Role of Imaging in Alzheimer Disease Trials

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Content of presentation

- Role of imaging in Alzheimer disease trials
- Issues related to imaging in AD trials
- Risk management strategies and imaging data standardization and optimization
Imaging modalities commonly utilized in AD trials

Imaging in AD trials is performed for:
- Patient eligibility
- ARIA (Amyloid Related Imaging Abnormalities)
- Efficacy

Imaging methodologies:
- MRI
- PET/PET-CT
  - FDG-PET
  - Amyloid imaging compounds
Concomitant exclusionary conditions

Imaging can provide information about conditions that can impact patient population and trial results

- Other causes of Dementia
  - Vascular dementia
- Multiple sclerosis
- Vascular pathology
- Micro and macro hemorrhages
- Neoplasms
- White matter disease
## Fazekas Rating Method

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None or a single punctate White Matter Hyperintensities (WMH) lesion</td>
</tr>
<tr>
<td>1</td>
<td>Multiple punctate lesions</td>
</tr>
<tr>
<td>2</td>
<td>Beginning confluency of lesions (bridging)</td>
</tr>
<tr>
<td>3</td>
<td>Large confluent lesions</td>
</tr>
</tbody>
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http://www.radiologyassistant.nl/en/43dbf6d16f98d
Amyloid Related Imaging Abnormalities (ARIA)
ARIA evaluations

Initially observed on brain MRI in trials of monoclonal antibody against amyloid-β (Aβ):

These include

- (ARIA E) Vasogenic edema
- (ARIA H) micro and macro hemorrhages, and superficial siderosis
- Mostly asymptomatic; symptoms include headache, worsening cognitive function, alteration of consciousness, seizures, unsteadiness, and vomiting.

Based on these findings, FDA has mandated that patients must frequently be followed by MRI in all AD trials.
ARIA-E

- Vasogenic edema is related to extravasated fluid due to increased permeability of brain capillaries
- Increased signal is seen on FLAIR sequences
- Usually transient and not associated with evidence of restricted diffusion, tissue necrosis or other sequelae of cytotoxic edema (as seen in acute infarction)
- Generally seen in parietal, occipital and frontal lobes and leptomeninges; also been observed in the cerebellum and brain stem
FLAIR sequence demonstrating increased signal in the right hemisphere

Sperling Alzheimer’s & Dementia 7 (2011) 367-385
ARIA-H (Hemorrhage & superficial siderosis)

**Hemorrhages:** Macro and Micro-Hemorrhages
- Micro-hemorrhage typically seen as focal, round, low intensity lesion in the brain parenchyma (5-10 mm)
- Represent small deposits of hemosiderin which originate from small leakage of blood from a blood vessel

**Superficial siderosis:** curvilinear low intensities that lie adjacent to brain surface – residua of leakage of blood into subarachnoid space or periadventitial compartment

**Seen on T2★ and Susceptibility-weighted sequences (SWI)**
2D GRE sequence, white arrows label small dark foci c/w mH

2D GRE sequence white arrows show curvilinear dark sulci as typically seen in superficial siderosis

FDA Recommendations for MRI for ARIA evaluation

- 1.5T magnet is the minimum standard
- Slice thickness of 5 mm or less
- ARIA-H: 2D GRE T2* weighted sequence should be used with TE 20ms or greater
- ARIA-E: T2 FLAIR sequence
FDA recommendations for ARIA

- Study drug should be discontinued if an imaging abnormality consistent with vasogenic edema, macrohemorrhage, or an area of superficial siderosis appears or a clinically symptomatic microhemorrhage is seen.

- If ARIA is observed, subjects must be rescanned more frequently after discontinuation of study drug to evaluate stability until imaging abnormalities are resolved.
Impact of ARIA monitoring

- Multiple additional visits (every 12-15 wks) and more frequently (6-8 wks) if ARIA is detected
  - Difficult for patient and care giver
- Need to coordinate with clinical follow-up visits
  - Imaging facilities are at different location
- Motion sensitive sequences (T2* weighted) can lead to non-evaluable images
  - Can lead to discontinuation of patient
  - Can impact sample size
- Quick turnaround time
Efficacy evaluations:

- MRI
  - Brain volume
  - Hippocampal volume
  - Ventricular volume
  - DTI

- PET
  - FDG PET
  - Amyloid imaging PET
  - Tau imaging agents
Brain Volume evaluations by MRI

- Intracranial volume
- Lateral ventricle volume
- Hippocampal volume

Courtesy: Dr. Chahin Pachai, BioClinica
FDG PET evaluation

- Evaluates glucose metabolism in brain

Cindee Madison and Susan Landau, UC Berkeley)
Factors impacting imaging in AD trials

- Site selection process
  - Traditionally focused on clinical capabilities
    - PI is interested, has resources and has patients
    - Not focused on imaging capabilities and requirements
      - Minimal information about imaging facility
        - Machine capabilities
        - Imaging protocols and reporting standards
        - Site radiologist and technologist
  - Communication with the patients
    - Inadequate explanation of imaging during clinical trials
      - Stress to care giver
      - Resulting in patient dropout
Image Review at Multiple, Unrelated Trial Sites

- Image Acquisition @ Site 1
  - Real-time QC of Images by Site 1 Technologist
  - Review of Images by Site 1 Radiologist
  - Site 1 Coordinator Reports Image Assessment

- Image Acquisition @ Site 2
  - Real-time QC of Images by Site 2 Technologist
  - Review of Images by Site 2 Radiologist
  - Site 2 Coordinator Reports Image Assessment

- Image Acquisition @ Site 3
  - Real-time QC of Images by Site 3 Technologist
  - Review of Images by Site 3 Radiologist
  - Site 3 Coordinator Reports Image Assessment

- Image Acquisition @ Site ‘n’
  - Real-time QC of Images by Site ‘n’ Technologist
  - Review of Images by Site ‘n’ Radiologist
  - Site ‘n’ Coordinator Reports Image Assessment
Standardization: With Independent Review
Risk mitigation strategies

Planning phase

1. Selection of image based inclusion and exclusion criteria
2. Standardization imaging protocol
3. Site selection process should include site imaging capabilities
   - Phantom data/Sample cases reviewed prior to FPI
   - Identify site radiologist and technologist and back ups
   - Ensure that baseline and follow-up evaluations are done on one machine
4. Development of standardized training program
   - Site radiologist, technologist, PI, study coordinator, readers
   - Clinical CRO training
Risk Mitigation Strategies

1. Clear explanation of imaging to patient/caregiver
   - Number of MRIs/PETs (increased frequency of MRI for ARIA)
   - Contrast injections
   - Duration of procedures
   - Sedation
   - Travel involved
   - Side effects of contrast injection

2. Central eligibility reads
   - Adjudication process

3. Central ARIA reporting

4. Robust communication plan
   - Communication between PI and imaging facility
   - Communication between CRO and core labs
Importance of imaging in AD research continues to grow
Questions