Alzheimer's Disease: Treatment Today and Tomorrow

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Abstract

Background and Aims: The scope of treatment in Alzheimer's Disease has widened in recent times with FDA approval of new drugs. This review looks at established treatments in AD as well as critically analyses the newer drugs available. **Methods:** Data in this review was gathered from PubMed; Google Scholar and MEDLINE from January-March 2023. Search words used were 'Alzheimer's Disease treatment' and 'Dementia treatment'. **Results:** Older time tested drugs like Acetyl Choline Receptor Inhibitors and NMDA Receptor antagonists remain the mainstay of pharmacological treatment in AD. Despite a lot of excitement about newer FDA approved drugs; we have to be cautious in their use. Aducanumab showed good reduction in CSF amyloid levels (biomarker of AD); but this did not necessarily translate into better clinical outcomes of patients. **Conclusion:** Despite the recent advances and approval of drugs in treatment of AD, we have to exhibit caution while prescribing these drugs. Even with a sound mechanism of action, these drugs do not always show improvement in clinical outcomes. More clinical trials are required for development of drugs in treatment of AD which explore various different mechanisms of action.

Keywords: Alzheimer's disease, advances, treatment

Alzheimer's disease (AD) is the most common cause of primary degenerative dementias, and it is conceptualized as a clinicopathological entity more than as a purely clinical entity. The primary pathological changes are neurofibrillary tangles and amyloid-ß (Aβ) neuritic plaques and are perceived as a dual proteinopathy. The surrogate biofluid markers of both these proteins are assessed *in vivo*, and AD diagnosis cannot be done without the positivity of these dual protein fluid biomarkers (A-beta 42 amyloid in Cerebro SPinal Fluid (CSF) or via brain positron-emission tomography (PET) and p-tau in CSF).

The disease sets in insidiously with initial symptoms of recent memory loss, language disturbances, mood swings, impaired judgment, and a slow change in personality. In its relentlessly progressive course, the individual fails to learn new information and recall (encoding, storage, and recall). The behavioral problems of wandering, agitation, aggression, and confusion get aggravated, and the individual develops sphincteric incontinence and profound motor weakness and becomes bedridden with total dependency on activities of daily living.[1] AD had profound effects on caregivers and places huge demands on the family. Age is a very important risk factor, and in 65- to 69-year age group up to 10% develop AD, and in beyond 85-year age group, more than 50% suffer from AD.[2,3] On the Mini-Mental Scale Examination (MMSE), approximately an annual decline of 3.5 points is observed. AD is conceptualized to have a very prolonged preclinical phase called minimal cognitive impairment (MCI) where the characteristic neuropathological changes are slowly but relentlessly accumulating leading to memory loss. MCI can be of two types: amnestic MCI (memory impairment with intact cognitive skills in other domains) and non-amnestic MCI (decline in non-memory cognitive functions such as language, executive function, and visuospatial), with most amnestic MCI patients progressing to full-blown AD. AD can be divided into stages: stage 1: preclinical or prodromal (mild recent memory changes without significant Activities of Daily Living (ADL) limitations with positive amyloid imaging or AD biomarker positivity in CSF); stage 2: mild AD: recent memory, mood changes, depressive symptoms, and disorientation to time and place; and stage 3: moderate AD: further worsening of memory, language, and dysexecutive features.

Pathophysiology

Risk factors for AD

Genetic

AD has a genetic predisposition due to mutations in amyloid precursor protein (APP), presenilin 1, and presenilin 2 and also the presence of apolipoprotein E4 alleles.

Acquired

There are other important exogenous and endogenous factors that have a role in either expression or prevention of AD.

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These are environmental toxins, head injury, physical activity, education with high cognitive reserve, intellectual challenges, diet, diabetes, cardiovascular risk factors, and menopause.

Amyloid protein is normally cleaved by alpha- and gamma-secretase enzymes and produces a water-soluble Aβ 40 (Aß-40) that gets easily washed away. Instead, if the amyloid protein is cleaved by a beta-secretase, then an insoluble toxic beta-amyloid is formed (Aß-42) that gets precipitated as toxic neuritic plaques in extracellular space.[4,5] Tau proteins are stabilizers of microtubules in cell, and their abnormal phosphorylation leads to the formation of neurofibrillary tangles that block axonal transport and cause cell death. The various therapeutic targets in the treatment of AD include 1) amyloid plaques, 2) tau proteins, 3) neurofibrillary tangles, 4) neuroinflammation, 5) secretases, 6) acetylcholine esterase (AChE-α-7-nAChR), 7) oxidative stress, 8) metal chelation, 9) Mono Amine Oxidase-B Inhibitors (MAO-B inhibitors), 10) NMDA receptor antagonists, and 11) angiotensin receptor antagonists. Some therapeutic targets have been enumerated in Table 1. Inhibitors of secretase enzymes and antisense oligonucleotides work at the level of cleavage of APP. The formation of amyloid aggregates in the form of oligomers, multimers, and diffuse plaques can be targeted by immunotherapy, copper chelators, and fibrillogenesis modulators.[6,7] The neuritic plaques elicit an inflammatory response in the extracellular matrix consisting of complement fragments, cytokines, and interleukins, especially Inter Leukin (IL)-1. Apolipoprotein E acts as a cholesterol transporter to the brain and plays a role in linking AD to hypercholesterolemia and cardiovascular diseases.[8]

Management of AD

The goals in the treatment of AD include delaying or preventing the onset, slowing progression, and improving memory, functional status, and behavioral symptoms.

Non-pharmacological interventions

FINGER is an ongoing multicenter randomized controlled trial in Finland, which compared nutritional guidance, physical exercise, cognitive training, social activities, and management of vascular and metabolic risk factors among elderly subjects with age-matched controls. After 2 years, subjects in the multi-domain intervention group showed 25% improvement in cognition.[9]

Table 1: Staging severity of Alzheimer's disease and FDA-approved treatment for each stage

	Mini-Mental State Exam (MMSE)	Montreal Cognitive Assessment (MOCA)	Clinical Dementia Rating (CDR)	FDA-approved treatment
Normal	>26	>16	<1	
Mild AD	19–26	12–16	1	Cholinesterase inhibitors, aducanumab
Moderate AD	10–18	4–11	2	Memantine
Severe AD	<10	<4	3	

1. Exercise: Exercise is speculated to enhance brain neurotrophic factors and modify apoptosis. Cohort studies have shown that less education increases the risk of AD. Therefore, it is important to emphasize the role of adequate physical activity and aerobic exercise in all patients.
2. Diet: Adherence to the Mediterranean diet (MeDi) was found to be associated with a lower risk of developing AD in a prospective community-based study in New York (hazard ratio, 0.91; $P = 0.015$).[10] A systematic review that looked at diet as a risk factor and disease-modifying factor in AD found that variation in the mean age of the subjects across trials was a major limitation in determining the influence of diet on AD. They found that 50 of 64 studies showed diet as a modifiable risk factor in AD.[11]
3. Cognitive reserve and engagement in cognitive activities: High levels of mental and social activity during a lifetime may help to maintain cognitive functioning even as we age.
4. Early education (including educational level attained)
5. Caregiver burden: Caregiver burden is a very big problem among caregivers of dementia patients. Caring for an AD patient is all consuming and can be ungratifying. Participation in caregiver support groups can help people to share their stories and connect with other caregivers to offer a sense of camaraderie.
6. Patient ID bracelets: A simple intervention of having AD patients wear a bracelet with their name, diagnosis of AD, and caregiver details can be very useful. Patients can be identified and returned to their homes if they wander away and get lost.

Pharmacological interventions

Cholinesterase inhibitors

Cholinergic hypothesis of AD was first proposed in the 1970s by Davies and Malone. The cholinergic system is involved in arousal and attention. In AD, there is selective destruction of cholinergic neurons located in the basal forebrain. Damage to the cholinergic system correlates with the severity of memory loss in AD. The four acetylcholinesterase inhibitors (AChE-I), which have been approved for the treatment of mild-to-moderate AD, include tacrine, donepezil, rivastigmine, and galantamine. The mechanism of action of these symptomatic therapies, indications, starting dose, and maximal dose are given in Table 2. Rivastigmine transdermal patch ensures a steady drug supply by avoiding the first-pass effect by the liver. Commonly experienced side effects are attributed to cholinergic side effects such as nausea, vomiting, salivation, diarrhea, weight loss, and muscle weakness. A Cochrane review comparing the three anticholinesterase inhibitors concluded that they were helpful in mild-to-moderate AD and were comparatively efficacious. One large trial showed fewer side effects with donepezil compared with rivastigmine.[12]

NMDA antagonists

Memantine is the other drug approved by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe

Table 2: Therapeutic targets in Alzheimer's disease

Mechanism of action	Choline esterase inhibitors			NMDA receptor antagonist
Drug	Donapezil	Galantamine	Rivastigmine	Memantine
Indication	Mild-to-moderate AD	Mild-to-moderate AD	Mild-to-moderate AD	Moderate-to-severe AD
Starting dose	5 mg qd	4 mg bd	1,5 mg bd patch 4.6 mg qd	5 mg qd
Maximal dose	10 mg qd	12 mg bd	6 mg bd	10 mg bd

AD. It is a : N- Methyl D-Aspartate Receptor (NMDA receptor) antagonist and can be used on its own or in combination with cholinesterase inhibitors. In mild-to-moderate AD, its effects are inconsistent. The main side effects are dizziness, headache, constipation, and confusion.[2,5,6] A Cochrane review established the beneficial role of memantine in moderate-to-severe AD, irrespective of treatment with ChEI. There was no benefit in mild AD.[13]

Neuroprotective agents

Latrepirdine is a nonselective antihistamine that can stabilize mitochondrial membrane potential and block mitochondrial permeability transition pore opening. Treatment with latrepirdine resulted in statistically significant improvement on all four efficacy endpoints at six months (orientation, memory, praxis, and language) with respect to placebo.[6] Drug–placebo treatment effects were stable or increasing over time. Results are supported by phase 2 study in mild-to-moderate Huntington's disease (HD) patients. HD patients treated with latrepirdine showed significant improvement in MMSE and significant improvement in cognitive symptoms compared with placebo, with a 6.9-point treatment difference on the Alzheimer's Disease Assessment Scale for cognition (ADAS-Cog) scale.[7] However, a meta-analysis of seven randomized control trials of latrepirdine concluded that while there was no effect of latrepirdine on cognition in mild-to-moderate AD, it appears to have a modest benefit for behavior.[8]

Immunological therapy

Of approximately 10,000 compounds discovered to be useful in AD, only 250 entered the preclinical stage over 3–6 years. Of these, five entered phase I clinical trials and only aducanumab and lecanemab were approved by FDA.

In AD, the basic pathology lies in abnormal accumulation of Aβ in the brain, which triggers downstream effects that lead to tau pathology, neurodegeneration, and subsequent cognitive decline.[14] In the normal brain, there is a delicate balance between the production of Aβ and its clearance. This balance is disrupted in AD. Treatment can be aimed at decreasing Aβ production using β-secretase inhibitors and γ-secretase inhibitors or to increase Aβ clearance by either active or passive immunization.[14,15]

Secretase inhibitors (BACE1)

Have been extensively studied; unfortunately, despite having a sound therapeutic basis, none have proven successful in the treatment of AD. In fact, Beta Secretase Inhibitors 1 (BACE1) levels in CSF have been used to distinguish AD from MCI and those without any cognitive impairment. Some studies have shown that in advanced AD, levels of BACE1 might decrease due to extensive neuronal and synaptic loss.[16] In experimental mice, 50% inhibition of BACE1 resulted in 20% lowering of cerebral Aβ production.[17] Aβ deposition begins more than a decade before the onset of symptoms of AD. BACE1 would be more effective in preventing AD, rather than treating it once significant Aβ deposition has already occurred. Their role in established AD might be limited by their inability to clear large amounts of already deposited amyloid plaques. BACE1 inhibition has been found to have certain toxicities such as hypomyelination, seizures, liver toxicity, axon guidance defects, memory defects, neurodegeneration, and neurogenesis abnormalities. Many trials were prematurely stopped due to worsening cognition in the drug arm compared with the placebo arm.[18] Thus, despite reducing the Aβ levels, these drugs were worsening cognition. This indicates a fallacy in the amyloid hypothesis. Apart from reduced production of Aβ, BACE1 also has other functions such as synaptic plasticity and synaptic homeostasis.[19] These functions might be adversely affected causing worsening of memory. The most important challenges in BACE1 inhibitors are the amount of inhibition required and to determine which stage of AD would they be most effective.

Gamma-secretase inhibitors

Semagacestat and Avagacestat both showed worsening cognition in those receiving the higher dose of drug compared with placebo, even though the former reduced CSF Aβ levels by 52%.[7,20] Tarenflurbil, a gamma-secretase modulator, also had worsening cognition compared with placebo.[21] This makes us question the amyloid hypothesis altogether.

Active immunization

Immunization with Aβ antigen reduced AD pathology in transgenic mice overexpressing the *APP* gene. This helped in clearing amyloid from the central nervous system.[22] Amyloid "vaccine" reduced plaque burden and memory loss in mice. Another trial of active immunization with an aggregated Aβ was terminated prematurely as 18 of 300 receiving AN-1792 developed a sterile meningoencephalitis related to cerebral T lymphocyte infiltration. Only 59 (19.7%) developed adequate Aβ response, and no clinical benefit was seen. Follow-up at one year showed that those who received at least one dose of the drug had an anti-Aβ antibody response and had slower rates of cognitive and functional decline and reduced CSF concentrations of tau protein compared with those who did not receive the drug.

Importantly, vaccination with AN-1792 first demonstrated reversal of AD neuropathology.[14,15]

Passive immunization

Monoclonal antibodies against amyloid are directed against one of the three domains of the Aβ protein: N-terminus, middle portion, or C-terminus. Drug efficacy and safety differ depending on which is the binding domain. Overall, there are seventeen phase III studies involving 12,285 patients. Salloway *et al.*[23] in 2014 and Vandenberghe *et al.*[24] in 2016 evaluated bapineuzumab in six studies, Doody *et al.*[25] in 2014 and Hongi *et al.*[26] in 2018 studied solanezumab tested in three Randomized Control Trials (RCTs), Ostrowitzki *et al.*[27] in 2017 studied gantenerumab in two studies, EMERGE/ ENGAGE investigators and Schneider in 2020 studied aducanumab in four studies,[28] and CREAD 1 and CREAD 2 in 2020 studied crenezumab in two studies.[29] Only aducanumab and crenezumab phase III trials had some statistically significant effects. A brief description of the monoclonal antibodies to treat AD is given below.

Solanezumab

It targets soluble forms of Aβ. In *post hoc* analyses of two large phase III trials, in certain subgroups potential benefit was seen. However, a recent trial assessing the role of Solanezumab in preclinical AD among 1169 subjects did not show any significant decline in cognition in the treatment arm (p value=0.26).[30]

Bapineuzumab

Bapineuzumab (AAB-001) is a humanized monoclonal antibody against the N-terminus of Aβ.[31,32] Bapineuzumab has been studied among 234 subjects in phase 2 randomized, multicenter trials. Though results favored the drug on ADAS-cog, Disability Assessment for Dementia (DAD), Neuropsychological Test Battery (NTB), and CDR-SB, the differences were not significant. According to a *post hoc* analysis, in E4 noncarriers, differences in ADAS-Cog, NTB, and Clincial Dementia Rating Scale Sum of Boxes (CDR-SB) significantly favored the drug. Two phase II trials also did not show any significant improvement in clinical outcomes, despite differences in biomarkers observed in Apolipoprotein E (APOE) ε4 carriers.[33-35]

Aducanumab

Aducanumab was tested in two (EMERGE and ENGAGE) 18-month randomized double-blind controlled phase 3 trials involving 3285 patients in early AD and MCI with confirmed amyloid pathology on PET scan or CSF biomarkers.[36] These two trials were tested together and were stopped when only 50–60 percent completed the schedule because 20 percent conditional power was not met. Contradictory data emerged from these two studies. There was a dramatic decrease in biomarkers, which did not translate into clinical effects. In EMERGE, there was a 22% less decrease in Clinical Dementia Rating Scale-Sum of Boxes Score (CRD-SB), the primary outcome {Test outcome:(-0.39 CI, - 0.69 to -0.09 $P = 0.012$; 22% decrease Control group. 012 (15%)}. Surprisingly, in ENGAGE trial none of these parameters showed any improvement. Amyloid-related imaging abnormalities (ARIAs), especially ARIA-E (vasogenic edema) and AIRA-H (microhemorrhage), were seen in 10 mg/kg monthly injection schedule, and these abnormalities were more often seen in APOE 4 positivity (66% in APOE 4 homozygotes).[37] The vast majority were asymptomatic (70%). Non-ARIA side effects included headache, falls, fatigue, confusion, dizziness, vision changes, and nasopharyngitis. FDA granted accelerated approval keeping in view unmet medical needs and surrogate marker response (reducing Aβ plaques on PET) that predicts clinical benefit. However, the European Medical Agency has not followed suit.[38] The indications, contraindications, and dosing schedule of aducanumab have been mentioned in Table 3.

Lecanemab

Lecanemab is a humanized version of murine mAb158 against Aβ protofibrils. In the phase III CLARITY AD trial, the treatment group received lecanemab intravenously every 2 weeks over 18 months.[39] Clinical deterioration as measured by the CRD-SB was 27% slowed in the lecanemab group (-0.45; $P < 0.0001$). A secondary endpoint of lowering Aβ levels on PET was also achieved (treatment group reduction by 55.48 centiloids; control group reduced by 3.64 centiloids).[40] Toxicities included ARIA-E (12.6% lecanemab; 1.7% placebo) and ARIA-H (17.3% lecanemab; 8.7% placebo). In January 2023, FDA granted accelerated approval for lecanemab for the treatment of AD.

Gantenerumab

Gantenerumab targets aggregated forms of Aβ. It is currently undergoing phase III trials. Aducanumab is available in India on a patient name basis and costs Rs 40 lakh per year. Both Lecanemab and Gantenerumab are not available in India. Table 4 gives a summary of the different monoclonal antibodies directed against Aβ.

E Antioxidants

Vitamin E

In the Alzheimer Disease Cooperative Study (ADCS) trial, vitamin E, selegiline, combination, and placebo were compared.[40] Vitamin E showed the delayed progression to institutionalization when compared to placebo (440 versus 670 days). Another trial of 613 patients compared vitamin E, memantine, combination, and placebo with mild-to-moderate AD.[41] At 2 years, patients treated with vitamin E experienced 3.15 units smaller decline in the ADCS-ADL Inventory compared with placebo (95% CI: 0.92–5.39). In prior studies, in people with cardiovascular disease, high-dose vitamin E supplementation (2000 IU per day) was sometimes associated with an absolute increase in mortality and heart failure. This was not seen among patients with AD. In view of its excellent safety and tolerability, it can be used to treat mild-to-moderate AD.

Table 3: Indications and contraindications for aducanumab[59]

Indications	Contraindications
1 Mild cognitive impairment or mild dementia: MMSE ≥21, MOCA ≥17, or CDR 0.5 to 1	1) Non-AD dementia (diffuse Lewy body disease, vascular dementia)
2 Documented amyloid pathology: by amyloid positron-emission tomography (PET) scan or lumbar puncture	2) Down syndrome with AD, avoid till more data are available
	3) High risk of hemorrhagic side effects:
	a) >4 microhemorrhages on MRI brain
	b) Any areas of superficial siderosis
	c) Prior macrohemorrhage
	d) Underlying brain lesion or vascular malformation
	e) Concomitant use of anticoagulant or antiplatelet use (other than aspirin 81 mg daily)
	f) Bleeding disorders
	g) Any other condition leading to increased risk of central nervous system hemorrhage
	4) Unstable medical conditions
	5) Unstable psychiatric conditions
	6) During pregnancy or breastfeeding
Protocol for aducanumab infusion	
Intravenous infusion once a week	
Doses 1–2 (weeks 0, 4)	1 mg/kg IV over 1 hour
Doses 3–4 (weeks 8, 12)	3 mg/kg IV over 1 hour
MRI brain before the 5th dose	
Doses 5–6 (weeks 16,20)	6 mg/kg IV over 1 hour
MRI brain before the 7th dose	
Dose 7 and above (weeks 24 and above)	10 mg/kg IV over 1 hour
MRI brain before the 10th dose	
MRI brain before the 12th dose	
Total duration of treatment is not known	
Stop aducanumab infusion if the patient progresses to moderate dementia	

Table 4: Clinical trials of recent monoclonal antibodies directed against Aβ tested in phase II trials

Trial name	Monoclonal antibody	No. of participants	Average cumulative dose per month in mg/month	Duration (weeks)	CDR-SB change
EMERGE	Aducanumab	1643	1500	78	-22%
ENGAGE		1653	1500	78	
CLARITY AD	Lecanemab	1906	1500	78	-27%
GRADUATE 1	Gantenerumab	984	1020	116	-8%
GRADUATE 2		975	1020	116	-6%

Clinical Dementia Rating Sum of the Boxes (CDR-SB)

Selegiline

In the ADCS trial, selegiline delayed progression of disease by a few days compared with placebo (655 versus 670 days).[40] A meta-analysis of 12 trials showed a beneficial effect of Selegiline in eight studies and three other studies there was an improvement in behavior and mood.[42] However, the magnitude of the benefits was small.

Management of vascular risk factors

Many patients have a mixture of both AD and vascular dementia called mixed dementia. In an observational study, treatment of vascular risk factors resulted in a slower decline in MMSE scores.[43] However, overzealous correction of vascular risk factors can have a detrimental effect, especially over-correction of blood pressure.[44] Randomized control trials of statins in preventing the progression of dementia have largely been futile.[45-47]

Behavioral disturbances

Behavioral disturbances due to AD adversely affect the patient, caregiver, and family. Early recognition and treatment with appropriate medication can greatly improve quality of life.

Stem cell therapy

Stem cell therapy for AD is in the nascent experimental stage, and all studies are in phase I or II trial and in animals.[48] Stem cells may be used to replace damaged neurons or to deliver therapeutic agents. Neural stem cells can be transplanted into the brain to transdifferentiate into neurons where there is damage and restore normal brain function. Mesenchymal stem cells have anti-inflammatory and regenerative properties and can be transfused intravenously, and they will home onto the brain areas of damage.[49] Transplantation of pluripotent stem cells is yet another modality, and the goal is the replacement of lost neurons in the brain. Exosomes are

small vesicles secreted by stem cells and are used to deliver therapeutic agents to the brain to reduce inflammation and improve cognitive function. All these studies are small, and thus, larger studies are required to establish the safety and efficacy of stem cell therapy in AD.

Biofeedback

Electronic monitoring devices are used to train AD patients to control some of the symptoms. Electroencephalogram (EEG) biofeedback therapy led to significant improvement in cognitive function including attention, memory, and executive functions. It should be included in a comprehensive treatment plan.[50]

Therapies of dubious benefit

Estrogen replacement

Estrogen is known to increase cerebral blood flow, reduce oxidative stress, and prevent atrophy of cholinergic neurons. Estrogen replacement in postmenopausal women has been used both to try to prevent dementia and in the treatment of dementia. Meta-analysis of four randomized control trials of estrogen in postmenopausal women found improvements in verbal memory, vigilance, reasoning, and motor speed but no enhancement of other cognitive functions.[51] Thus, there is no evidence for initiating estrogen replacement in postmenopausal women to either prevent or treat dementia.

Anti-inflammatory drugs

In AD, there is a deposition of amyloid plaques and amyloid-induced inflammatory reaction with microglial activation and cytokine release has been postulated.[52] Some observational studies have found that patients taking NSAIDs have a lower risk of developing AD.[53,54] Only one trial of Indomethacin showed some clinical benefit.[55]

Long-term use of NSAIDs, specifically Cyclo oxygenase (COX-2) inhibitors, is associated with increased cardiovascular events.

Ginkgo biloba

A plant derivative, ginkgo biloba, has been found to be safe but without strong evidence of improving cognitive abilities.[56]

Dietary supplements

Vitamin B

A randomized controlled trial of vitamin B complex supplementation in mild-to-moderate AD did not show any benefits.[57]

Omega-3 fatty acids

Observational studies have suggested the role of omega-3 fatty acid intake in lowering the risk of dementia. This has not been proven in any clinical trial.[58]

Donanemab

It is a humanized antibody that reduces Aβ plaque. The recently published TRAILBLAZER-ALZ 2 randomized control phase 3 trial studied 1736 subjects with mild cognitive impairment (91.5% whites). The test drug was able to successfully clear amyloid plaques in 80% of treatment group at the end of 76 weeks. Donanemab was found to delay progression to AD by 4 months (as assessed by integrated AD Rating Scale). In the treatment group 3 deaths occurred due to amyloid related imaging abnormalities (bleeding and cerebral oedema).[60] The few blacks and Hispanic subjects included in this trial showed accelerated cognitive and functional decline; but numbers were too few to draw any conclusions.[61]

Conclusion

In recent decades, the pathophysiology of AD is better understood and the present concept of dual proteinopathy nature and *in vivo* study of amyloid proteins and tau proteins lead to the development of new therapies. Accelerated approval has been given to immunotherapies, which showed a reduction in surrogate markers without definite clinical benefit, with the hope of a presumed clinical benefit. These approvals require to be followed up with further phase III clinical trials. Though these are very exciting developments, caution is to be exercised when using these drugs. Future research in AD needs to be fuelled by the audacity to challenge assumptions, explore innovative avenues, and embrace interdisciplinary approaches. We hope that the future will open new avenues toward early detection, effective prevention strategies, and transformative treatments that will offer hope and solace to the millions affected by AD.

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Conflicts of interest

There are no conflicts of interest.

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