ISCTM 2014 presentation
20 Years of Clinical Trials in AD: Some Lessons Learned

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Clinical Presentation of Dementia
Outcomes of Relevance in Trials May Vary by Dementia Type
Eventually the Field Reconceptualized AD disease as a Continuum; Criteria Are Evolving
Initial Registration Trial Designs:
“Symptomatic”

• Neurotransmitters as targets
• Assess effects over 3-6 months
• Rely on change scores for efficacy
• 2 co-primary outcomes
  • Cognition (FDA, EMA) (e.g., ADAScog)
  • Function (EMA)
  • Global status (FDA)
• Superiority over active comparator not required
• Gradual increased in use of stratification variables
  • Severity of dementia
  • APOE e4 status
• The approach worked: 4 cholinesterase inhibitors and memantine approved
  • Beware of the canard: “these are not important”
Initial Registration Trial Designs

- Used diagnostic criteria from 1984; not updated until 2011
- Impact of inclusion of at least 20-30% subjects with non-AD dementia
- Mostly mild-moderate severity of dementia
  - Viewed as the salient clinical population, early success of tacrine
- Most cognitive measures also from 1980’s
  - Incremental changes in measures (role of ADCS)
  - Relatively effort to optimize quality
- Why did we wait?
  - Conservatism? (“It is a safe path forward”)
  - Sled dog phenomenon?
  - Could we have found better measures and methods, sooner?
- Mainly ignored background therapy
- Registration trials tend not to inform practice
  - Not their goal
  - Examples: what drug is most effective; how long to treat; what about other doses, combinations; long term safety
Examples of Efficacy results with ChEI Monotherapy in Mild to Moderate AD

Cognition: MMSE

Function: ADCS-ADL

Global: CIBIC-Plus

*P<.05; †P<.01; ‡P≤.001.
CIBIC-Plus = Clinician's Interview-Based Impression of Change with caregiver input; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living inventory.
Memantine Monotherapy in Moderate to Severe AD: Efficacy

**Cognition: SIB**

- Difference in score
- Week 0, 4, 12, 28
- End Point (LOCF)
- *P* = .068, *P* < .001
- *P* = .002, *P* < .001

**Function: ADCS-ADL**

- Difference in score
- Week 0, 4, 12, 28
- End Point (LOCF)
- *P* = .145, *P* = .106
- *P* = .003, *P* = .02

**Global: CIBIC-Plus**

- Percentage of Patients
- CIBIC-Plus Global Score
- Week 0, 4, 12, 28
- *P* = .003, *P* = .001
- *P* = .068, *P* = .002

SIB = Severe Impairment Battery.

Evolving Registration Trial Designs

- General failure in “anti-dementia” trials to grapple with behavioral outcomes
- Gradually explored more severe and milder AD dementia
- Other dementias: VaD, DLB, PD; some FTD
  - But few “mixed” dementia studies
- Typically longer duration
- New regulatory and design questions
  - How long to treat?
  - How to measure change?
- Began to address other pathobiological targets
- Eventual MCI studies
  - A recognized condition?
Treating Behavioral Changes in Dementia: A Vexing Public Health Issue

- Cardinal features of dementia
  - Impact of specific dementia diagnosis
  - Major cause of morbidity, medical involvement
  - Driver of cost
  - Exaggerate functional/cognitive deficits
- Most trials show limited/no benefit
  - Disconnect between data showing limited/no efficacy and clinical practice
- No treatment is FDA approved
  - Disconnect between clinical indication and regulatory approval
- Overall, an example of inherent limitations of “evidence based medicine”
  - Blending different outcomes/goals/purposes
Finding Targets: A Proposed Temporal Progression Of AD

Genetic Factors
- APP mutations
- Presenilin 1,2 mutations
- APOE4 alleles
- Family history
- APOE2 alleles protects
- APP/BACE mutation protects

Environmental Factors
- Head Injury
- Toxins

Age

Endogenous Factors
- Diet
- Cardiovascular risk factors
- Diabetes
- Smoking
- Education
- Menopause
- Physical/Mental Activity

Protective Factors
- Estrogen?
- Anti-inflammatory Drugs?

Net effect = stress and vulnerability to stress

Molecular Phenotype

INITIAL STRESSORS
- Proximal Apoptosis
- APP dysregulation
- Impaired neurotrophic function
- Oxidative stress
- Excitotoxicity

FAILED STRESS RESPONSE
- Cell cycle dysregulation
- Kinase/phosphatase dysfunction
- Protein misfolding
- Altered DNA repair
- Vascular/membrane dysfunction

CELL INJURY
- Inflammation
- Cytoskeletal dysfunction
- Synaptic dysfunction
- Mitochondrial damage

CELL DEATH
- Distal apoptosis
- Neurotransmitter failure

Neuropathology

Normal

Clinical Phenotype

Normal

Normal

Normal

Mild Cognitive Impairment

Dementia

The figure depicts apparently continuous processes, though they are likely to be asynchronous. Yaari and Tariot 2008
Using Information From Multiple Sources to Improve Diagnosis and Assess Treatment

- Neuronal Activity
  - FDG PET
- Fluid Biomarkers
- Cognitive Reserve
  - fMRI
- Plaque Load
  - Amyloid PET
- Brain Atrophy
  - Structural MRI
- Genetic Risk Profile
- Cognitive, Functional Profile
How Might Promising Advances in AD Treatment Address Unmet Needs?

- **Symptomatic**
  - Improved efficacy
    - Cognition
    - Function
    - Behavior
  - Being pursued in several trials now
  - Enduring response
  - Fewer side effects
  - Simple to administer
  - Reduced number of treatment unresponsive patients

- **“Disease modification”**
  - Increase neuroprotection against pathology, e.g.:
    - Impact Aβ dysregulation
    - Impact processes leading to neurofibrillary tangles
  - Reverse existing neuronal damage?
  - Address other aspects of pathobiology

- **Slow, delay or even prevent disability**

Trial Designs for Emerging Therapies Aimed at Slowing Progression

- **Phase 2** data become more important, but what to use as go signal?
  - Is there a translatable pharmacodynamic signal?
  - Are there interpretable effects on disease related or “downstream” biomarkers in humans?
  - Is there any clinical signal?
    - Or must we go to phase 3 to get answers?
  - Are dosing, safety and tolerability clarified?

- **Phase 3** designs use clinical outcomes:
  - Assess treatment over extended time period, e.g., 12-36 months
  - Compare change scores? slope of performance over time?
  - Prior FDA design suggestion: staggered start or stop
  - Survival approaches?

- **Biomarkers** embedded in phase 2/3 to explore response to treatment, relationship with clinical outcomes, possible predictive utility
  - In some cases, used as outcomes
Phase 2 Clinical Results as Basis for Phase 3: Tarenflurbil (gamma secretase modulator) Cognition in Mildly Impaired AD Subjects

Mean Change in ADAS-cog

Mean Change in ADAS-cog

Effect Size ($d=52\%$)
Slope Comparison*:

- $p=0.109$ (800 vs. placebo 0-12)
- $p=0.013$ (800 vs. 400)

Negative Tarenflurbil Phase 3 Results

Figure 2. Alzheimer Disease Assessment Cognitive Subscale and Alzheimer Disease Cooperative Studies–Activities of Daily Living Scale Scores by Visit

Values represent means using imputed last observation carried forward. Error bars represent 95% CIs.

Source: Green et al JAMA 2009
Anti-amyloid Immunotherapy AN 1792: Amyloid “Vaccine” Reduces Plaque Burden and Memory Loss in Transgenic Mouse Model of AD

Amyloid Stain (Mouse Brain)

Unvaccinated

Vaccinated

Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse


Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA

AN 1792 Vaccination in Humans: Reversal of AD Neuropathology, But New Toxicity, No Clinical Benefit

Neuropathology of human Alzheimer disease after immunization with amyloid-β peptide: a case report

JAMES A.R. NICOLL1,2, DAVID WILKINSON1, CLIVE HOLMES3, PHIL STEART6, HANNAH MARKHAM1,2 & ROY O. WELLEH1,2

Parietal neocortex, non-immunized patient at comparable stage of AD

Parietal neocortex, immunized AD patient in Elan AN-1792 Trial

Bapineuzumab Phase 2 Clinical Outcomes as Partial Basis for Phase 3 (Salloway et al 2009)
Bapineuzumab Phase 2 PIB-PET Data (Rinne et al 2010)

*Figure 2: Estimated change from baseline over time in mean $^{11}$C-PiB PET
Data are least squares means and 95% CIs. *Difference between patients in the placebo group and those in the bapineuzumab group at week 78 = $-0.24$ (p=0.003). PiB=Pittsburgh compound B.*
Bapineuzumab Phase 2 Safety: Vasogenic Edema (ARIA-E)

• 12/124 (9.7%) patients on bapi (vs 0 on placebo) developed vasogenic edema (VE)
  • Most frequently detected by MRI, with few or no clinical symptoms in most cases, and resolved in weeks to months
Negative Bapineuzumab Phase 3 Results

A. ADAS-cog11

B. DAD
Solanezumab Phase 2: Safety and Pharmacodynamic Data as Basis for Phase 3

• Safety, tolerability and biomarker effects in AD patients and controls
  • AD patients: 12 weekly infusions, 4 doses vs placebo
  • Controls: 1 single dose-100 mg solanezumab

• Total (bound + unbound) plasma Aβ_{1-40} and Aβ_{1-42} increased, dose-dependent manner

• Total CSF Aβ_{1-40} and Aβ_{1-42} increased
  • Viewed as proof of concept
  • Peripheral sink hypothesis

• Well tolerated

"Negative" Solanezumab Phase 3 Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean Change from Baseline to Wk 80 (95% CI)</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-cog11 score‡</td>
<td>4.5 (3.3 to 5.8)</td>
<td>3.8 (2.5 to 5.0)</td>
<td>-0.8 (-2.1 to 0.5)</td>
</tr>
<tr>
<td>ADAS-cog14 score‡</td>
<td>5.8 (4.3 to 7.3)</td>
<td>4.5 (2.9 to 6.0)</td>
<td>-1.4 (-2.9 to 0.2)</td>
</tr>
<tr>
<td>ADCS-ADL score‡</td>
<td>-8.7 (-10.4 to -7.0)</td>
<td>-9.1 (-10.9 to -7.4)</td>
<td>-0.4 (-2.3 to 1.4)</td>
</tr>
<tr>
<td>CDR-SB score§</td>
<td>1.8 (1.3 to 2.3)</td>
<td>2.0 (1.5 to 2.4)</td>
<td>0.1 (-0.3 to 0.6)</td>
</tr>
<tr>
<td>NPI score¶</td>
<td>0.6 (-1.5 to 2.6)</td>
<td>-0.3 (-2.4 to 1.7)</td>
<td>-0.9 (-2.6 to 0.8)</td>
</tr>
<tr>
<td>MMSE score</td>
<td>-2.0 (-2.8 to -1.2)</td>
<td>-1.4 (-2.2 to -0.6)</td>
<td>0.6 (0.0 to 1.2)</td>
</tr>
<tr>
<td>Free Aβ₄₀ in CSF — pg/ml</td>
<td>80.9 (-2100.5 to 2262.3)</td>
<td>-1127.3 (-3272.4 to 1017.9)</td>
<td>-1208.2 (-2132.4 to -283.9)</td>
</tr>
<tr>
<td>Free Aβ₄₂ in CSF — pg/ml</td>
<td>-28.5 (-160.0 to 102.9)</td>
<td>-54.4 (-186.7 to 77.9)</td>
<td>-25.8 (-88.3 to 36.9)</td>
</tr>
<tr>
<td>Total Aβ₄₀ in CSF — pg/ml</td>
<td>-1902.1 (-6660.1 to 2855.8)</td>
<td>1325.4 (-3162.0 to 5812.9)</td>
<td>3227.6 (1253.6 to 5201.5)</td>
</tr>
<tr>
<td>Total Aβ₄₂ in CSF — pg/ml</td>
<td>-242.3 (-1144.4 to 659.7)</td>
<td>471.4 (-436.0 to 1378.8)</td>
<td>713.7 (309.1 to 1118.4)</td>
</tr>
</tbody>
</table>
Phase 2 Biomarker Data as Basis for Phase 3: Semagacestat Decreased CNS Aβ Production in Normals (Phase 3 showed no clinical benefit, and mild cognitive (and other) toxicity)

Bateman et al Ann Neurology 2009
Some Lessons From More Recent Trials

- Most now using updated AD diagnostic criteria
  - For AD dementia, MCI, and “preclinical” AD
- Will more refined cognitive (and functional, global, behavioral) measures and methods work better?
  - Empirically derived cognitive composite measures
  - Centralized expert raters
  - Computerized testing
  - Home based, telephonic, internet based assessments
- Translation of animal data to human, e.g., transgenics, remains problematic
- Phase 2 design/decision making still challenging
- New approaches to enrollment needed, including minorities
  - Alzheimer’s Association TrialMatch
Role of Biomarkers Evolving: Humility Needed

- **Diagnostic:**
  - CSF, fDG PET, amyloid PET can have a role in improving *diagnostic* accuracy
  - e.g., about 35% of amyloid (-) APOE4 noncarriers in bapi, sola
  - suggests utility of enrolling amyloid (+) patients in anti-Aβ trials
  - But emerging information about “indeterminate” amyloid PET results (27%, K. Johnson, 2013 CTAD)

- **Prognostic:**
  - e.g., more rapid decline in amyloid (+) subjects; offers rationale for trial inclusion criterion

- **Pharmacodynamic:**
  - Fluid biomarkers offer PD signals for some drug development decisions, e.g., BACE inhibitors show lowering of CSF AB; fluid antibody levels increase with passive immunization
  - Utility of amyloid PET for PD uncertain

- **Predictive and theragnostic potential:** unknown
“Prevention” Research

- Lack of clinical impact of anti-Aβ therapies so far may reflect weak and/or off-target effects
  - and/or lack of potential for effect once brain is ravaged
- A preclinical stage of AD exists during which silent pathobiological and neuropathological changes occur
- Earlier treatment *may* slow the progression of AD in this silent phase
- Prior trials using survival to dementia failed to show benefit
  - Gingko biloba, NSAID’s, HRT
- New prevention trials are already underway or planned
  - Different approaches to enrichment, outcomes
  - “Coalition for Alzheimer’s Prevention”
- New FDA guidance
  - Possibly change in cognitive performance alone
  - Role of biomarkers TBD
Double-blind, placebo-controlled 5 year trial crenezumab 300 mg SC every 2 weeks

Primary endpoint: change in the API composite cognitive score
24-mo interim analysis: florbetapir PET, FDG PET, MRI, CSF & cognitive/clinical endpoints

300 PSEN1 E280A kindred participants from Colombia

Launched 2013
The optimal ages to track preclinical AD cognitive decline:
60-75 in homozygotes; 70-80 in heterozygotes

Ayutyanont et al, AAIC Abstr 2013
API APOE4 Trial

- 650 participants
  - All APOE4 homozygotes
  - Will disclose genetic status and monitor impact of disclosure
- 5 year trial to study efficacy of a TBD treatment by comparing change in cognition (& biomarkers)

Interested individuals who either know APOE4 status or willing are willing to undergo genetic testing and disclosure

325 TREATMENT ARM

325 PLACEBO ARM

Trial estimated to begin 2015
Other New Prevention Studies

- **TOMMOROW**
  - Examine genetic profile as predictor of risk for developing MCI due to AD in cognitively unimpaired people
    - APOE, TOMM40, Age (65-83)
  - Test safety and effectiveness of low dose pioglitazone in delaying the onset of MCI
    - n>5000
    - about 5 years’ duration of treatment (survival approach)

- **ADCS A4**
  - Test safety and effectiveness of solanezumab in cognitively unimpaired people with amyloid positive PET scan
    - about 1100 (400 amyloid (-) /100 amyloid indeterminate will be followed); age 65-85
  - Cognitive outcome, 3 years treatment

- **DIAN**
  - Test solanezumab & gantenerumab in people with different ADAD mutations
    - Small n
    - Biomarker outcome, 1-2 years treatment
• Alzheimer’s Prevention Registry
  • [Website: www.endALZnow.org](http://www.endALZnow.org)
  • [Phone: 1-888-STOP-ALZ](tel:1-888-STOP-ALZ)
  • [Email: info@endALZnow.org](mailto:info@endALZnow.org)
Some Lessons Learned

- Early AD drug development “worked”
  - Drugs undervalued
- Relying on outdated diagnostic criteria
- Slow to deal with pathological heterogeneity
- Using outdated clinical tools
- Slow adoption of:
  - “modern” QI methods
  - novel outcomes
  - novel designs
- Failing our patients with neuropsychiatric symptoms
- How best to inform practice?
- Many new targets
  - e.g., AlzForum Therapeutics Home Page
  - Will we move beyond “pathology focus?”
  - Non-drug interventions
- Evolution of biomarkers, understanding their use in drug development
- Phase 2 decision making remains treacherous
Some New Themes and Questions

- Ethical issues: disclosing genetic or biomarker risk; possible changes in community standards for disclosure
- Data and sample sharing: NIH requirement
- Assuring that all stakeholders are involved
- Precompetitive collaboration
  - Sharing placebo data, discovery/development, methods
- New approaches to enrollment
  - Including prospective cohort studies?
- New approaches to funding
  - Private/private
  - Public/private
  - Impact of philanthropy
- Potential for adaptive designs
  - Other designs: e.g., run-in?
- Non-drug interventions; or targeting nonpathological factors?
- Incorporating new data gathering technologies?
- Risk-based monitoring?
- Enrichment strategies: biomarker, genetic (DTC), DBS, TBI
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