Multiple Sclerosis: Using Biomarkers/Surrogates

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Overview

• Unique Challenges in Neurological Disorders
• Biomarkers – Making the diagnosis and beyond?
• Surrogate Measures
• Imaging Modalities as Surrogates
• Limitations
• Future directions
Clinical Translational Trials in Neurological Disease: Unique Opportunities and Challenges

• Long prodromes/preclinical phase
  o Parkinson’s Disease, Alzheimer’s Disease, Multiple Sclerosis
• Diagnosis determined clinically
• Progression occurs over years
• Tissue of interest testable only indirectly
• Clinical manifestations modifiable
  o Plasticity
  o Education/IQ
What is a Good Biomarker?

- A test or measure that reflects a physiological process of interest
- Displays high sensitivity and specificity
- Can be used to enrich/refine study populations enrolled
- Not all biomarkers can function as surrogate outcome measures
What is a Surrogate Clinical Outcome?

• A surrogate outcome is correlated with the true clinical outcome

• The impact of the intervention on the true clinical outcome is captured by the effect on the surrogate outcome
Four Categories of Biomarkers

Drug Development:

Target
Mechanism
Pathophysiology
Diagnostic

Hampel et al. Nature Reviews 2010, 9:560-574
Biomarker as Diagnostic tool: Multiple Sclerosis

• CNS demyelinating disease
  ~350,000 affected in US
  ~8,500–10,000 new cases yearly

• Women:Men, 2:1
• Age at onset 20-40
• Fluctuating neurological symptoms
• T-cell mediated autoimmune disease
• Diagnosis is a combination of clinical and paraclinical findings
Diagnostic Criteria: Evolution

- Schumacher 1965 - Exam based
- Poser 1983 - Paraclinical evidence accepted (MRI, EPs)
- McDonald 2001 - Evaluation of monosymptomatic patients, Increased role of MRI

*Dissemination in time and space is still the basis for diagnosis
*Must exclude other possible causes
Dissemination in Space (DIS)
FLAIR lesions

FLAIR = fluid-attenuated inversion-recovery.
Dissemination in Time (DIT)

Gadolinium enhancing lesion
Pathology of MRI Gd-Enhancing Lesion

Gd = gadolinium; Dhib-Jalbut S (2002), Neurology 58(8 suppl 4):S3-S9
Current Use of MRI in Multiple Sclerosis

• Assist in Diagnosis
• Assist in Prognosis
• Monitor Treatment Response
• Better Understanding of Disease Process
• Evaluate New Therapies
MS Subtypes - determined by clinical course

- Relapsing Remitting: 85%
- Primary Progressive: 10%
- Progressive Relapsing: 5%

- Secondary Progressive - 50% of RRMS become SP after 10 years, 90% after 30 years
Natural History of MS

- Measures of brain volume
- Relapses and impairment
- MRI burden of disease
- MRI activity

Time
Differential Diagnosis - MS Variants

• Primary Progressive MS
• ADEM
• Neuromyelitis optica (Devic’s Disease)
• Marburg’s (Acute MS)
• Schilder’s Disease
• Balo’s concentric sclerosis - rings of demyelination
Neuromyelitis Optica (Devic’s Disease)

• Bilateral optic neuritis
• Transverse myelitis: Multiple segments involved, cord swelling, and massive inflammation/necrosis
• Clinical Diagnosis
• Previous criteria – spinal lesions only
Neuromyelitis Optica (Devic’s Disease)

• NMO-IgG antibody identified as biomarker

• Antigen is aquaporin-4, a water channel

• Many NMO-Ab patients have brainstem/other brain lesions and clinical manifestations more widespread than previously recognized
  o Vomiting, brainstem involvement

• Best treatment is immunosuppression—not traditional MS medications

• Example of biomarker but not surrogate
neuromyelitis optica
MRI as a Surrogate Outcome for MS Relapses

- Relapses are a key short term clinical outcomes of interest

- Disability accumulation is the ultimate clinical outcome of interest

- Gadolinium enhancing (Gd+) lesion counts are a key MRI surrogate outcome measure for relapses in MS.

- All of the currently approved therapies (and those in Phase II and III testing currently) have demonstrated an effect of decreasing Gd+ lesions in MS.
Gd-Enhanced Lesions

• Frequent in subclinical phase of MS and in clinically silent periods between relapses

• 5–10 times more frequent than relapses

• Usually resolve within 4–6 weeks and leave behind a T2 hyperintense lesion

• Evolve into new and enlarging T2 lesions
Effect of IFN-β1b on Gadolinium Enhancing Lesions

Total Enhancements

Months on Study (27 Participants)

Interferon-β1b Initiated

80-90% Response

Stone LA et al. (1997), Neurology 49(3):862-869
Trials in RR MS

IFN-β1a vs. Placebo: Dose Effect

Weekly Dose | IFN-β1a Regimen | Exacerbation Rate Reductions (1 Year)
--- | --- | ---
22 mcg | IFN-β1a 22 mcg SC QW | 0%
30 mcg | IFN-β1a 30 mcg IM QW | 9.6%
44 mcg | IFN-β1a 44 mcg SC QW | 19%
66 mcg | IFN-β1a 22 mcg SC TIW | 33%
132 mcg | IFN-β1a 44 mcg SC TIW | 37%

EDSS: Progression to Disability

10.0 = Death due to MS
9.0–9.5 = Completely dependent
8.0–8.5 = Confined to bed/chair; self-care with help
7.0–7.5 = Confined to wheelchair
6.0–6.5 = Walking assistance is needed
5.0–5.5 = Increasing limitation in ability to walk
4.0–4.5 = Disability is moderate
3.0–3.5 = Disability is mild to moderate
2.0–2.5 = Disability is minimal
1.0–1.5 = No disability
0 = Normal neurologic exam

Walking Ability
- Confined to a wheelchair or bed
- Walks with aid (<5 yards)
- Walks with assistance (22–220 yards or more)
- Walks unaided (110–220 yards or more)
- Walks unaided (330–550 yards or more)
- Fully ambulatory

Modest delay in time to first EDSS progression in Relapsing Remitting MS

Figure 2. Kaplan–Meier curves for time to confirmed progression in disability for years 1 through 4 (all patients). Proportions of patients are those free from progression. The patients receiving highest cumulative dose of therapy have the lowest rate of progression as opposed to those receiving the lowest dose who had the highest rate of progression. Late treatment was not associated with a catch-up of benefit to early therapy.
But No Effect on Disability Progression in Secondary Progressive MS

Figure 2. Time to 6-month confirmed progression. The time to 6-month confirmed progression was not delayed in interferon β-1b (IFNβ-1b)–treated patients (p = 0.712 for all IFNβ-1b vs placebo). Time to the 30% quantile was 750 days for the placebo group, 981 days for the 250-µg group, and 668 days for the 160-µg/m² group. The differences between the 250-µg and placebo groups (p = 0.606) and between the 160-µg/m² and placebo groups (p = 0.261) were not significant.
Disability and $T_2$ MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis.

L. K. Fisniku,¹,² P. A. Brex,⁴ D. R. Altmann,¹,⁵ K. A. Miszkiel,⁶ C. E. Benton,⁶ R. Lanyon,¹,² A. J. Thompson¹,³ and D. H. Miller¹,²
Examples of Surrogates

When surrogates fail:

1. Treatment has an effect on the disease but not the surrogate

2. Treatment has an effect on the surrogate but not on the disease process

3. Treatment has apparent effect on the true clinical outcome but is only provides symptomatic relief
Disease modification or symptomatic improvement?

Hampel et al. Nature Reviews 2010, 9:560-574
# Correlation between Stage, MRI parameters and Clinical Outcome

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<thead>
<tr>
<th>Stages</th>
<th>MRI Monitored parameter</th>
<th>Major Correlate</th>
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<tbody>
<tr>
<td>Early</td>
<td>T2 and T1 images (Gd-enhanced)</td>
<td>Relapses</td>
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<tr>
<td></td>
<td><em>Inflammation and Demyelination</em></td>
<td></td>
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<tr>
<td>Late</td>
<td>Persistent lesions seen on T2</td>
<td>Disability</td>
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<td><em>Chronic Demyelination</em></td>
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<td>Black Holes on T1 images</td>
<td>Cognitive Impairment</td>
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<td><em>Permanent Axonal loss, Atrophy</em></td>
<td>Severe Disability</td>
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Disability/MRI Dissociation

• Enhancing lesions are predictive of relapses (with caveats)
• Measures of disability (EDSS) are poorly correlated with T2 lesion volumes
• Long term follow-up studies (Brex et al NEJM 2002) show only modest association of T2 volumes with future disability

• T2 lesions represent nonspecific pathology
  • Demyelinated axons
  • Remyelinated axons
  • Gliosis
  • Tissue Loss
• Functional Compensation

• Hidden Pathology - beyond the lesions
Axonal Transection in MS

• Proposed correlation of MS clinical course, axonal loss, and neurologic disability

Brain Atrophy

Promise and Pitfalls
These images were acquired over the course of 7 years from a single untreated MS patient.
Brain Atrophy

- Rate of global brain atrophy accelerated in MS: 0.8%–1.2% annualized vs healthy control rate 0.1%–0.3%
- Assessing treatment effects complicated by:
  - Initial pseudoatrophy associated with resolution of inflammation
  - Relatively short treatment trials
- Studies\(^1,2\) demonstrate different atrophy rates in specific tissue compartments
  Gray-matter atrophy continues throughout disease course

Gray Matter Atrophy
**Thalamus**

- Deep nuclei affected: Thalamus and basal ganglia (Cifelli 2002,¹ Wylezinska 2003,² Inglese 2004³)

- Total thalamic volume correlated with cognitive function in MS including Information processing speed, verbal and spatial memory⁴,⁵

- Third ventricular width linked to thalamic atrophy

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Third Ventricular Enlargement
Hippocampal Imaging Protocol

A. Sagittal T2-weighted scout image with the superimposed slice prescription for the 16 coronal high-resolution structural images covering the medial temporal lobe.

B–C. Coronal T2-weighted scan acquired at 3T with in-plane resolution of 400 µm x 400 µm

D. Subregional segmentation

Hippocampus in 3D

Cole et al. J Affective Disorders 2010
Tracking Hippocampal Atrophy with Surface Projection Techniques

Surface mapping technique detects changes between groups/over time, allowing for monitoring of disease progression/treatment effects in large cohorts.
Cortical Lesions

- Several types recognized on pathological specimens
- Do not demonstrate inflammatory infiltrate
- Higher volumes in progressive MS
- Progressive increase without Gd enhancement demonstrated
- Effect of DMAs on cortical plaques largely unknown
- Likely better predictor of disability

cortical lesions

Type I

Type II

Type III
Cortical demyelination and diffuse white matter injury in multiple sclerosis

Alexandra Kutzelnigg, Claudia F. Lucchinetti, Christine Stadelmann, Wolfgang Brück, Helmut Rauschka, Markus Bergmann, Manfred Schmidbauer, Joseph E. Parisi and Hans Lassmann
Inflammatory Cortical Demyelination in Early Multiple Sclerosis

Figure 1. Representative Types of Cortical Demyelinated Plaques in Early Multiple Sclerosis on Immunohistochemical Staining for Proteolipid Protein.

Panel A shows leukocortical demyelination; Panel B subpial demyelination (arrows delineate an area of cortex with preserved myelin); Panel C intracortical demyelination (arrows), with neurons in the demyelinated lesion (inset); and Panel D subpial and leukocortical demyelination in the same tissue section.
Spinal Cord Atrophy

• Atrophy at the cervical level is clinically relevant

Benign MS
EDSS 3
Cord area = 85 mm²

Progressive MS
EDSS 8
Cord area = 55 mm²

spinal cord
d structure vs. dysfunction

Zackowski et al., Brain (2009)
Diffusion Tensor Imaging Metrics

• Mean Diffusivity (MD) - average of diffusion in all directions

• Axial Diffusion (AD) - $\lambda_1$ first eigenvalue - parallel to tract $\lambda_\parallel$

• Radial Diffusion (RD) - $\lambda_{2,3}$ average of 2nd and 3rd eigenvalues - perpendicular to tract - $\lambda_\perp$

• Fractional Anisotropy (fA) - dimensionless number ranging from 0 (isotropic) to 1 corresponding to the degree of preferential flow
Tract Based Spatial Statistics (TBSS) Skeletons
Group Differences: Fractional Anisotropy in RRMS vs Controls
Radial Diffusivity: Group comparisons and correlations with 9HPT
Radial Diffusivity: correlations with right hand 9-Hole Peg Test (9HPT) performance
Compensation or Disinhibition?

fMRI during finger movements
Conclusions

• Biomarkers serve important roles in aiding diagnosis and treatment response

• Not all biomarkers can function as surrogate clinical outcome measures

• Neurodegenerative disease present unique opportunities and challenges in clinical translational research

• Better understanding of disease pathophysiology is a critical component in the development of relevant biomarkers/surrogate outcome measures

• Short term clinical trials may not be adequate to assess long term outcomes in neurodegenerative diseases
Thank you for your attention!