CLINICAL TRIALS IN ALZHEIMER’S DISEASE

Drama or Dramamine?

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1906

Amyloid Plaques

Tau Tangles
The Creation of Amyloid

Amyloid (Aβ) Fragment
The Toxic Effect of Amyloid

Amyloid (Aβ) Fragments → Amyloid Oligomers → Amyloid Plaques

Brain Toxicity
Development of Alzheimer’s Disease

Genetic Factors → Abnormal Amyloid Deposition → Tau Tangle Formation → Neuron Loss → Dementia

Environmental Factors

Age
Prevalence of AD

- Aged 65: 2.5%
- Aged 70: 5%
- Aged 75: 10%
- Aged 80: 20%
- Aged 85: 40%

- Doubling of prevalence with every 5 years of age after age 65
- Dementia due to Alzheimer’s disease (AD) is a clear threat to an aging population
The Threat of Alzheimer’s

- US prevalence


4.5 million (2000) → 13.2 million (2050)
The Threat of Alzheimer’s

- In Canada
  - 2012: Estimated 747,000 Canadians have Alzheimer's or a related dementia
  - 2038: Estimated 1,125,000 Canadians will have Alzheimer's or a related dementia
    - Economic cost rising from $15 billion in 2008 to $150 billion in 2038

Alzheimer Society of Canada “Rising Tide” Study (January 2010)
Support of the “Amyloid Hypothesis”

- Mutations associated with early-onset plaque/tangle dementia all lead to excessive amyloid production
  - Amyloid-precursor Protein (APP)
  - Presenilin-1 (gamma-secretase)
  - Presenilin-2 (gamma-secretase)
- Down Syndrome (APP located on 21)

- Amyloid oligomers induce tau hyperphosphorylation and neurodegeneration in vitro and in vivo
Anti-amyloid vaccination
Anti-amyloid vaccination

- **AN1792**
  - Amyloid fragment+adjuvant SC
  - Induced anti-amyloid antibody titre (in most)
  - Induced meningoencephalitis in 6% of subjects (headache, encephalopathy, ataxia, focal)
  - Study halted in 2002

- Long-term follow-up of cases
  - Plaque load decreased
  - Small but statistically significant difference in functional decline in antibody responders (1/2200) after 4.6 years

Alzhemed/tramiprosate

- Developed in QC
- Binds amyloid in vitro and in vivo (crosses blood-brain barrier)
- Prevents oligomerization

- n=1052; randomized, placebo-controlled, double-blinded
- Oral BID dosing; 18 months
- ADAS-Cog and CDR-SB endpoints

- No safety concerns
- No statistically significant difference found between treated and placebo groups

Flurizan/tarenflurbil (flurbiprofen)

- Inspired by epidemiological studies indicating less dementia in patients taking NSAIDs and ibuprofen
- Flurbiprofen found to modulate γ-secretase and lower amyloid levels in vitro

- n=1649; randomized, placebo-controlled, double-blinded
- Oral BID dosing; 18 months
- ADAS-Cog and ADCS-ADL endpoints

- Mild dizziness, anemia, increased infection rate
- No statistically significant difference found between treated and placebo groups

JAMA. 2009 Dec 16;302(23):2557-64.
Anti-amyloid Antibodies

- Passive immunization by way of intravenous infusion qmonthly or q3monthly
- Each targeted against different epitope of amyloid peptide, some binding monomers > fibrils or vice-versa
- Highly effective in reversing cognitive decline in mouse models of AD

- Bapineuzumab
- Solanezumab
- Crenezumab
- Gantenerumab
- Aducanumab
Bapineuzumab

- Anti-amyloid antibody against fibrillar form of Aβ
- Phase 2 studies showed occurrence of vasogenic edema, especially in ApoE4 carriers
- Renamed ARIA (amyloid-related imaging abnormalities)

- Occurred in ~10%
- Half mildly symptomatic (headache, ataxia)
- Resolves with suspension of treatment
Amyloid-related Imaging Abnormalities (ARIA)

Temporal course of ARIA on MRI

Baseline 1st Dose Week 6 Dose Suspension Week 16

ApoE ε 4/4 carrier in 1.0mg/kg in phase 2 bapineuzumab trial; asymptomatic
Bapineuzumab

- n=1121 (ApoE4 carriers) + 1331 (ApoE4 non-carriers)
- 1-hour IV infusion q3monthly; 18 months
- ADAS-Cog and DAD endpoints

- ARIA-E occurred more frequently in ApoE4 carriers (~10%)
- No statistically significant difference found between treated and placebo groups

Solanezumab

- n=1012 and n=1040
- 1 hour IV infusion qmonthly; 18 months
- ADAS-Cog and ADCS-ADL endpoints

- ARIA-E occurred infrequently (~1%)
- No statistically significant difference found between treated and placebo groups

A Ray of Hope?

Pooled Phase 3 Solanezumab trials, mild AD (MMSE 20-26) patients only (n=1322)

Crenezumab

- n=247
- IV infusion qmonthly; 68 weeks
- ADAS-Cog and CDR endpoints
- ARIA occurred in only one case
- No statistically significant difference found between treated and placebo groups
Crenezumab
Aducanumab

Slowing of Decline on CDR-sb with Aducanumab

Adjusting mean change from baseline (±SE)

Placebo (n=36, 36, 31)
Aducanumab 1 mg/kg (n=28, 28, 23)
Aducanumab 3 mg/kg (n=30, 30, 27)
Aducanumab 6 mg/kg (n=27, 27, 26)
Aducanumab 10 mg/kg (n=28, 28, 23)

Difference from placebo at Week 54
-0.15
-0.50
-0.76
-1.24

Analysis visit (weeks)

Test of linear trend of dose response p < 0.05

Alzheimer’s Association International Conference 2015
Nature 537, 50–56 (01 September 2016)
Reasons for Overall Failure

- Patients too advanced
  - Too much neurodegeneration has already occurred

- Patients too heterogeneous
  - Alzheimer’s disease vs. “mixed vascular dementia”

- Dosing Inadequate (due to side effects)

- Cognitive Measures Inadequate

- “Amyloid Hypothesis” is incorrect
Mild Cognitive Impairment (MCI)

<table>
<thead>
<tr>
<th></th>
<th>Normality</th>
<th>MCI</th>
<th>Dementia</th>
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<tbody>
<tr>
<td>Cognitive Symptoms</td>
<td>Yes or No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cognitive Testing</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Functional (ADL)</td>
<td>Intact</td>
<td>Intact</td>
<td>Impaired</td>
</tr>
</tbody>
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Natural History of MCI

Purpose of MCI Diagnosis

- MCI diagnosis provides “warning state” for increased risk of future worsening of cognitive symptoms

- Rate of decline to dementia is ~10-15% per year in MCI, while only ~1-2% in general population (aged 65 or older)
  

- Most, but not all cases progress

- Patient’s mild cognitive concerns are not dismissed, and increased follow-up can be provided
Treatment of MCI

- Multiple treatment trials have been negative
  - Aricept/donepezil
  - Exelon/rivastigmine
  - Reminyl/galantamine
  - Rofecoxib
  - Piracetam
  - Ampakine CX516

- No treatment currently approved for MCI
Amyloid Imaging

- Pittsburgh compound-B (PiB) or florbetapir, IV injection (10 mL) followed by PET acquisition 50 minutes later lasting 10 minutes.
Solanezumab Second Phase 3

- Mild dementia only (MMSE=20-26)
- Amyloid presence confirmed via amyloid-PET or CSF measures
- n=1822
- IV infusion qmonthly; 76 weeks
- ADAS-Cog primary endpoint
- Results released November 2016
Solanezumab Second Phase 3

EXPEDITION3: Solanezumab Initiated in Mild AD Dementia

Change in Cognition - ADAS-Cog$_{14}$ (Primary)

- Placebo n=1067
- Solanezumab n=1053

*p≤0.05; **p≤0.01

11% Slowing in Decline

Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study.

Abbreviations: AD=Alzheimer's disease; ADAS-Cog$_{14}$=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error.
Solanezumab Second Phase 3

EXPEDITION3: Solanezumab Initiated in Mild AD Dementia
Change in Composite Scale - CDR-SB

Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD = Alzheimer’s disease; CDR-SB = Clinical Dementia Rating Sum of Boxes; LS = least squares; n = number; SE = Standard Error.
Currently in Phase 3

- **Crenezumab**
  - Phase 3 in MCI and mild dementia/AD (Amyloid+ proven)
  - Begun 2016
  - Additional study underway in “pre-symptomatic” autosomal dominant AD mutation carriers in Colombia, South America

- **Aducanumab**
  - Phase 3 in MCI and mild dementia/AD (Amyloid+ proven)
  - Begun 2016
β-secretase (BACE) Inhibitors

- Verubecestat
- LY3314814

- Oral once-daily administration
- Currently in Phase 3 studies in MCI and mild dementia/AD
A4 (Anti-Amyloid Asymptomatic Alzheimer’s) Study

- Asymptomatic patients
- Normal neuropsychological profile
- Evidence of amyloid positivity on amyloid-PET

- Randomized to IV solanezumab vs. placebo

- Followed cognitively over 4+ years
Tau Imaging

- AV-1451 Tau-PET tracer (flortaucipir)
Tau-directed therapy

- Tau-aggregation Inhibitor (TAI)
  - TRx0237
  - Oral BID dosing
  - Phase 3 studies in mild/moderate dementia/AD and bvFTD
  - July 2016: Negative results in AD
  - August 2016: Negative results in bvFTD

- Anti-Tau antibody in Phase 1 studies
Conclusions

- The “amyloid hypothesis” remains under intense investigation by way of numerous Phase 3 studies
  - Intravenous anti-amyloid antibodies
  - Oral β-secretase (BACE) inhibitors
- Studies are selecting for mildly affected or asymptomatic patients, with biomarker-proven amyloidopathy (i.e. amyloid-PET, CSF)
- Anti-tau therapies also in development
- Results continue to be forthcoming