Monoclonal Antibodies: An Overview

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Disclosure

- Kimiko Domoto-Reilly has the following financial relationships to disclose:
  - Speaker's Bureau for: MedBridge

Anti-amyloid Monoclonal Antibodies (mAbs)

- We have entered a new era of disease modifying therapies for Alzheimer's disease
  - Donepezil approved in 1996
  - Memantine approved in 2003

- mAb infusion therapy can be prescribed for mild cognitive impairment or early-stage dementia due to Alzheimer's disease (AD)
  - Importance of early diagnosis
  - Requirement for identification of AD neuropathologic change via molecular biomarker

- mAbs *do not replace* current treatments including cholinesterase inhibitors (eg donepezil) and non-pharmacologic interventions

Terminology Refresher

- Mild Cognitive Impairment (MCI)
- Dementia
- Alzheimer's disease

Syndrome

Underlying neuropathology (amyloid & tau)

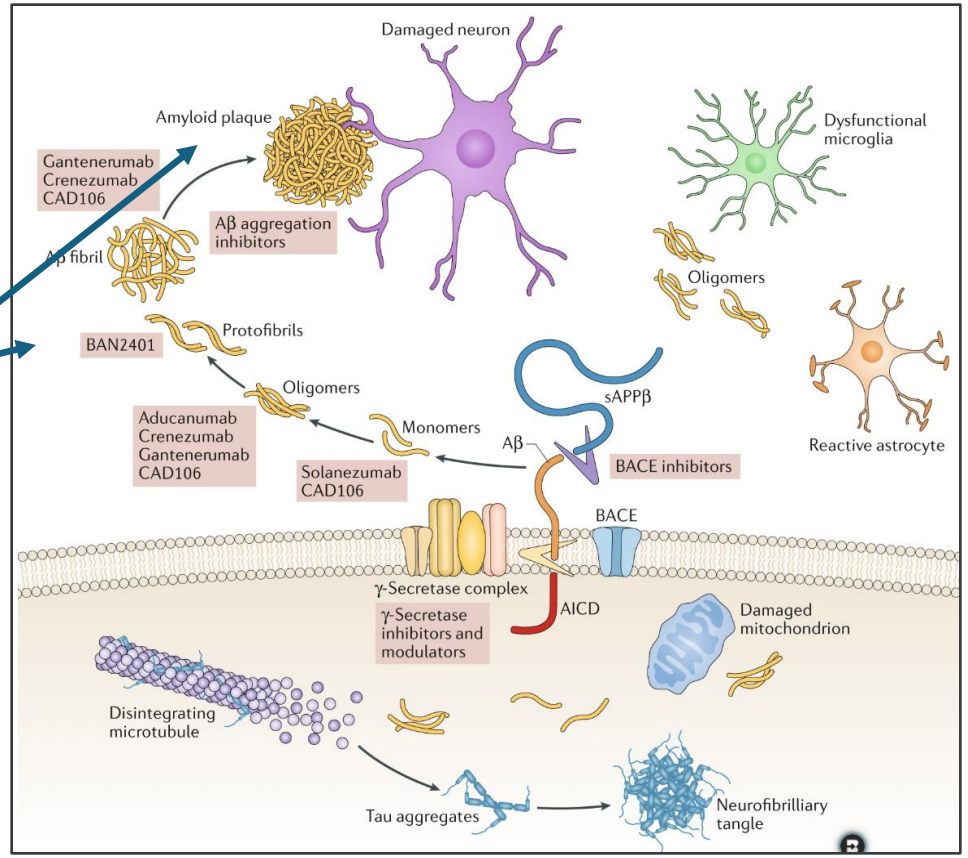
- Dementia stages: Mild / Moderate / Severe
  - Instrumental versus basic ADLs
- Dementia onset: Early / Late
  - Age at symptom recognition (65yo)

Anti-amyloid Monoclonal Antibodies (mAbs)

- Each monoclonal antibody facilitates clearance of different amyloid aggregates

- Lecanemab (Leqembi®)
  - FDA approval 2023
  - Targets protofibrils

- Donanemab (Kisunla™)
  - FDA approval 2024
  - Acts on plaques



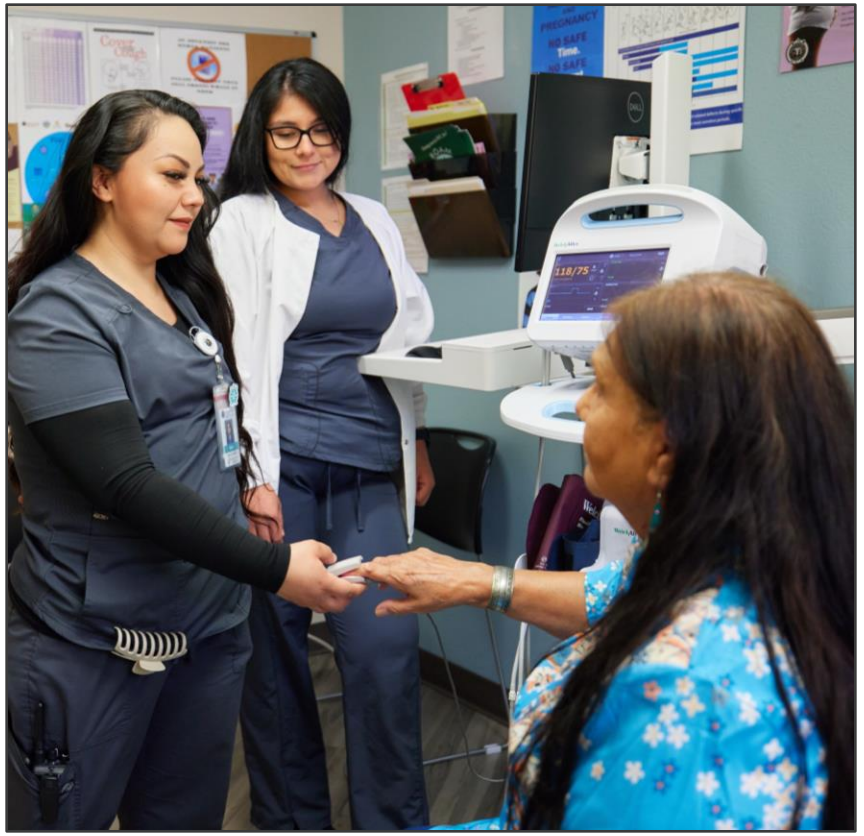
Treatment Approach: Initial Screening

A person diagnosed with MCI or mild stage dementia due to AD may be eligible for treatment with anti-amyloid mAb

- Imaging or fluid biomarkers indicative of brain amyloid pathology
  - Amyloid PET scan
  - Cerebrospinal fluid
  - Serum biomarkers may be used for initial screening

mAb Treatment: Basic Exclusion Criteria

- Anticoagulated
- Unable to undergo repeated brain MRIs
- Other major medical issues such as recent stroke or seizure, poorly controlled diabetes
- Strict precautions to avoid anticoagulation during treatment



Monoclonal Antibody Treatment Risks

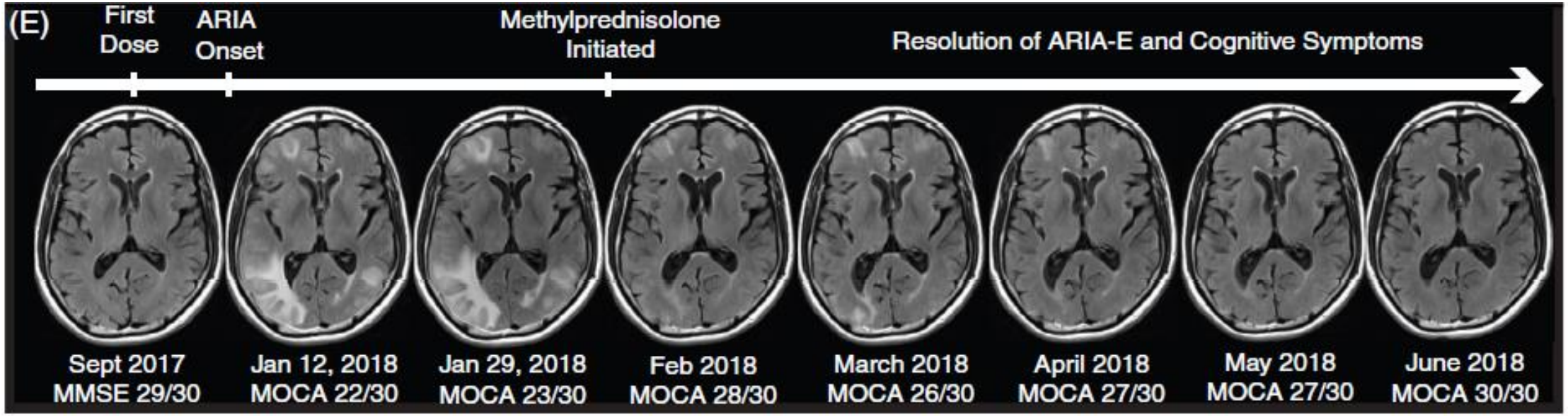
- Amyloid-related imaging abnormalities (“ARIA”)
  - Brain swelling or bleeding
- Headache most common symptom
  - Often clinically silent, but can be fatal
- Symptoms can be stroke-like
  - Must avoid anticoagulation

Medical Alert:
Report monoclonal antibody use if experiencing a medical emergency

Safety Screening Tests

- AD risk gene: apolipoprotein E (*ApoE*)
  - 2 ε4 copies (*ApoE*ε4 homozygote) at highest risk

- MRI with specific protocol

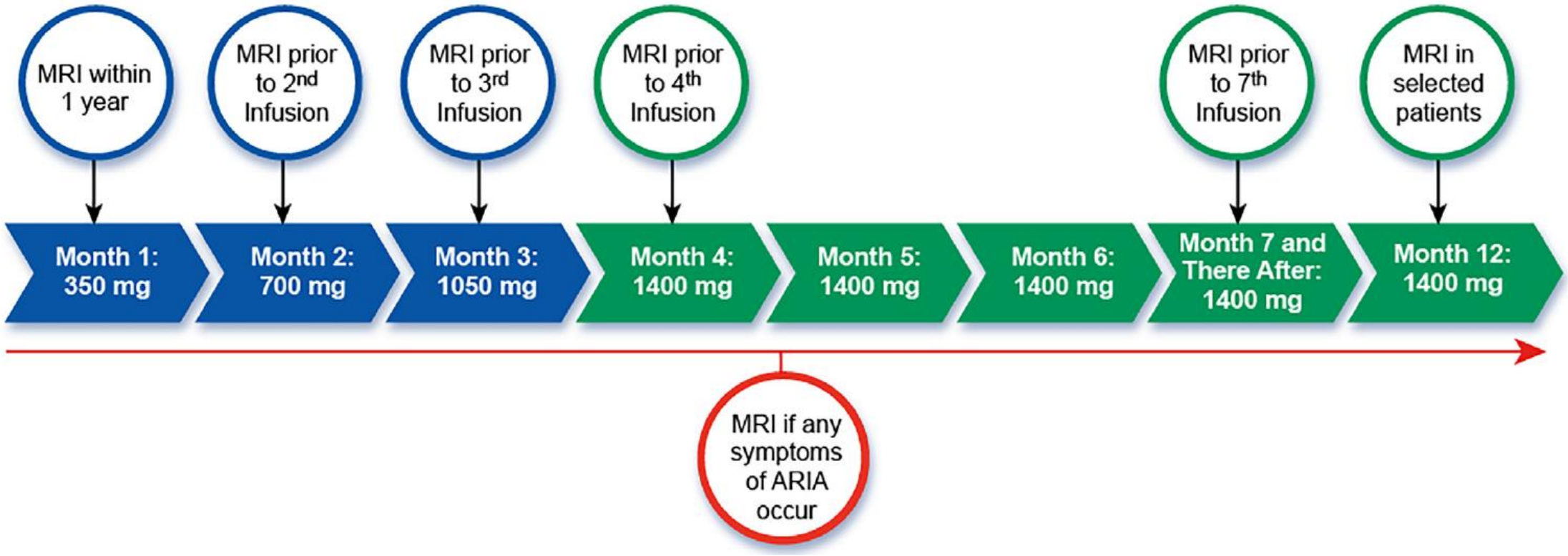


Treatment Protocol

- Infusion schedule
  - 1 x monthly for donanemab or 2 x monthly for lecanemab
  - Watch for infusion reactions, especially first and second doses
- Surveillance MRIs
  - Multiple scans at start of treatment, and for any concerning symptoms
  - Ideally same scanner across time; radiologists must be trained

Highest risk for ARIA in first 6 months, but risk remains throughout treatment

Sample Treatment Schedule



Rabinovici et al *JPAD* 2025

Care Considerations and Future Directions

- Important to counsel that although mAbs are disease modifying therapy, they are NOT curative (also not experimental)
  - Continued slowly progressive decline is expected
- Consider timing of *ApoEε4* testing and counseling
- Emphasize shared decision making, ideally together with the healthcare designated power of attorney
- Advise carrying a medical alert wallet card
- Future directions
  - Debates about duration of therapy
  - Possible injectable options