation end-products inhibition, and metabotropic glutamate receptor 5 modulation, aiming to reverse or inhibit Aβ pathology or dementia. A summary of the drugs in clinical trials developed for AD treatment is provided in Table 2.

Table 1. List of drugs for Alzheimer's disease treatment with approval status by the United States Food and Drug Administration

Drug name (brand name)	Company	Mode of action and effect	Approval status
Aducanumab (Aduhelm)	Biogen, Neurimmune	Eliminate aggregated Aβ plaques	Approval in progress[17,57,94]
Lecanemab (Leqembi)	BioArctic AB, Biogen, Eisai	Reduce soluble Aβ protofibrils	Fully approved[17,57]
Donanemab (Kisunla)	Eli Lilly and Company	Eliminate aggregated Aβ plaques	Application for full approval[17,57]

Abbreviation: Aβ: Amyloid-beta.

Several potential factors contributed to the failures in clinical trials, whether by faulty drug development processes or the lack of a clear understanding of the complex regulatory mechanisms underlying AD pathology. The main reasons for failures include (i) insufficient evidence to justify clinical trials, (ii) inadequate clinical trial designs, (iii) inappropriate drug designs that fail to align with the rational drug development principles specifically designed for AD therapeutic development,

Table 2. List of drugs developed for Alzheimer's disease treatment

Drug name	Mode of action and effect	Trial phase status	Side effects/outcome
Lenalidomide	BACE1 inhibition, inflammation reduction	Ongoing phase II	Yet to be available[95,96]
CT1812	Aβ aggregation inhibition, Aβ oligomer reduction, behavioral improvement	Ongoing phase II	Yet to be available[97,98]
ALX-001	mGluR5 modulation, synaptic function, and behavioral enhancement	Ongoing phase I	Yet to be available[99,100]
Buntanetap	Aβ production inhibition, Aβ generation reduction	Ongoing phase III	Yet to be available[101,102]
GV-971	Aβ dissociation, Aβ plaque burden reduction	Ongoing phase II	Yet to be available[103,104]
Nasal insulin	Aβ toxicity modulation, memory improvement	Ongoing phase II/III	Yet to be available[105-107]
Simufilam	Disrupts famin A aberrant linkage to the α7 nicotinic acetylcholine receptor (α7nAChR), and blocks soluble amyloid signaling via α7nAChR that hyperphosphorylated tau	Ongoing phase III	Yet to be available[108,109]
Varoglutamstat	Glutaminyl cyclase inhibition, amyloid pathology, and pGlu-Aβ reduction	Ongoing phase II	Yet to be available[110,111]
Aducanumab	Passive immunization, plaque clearance	Approved and ongoing phase III	Application for full approval[17,94]
Lecanemab	Passive immunization, brain, and CSF Aβ protofibril reduction	Approved and ongoing phase III	Approved[17,57]
Donanemab	Passive immunization, plaque clearance	Approved and ongoing phase III	Approved[17,57,112]
Thalidomide	BACE1 inhibition, amyloid pathology, and gliosis reduction	Completed phase III	Adverse consequences[96]
CHF5074	γ-secretase modulation, Aβ reduction	Completed phase II	Decision unavailable[113]
PBT2	RAGE inhibition, spine density, and synaptic protein level improvement	Completed phase II	Lack of efficacy[114]
Contraloid	Aβ aggregation inhibition, amyloid deposition reduction	Completed phase I	Yet to be available[115]
Acitretin	Aβ production inhibition, Aβ reduction	Completed phase II	Yet to be available[116,117]
Bexarotene	Anti-ApoE, Aβ reduction, cognitive deficit improvement	Discontinued phase II	Adverse outcomes/lack of efficacy[118,119]
AN-1792	Active immunization, amyloid plaque formation reduction	Discontinued phase II	Adverse events[120]
ACC-001	Active immunization, amyloid plaque formation prevention	Discontinued phase II	Adverse incidents[121]
CAD106	Active immunization, amyloid accumulation in brain reduction	Discontinued phase II	No results available[122]
Ponezumab	Passive immunization, cerebral blood vessel amyloid deposition reduction	Discontinued phase II	Lack of efficacy[123]
Gammagard	Passive immunization, Aβ reduction	Discontinued phase II	Lack of efficacy[124,125]
Bapineuzumab	Passive immunization, plaque burden reduction	Discontinued phase II	Lack of efficacy[76]
Crenezumab	Passive immunization, localized to Aβ oligomers	Discontinued phase II	Lack of efficacy[126]
Gantenerumab	Passive immunization	Ongoing phase III	Yet to be available[127,128]
Atabecestat	BACE1 inhibition reverses amyloid pathology and cognitive deficit	Discontinued phase II/III	Clinical worsening[76,129]
Elenbecestat	BACE1 inhibition, brain, CSF, and plasma Aβ reduction	Discontinued phase III	Unfavorable risk-benefit ratio[124]
LY2886721	BACE1 inhibition, dose-dependent Aβ reduction	Discontinued phase II	Adverse consequences[122]
Lanabecestat	BACE1 inhibition, Aβ reduction	Discontinued phase III	Lack of efficacy[123]
PF-06751979	BACE1 inhibition, CSF Aβ42 reduction	Discontinued phase I	Pfizer ended R&D in neurology[130,131]
RG7129	BACE1 inhibition, Aβ reduction	Discontinued phase I	Adverse incidents[121,132]
Verubecestat	Dose-dependent Aβ40 and Aβ42 reduction	Discontinued phase III	Clinical worsening[133-135]
Avagacestat	γ-secretase inhibition, CSF Aβ reduction	Discontinued phase II	Clinical worsening/adverse events[127,128]

(Cont'd...)

Table 2. ***(Continued)***

Drug name	Mode of action and effect	Trial phase status	Side effects/outcome
PF-06648671	γ-secretase inhibition, brain Aβ42 reduction	Discontinued phase I	Pfizer ended R&D in neurology[112,136]
Semagacestat	γ-secretase inhibition, soluble Aβ, and plaque reduction	Discontinued phase II	Clinical worsening/adverse events[126]
Azeliragon	γ-secretase modulation, Aβ load reduction, behavioral improvement	Discontinued phase III	Lack of efficacy[137]
Tarenflurbil	γ-secretase modulation, Aβ reduction	Discontinued phase III	Lack of efficacy[94]
Ibuprofen	γ-secretase modulation, Aβ reduction	Discontinued phase II	Lack of efficacy[138]
Clioquinol	Aβ aggregation inhibition, amyloid deposition reduction	Discontinued phase III	Toxic contaminants in manufacturing process[139,140]
ELND005	Aβ aggregation inhibition, amyloid pathology reduction, learning deficit restored	Discontinued phase II	Lack of efficacy[141]
Tramiprosate	Aβ aggregation inhibition, Aβ40 reduction	Discontinued phase III	Lack of efficacy[142,143]

Abbreviations: Aβ: Amyloid-beta; BACE1: Beta-secretase 1; CSF: Cerebrospinal fluid; mGluR5: Metabotropic glutamate receptor 5; pGlu-Aβ: Pyroglutamate Aβ; RAGE: Receptor for advanced glycation end-products; R&D: Research and development.

and (iv) limited therapeutic efficacy.[54] For example, bapineuzumab and solanezumab advanced to phase III trials despite unconvincing phase II results, ultimately leading to failure.[75-77] A critical human error that could have been avoided is the lack of learning from past clinical trials, leading to recurring challenges, negative outcomes, and diminished confidence in AD drug development.[78] Additional factors such as delayed intervention in symptomatic dementia, inappropriate therapeutic targets, and flawed clinical methodologies have further impeded success in AD clinical trials.[79] To overcome these challenges, both clinical and basic research, along with a more intelligent and holistic approach, are crucial in the search for effective treatment of AD and RD.

3.3. Current progress in clinical trials

While most drugs have failed, a few continue to show promising signs and hold hope for success. Three FDA-approved drugs – aducanumab, lecanemab, and donanemab – that target Aβ plaques and protofibrils are still undergoing phase III clinical trials to further examine preventive effects. Comparing the therapeutic effects and data from these trials is expected to help guide future AD drug development. Aducanumab, a human immunoglobulin gamma 1 (IgG1) monoclonal antibody derived from aged donors resistant to AD, binds to the N-terminus of Aβ fibrils but not to Aβ monomers, thereby blocking Aβ aggregation.[80,81] Initially, further clinical trials of aducanumab were terminated due to failure to meet the primary endpoint in Clinical Dementia Rating Scale Sum of Boxes scores.[57] However, two recent phase III clinical trials, the ENGAGE and EMERGE studies, showed significant slowing of cognitive decline at the highest dose. While the EMERGE trial reached statistical significance, the ENGAGE trial did not meet the primary endpoint.[17] Based on these results, the US FDA approved aducanumab, through an "accelerated approval pathway," for the treatment of MCI and mild dementia in AD patients in June 2021, under the brand name Aduhelm by Biogen.[82] Both trials showed intermediate effects on biomarkers, including amyloid removal, which may contribute to the clinical benefit of aducanumab. The phase phase IIIb/IV ENVISION trial (ClinicalTrials.gov ID: NCT05310071) is currently ongoing.[17,57]

Donanemab is another humanized IgG1 monoclonal antibody developed from mouse mE8-IgG2a, which targets the Aβ (3 – 42), a pyroglutamate form of Aβ, that is abundant in the brains of AD patients.[83,84] Interestingly, donanemab can bind to approximately one-third of Aβ plaques in post-mortem AD and Down syndrome brains, strongly reacting with plaque cores.[85] In the phase II TRAILBLAZER-ALZ study (https://clinicaltrials.gov/study/NCT04437511), combination therapy using donanemab and BACE1 inhibitor LY3202626 was administered to target the pyroglutamate form of Aβ. The treatment met the primary endpoint of delaying cognitive decline as assessed by the Integrated AD Rating Scale.[17,57] Reduction of Aβ burden was correlated with improvement in the scores but only in APOE4 carriers.[86] Donanemab also reduced tau aggregation in the temporal, parietal, and frontal lobes and significantly lowered plasma pTau217 levels.[87] Phase I clinical trials of donanemab demonstrated sustained reduction in cortical amyloid load, with the treatment being well tolerated.[88] While phase II trials of donanemab replicated phase I results with no adverse effects, patients were more likely to exhibit amyloid-related imaging abnormalities amyloid-related imaging abnormalities with vasogenic

edema, and amyloid-related imaging abnormalities with microhemorrhages.[89] Phase III clinical trials for donanemab are currently ongoing.

On the other hand, LY3202626 and most BACE1 inhibitors were excluded from further trials due to insufficient evidence of safety and efficacy, except lenalidomide.[57] The US FDA granted traditional approval for lecanemab under the brand name Leqembi, in July 2023 for the treatment of AD.[90] Lecanemab, a humanized IgG1 antibody derived from mAb158, selectively binds to soluble Aβ protofibrils.[91,92] In phase II clinical trials involving AD patients with MCI or mild dementia, confirmed by amyloid pathology through amyloid positron emission tomography scan or CSF Aβ(1-42) levels, the results showed a significant dose-dependent reduction in Aβ plaque.[91] Positive outcomes were observed across all primary and secondary measures, including the AD Assessment Scale–Cognitive Subscale, AD Composite Score, and AD Cooperative Study-MCI-Activities of Daily Living Inventory scores.[93] The phase III clinical trial for lecanemab is currently ongoing. These findings suggest that while a definitive drug or treatment for dementia related to AD and RD remains unavailable, there is still hope for progress in the field.

4. Discussion

The regulatory mechanisms underlying the pathology of dementia in AD and RD are highly complex, and no effective treatment is currently available. A more detailed investigation is needed to uncover unknown pathways that could facilitate drug design for the treatment of cognitive impairments caused by AD and RD. Despite significant efforts and extensive studies aimed at understanding disease pathology and finding a cure, no breakthrough therapy has been established. However, research has greatly expanded our knowledge of the regulatory mechanisms involved, identifying multiple potential pathways that contribute to mild, moderate, or severe cognitive deficits in AD and RD. Although several drugs have been developed to target cognitive impairment, the challenges remain profound due to the intricate regulatory pathways of these diseases. In addition to gaps in understanding disease pathology, the design and methodology of clinical trials have been critically examined and debated as contributing factors to drug development failures. Three promising drugs – aducanumab, lecanemab, and donanemab – are still undergoing phase III clinical trials to assess their preventive effects. While lecanemab has received US FDA approval, aducanumab and donanemab are still in the process of regulatory review. Comparing the therapeutic effects across these trials is expected to guide future AD drug development.

Although most drug candidates have failed to demonstrate efficacy, the positive outcomes of a few drugs keep the hope of success alive. Current clinical trials primarily focus on disease-modifying therapies. To enable preventive interventions before irreversible brain damage occurs, early-stage participant recruitment is crucial. This highlights the importance of fundamental research on AD pathology in its early stages. Most drug designs have focused on inhibiting toxic Aβ and pTau aggregation. However, expanding research has introduced new therapeutic possibilities, including the promising outcomes of aducanumab, lecanemab, and donanemab, which successfully clear Aβ plaques and protofibrils. A vast number of studies have demonstrated that modulating chronic neuroinflammation, regulating microglial phagocytosis, and promoting myelination improve Aβ clearance. These findings suggest that passive immunotherapy targeting neuroinflammatory responses holds significant therapeutic potential. Moreover, early detection of AD could allow for timely therapeutic intervention.

Other monoclonal antibody drugs currently in phase III trials are remternetug (ClinicalTrials.gov identifier: NCT05463731) and solanezumab (ClinicalTrials.gov identifier: NCT01760005). Inflammatory pathways involving inflammasomes that are associated with potential AD biomarkers, such as nuclear factor kappa B, NLR family pyrin domain-containing 3, and triggering receptor expressed on myeloid cells 2, have emerged as potential drug targets for AD.[144] Given that multiple pathways contribute to neurodegeneration, leading to cognitive deficits in AD and RD, single-target drug approaches have proven insufficient. A more effective strategy would involve the simultaneous application of multiple drugs targeting different regulatory pathways.

Research has also revealed common disease pathways among neurodegenerative diseases,[145] suggesting that the findings from AD studies may be applicable to other dementias. Understanding the histopathologic changes underlying neurodegenerative diseases is crucial for advancing AD and RD research and developing effective treatment, as it can reveal key mechanisms of neurodegeneration that contribute to dementia. Furthermore, the persistent failures in AD clinical trials necessitate a thorough reassessment of drug design strategies and clinical trials methodologies. Moving forward, both basic and clinical research must be expanded, integrating diverse approaches to unravel the complex causes of AD and RD and develop more effective treatments.

5. Conclusion

AD and RD are complex neurodegenerative diseases that severely affect the lives of millions globally, with mortality

rates continuing to increase over the years. Moreover, individuals with dementia require lifelong caregiving. These diseases demand urgent attention to develop effective preventive and curative treatments. Through in-depth research, innovative drug design, and systematic clinical trials, the discovery of effective treatments for AD and RD may become a reality in the near future.

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Writing – review & editing: All authors

Ethics approval and consent to participate

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