Primary Endpoints in “Alzheimer’s Dementia”

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Critique on Regulatory Decisions in Dementia

- Trend to question the clinical relevance of improvement shown with AchEI and Memantine
  - All studies methodological flawed
    - Assessment tools
    - Endpoints
    - Drop outs/missing data
    - Statistical evaluation
  - Overestimation of effects of active treatment
  - Despite of these limitations treatment effects are small and not clinically meaningful
  - Long-term safety issues
Possible Cornerstones in the Treatment of Patients with Dementia

• NfG on Medicinal Products for Treatment of Alzheimer‘s Disease
  – Symptomatic Improvement
  – Slowing or arrest of progression
  – Primary prevention

NEW: http://www.emea.europa.eu
Clinical Milestones in Alzheimer’s Disease

• Emergence of cognitive symptoms
• Conversion from amnestic MCI/preclinical dementia to diagnosable dementia
• Loss of „instrumental activities of daily living“
• Further deterioration in cognitive and functional domains to worse than expected
• Emergence of behavioural abnormalities
• Nursing home placement
• Loss of self-care ADL
• Death
Disease Course and Symptoms in the different domains

modified from: Gauthier, S: Trial Designs and Outcome in Dementia Therapeutic Research, Taylor & Francis 2006, p.38
Which population do we study?

- **Diagnostic criteria**
  - MCI / aMCI / preclinical DAT / prodromal DAT
  - DAT

- **Severity**
  - Mild
  - Moderate
  - Severe

- **Study design**
  - Assessment tools
  - Domains of assessment
  - Duration of trials
  - Placebo/active comparator/add-on
  - Statistical evaluation
  - Clinical relevance
MCI is Prodromal Dementia?

- Normal Cognition
- Prodromal Dementia
- Dementia
  - Other Dementias
  - Mixed
  - Alzheimer's Disease
    - Mixed
  - Vascular Dementia
    - Mixed

Brain Aging

Mild Cognitive Impairment

Stable or Reversible Impairment
Clinical Heterogeneity of MCI

**MCI**
- Amnestic
- Single non-memory domain or Multiple domains slightly impaired

**MCI**

- Alzheimer’s disease
- Normal Aging
- Alzheimer’s disease
- Vascular dementia
- Frontotemporal dementia
- Lewy body dementia
- Primary progressive aphasia
- Parkinson’s disease
Revision of Diagnostic Criteria
Dubois B, Feldman HH, Jucova C et al. 2007

• Core diagnostic Criterion:
  Early and significant episodic memory impairment

• At least one supportive criterion of
  – MTL atrophy shown with MRI
  – Abnormal CSF (amyloid-ß, tau, phospho-tau)
  – Specific pattern shown with PET
  – Proven DAT mutation

• Validation studies necessary !!!
Revision of the Guidance Document

- will address different types of dementia
- differences in severity
  - MCI/preclinical/prodromal/very mild
  - mild
  - moderate
  - severe
- disease modification
- discussion on biomarkers as surrogate endpoints
- discussion on adequate study designs
Alzheimer’s Disease: Efficacy (Symptomatic Improvement)

- **2 primary Endpoints**
  - mandatory: cognitive domain
    functional domain
  - both endpoints should show significant differences

- **Response criteria for clinical relevance:**
  proportion of patients with meaningful benefit?

- **Duration of treatment:** at least 6 months

- **secondary endpoints**
  - global domain
  - additional symptoms
Scales used in Clinical Trials

**Cognition**
- ADAScog
- Neuropsychological Test Battery (NTB)
- Severe Impairment Battery (SIB)

**Functional**
- Alzheimer Disease Cooperative Study ADL Scale (ADCS-ADL)
- Alzheimer’s Disease Functional Assessment and Change Scale (ADFACS)
- Disability Scale in Dementia (DAD)
- Nurses Observation Scale for Geriatric Patients (NOSGER)

**Global**
- CIBIC-plus
Assessment of overall benefit

• Response-Criteria:
  e.g.. ADAScog ≥ 4 + Score ≤ 3 of CIBIC
  + no change in DAD

• Effect size

• Numbers Needed to Treat
  (e.g. patients showing improvement of ADAScog ≥ 4)
Alzheimer’s Disease: Efficacy (Disease Modification)

- **2 primary Endpoints**
  - mandatory: cognitive domain
  - functional domain
  - both endpoints should show significant differences

- **Response criteria for clinical relevance:**
  proportion of patients with meaningful benefit?

- **Duration of treatment:** 18 months (?)

- **secondary endpoints**
  - global domain
  - Biomarkers
    - e.g. serial volumetric MRI
  - Quality of Life
  - additional symptoms
Design Issues

- study population/add-on populations
- study duration
- which type of endpoints
- type of analysis
  - slope analysis
  - survival analysis
  - randomized start designs /randomized withdrawal
  - missing data/drop outs/LOCF
- valid and reliable scales
"Randomized withdrawal design"

Cognition

Active Treatment Phase

Structural Effect

Natural Course

Symptomatic Effect

Time
Deterioration in Cognition in different stages of Disease Severity

modified from: Gauthier, S: Trial Designs and Outcome in Dementia Therapeutic Research, Taylor & Francis 2006, p.39

ADAS-cog

- Normal range
- Mild range
- Moderate range
- Severe range

(1 year) Mild disease
(1 year) Moderate disease
(1 year) Severe disease

Treatment
Untreated progression
Disease Course and Symptoms in the different domains

Progression of Alzheimer's disease

modified from: Gauthier, S: Trial Designs and Outcome in Dementia Therapeutic Research, Taylor & Francis 2006, p.38

2nd Workshop on Neurodegenerative Disorders, Feb. 11, 2008 EMEA
Biomarkers can be used as tools to

- Understand the biology of a disease
- Understand the effects of medicinal products
- Provide information on sub-populations of patients that might respond to treatment or be susceptible to side effects (individualized medicine)
- Developing better diagnostics and medicinal products
- Improve methodology of clinical trials
Primary Endpoints in Clinical Trials

• Clinical Endpoints of interest may be difficult to use
  - Long follow-up measurement
  - Expensive measurements
  - Rare events

• Surrogate (replacement) Endpoint
  - Easier/quicker to measure
  - Reduce trial duration, size and expenditures
  - Should be measured accurately and reproducible
  - Change in proportion to what it represents

• Common Misunderstanding: correlation between outcome and clinical endpoint reflects not a valid surrogate
Ideal Surrogate Endpoints (1)
Temple R, JAMA, 1999

• …endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinical meaningful endpoint that measures directly how a patient feels, functions or survives

• Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint
Ideal Surrogate Endpoints (2)
Fleming TR, Ann Int Med, 1996

• ...proposed surrogate endpoint must not merely be a correlate of the true clinical outcome
• effect of intervention on a valid surrogate endpoint must reliably predict the effect on a clinical outcome of interest
• treatment effect on the clinical outcome should be explained by its effect on the surrogate marker
Questions on Surrogate Markers in Dementia

- for which clinical outcome the biomarker is used?
- does the biomarker reliably predict the clinical outcome?
- does the biomarker reflect effects on pathology and/or pathophysiology for a claim of disease modification?
- are the effects seen in the biomarkers clinically relevant?
- allow results seen short-term generalization to long-term?
phospho-tau and MCI

from:
Ewers M et al.
Neurology, 69, 2205-2212 (2007)

A priori cut off point:
27,32pg/ml

Centers: München, Heidelberg, Amsterdam, Pitea
Surrogate Endpoints: Neuroimaging

- **Structural MRI**
  - Hippocampus
  - Entorhinal cortex

- **Functional Imaging**
  - PET/SPECT
  - MRS
  - fMRI

- **Links need to be established:**
  - Imaging tool and desired clinical outcome
  - Imaging tool and disease modification
A new PET ligand for drug development in AD

- PET radioligand \([^{11}\text{C}]\text{xyz}****\) for amyloid quantification
- Highly specific and reversible binding
- Early diagnosis and patient selection
- Confirm amyloid-lowering therapies at a biochemical level in man

AD Patient

Cooperation Pharmaceutical Industry-Academic PET-Centers

2nd Workshop on Neurodegenerative Disorders, Feb. 11, 2008 EMEA
Open Regulatory Issues

• **Study population / add-on populations**
  - Diagnostic criteria
    • Subtypes of dementia
    • Level of severity and impairment
  - Placebo / active control

• **Study design**
  - Which type of endpoints
    • Valid and reliable scales
    • Time to progression of ?
  - study duration
  - type of analysis
    • slope analysis
    • survival analysis
    • Randomized start designs /randomized withdrawal
    • missing data / drop outs / LOCF