Dementia: Study Designs, Methodologies & Regulatory Perspectives – One Size Does Not Fit All

Chairs
Prof Pierre Tariot
Dr Jill Rasmussen
Defining the Problem
Session Overview

Dr Jill Rasmussen
Declarations of Interest

Jill Rasmussen

NHS:
- East Surrey CCG Commissioning Lead for Mental Health Learning Disability and Dementia
- Strategic Clinical Network Lead Dementia SE Coast
- Co-developer of MoodHive (Depression Anxiety Pathway)

Royal College of General Practitioners:
- Chair Learning Disability Special Interest Group
- Clinical Champion Dementia

Consultancy / Advisory Boards / Speakers Bureau:
- Chair Lewy Body Society, Advisor to Alzheimer’s Society
- Autism Therapeutics, AstraZeneca, Chronos, Lilly, Napp, Novartis, Otsuka, Pfizer, Roche, Servier, Targacept, TauRX
Considerations in Dementia

Ref: Changing the Trajectory of Alzheimer’s Disease: A National Imperative Alzheimer’s Assoc 2010.
Considerations in Dementia

Figure 5: Impact of a 5-Year Delay in Onset by Stage of Disease, Americans Age 65 and Older with Alzheimer’s Disease, 2050

- 2050 Current Trajectory:
  - Mild: 23%
  - Moderate: 29%
  - Severe: 48%
  - Total: 13.5 Million

- 2050 Delayed Onset:
  - Mild: 25%
  - Moderate: 30%
  - Severe: 45%
  - Total: 7.7 Million

Ref: Changing the Trajectory of Alzheimer’s Disease: A National Imperative Alzheimer’s Assoc 2010.
Considerations in Dementia

Ref: Changing the Trajectory of Changing the Trajectory of Alzheimer’s Disease: A National Imperative Alzheimer’s Assoc 2010.

Figure 6: Impact of a 5-Year Delay in Onset on Costs, Americans Age 65 and Older with Alzheimer’s Disease, 2010–2050

Cost in Billions of Dollars

- **Current Trajectory**: $172, $202, $240, $297, $408, $547, $717, $906, $1,078
- **Delayed Onset**: $172, $202, $190, $196, $239, $311, $407, $522, $831
- **Reduced Cost**: $0, $0, $50, $111, $170, $236, $310, $384, $447

*All cost figures are reported in constant, 2010 dollars and do not include inflation. Costs of care include the same categories of costs for medical care, nursing home and other residential care, paid in-home and community-based services, and medications that were included in the current trajectory costs.*
Dementia Differential Diagnosis

Vascular dementias
- Multi-infarct dementia
- Binswanger’s disease

Dementia with Lewy bodies
- Parkinson’s disease
- Diffuse Lewy body disease
- Lewy body variant of AD

AD and dementia with Lewy bodies

Other dementias
- Frontal lobe dementia
- Creutzfeldt-Jakob disease
- Corticobasal degeneration
- Progressive supranuclear palsy
- Many others

Alzheimer’s Disease

5% 10% 65% 5% 7% 8%
Considerations in Dementia

- Although Alz Dis is commonest cause of dementia and pure form does exist it commonly exists with diseases that contribute to cognitive impairment:
  - Lewy Body disease, vascular brain injury, hippocampal sclerosis, TDP-43 inclusions
  - Also Physical co-morbidity

- The extent to which Autosomal dominant (PSEN1, PSEN2 and AP) gene mutations, ApoE and other genetic variations & environmental risk factors impact neuropathological changes is unknown

- Many other neurodegenerative disorders that can cause dementia may be co-morbid with Alz disease:
  - Tauopathies (FTLD and its subtypes)
  - Prion disease

Considerations in Dementia

- Lewy Body disease characterised by accumulation of $\alpha$-synuclein includes:
  - Parkinson’s disease
  - Dementia with Lewy Bodies:

- Cerebrovascular disease (CVD) and Vascular brain injury (VBI) with age and are commonly seen in in people with dementia.
  - Ability to assess relative contributions of CVD / VBI to AD or other pathology is limited

- Recommendation that biomarkers and genetic risk be used to complement neuropathological data
  - ? Also medications, vascular risk
  - Implications for Follow-up of pts in clinical trials

Example of Hypertension:

- Chronic hypertension is associated with ↑ risk of dementia
- Antihypertensive medications associated with ↓ dementia risk
  - ACE inhibitors/ ARBs

In clinical trial data:

- Are the appropriate demographic data collected?
- Do the data go far enough back into pt history?
- Are the relevant subgroups identified and analysed?

Questions:

- How are these factors controlled in clinical trials?
- How have these factors contributed to the failure to differentiate from placebo?

ApoE not only relevant for Alz Disease

- Need to understand neurobiological mechanisms
  - ↑ brain variability because of ↓ brain repair mechanisms
  - Cognitive impairment in a number of neurological diseases

- Also associated with FTLD
  - Genetic risk factor 2 fold increase
  - Modulation inflammation, neuronal toxicity, synaptic plasticity (pre-clinical studies)
  - Dose-dependent effect on behavioural symptoms
  - Potential role in tau hyperphosphorylation

ADAS-cog Trajectories

Ref: Gomeni et al, Alzheimer's & Dementia 2012; 8:39-50
FINGER Protocol

Considerations in Dementia

Epigenetics

- May help to explain:
  - Differential regulation of AD / FTD risk
  - Link between PD risk factors and disease

- Unlike mutations / genetic abnormalities these modifications are dynamic and modifiable (drugs / therapeutic approaches)
  - DNA methylation-based therapy, Histone modifying enzymes

Challenges

- Off-target effects
- Need to be assessed prior to clinical development

Issues in Clinical Trial Methodology

• Learning from past experience
• Identifying the problem(s)
• Improving the predictive value of early Phase trials
• Enroll the appropriate participants
• Demographic data / subgroups
  – Genetics
  – Biomarkers
• Conduct longer trials
• Biomarkers as outcomes
• Better assessment tools
Considerations in Dementia

Session Overview

- Defining the Problem and Session Overview
  - Jill Rasmussen

- 20 Years of Clinical Trials in AD: Some Lessons Learned
  - Pierre Tariot

- Pathobiological Targets in AD Trials: Where We Have Been and where We’re Headed
  - Marty Jefson

- Discussion

- Design of Trials in DLB and PDD
  - Ian McKeith

- Clinical Trials in Frontotemporal Lobar Degeneration: Focus on Tau
  - Adam Boxer

- Discussion

- Regulatory Challenges Across Dementia Subtypes
  - Marion Haberkamp EMA
  - Nicholas Kozauer FDA

- Panel Discussion