Aducanumab (Aduhelm) Discussion: WAI Clinic Network

June 30, 2021

Talking points for the meeting:

- Who are potential candidates for aducanumab?
- Engaging patients and families - establishing expectations regarding aducanumab's efficacy and adverse effects
- Logistics of aducanumab's administration and monitoring
- Network members sharing event information and resources
- Next steps- what are the needs among our Network providers?

Who are potential candidates for aducanumab?

- Biogen's Phase 3 trials enrolled people with amnestic MCI or mild dementia due to AD, all with PET-confirmed amyloid buildup in the brain
- FDA prescribing label specifies only "Alzheimer's disease"
  - No contraindications listed despite higher risk of ARIA-related complications in persons numerous prior microhemorrhages or those on blood thinners
  - No information on what to do with patients who also have cerebral amyloid angiopathy or cerebrovascular disease
- Label does not require that the prescribing physician confirm the presence of brain amyloid
- No data on the safety and effectiveness of aducanumab in in the preclinical phase or moderate or severe AD

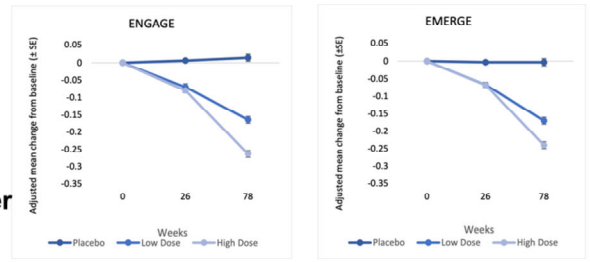
https://www.alzforum.org/news/research-news/how-will-aducanumab-approval-change-clinical-practice

Engaging patients and families - establishing expectations regarding aducanumab's efficacy and adverse effects

Does aducanumab slow Alzheimer's disease?

Biomarker

Figure 3.3. Change from Baseline in Aβ PET Composite SUVR in EMERGE and ENGAGE[22]



SE: standard error

Cognition

Mean change in CDR-SB* aducanumab vs placebo

	ENGAGE	EMERGE
High dose	0.39, p=0.01	not significant
Low dose	not significant	not significant

*CDR-SB = Clinical Dementia Rating scale, Sum of Boxes, 0-18; mean 2.4-2.5 at baseline; Lin et al. *Institute for Clinical & Economic Review* 5/5/21

Slide courtesy of Art Walaszek, MD

Logistics of aducanumab's administration and monitoring: How about the cost?

- the drug itself: $56,000 per year
- other costs:
  - amyloid PET or other way to establish amyloid positivity
  - infusion costs
  - baseline & surveillance MRIs
  - costs of managing ARIA
- who will pay?
  - Medicare
  - other payors
  - patients themselves

Slide courtesy of Art Walaszek, MD

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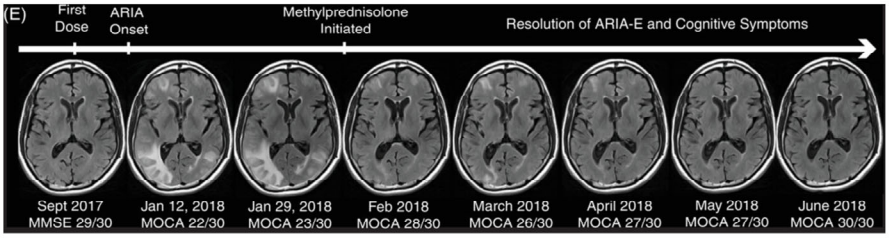
Wisconsin Alzheimer's Institute
Wisconsin Alzheimer's Disease Research Center

Sachs R, *Health Affairs* blog 6/10/21; Cubanski & Neuman, *Kaiser Family Foundation* 6/10/21: https://go.wisc.edu/qq32qf

If 1 million Medicare beneficiaries receive Aduhelm, which may even be on the low end of Biogen's expectations, spending on Aduhelm alone would exceed $57 billion dollars in a single year – far surpassing spending on all other Part B-covered drugs combined. In fact, this amount is roughly the same that Medicare paid for all hospital outpatient services in 2019. Medicare beneficiaries would face about $11,500 in coinsurance for one year of Aduhelm treatment, which represents nearly 40% of the $29,650 in median annual income per Medicare beneficiary in 2019. Because Aduhelm is not a cure for Alzheimer's disease, patients could incur these annual out-of-pocket costs over multiple years.

Logistics of aducanumab's administration and monitoring: What are the risks?



- ARIA-E* 35.0%
  - serious ARIA-E 1.0%
  - led to d/c 6.1%
  - higher risk if APO-e4(+)
  - higher risk with higher dose
- ARIA-H* 28.3%
- baseline MRI, plus at least 2 follow-up MRIs

- no contraindications listed in label, but may need to exclude:
  - people with history of CNS hemorrhage or extensive cerebrovascular disease
  - those who can't get an MRI
  - people taking anticoagulants

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* ARIA=amyloid-related imaging abnormalities, E=edema, H=hemorrhage; VandeVrede et al., *Alzheimer's & Dementia: DADM* 2020.

In 2016, he enrolled in the ENGAGE trial for aducanumab, and he was randomized to the placebo arm for the 78 weeks of the trial. Afterward, he entered the open-label extension and began uptitration toward a target dose of 6 mg/kg. He received two monthly doses of aducanumab at 1 mg/kg and two doses at 3 mg/kg, after which time, he developed sudden-onset explosive headaches and fluctuating confusion, and he self-diagnosed alexia without agraphia. He presented to the hospital, where his systolic blood pressure was 206/116 on admission to the intensive care unit (ICU) … On MRI, T2 fluid-attenuated inversion recovery (FLAIR) sequences revealed focal, confluent hyperintensities consistent with ARIA-E, and susceptibility weighted imaging (SWI) showed microhemorrhages consistent with ARIA-H … Approximately 1 month later, his alexia without agraphia worsened, and repeat MRI showed increasing FLAIR hyperintensities in the left inferior temporal lobe, corresponding to the focal neurologic symptoms. Electroencephalogram (EEG) revealed left temporal sharp waves (Figure **2D**), and he was started on levetiracetam and treated with intravenous methylprednisolone 1000 mg for 5 days without oral taper … In 2018, almost 1 year after his episode of ARIA, he returned to UCSF for repeat evaluation. He remained high-functioning, though he noticed worsening lexical memory and new facial recognition difficulties.

The sequence above shows: Sequential T2 FLAIR at the level of maximal edema, with subsequent resolution after treatment with intravenous steroids, with cognitive assessment showing resolution in parallel with ARIA-E.

- How can WAI help Clinic Network Providers?
  - Network members sharing event information and resources
    - Alzforum is great resource: https://www.alzforum.org/
  - Next steps- what are the needs among our Network providers?