Research America!

Anti-Amyloid Monoclonal Antibodies are Transforming Alzheimer Care and Research

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- History of Alzheimer and amyloid research
- What are anti-amyloid monoclonal antibodies?
- What’s next
History of Alzheimer and Amyloid Research

- Alois Alzheimer describes neurofibrillary tangles and “miliary foci” (amyloid plaques) in the brain of a woman with early onset dementia (1906)
- Named in honor of Dr. Alzheimer based on this early observation (Kraeplin, 1910)
- Sir Martin Roth discovers that the pathology of “senile dementia” is the same as that of Alzheimer’s disease (previously thought to be characteristic of rare early onset dementia)(1968)
- Robert Katzman notes the aging of the population and the high prevalence of “senile dementia/Alzheimer’s disease” and sees the coming epidemic
- Protein substance found to be amyloid (George Glenner, 1984)
- “Amyloid hypothesis” formulated (Hardy and Allsop, 1991; Hardy and Selkoe and Hardy, 2002)
The Amyloid Cascade Hypothesis

- AB Protein Aggregated in Plaques
- Neurofibrillary Tangles
- Inflammation
- Neuronal Death

2003-2016

- All clinical trials were negative
  - $A\beta$-directed
  - Non-$A\beta$-directed
- Enormous learnings about $A\beta$ were accruing
- Molecular biology studies showed that there were several “species” of amyloid
- Species have different toxicities and different treatment implications
Amyloid Brain Imaging: A Major Technological Advance

- First published 2005\(^1\)
- First amyloid PET approved by FDA 2012\(^2\)
- 2 more types of amyloid PET approved since
- All show amyloid plaque, not other species of amyloid

Immunotherapy Emerges

• Vaccination with $\alpha\beta$ produces marked reduction of brain amyloid plaques$^1$

Upper panels; amyloid deposition in mouse model of Alzheimer’s (no vaccination)

Lower panels; amyloid deposition in mouse model of Alzheimer’s (vaccinated)

Human Immunotherapy Trials: A Learning Process

• First human vaccination study (AN1792) is terminated early; 6% of patients develop an immune encephalitis\(^1\)

• Passive immunotherapy (with monoclonal antibodies targeting \(A\beta\)) trial with bapineuzumab is negative\(^2\)

• Other antibodies fail to show a drug-placebo difference in trials, none are directed at amyloid plaques or protofibrillar species of amyloid\(^3,4,5\)

• Study observations suggests the dose of the monoclonal antibodies is too low and that plaque reduction is important\(^6,7\)

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Aducanumab (Aduhelm®): The Turning Point\textsuperscript{1,2}

- Plaque focused
- Dose range explored to high dose
- Phase 1
  - High dose produced marker $A\beta$ reduction
  - Clinical measures supported disease slowing
- Phase 3
  - Trials prematurely terminated for erroneous interpretation of futility
  - Marked $A\beta$ plaque reduction
  - Clinical benefit in 1 study (Emerge) not the other (Engage)
- Controversial accelerated approval by the FDA

Consider This!

Lecanemab (Leqembi®) and Donanemab Confirm the Relationship Between Amyloid Lowering and Slowing of Clinical Decline

• Lecanemab (Phase 3)\(^1\)
  • Marked amyloid plaque lowering
  • Positive on primary clinical trial outcome (slowing of decline as measured by Clinical Dementia Rating Scale Sum or Boxes (CDR-SB))
  • Positive on all secondary outcomes (cognition, function)
  • Accelerated approval based on Phase 2; standard approval to be considered by FDA

• Donanemab (Phase 2)\(^2\)
  • Marked amyloid plaque lowering
  • Positive on primary clinical trial outcome (slowing of clinical decline as measured by integrated Alzheimer’s Disease Rating Scale (iADRS))
  • Phase 3 positive; details on yet published

ARIA: A Challenge that Must Be Managed

ARIA: amyloid related imaging abnormalities

Thought to result from amyloid removal from the blood vessel

Leakage of fluid or blood into the brain

15-30% of patients

Symptoms in 3-5% of patients

Rarely can be serious or fatal

80-90% recover and treatment can be continued

Must be monitored with periodic MRI

Immunotherapies are Unprecedented Therapies that Make New Demands on Health Care

- Early Alzheimer’s: must be recognized and diagnosed
- Alzheimer’s must be confirmed with lumbar puncture/spinal fluid studies or amyloid PET
- Patients must have MRI prior to treatment to ensure they do not have excessive brain vascular disease
- Treatments are given intravenously 1/m (donanemab) or 2/m (lecanemab)

- MRI must be obtained periodically in first 6-12 months
- ARIA can occur
- Reimbursement by CMS is uncertain
Where are We Now?

• Anti-amyloid monoclonal antibodies slow the progression of AD!
• These agents are the first disease-modifying therapies for AD
• These drugs are approved by FDA for the treatment of early AD confirmed to have brain amyloid
• Monoclonal antibodies require infusion and MRI monitoring
• Monoclonal antibodies have rare but important side effects (ARIA)
• Reimbursement of treatment with monoclonal antibodies is uncertain
What’s Coming Next?

• Monoclonal antibodies
  • Subcutaneous administration (to avoid IV requirement)
  • Diagnosis by blood test (to avoid lumbar puncture or amyloid PET)
  • Likely 2-3 year time frame

• Other types of treatment
  • Anti-tau ASO (administered through spinal tap every 3-6 months)
  • Anti-inflammatory agents
  • Synaptic agents
  • Metabolic agents
Some Larger Points

• Great demonstration of research and discovery leading to new therapies
• Illustration of the importance of breakthrough technology (amyloid PET)
• Reveals the need for health care system planning to incorporate unprecedented therapies for new (previously untreatable) patient populations
• Science forward!
Thank you
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