Alzheimer’s Disease: Focus on Diagnosis and New Treatments

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Disclosures

Consultant: Janssen Alzheimer Immunotherapy Research & Development, LLC
Learning Objective

Evaluate the emerging treatments for Alzheimer’s disease and applicability to current practice

Keeping Expectations Modest

- If your primary goal is cure, switch to ophthalmology or orthopedics
- Maintaining quality of life and function and relieving distress are important accomplishments
- Slowing disease progression is a primary goal

Definitions of Cognitive Syndromes

- **Dementia**: Impairment of memory and other cognitive functions caused by damaged brain structure
- **Delirium**: Impairment of attention and level of consciousness caused by disrupted brain physiology

One in Eight Older Americans Has Alzheimer's Disease

- Alzheimer’s disease (AD) is the most common cause of the dementia syndrome in later life
- 5.4 million cases in the United States


Differential Diagnosis of Alzheimer’s Disease

- Dementia with Lewy bodies
- Vascular dementia
- Frontotemporal dementia
- Alcoholism-related dementia
- Severe depression


The Clinical Diagnosis of Typical AD

- First, insidious onset of gradually progressive memory and executive function impairment
- Then, worsening language function
- Then, episodic disruptive agitation and other behavioral problems

Neuropathology of AD

- Neuritic plaques of aggregated beta-amyloid
- Neurofibrillary tangles of hyperphosphorylated tau

Genetics of AD

- The ε4 allele variant of apolipoprotein E is a major risk factor for AD
- Three rare, autosomal-dominant mutations cause early-onset AD (mutations in presenilin 1, presenilin 2, and amyloid precursor protein genes)

AD Biomarkers

- PET imaging of brain beta-amyloid protein in aggregated form
- Cerebrospinal fluid decreased beta-amyloid and increased tau concentrations
Beta-Amyloid PET Imaging Ligands

- $[^{11}\text{C}]$ Pittsburgh Compound B (PIB)
  - Currently available, but short half-life (20 minutes), requires close proximity to cyclotron
- $[^{18}\text{F}]$–AV-45
  - Recently approved by FDA
  - Longer half-life (110 minutes), enhances availability


Role of Beta-Amyloid

- Genetic and preclinical data support pathogenic role of beta-amyloid in AD
- Question: If beta-amyloid is pathogenic in AD, would drugs be effective “disease modifying” treatments if they either:
  - Decrease beta-amyloid production?
  - Increase beta-amyloid removal?


Decreasing Beta-Amyloid Production Is Not Beneficial in AD

- Gamma secretase inhibitors not superior to placebo, and can potentially be harmful at high doses

The Anti-Amyloid Antibodies Approach to Treating AD

- Transgenic AD mice show marked reduction in amyloid plaque deposition when actively immunized against beta-amyloid
- Active beta-amyloid immunization in humans produced apparent reduction of amyloid plaque density, but no clear cognitive benefits
- 6% incidence of meningoencephalitis


Would Passive Monoclonal Anti-Amyloid Antibody Approaches Be More Effective and Less Toxic?

- Bapineuzumab*: N terminus-directed beta-amyloid monoclonal antibody in clinical trials
  - Primary efficacy outcomes in Phase 2 trial not significant
  - Signal for efficacy in ε4-negative subjects in Phase 2 trial
- Solanezumab*: Mid-domain-directed beta-amyloid monoclonal antibody in clinical trials
  - Antibody design targets soluble beta-amyloid

* Investigational agents for use in AD; not FDA-approved for the prevention or treatment of AD


Recently Reported News

- Bapineuzumab was not superior to placebo in phase 3 trials in either ε4-positive or ε4-negative subjects
- Solanezumab not superior to placebo in two large, phase 3 trials
  - But, analysis of the combined samples suggested small slowing effect on cognitive function at 18 months in the subjects with milder AD (this effect substantially smaller than seen with cholinesterase inhibitors)
  - Would a higher dose of solanezumab produce a more clinically meaningful benefit?

Cholinesterase Inhibitor Clinical Experience and Clinical Trials Support Its Reduction of AD Progression

- Persistent “symptomatic” treatment appears to slow clinical progression
- Delayed-start design: persons first on placebo and then switched to a cholinesterase inhibitor do not catch up
- Sounds like disease modification to me


Persistent Treatment With Cholinesterase Inhibitors and/or Memantine Slows Progression of AD

- 641 AD patients followed at Baylor College of Medicine for over 20 years
- Persistent treatment with donepezil, other cholinesterase inhibitors, and memantine slowed AD progression as assessed by multiple cognitive, functional, and global measures


Galantamine Shows Sustained Cognitive Benefits in AD Over 12 Months Including a Delayed Start Time

ADAS-Cog = Alzheimer's Disease Assessment Scale—Cognitive
### Long-Term Data:
Change From Baseline in ADAS-Cog/11 Scores

![Graph showing Long-Term Data: Change From Baseline in ADAS-Cog/11 Scores]

ADAS-Cog = Alzheimer’s Disease Assessment Scale—Cognitive

### Memantine in AD

- Memantine, a drug of unknown mechanism, has received FDA approval for moderate to severe AD\(^1\)
- Some studies support adding memantine to a cholinesterase inhibitor\(^*\) for long-term management of AD\(^2\)

\(^*\) Not an FDA-approved use of this agent


### Clinical Connections

- There remain many unknowns in understanding Alzheimer’s disease
- New treatments offer hope but progress is slow
  - Is beta-amyloid the basic cause or a “downstream” result?
  - Will drugs targeting the hyperphosphorylated tau of neurofibrillary tangles be effective?
Bapineuzumab Decreases $^{11}$C-PIB Aβ Load

- 28 AD patients assigned to bapineuzumab (n=20) or placebo (n=8).
- Treatment with bapineuzumab for 78 weeks reduced cortical $^{11}$C-PIB amyloid load compared to baseline and placebo.
- But, in this small subsample, effects on clinical endpoints were disappointing and did not appear related to effects on Aβ binding.


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Role of Beta-Amyloid (cont’d)

- If beta-amyloid is pathogenic in Alzheimer’s disease, would drugs be effective treatment if they either:
  1. Decrease beta-amyloid production
  2. Increase beta-amyloid removal

36-Month Galantamine Trial

- Does a greater rate of cognitive decline in dropouts than in 36-month completers explain results?
- No! Rate of decline prior to galantamine discontinuation in dropouts was the same as in completers.


Comparison of Slopes of ADAS-Cog Decline Between Dropouts and Completers

ADAS-Cog = Alzheimer’s Disease Assessment Scale—Cognitive