UT Southwestern Medical Center

Anti-Amyloid Therapies: Patient Selection and Complication Management

Brain Summit 2026

Trung P. Nguyen, MD, PhD

Disclosure

- I have no actual or potential conflicts of interest in relation to this presentation

Objectives

Objectives

- Review the currently available anti-amyloid therapies (AAT)
- Evaluate patients to determine candidacy for AAT
- Assess and manage complications associated with AAT

Anti-Amyloid Therapies

Anti-Amyloid Therapies

- Monoclonal antibodies designed to help clear amyloid plaques from brain
- Approved for treatment of patients with mild stage Alzheimer disease (AD)
  - Mild cognitive impairment (MCI)
  - Mild dementia
- Slows cognitive and functional decline
- Side effects
  - Amyloid-related imaging abnormalities (ARIA)
  - Infusion reactions
- Appropriate use recommendations (AUR) available to guide implementation

Anti-Amyloid Therapies

Lecanemab / LEQEMBI

- Approved July 6, 2023
- Initial infusion Q2W
- Maintenance
  - Q2W vs Q4W
  - QW subcutaneous injections
- Initial subcutaneous injections*

Donanemab / Kisunla

- Approved July 2, 2024
- Infusions Q4W with initial titration
- Discontinue by amyloid PET criteria
  - 1 amyloid PET < 11 centiloids
  - 2 amyloid PETs < 25 centiloids
  - Negative
- Consider discontinuation at 18 months

Appropriate Use Recommendations

J Prev Alz Dis 2023;3(10):362-377
Published online March 27, 2023, http://dx.doi.org/10.14283/jpad.2023.30

Review

Lecanemab: Appropriate Use Recommendations

J. Cummings[1], L. Apostolova[2], G.D. Rabinovici[3], A. Atri[4], P. Aisen[5], S. Greenberg[6], S. Hendrix[7], D. Selkoe[8], M. Weiner[9], R.C. Petersen[10], S. Salloway[11], For the Alzheimer's Disease and Related Disorders Therapeutics Work Group

1. Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas (UNLV), Las Vegas, NV; USA; 2. Departments of Neurology, Radiology, Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA; 3. Memory and Aging Center, Department of Neurology, Weill Institute for Neurosciences and Department of Radiology and Biomedical Imaging; University of California, San Francisco, San Francisco, CA, USA; 4. Banner Sun Health Research Institute, Banner Health, Sun City, AZ; Center for Brain/Mind Medicine, Harvard Medical School, Boston, MA, USA; 5. Alzheimer's Treatment Research Institute, University of Southern California, San Diego, CA, USA; 6. Deparment of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; 7. Pentara Corporation, Millcreek Utah, USA; 8. Ann Romney Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; 9. Departments of Radiology and Biomedical Imaging, Medicine, Psychiatry and Neurology, University of California San Francisco, San Francisco, CA, USA; 10. Department of Neurology, Mayo Clinic, Rochester, MN, USA; 11. Butler Hospital and Warren Alpert Medical School of Brown University, Providence RI, USA

Corresponding Author: Jeffrey Cummings, MD, ScD, 1380 Opal Valley Street, Henderson, NV 89052, USA, jcummings@cnsinnovations.com, T: 702-902-3939

Appropriate Use Recommendations

The Journal of Prevention of Alzheimer's Disease 12 (2025) 100150

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad



Special Article

Donanemab: Appropriate use recommendations



G.D. Rabinovici[a,*], D.J. Selkoe[b], S.E. Schindler[c], P. Aisen[d], L.G. Apostolova[e], A. Atri[f,g], S.M. Greenberg[h], S.B. Hendrix[i], R.C. Petersen[j], M. Weiner[k], S. Salloway[l,1], J. Cummings[m,1]

[a] *Memory & Aging Center, Departments of Neurology, Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA*
[b] *Ann Romney Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[c] *Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA*
[d] *Alzheimer's Treatment Research Institute, University of Southern California, San Diego, CA, USA*
[e] *Departments of Neurology, Radiology, Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA*
[f] *Banner Sun Health Research Institute, Banner Health, Sun City, AZ, USA*
[g] *Center for Brain/Mind Medicine, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[h] *Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[i] *Pentara Corporation, Millcreek UT, USA*
[j] *Department of Neurology, Mayo Clinic, Rochester, MN, USA*
[k] *Departments of Radiology and Biomedical Imaging, Medicine, Psychiatry and Neurology, University of California San Francisco, San Francisco, CA, USA*
[l] *Butler Hospital and Warren Alpert Medical School of Brown University, Providence RI, USA*
[m] *Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, Kirk Kerkorian School of Medicine, University of Nevada Las Vegas, Las Vegas, NV, USA*

Patient Selection

Inclusion Criteria

- AD as primary etiology for cognitive impairment
- Typical (amnestic) and atypical (non-amnestic) phenotypes
  - Posterior cortical atrophy
  - Logopenic primary progressive aphasia
  - Dysexecutive variant
- Positive amyloid PET or CSF biomarkers for AD
- Mild disease stage
  - MCI (AD Clinical Stage 3)
  - Mild dementia (AD Clinical Stage 4)
  - Objective impairment in one or more cognitive domains
  - Independent with basic ADLs
  - MMSE ≥20 (don) or ≥22 (lec)
  - MoCA ≥13 (don) or ≥16 (lec)

Exclusion Criteria: Neurologic

- Other neurologic diseases affecting cognition
  - Vascular cognitive impairment
  - Parkinson/Lewy body disease
  - Normal pressure hydrocephalus
  - Multiple sclerosis
- Stroke or TIA in past 12 months
- Any history of seizures

- Baseline MRI brain findings
  - Edema/effusions
  - > 4 cerebral microhemorrhages
  - Superficial siderosis
  - ICH or infarcts > 1 cm; > 2 lacunes
  - Severe white matter disease (Fazekas scale 3)
- Check APOE

Exclusion Criteria: Non-Neurologic

- Medical or psychiatric condition significantly contributing to cognitive impairment
- Active cancer interfering with ability to comply with treatment
- History of immunologic disease or systemic treatment with immunosuppressant, immunoglobulins or monoclonal antibodies or their derivatives
- Bleeding disorders
- Anticoagulation
- Unstable medical conditions

Complication Management

Amyloid Related Imaging Abnormalities

ARIA-E (Edema)

- Vasogenic edema or sulcal effusions
- Extensive cases with mass effect, cortical swelling, sulcal effacement
- Usually resolves in 3-4 months
- MRI features
  - T2 FLAIR hyperintensities in white matter, may involve gray matter
  - No restricted diffusion
  - No contrast enhancement
- MRI Severity – Mild:
  - 1 site < 5 cm
- MRI Severity – Moderate:
  - 1 site 5-10 cm
  - >1 site, each < 10 cm
- MRI Severity – Severe:
  - 1 site > 10 cm with gyral swelling and sulcal effacement
  - One or more sites of involvement may be noted

ARIA-H (Hemorrhage)

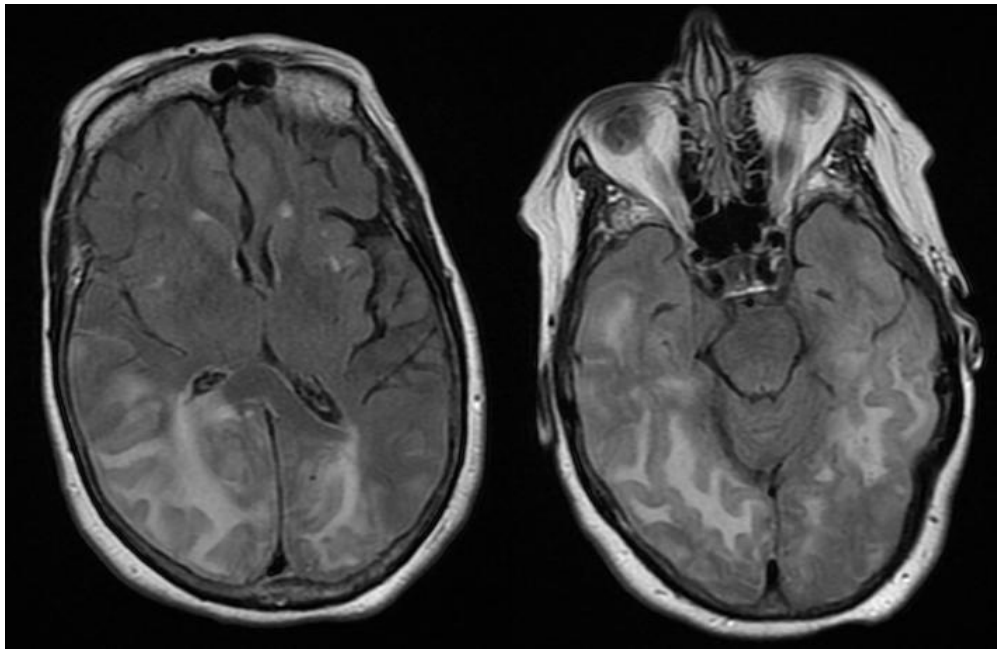
- Microhemorrhages
- Superficial siderosis
- Macrohemorrhages
- MRI
  - T2*-weighted imaging
  - Susceptibility-weighted sequences
  - Usually permanent

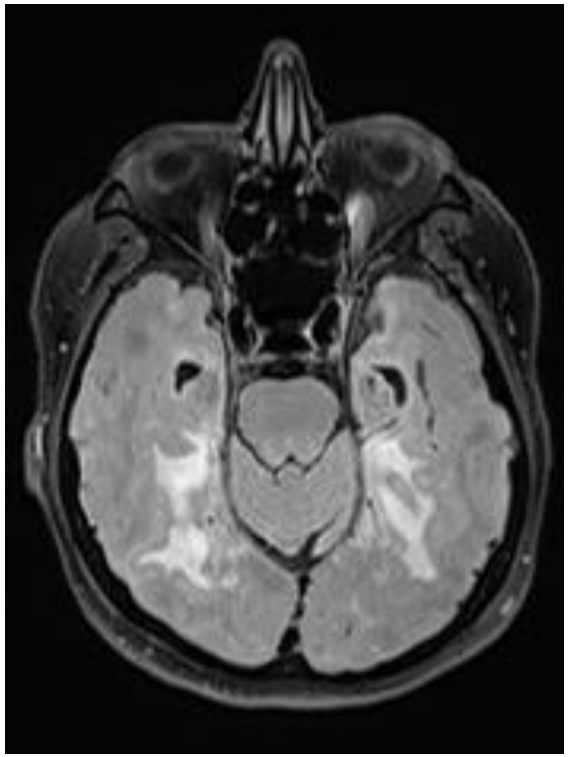
- Microhemorrhage
  - MRI Severity - Mild: ≤ 4
  - MRI Severity - Moderate: 5-9
  - MRI Severity - Severe: 10+
- Superficial siderosis
  - MRI Severity - Mild: 1 focal area
  - MRI Severity - Moderate: 2 focal areas
  - MRI Severity - Severe: > 2 areas

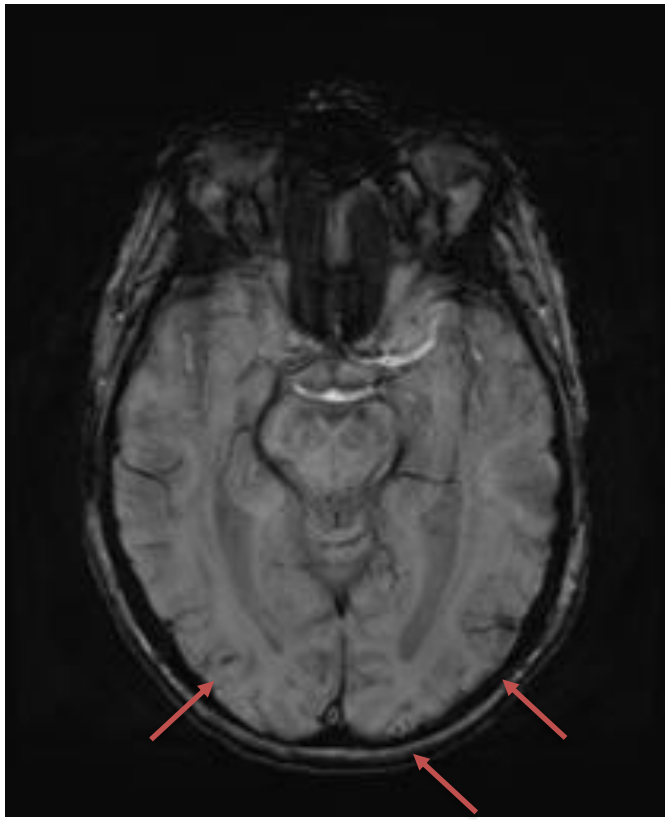
ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/ independent sites of involvement may be noted.
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 areas of superficial siderosis

Examples of ARIA







ARIA Clinical Manifestations

- 3-6% of clinical trial participants with symptomatic ARIA
  - 75% of ARIA incidental/asymptomatic
  - 10% - 23% of ARIA mild-moderate
  - 1% - 2% of ARIA severe
- Symptoms:

Headache	Visual disturbances
Confusion	Gait difficulties
Disorientation	Encephalopathy
Dizziness/vertigo	Seizures
Nausea/vomiting	Focal neurologic deficits
Fatigue	

- Mild
  - Discomfort noticed
  - No disruption of normal daily activity
- Moderate
  - Discomfort
  - Sufficient to reduce or affect normal daily activity
- Severe
  - Incapacitating
  - Inability to work or to perform normal daily activity

ARIA Monitoring and Detection

- Baseline MRI with T1, T2 FLAIR, DWI, GRE T2*/SWI
- Surveillance MRIs
  - Lecanemab: prior to 3rd, 5th, 7th and 14th infusions
  - Donanemab: prior to 2nd, 3rd, 4th and 7th infusions
- Evaluate for potential symptomatic ARIA prior to next infusion

Dosing Recommendations for ARIA

ARIA-E

- May continue if imaging: mild and no or mild symptoms
- Suspend dosing
  - Imaging: moderate or severe
  - Symptom: moderate or severe
- Consider resuming
  - Radiographic resolution (MRI in 2-4 mo)
  - Symptoms resolve
  - Clinical judgement

ARIA-H

- May continue if imaging: mild and asymptomatic
- Suspend dosing
  - Imaging: moderate or severe
  - Symptomatic
- Consider resuming
  - Radiographic stabilization (MRI in 2-4 mo)
  - Symptoms resolve
  - Clinical judgement
- Consider discontinuation if imaging: severe

ARIA-E Management

Clinical Symptom Severity	ARIA-E Severity on MRI Mild	Moderate	Severe
Asymptomatic	May continue dosing at current dose and schedule	Suspend dosing [a]	Suspend dosing [a]
Mild	May continue dosing based on clinical judgement	Suspend dosing [a]	Suspend dosing [a]
Moderate or Severe	Suspend dosing [a]	Suspend dosing [a]	Suspend dosing [a]

[a] Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment.

ARIA-H Management

Clinical Symptom Severity	ARIA-H Severity on MRI Mild	Moderate	Severe
Asymptomatic	May continue dosing at current dose and schedule	Suspend dosing [a]	Suspend dosing [b]
Symptomatic	Suspend dosing [a]	Suspend dosing [a]	Suspend dosing [b]

[a] Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment; consider a follow-up MRI to assess for stabilization 2 to 4 months after initial identification.

[b] Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Use clinical judgment when considering whether to continue treatment or permanently discontinue treatment.

ARIA Management per AURs

- Continue dosing in imaging mild and asymptomatic ARIA
  - Monitor for symptoms
  - Monthly MRI scans until ARIA-E resolves or ARIA-H stabilizes
- Suspend dosing in imaging moderate-severe or symptomatic ARIA
  - Monitor for symptom resolution
  - Monthly MRI scans until ARIA-E resolves or ARIA-H stabilizes
- Restarting can be considered based on discussion of
  - Risk and benefits
  - Recurrence risk
  - Severity of imaging changes
  - Severity of symptoms
  - *APOE* genotype
  - Co-morbidities
  - Concurrent medications

ARIA Management per AURs

ARIA Severity on MRI	Symptom Description			
	No Symptoms	Mild	Moderate	Severe
ARIA-E				
Mild	Continue	Suspend	Suspend	Discontinue
Moderate	Suspend	Suspend	Suspend	Discontinue
Severe	Discontinue	Discontinue	Discontinue	Discontinue
ARIA-H				
Mild	Continue	Suspend	Suspend	Discontinue
Moderate	Suspend	Suspend	Suspend	Discontinue
Severe	Discontinue	Discontinue	Discontinue	Discontinue

Serious and Severe ARIA

- Characteristics
  - 0.7% - 0.8% of dosed subjects in trials
  - Usually within the first several months
  - Large areas of edema +/- mass effect
  - Can have microbleeds
  - Can have punctate restricted diffusion
  - Usually (but not always) symptomatic
  - Resembles cerebral amyloid angiopathy-related inflammation
- Management
  - Admission to hospital/ICU for stabilization, monitoring, treatment
  - High-dose glucocorticoid treatment
    - Methylprednisolone 1g IV daily for 5 days, then
    - Oral steroid taper over several weeks
  - Monitor for neurologic status, seizures, other complications

AAT and Ischemic Strokes

AAT and Ischemic Strokes

- Differentiate ARIA from acute stroke
- IV thrombolytics in patients treated with AAT associated with severe outcomes
  - Intracerebral hemorrhage
  - Death
- Recommend IV thrombolysis not be administrated in patients treated with AAT without MRI unequivocally excluding ARIA
- Mechanical thrombectomy without thrombolytic should be considered for acute stroke due to large-vessel occlusion

Infusion Reactions

Infusion Reactions

- Characteristics
  - 9% - 26% of subjects in clinical trials
  - Typically mild to moderate
  - During the first several infusions
  - At infusion or up to several hours later
  - Resolves in 24 hours
- Symptoms:
  - Fevers
  - Chills
  - Flu-like symptoms
  - Headache
  - Rash
  - Nausea/vomiting
  - Blood pressure elevation
- Consider hypersensitivity reactions
  - Angiodedema
  - Bronchospasm
  - Anaphylaxis

Grading of Infusion Reactions

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 (e.g., antihistamines, acetaminophen, NSAIDs, narcotics, i.v. fluids); prophylactic medication indicated for < 24 hours	Prolonged recurrence of symptoms following initial improvement; hospitalization may be indicated for clinical sequelae (e.g., poorly controlled hypertension)	Life-threatening consequences; urgent intervention indicated (may require pressor or ventilatory support)	Death

Management of Infusion Reactions

- Grade 2: stop infusion and treat
  - Mild:
    - Diphenhydramine and acetaminophen
    - Repeat every 4-6 hours as needed until symptoms fully resolve
  - Significant:
    - Dexamethasone (0.75 mg / day for 2-3 days)
    - Methylprednisolone (80 mg twice per day for 2-3 days)
  - Follow-up to determine if symptoms have resolve
- Pretreatment for future infusions
  - Diphenhydramine and acetaminophen
  - Oral steroids if above not effective
  - Continue until asymptomatic for 2-4 infusions
- Grade 3 or higher: discontinue

Conclusion

Summary

- AAT are approved for treatment of patients in mild stages of Alzheimer disease (mild cognitive impairment, mild dementia)
- Diligent assessment of inclusion and exclusion criteria for each patient is required
- Patient treated with AAT require surveillance MRI scans and clinical monitoring for adverse reactions including ARIA and infusion reactions
- Guidance for patient selection and management of complications can be found in published appropriate use recommendations