Monoclonal Anti-Amyloid Treatments

The Good, The Bad, and The Difficult

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Potential Conflicts of Interest

I provide or have provided consultative and/or educational services to:

- Alzheon
- Biogen
- C2N
- Eisai
- Genentech
- Lilly
- Roche

Any reimbursement I receive for such work is donated to Dream Foundation (Adult “Make-A-Wish”)

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The Good

Memory Lane…
AZT (1987)
Methotrexate (1989)
Tacrine (1994)

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Aducanumab (Aduhelm)

- Approved by FDA 2021 via “accelerated pathway”
- Indicated for treatment of Alzheimer’s Disease
  - Mild Cognitive Impairment or
  - Mild dementia stage of the disease
- Approval based on reduction of amyloid beta plaques
- Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s)

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Aducanumab Clinical Pharmacology

- Mechanism of action
  - Human immunoglobulin gamma 1 (IgG1) monoclonal antibody
  - Directed against aggregated and insoluble forms of amyloid beta
- Pharmacodynamics
  - Reduces beta amyloid plaque in a dose-related manner compared to controls
  - Magnitude of plaque reduction is time and dose dependent
  - CSF p-tau was lower in sub-studies of two of the three efficacy trials
  - PET imaging showed tau reduction in several areas of the brain

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Lecanemab (Leqembi)

- Approved by FDA 2023 via “accelerated pathway”
- Indicated for treatment of Alzheimer’s Disease
  - Mild Cognitive Impairment or
  - Mild dementia stage of the disease
- Approval based on reduction of amyloid beta plaques
- Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial

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Lecanemab Clinical Pharmacology

- Mechanism of action
  - Human immunoglobulin gamma 1 (IgG1) monoclonal antibody
  - Directed against aggregated soluble and insoluble forms of amyloid beta
- Pharmacodynamics
  - Reduces beta amyloid plaques compared to controls
  - Magnitude of plaque reduction is time and dose dependent
  - Reduction in clinical decline CDR-SB and ADAS-Cog 14
  - Association seen between plaque reduction and clinical decline on CDR-SB
  - p-tau 181 was lower in a sub-study

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Donanemab

- Accelerated pathway approval rejected by FDA
- Targets aggregated amyloid deposited in plaques
- Regular FDA approval track filing expected this summer

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Donanemab: Press release May 3, 2023

- Phase III study positive results
  - Significantly slowed cognitive and functional decline in early AD
  - Use Integrated Alzheimer's Disease Rating Scale (iADRS)
  - All secondary efficacy endpoints of cognitive and functional decline were also met at the 18th month timepoint
  - 71% of patients had clearance of amyloid plaque by 12th month
- Participants stratified by level of tau in the brain
- Primary analysis population had an intermediate level of tau
- High tau level patients had lower difference in function decline

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The Bad

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Amyloid-Related Imaging Abnormalities (ARIA)

- Two forms, ARIA-E (edema) and ARIA-H (micro-hemorrhage)
- ARIA worse in APOE-4/4, incidence and severity
- Aducanumab:
  - ARIA-E in 35% of patients compared to 3% controls
  - ARIA-H in 21% of patients compared to 1% (?) of controls
- Lecanemab:
  - ARIA-E in 13% of patients compared to 2% controls
  - ARIA-H in 17% of patients compared to 9% of controls
- Donanemab:
  - ARIA-E in 24% of patients compared to 6% controls
  - ARIA-H in 31% of patients compared to 14% of controls

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Symptoms and signs consistent with ARIA that should trigger consideration of out-of-sequence MRI for patients

- • Acute or subacute onset of new focal neurological signs or symptoms
- • Headache
- • Confusion/altered mental status/delirium/disorientation
- • Dizziness/vertigo
- • Nausea
- • Vomiting
- • Fatigue
- • Blurred vision
- • Vision disturbance/impairment
- • Gait disturbance
- • Seizures

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Other Adverse Effects

- Deaths:
  - None related to product for Aducanumab to date
  - 2 certain plus one probably product-related for lecanemab
  - 3 ARIA – related for donanemab
- Infusion reactions (mostly mild and first infusions)
  - Rare with aducanumab
  - 26% with lecanemab
  - 9% with donanemab

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The Difficult

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Selecting the Patient

1. Chart review (“Appropriate Use” for Aduhelm and Leqembi):
    a. Diagnosis of MCI or early/mild Alzheimer's Disease
        i. > 21/30 MMSE for Aduhelm; > 22/30 for Leqembi
        ii. Biomarker for AD: FDG-PET, CSF
    b. Confirmation of amyloid : scan, CSF (blood?)
    c. Med review for antiplatelet or anticoagulant drugs, herbals
    d. ARIA and vascular screen on recent MRI (< 1year)
    e. Genetic testing APOE-4 (required for Leqembi)
    f. Other considerations : exercise, diet, expectations
    g. Lab review for A1C, TSH, CMP, vitamin deficiencies

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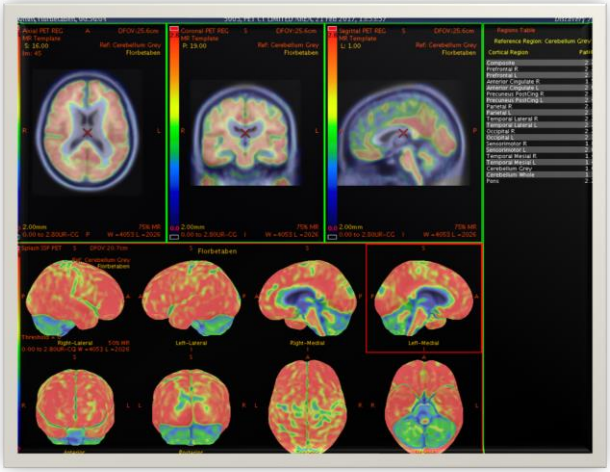
Positive Amyloid PET; AD



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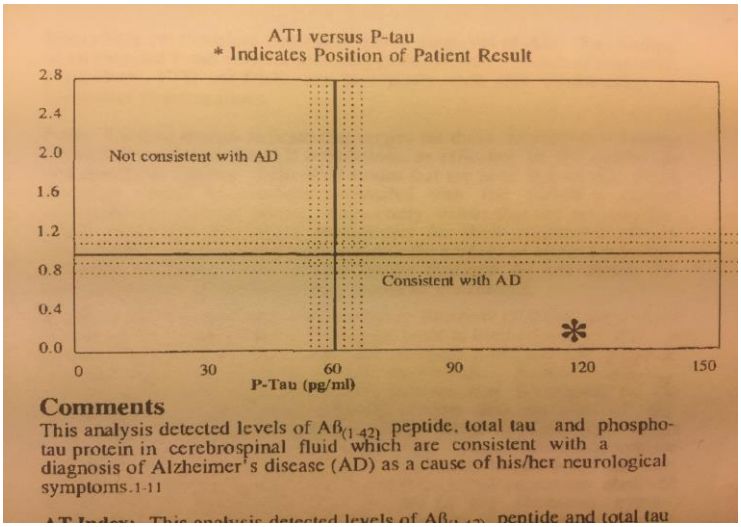
CSF biomarker



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Informing the Patient

2. Patient Visit 1 (in person or video/telephone):
   a. Verbal information about both monoclonal treatments
      i. FDA approval, controversies
      ii. Limited possible benefits, certain potential side effects
      iii. Number of infusions, number of MRIs
   b. Where to get information: Alzheimer's Association, AlzForum
   c. Cost considerations, patient assistance, Infusion center charge
   d. Travel considerations: infusion centers, MRIs, follow-up visits

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Preparing the Patient

3. Patient visit 2: in person, family members, phone attendees
    a. Review meds, update history, discuss last visit information
    b. Exam for neurologic, cardiac, psychiatric; understanding
    c. Review of medication information sheets, side effects
    d. Go through process for handling possible side effects
        i. Who to contact
        ii. When to go to ED; UW/ED prepped by referring physician

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Starting Treatment

4. Patient wants treatment, discuss what happens next:
    i. Patient assistance (1 page Aduhelm, 8 pages Lequembi) sent in
    ii. Company calls patient to discuss cost of drug (pharmacy?)
    iii. Patient informs us that they want treatment
    iv. Order form sent to Infusion Center
    v. Infusion center (found and prepped for treatment):
        1. Calls patient to set up first infusion
        2. Contacts patient evening of Leqembi infusion to check for reactions
        3. Informs prescriber of each treatment
        4. Calls prescriber with infusion issues
        5. Notifies prescriber when MRIs are due

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On Treatment

1. Between infusions:
   a. Order monitoring MRIs per Appropriate Use recommendations
   b. Stop infusions with ARIA: assess seriousness
   c. For side effects consider MRI
   d. Discuss risks of restarting treatment if stopped for ARIA
   e. See patient on regular basis (3-6 months)
   f. Regular meetings with Biogen and Eisai
   g. Determine if going beyond 18 months of treatment

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Quartz PA: Criterial for Coverage (7/3/23)

- Diagnosis of Alzheimer's disease with mild cognitive impairment or dementia confirmed by any of the follow
  - Mini Mental State Exam (MMSE) score between 21 and 30
  - Clinical Dementia Rating Global Score (CDR-GS) of 0.5
  - Montreal Cognitive Assessment (MoCA) score of ≥ 16
- Prescribed by or in consultation with a Neurologist, Geriatrician, Psychiatrist, or other Alzheimer's disease specialist
- Age 50 to 90 years
- Positive amyloid confirmed by a Positron Emission Tomography (PET) scan or lumbar puncture (Cerebral Spi Fluid)
- Other causes of symptoms are ruled out (e.g. Lewy body dementia, Parkinson's disease, vitamin B12 deficie etc.)
- Person does not have any of the following:
  - Use of antiplatelet or antithrombotic drugs (except prophylactic aspirin or clopidogrel)
  - History of cerebrovascular abnormalities, bleeding disorder, clotting disorder, or brain hemorrhage
  - Diagnosis of stroke, seizures, transient Ischemic attack within the previous 12 months

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Criterial for Continuation of Coverage

- Magnetic Resonance Imaging (MRI) scans before the 5th, 7th and 14th dose confirming there are not amyloid-related imaging abnormalities (ARIA)
- Clinical documentation of a decrease in brain amyloid plaques
- Person does not have any of the following:
  - Use of antiplatelet or antithrombotic drugs (except prophylactic aspirin or clopidogrel)
  - History of cerebrovascular abnormalities, bleeding disorder, clotting disorder, or brain hemorrhage
  - Diagnosis of stroke, transient Ischemic attack, unstable angina, myocardial infarction, unexplained loss of consciousness within the previous 12 months

Note:
Continuation of therapy criteria will not be applied to persons who are not new to the plan who were not previously approved for coverage of their current therapy (such as those who initiate therapy through provider samples or manufacturer-sponsored free drug programs).

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To treat, or not to treat, That is the (*ethical*) question

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