

Detecting Relevant Changes in The Brain:

Sensitivity and Specificity in Real Patients

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Background

Neuroimaging tools are increasingly used to monitor treatment effect in CNS disorders like multiple sclerosis (MS) and Alzheimer's disease (AD). Systematic development of therapeutics requires a phase I clinical trial safety assessment, followed by preliminary efficacy assessment and evaluation of 'proof of concept', usually in the context of phase IIa and IIb randomized clinical trials (RCT). For example in MS, the duration of phase II trials in MS is typically only 4–6 months, during which it is not possible to achieve reliable clinical outcomes - so nonclinical biomarkers are often used. Gadolinium-enhancing lesions seen on brain MRI provide a sensitive, non-invasive means of tracking changes attributable to inflammatory pathology in MS, and have been widely adopted to demonstrate proof of concept for agents that target the inflammatory component of the disease. Valid, reliable and sensitive MRI outcomes are available that facilitate efficient testing and ultimately regulatory approval of new therapies [Miller].

Monitoring disease progression and therapy in MS

The number of new lesions on serial MRI is ~10 times higher than the number of clinical events, and can be measured reliably using simple visual analysis.

Use of image registration and subtraction may further improve reliability and sensitivity [Moraal]. Depending on the phase of the disease and the type of intervention, various MRI outcome measures are being used in RCTs:

- CIS – new (enhancing) lesions and conversion to McDonald MS
- RR-MS – active lesions counts/volume and brain volume change

In phase II trials, MRI outcomes are often used as the primary outcome of the study, with sample sizes of 50-100 patients per arm, depending on expected treatment effect. By contrast, in phase III RCTS, the primary outcome is clinical. Given the greater power of MRI outcomes, they can be used in phase III to

- Support the primary clinical outcome
 - Improve understanding of mechanism of action
- Perform subgroup analyses
 - Identify responders/non-responders
- Measure side-effects (safety)

Finally, imaging outcomes are increasingly used to monitor the neurodegenerative aspects of MS, especially relevant in progressive disease phases [Barkhof].

Monitoring disease progression and therapy in AD

The spread of pathology in the brains of Alzheimer patients follows a predictable pattern, starting in the medial temporal lobe (MTL), especially hippocampus, subsequently spreading to temporo-parietal neocortex. The rate of hippocampal volume (HCV) and whole brain volume (WBV) are sensitive and clinically relevant markers of disease progression, that are being considered more frequently in the context of RCTs in AD, especially with a shift from symptomatic (e.g. choline-esterase inhibitors) to disease modifying treatments (e.g. anti-amyloid strategies).

Depending on the phase of the disease, the type of intervention, various MRI outcome measures are being used in RCTs:

- MCI – HCV and WBV from 6-12 monthly MRI
- AD – WBV from 6-12 monthly MRI

Unlikely the situation in MS, imaging outcomes have a less well established role in AD, and are only used as secondary outcome measures presently. MRI outcomes generally have greater power though than clinical outcomes, and their role in phase III trials can be:

- Supporting the primary clinical outcome
 - Corroborating proposed mechanism of action
- Screening patients for inclusion criteria
 - Exclusion of vascular dementia, enrichment with fast progressors
- Safety assessment (e.g. vasogenic edema and microbleeds)

References

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