Amyloid-Targeting Treatments

General Overview for Healthcare Providers

Unmet Needs in AD[1]

- Alzheimer's disease (AD) is the leading cause of dementia, presenting a significant unmet medical need worldwide.
- Traditional treatments for AD primarily manage symptoms without altering disease progression
- There remains an unmet need for additional amyloid-targeting therapies (ATTs) that can target the pathology and alter the progression of AD
- Amyloid-targeting treatments have recently emerged as options for DMTs in early symptomatic AD, helping to address this need

Need for Early Patient Identification

AD is the most frequent cause of dementia, accounting for about 60%–80% of all cases.[2]

In early stages of the disease, where symptoms are mild, AD seems more likely to be overlooked.[3]

Diagnosis delayed by approximately 3.6 years after symptom onset and often made only in the later stages of the disease.[4]

Early and accurate identification of patients and timely intervention are crucial in slowing the progression of AD.[5]

Current Diagnostic-Therapeutic Paradigm[6,7]

The 2024 revised criteria by the Alzheimer's Association Workgroup supports the paradigm shift that clinical presentation alone is not diagnostic of AD. Amyloid PET, plasma assays, and CSF biomarkers (Aβ42/Aβ40, P-tau181/Aβ42, T-tau/Aβ42) can be diagnostic of AD. Biomarkers are not used as standalone tests but are needed for confirming biological evidence of AD.

AD Biomarkers	
Aβ plaques	Established biomarkers include: • Aβ42 and Aβ42/Aβ40 ratio (determined in CSF and blood) • Amyloid plaque accumulation (determined via amyloid PET)
Tau	Established biomarkers include: • Increase in P-tau, P-tau/Aβ42 ratio, and T-tau/Aβ42 ratio (determined in CSF and blood) • Tau tangle accumulation (determined via Tau PET)
Neurodegeneration	Assessed through structural MRI and FDG-PET • Neurodegeneration is not specific to AD, it cannot be used to diagnose AD in isolation

Diagnostic Treatment Pathway[5,8,9]

Initial Assessment	Diagnosis[a]		Treatment Initiation	Monitoring
Clinical evaluation of the patient and medical history.	**Cognitive Assessments** MMSE, CDR, MoCA, other validated tests.	**Biomarker Testing[b]** CSF, blood, or Imaging[b]-based Biomarkers.	• Amyloid-targeting treatments (ATTs) • Symptomatic treatments • Non-pharmacological interventions	• Longitudinal cognitive testing • Periodic MRI (for Amyloid-targeting treatments only)

[a]Cognitive assessments and biomarker tests are tools that help healthcare providers in making diagnoses.[5]
[b]Biomarker testing may be considered when cognitive impairment is present and AD is suspected.[5] Not all biomarker testing modalities may be approved and/or readily available for use in every clinical setting.

The diagnosis of AD is followed by appropriate treatment and/or follow-up care. Disease-modifying treatments (DMTs) inhibit or delay the development of AD neuropathology in patients with mild cognitive impairment (MCI) or mild dementia stage of disease. As a result, DMTs can delay disease progression and slow cognitive and functional decline.

Abbreviations: Aβ=amyloid beta peptide; AD=Alzheimer's disease; CDR=Clinical Dementia Rating; CSF=cerebrospinal fluid; DMT=disease modifying therapy; FDG=fluorodeoxyglucose; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MRI=magnetic resonance imaging; PET=positron emission tomography; P-tau=phosphorylated tau; T-Tau=total tau.

References: 1. Huang LK, et al. *J Biomed Sci.* 2023;30(1):83. 2. https://www.alz.org/alzheimers-dementia/what-is-alzheimers (Accessed September 11, 2024). 3. Boustani M, et al. *Ann Intern Med.* 2003;138(11):927- 937. 4. Kusoro O, et al. *Int J Geriatr Psychiatry.* 2025;40(7):e70129. 5. Porsteinsson AP, et al. *J Prev Alzheimers Dis.* 2021;8:371-386. 6. Jack CR Jr, et al. *Alzheimers Dement.* 2024;20(8):5143-5169. 7. Madnani RS. *Front Neurol.* 2023;14:1178588. 8. Hampel H, et al. *Nat Aging.* 2022;2:692-703. 9. Atri A, et al. *Alzheimers Dement.* 2024;1-20.

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Symptomatic Treatments & Amyloid-Targeting Treatments

Symptomatic Treatments[1,2]

- Provide symptomatic relief by preventing NMDA receptor overactivation or by inhibiting acetylcholinesterase to increase acetylcholine
- Indicated for use in mild to severe dementia stages of AD

Alzheimer's Disease Continuum[a,2]

Preclinical AD

▼

MCI due to AD

▼

Mild dementia due to AD

▼

Moderate dementia due to AD

▼

Severe dementia due to AD

Amyloid-Targeting Treatments[3]

- Target and reduce β-amyloid plaques from the brain slowing cognitive and functional decline in patients with early symptomatic AD
- Indicated for use in MCI or mild dementia stage of AD

[a]Alzheimer's disease continuum based on the National Institute on Aging-Alzheimer's Association (NIA-AA) classification.[2]

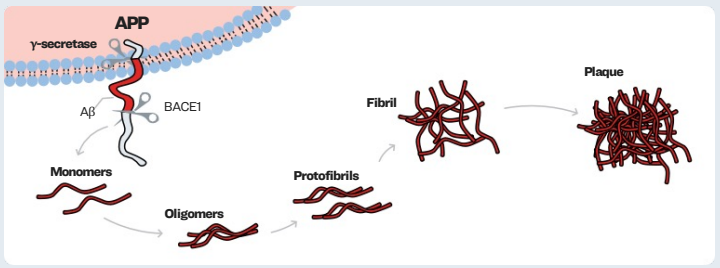
Amyloid Pathology

A hallmark of AD is the accumulation of Aβ peptide.[4] All amyloid-targeting treatments bind to Aβ, but they differ in their primary targets (see the figure below).[5-7]

Binding to Aβ plaques

Slowing Aβ plaque build-up

Promoting clearance of Aβ plaques

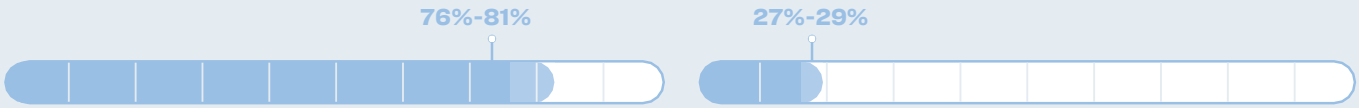


Efficacy of Amyloid-Targeting Treatments[8,9]

Randomized controlled trials with amyloid-targeting treatments show:

Amyloid clearance ranged from 76%-81%[b]

27%-29% slowing of clinical progression as measured by the Clinical Dementia Rating–Sum of Boxes (CDR-SB)[c]



The data presented are an aggregate of approved, commercially available agents in the US. No head-to-head trials or direct comparisons were conducted.

[b]Amyloid clearance rates estimated at 76-78 weeks among participants receiving amyloid-targeting treatments in the phase 3 placebo-controlled studies. Amyloid status (positive vs. negative) determined via PET imaging.

[c]CDR-SB estimated at 76-78 weeks by sum of boxes of the Clinical Dementia Rating Scale (CDR-SB) in the overall/combined population of participants receiving Amyloid-targeting treatments in placebo-controlled studies. The CDR-SB assessment is based on six domains that focus on cognition and function. Scores range from 0 to 18 with higher scores corresponding to greater levels of impairment.

Common adverse effects included amyloid-related imaging abnormalities (ARIA) (ranging 21%-37%) and infusion-related reactions (ranging 8%-26%).[8,9]

Abbreviations: Aβ=Amyloid beta peptide; AD=Alzheimer's disease; APP=amyloid precursor protein; ARIA=amyloid-related imaging abnormalities; BACE1=Beta-site APP Cleaving Enzyme 1; CDR-SB=Clinical Dementia Rating-Sum of Boxes; DMT=disease-modifying therapies; MCI=mild cognitive impairment; NMDA=N-methyl-D-aspartate; PET=positron emission tomography.

References: 1. Abeysinghe AADT, et al. *Life Sci.* 2020;256:117996 2. Porsteinsson AP, et al. *J Prev Alzheimers Dis.* 2021;8:371-386. 3. https://www.alz.org/professionals/health-systems-medical-professionals/amyloid-targeting (Accessed September 09, 2024). 4. Mintun MA, et al. *N Engl J Med.* 2021;384(18):1691-1704. 5. Cai H, et al. *Ageing Neur Dis.* 2023;3:13. 6. Zampar S, et al. In: Huang X, ed. Alzheimer's Disease: Drug Discovery. Exon Publications; 2020. Chapter 2. 7. Panza F, et al. *Nat Rev Neurol.* 2019;15:73-88. 8. Sims JR, et al. *JAMA.* 2023;330(6):512-527. 9. Van Dyck CH, et al. *N Engl J Med.* 2023;388(1):9-21.

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Amyloid Related Imaging Abnormalities (ARIA)

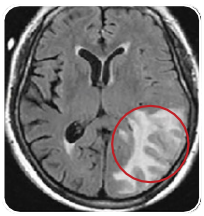
- ARIA refers to a spectrum of MRI signal abnormalities associated with amyloid clearance in the brain[1-3]
- ARIA can occur spontaneously, but it is more frequently observed during treatment with amyloid-targeting treatments[1-3]
- ARIA is usually asymptomatic, although rarely serious, life-threatening events can occur[2,4]
- ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke; treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient receiving an amyloid-targeting treatment[5,6]
- ARIA is usually identified via protocol-specified surveillance MRI scans[3,4]
- Identification of ARIA prior to initiation of therapy and ongoing monitoring via MRI imaging are crucial during treatment with amyloid-targeting therapies[1-3]
- Patients who are *APOE* ε4 homozygotes have a higher incidence of ARIA[5,6]

Types of Imaging Abnormalities[7]

MRI Findings:

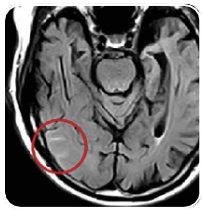
ARIA-E Vasogenic Edema and/or Sulcal Effusion

Edema



Parenchymal hyperintense signal on T2 FLAIR

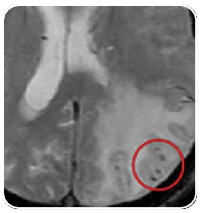
Effusion



Leptomeningeal sulcal surface hyperintense signal on T2 FLAIR

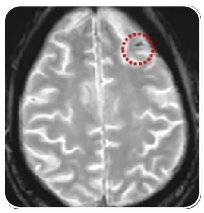
ARIA-H Hemosiderin Deposits

Microhemorrhage



Punctate foci of signal void on T2[a] GRE

Superficial Siderosis



Sulcal signal hypointensity on T2[a] GRE

Clinical Symptom Severity Monitoring[a,8-10]

Common

- Headache
- Confusion/ dizziness
- Nausea

Less common

- Neuropsychiatric symptoms
- Visual disturbance/ blurred vision
- Gait disturbance

Least common

- Seizure/status epilepticus, encephalopathy, stupor, coma, stroke-like symptoms/focal neurological deficits

Asymptomatic	Mild	Moderate	Severe
No symptoms noted, no disruption of daily activities.	Symptoms noted, no disruption of daily activities.	Symptoms sufficient to reduce or affect normal daily activities.	Incapacitating with inability to perform normal daily activities.

Clinical Implications[1-3,8-10]

- Baseline ARIA evaluation and periodic monitoring with MRI are recommended during treatment with amyloid-targeting therapies. Patients experiencing symptoms suggestive of ARIA should undergo clinical evaluation, including MRI if indicated
- If ARIA is observed on MRI, careful clinical evaluation should be performed
- Dose suspension or discontinuation may be considered based on the presence of symptoms and/or radiographic severity; in this case, treatment of ARIA revolves around close monitoring of neurologic status
- Use of high-dose corticosteroids may be considered for treatment of severe ARIA

[a]*ARIA can result in severe and potentially fatal symptoms. While most cases are asymptomatic or mild, some individuals may experience serious side effects like intracranial hemorrhage (>1 cm), severe headaches, confusion, dizziness, nausea, visual disturbances, and seizures. Immediate medical attention is required for any severe or lifethreatening symptoms.*[2,4,8-10]

Abbreviations: *APOE* ε4=apolipoprotein ε4 allele; ARIA=amyloid related imaging abnormalities; ARIA-E=amyloid related imaging abnormalities-edema/effusion; ARIA-H=amyloid related imaging abnormalities-hemosiderin deposits; FLAIR=fluid-attenuated inversion recovery; GRE=gradient recalled echo; MRI=magnetic resonance imaging.

References: 1. Salloway S, et al. *JAMA Neurol*. 2022;79:13-21. 2. Filippi M, et al. *JAMA Neurol*. 2022;79:291-304. 3. Sperling RA, et al. *Alzheimers Dement*. 2011;7:367-385. 4. Sperling RA, et al. *Lancet Neurol*. 2012;11:241-249. 5. Vukmir RB. *Ann Clin Transl Neurol*. 2024;11(7):1669-1680. 6. Cogswell PM, et al. *Am J Neuroradiol*. 2024:ajnr.A8469. 7. Figures adapted from Barakos J et al. J Prev Alz Dis. 2022;9:211-220. Copyright © licensed under CC-BY-4.0 (https://creativecommons.org/licenses/by/4.0/). Modified from original by cutting. 8. Cummings J, et al. *J Prev Alz Dis*. 2023;10:362-377. 9. Cummings J, et al. *J PrevAlz Dis*. 2022;9:221-230. 10. Cummings J, et al. *J Prev Alz Dis*. 2021;4:398-410.

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Infusion-Related Reactions (IRR)

- IRRs are common potential adverse effects when monoclonal antibodies are infused[1]
- Symptoms can range from mild discomfort to severe reactions, requiring immediate medical attention[1]
- Anaphylaxis is a life-threatening, acute allergic reaction. It occurs within minutes of the infusion, and it is characterized by shortness of breath, chest tightness, suffocation, hypotension, bronchospasm, and urticaria[1]
- IRRs usually occur during the first 2-4 treatments and are seen during the infusion or up to several hours following the infusion.[4] Proper management is crucial to ensure patient safety, comfort, and adherence to treatment[1]

Type of Reactions[2-4]

Signs and symptoms:


Chills


Erythema


Nausea


Dyspnea


Headache


Chest pain


Elevated blood pressure


Sweating

Please note this is not a complete list of all possible signs and symptoms associated with infusion-related reactions.

Grading of Infusion-Related Reactions[4]

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild transient reaction; infusion interruption not indicated; intervention not indicated	Infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, acetaminophen, NSAIDs, narcotics, IV fluids); prophylactic medication indicated for <24 hrs	Prolonged recurrence of symptoms following initial improvement; hospitalization may be indicated for clinical sequelae (eg, poorly controlled hypertension)	Life-threatening consequences; urgent intervention indicated (may require pressor or ventilatory support)	Death

Management and Prevention[2-4]

In the event of an infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated.

Pre-treatment with antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs or corticosteroids prior to subsequent dosing may be considered.

Amyloid-Targeting Treatments General Overview for Healthcare Providers: Key Takeaways

- **Amyloid-targeting treatments** reduce **Aβ plaques** in the brain, thereby **slowing cognitive and functional decline** in people living with early symptomatic AD, including MCI and mild dementia stages of AD
- **ARIA and IRRs** are risks associated with the amyloid-targeting treatment class.
- **ARIA** is usually **asymptomatic,** although rarely **serious, life-threatening events can occur.**
- **Identification of ARIA** prior to initiation of therapy and ongoing monitoring via **MRI imaging** are crucial during treatment with amyloid-targeting treatments.
- **IRR symptoms** can range from mild discomfort to severe reactions, requiring immediate medical attention.

Abbreviations: Aβ=amyloid beta peptide; AD=Alzheimer's disease; ARIA=amyloid related imaging abnormalities; IRR=infusion-related reactions; IV=intravenous; MCI=mild cognitive impairment; MRI=magnetic resonance imaging; NSAIDS=non-steroidal anti-inflammatory drugs.

References: 1. Cáceres MC, et al. *Ther Clin Risk Manag.* 2019;15:965-977. 2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761248s000lbl.pdf (Accessed February 27, 2025). 3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269s000lbl.pdf (Accessed February 27, 2025). 4. Cummings J, et al. *J Prev Alz Dis.* 2023;3(10):362-377.

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