Clinical and research application of MRI in diagnosis and monitoring of multiple sclerosis
What is to be considered Treatment Failure in MS?

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Background

- Several therapeutic opportunities for MS patients
- Current MS treatments reduce frequency of relapses, disability progression and disease activity (as measured by MRI).
- Response varies among patients. Difficult to assess
- How to switch after suboptimal response?
Assessment of treatment response

Disease progression

Disability

Relapses

MRI activity

Focal inflammation
(relapses / MRI lesions)

Diffuse damage accumulation
(neurodegeneration / failure of repair; disability / atrophy)
The growing availability of drugs active against MS over years leads to greater expectations.
NEDA – Clinical trial data

✧ NEDA at 1 year
  ✧ 34% for PegInterferon (ADVANCE)
  ✧ 47% for Natalizumab (AFFIRM)
  ✧ 39% for Daclizumab (SELECT)

✧ NEDA at 2 years
  ✧ 37% for Natalizumab (AFFIRM)
  ✧ 39% for Alemtuzumab (CARE-MS I)
  ✧ 32% for Alemtuzumab (CARE-MS II)
  ✧ 46% for Cladribine (CLARITY)
  ✧ 28% for Dimethyl Fumarate (DEFINE)
  ✧ 33% for Fingolimod (FREEDOMS)
  ✧ 18% and 23% for Teriflunomide 7mg and 14mg (TEMSO)

✧ NEDA at 3 years
  ✧ 19% for Glatiramer Acetate (CombiRx)
  ✧ 21% for IFN-B 1a (CombiRx)
  ✧ 33% for Glatiramer Acetate+IFNB1a (CombiRx)

✧ NEDA-4: 20% for Fingolimod (FREEDOMS+FREEDOMS II)
NEDA

✧ NEDA is an important therapeutic goal in MS care.
✧ Data from clinical trials show that NEDA is a very interesting outcome measure, showing clear difference between placebo and treated arms. However, only a minor portion of patients (range 18-46%) are NEDA in the short term after treatment with current DMT’s.
✧ In clinical settings, NEDA is difficult to sustain in the long term. Should we aim for “minimal evidence of disease activity” (MEDA)?
✧ The definition of NEDA should evolve as new metrics are adopted into clinical practice (e.g., T25FW, SDMT, brain atrophy, etc.)
Defining treatment response is challenging: the proportion non-responders varies depending on definition

<table>
<thead>
<tr>
<th>Non-responder definitions</th>
<th>% non-responders</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  ≥ 1 EDSS point confirmed at 6 months</td>
<td>18</td>
<td>39.623</td>
</tr>
<tr>
<td>B  Presence of any relapse</td>
<td>45</td>
<td>6.366</td>
</tr>
<tr>
<td>C  ≥ 2 relapses</td>
<td>20</td>
<td>4.562</td>
</tr>
<tr>
<td>D  A decrease in relapse rate of &lt; 30% compared with the 2 years before therapy</td>
<td>16</td>
<td>4.830</td>
</tr>
<tr>
<td>E  A decrease in relapse rate of &lt; 50% compared with the 2 years before therapy</td>
<td>20</td>
<td>4.009</td>
</tr>
<tr>
<td>F  No decrease in or identical relapse rate compared with the 2 years before therapy</td>
<td>15</td>
<td>4.620</td>
</tr>
<tr>
<td>G  Definition A or B</td>
<td>49</td>
<td>10.028</td>
</tr>
<tr>
<td>H  Definition A or E</td>
<td>30</td>
<td>19.869</td>
</tr>
<tr>
<td>I  Definition A and B</td>
<td>13</td>
<td>41.143</td>
</tr>
<tr>
<td>J  Definition A and E</td>
<td>7</td>
<td>24.544</td>
</tr>
</tbody>
</table>

Assessing treatment response to interferon-β
Is there a role for MRI?

ABSTRACT

Objective: Interferon-β (IFN-β) has been shown to reduce relapse rates in multiple sclerosis; however, the clinical response appears to vary among individuals. Can early MRI be used to identify those patients who have a poor response to treatment?

Methods: A systematic review of studies examining differential treatment response and clinical endpoints in groups defined as responders or nonresponders to IFN-β was performed. Metaanalytic techniques were used to combine study results where appropriate.

Results: Patients with MRI evidence of poor response to IFN-β treatment as defined by either ≥2 new hyperintense T2 lesions or new gadolinium-enhancing lesions had significantly increased risk of both future relapses and progression as defined by the Expanded Disability Status Scale. There appeared to be an increased risk of poor outcomes 16 years after treatment initiation in those with an initial poor response to treatment. Previous evidence has shown this not to be the case in placebo arms of clinical trials.

Conclusions: For those patients starting IFN-β, early MRI, within 6 to 24 months after starting treatment, has the potential to provide important information when counseling patients about the likelihood of future treatment failure. This can inform treatment decisions before clinical relapses or disease progression. Neurology® 2014;82:248-254
## Table 3: Recommendations for determining the level of concern when considering treatment modification based on annual MRI findings

<table>
<thead>
<tr>
<th>Activity on MRI*</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Gd-enhancing lesions OR Accumulation of new T2 lesions per year</td>
<td>1 lesion</td>
<td>2 lesions</td>
<td>≥3 lesions</td>
</tr>
</tbody>
</table>

*Note: Routine follow-up MRI with gadolinium (Gd) is recommended 6-12 months after initiating therapy for RRMS (or in CIS if therapy is not initiated). Note: New T2 lesions that are also enhancing on the same scan are only counted once as unique active lesions. *The presence of Gd-enhancing lesions is more reliable than new T2 lesion counts. New T2 lesion counts require high-quality comparable MRI scans and interpretation by highly qualified individuals."
MRI and identification of responders

242 RRMS patients with IFN beta-1a treatment (follow-up 4.3 ± 2.3 anni)

Definition of not responder:
2 or more clinical relapses during follow-up (35% dei pazienti)

Pozzilli et al., Neurol Sci 2005
One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis

L. Prosperini\textsuperscript{a}, V. Gallo\textsuperscript{a,b}, N. Petsas\textsuperscript{c}, G. Borriello\textsuperscript{a} and C. Pozzilli\textsuperscript{a}

\textsuperscript{a}Multiple Sclerosis Centre, Department of Neurological Sciences, S. Andrea Hospital, “La Sapienza” University, Rome, Italy; \textsuperscript{b}Division of Epidemiology, Public Health and Primary Care and Division of Neuroscience and Mental Health, Imperial College London, London, UK; and \textsuperscript{c}Neurological Centre of Latium, Rome, Italy

Poor Response defined as an increase of at least 1 point of EDSS confirmed at 6 months
Combined MRI lesions and relapses as a surrogate for disability in multiple sclerosis

**PRISMS study (scIFNβ-1a)**

![Graph showing progression free survival](image)
Measures in the first year of therapy predict the response to interferon β in MS

J Río¹, J Castilló², A Rovira³, M Tintoré¹, J Sastre-Garriga¹, A Horga¹, C Nos¹, M Comabella¹, X Aymerich² and X Montalbán¹

Table 3  Risk of new relapses and increase of disability during the period of follow-up (months 12–36) according the positivity for the different variables after 12 months of therapy

<table>
<thead>
<tr>
<th>N</th>
<th>Relapses</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (CI)</td>
<td>Significance</td>
</tr>
<tr>
<td>R+/P+/MRI+</td>
<td>11</td>
<td>9.8 (2.6–53.4)</td>
</tr>
<tr>
<td>R+/P-/MRI+</td>
<td>18</td>
<td>8.3 (2.9–28.9)</td>
</tr>
<tr>
<td>R-/P+/MRI+</td>
<td>7</td>
<td>3.3 (0.8–15.6)</td>
</tr>
<tr>
<td>R+/P+/MRI-</td>
<td>5</td>
<td>1.8 (0.3–9.9)</td>
</tr>
<tr>
<td>R-/P+/MRI-</td>
<td>10</td>
<td>1.2 (0.3–4.3)</td>
</tr>
<tr>
<td>R+/P-/MRI-</td>
<td>17</td>
<td>1.1 (0.4–3.2)</td>
</tr>
<tr>
<td>R-/P-/MRI+</td>
<td>35</td>
<td>1.5 (0.7–3.4)</td>
</tr>
<tr>
<td>R-/P-/MRI-</td>
<td>119</td>
<td>1 *</td>
</tr>
</tbody>
</table>

*Reference category
Scoring treatment response in patients with relapsing multiple sclerosis

MP Sormani¹, J Rio², M Tintorè², A Signori¹, D Li³, P Cornelisse⁴, B Stubinski⁴, ML Stromillo⁵, X Montalban²* and N De Stefano⁵*
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Training set (PRISMS)

Validation set (Barcelona)
Scoring treatment response in patients with relapsing multiple sclerosis

MP Sormani¹, J Rio², M Tintorè³, A Signori¹, D Li³, P Cornelisse⁴, B Stubinski⁴, ML Stromillo⁵, X Montalban²* and N De Stefano³*

Training set (PRISMS)

1 relapse or >=2 new T2 lesions in month 12-18

No relapse and <2 new T2 lesions in month 12-18
Defining and scoring response to IFN-β in multiple sclerosis

Maria Pia Sormani and Nicola De Stefano

**Figure 1** | An evidence-based quantitative algorithm to monitor response to IFN-β. This proposed algorithm is based on the Modified Rio Score for the assessment of the risk of progression over 4 years in patients with multiple sclerosis treated for 1.5 years with IFN-β therapy. *Substantial new T2 activity is defined as >4–5 new T2 lesions in 1 year of treatment, or >1–2 new T2 lesions if the reference MRI scan to assess new T2 lesion formation is obtained at least 6 months after initiating therapy.*
Assessing response to Interferon in a large multicentre clinical
dataset of patients with multiple sclerosis

the MAGNIMS study group.

**Conclusion:** Results of the study suggest that substantial MRI activity, better if in combination with clinical relapses, is needed during the first year of treatment with Interferon to significantly increase the risk of disability worsening in the short-term.

**Accepted Neurology**
MAGNIMS Project - Participating Centers
In the statistical analysis, centers with small sample size (<10% of the whole group) were grouped to allow heterogeneity tests among centers.
Disability progression across centers

0 new T2 lesions

1 or more new T2 lesions

Progression free survival

Years

0 1 2 3

Progression free survival

Years

0 1 2 3

Rome

Milan

Barcelona

Other MAGNIMS

p<0.001

p<0.001
### Optimized score

Multivariate Cox model on the merged MAGNIMS dataset for risk of 3-year disability progression (n=1280)

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NewT2 lesions=0</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>NewT2 lesions=1</td>
<td>0.93 (0.62-1.4)</td>
<td>0.73</td>
</tr>
<tr>
<td>NewT2 lesions=2</td>
<td>1.09 (0.71-1.68)</td>
<td>0.68</td>
</tr>
<tr>
<td>NewT2 lesions=3</td>
<td>1.65 (1.01-2.70)</td>
<td>0.04</td>
</tr>
<tr>
<td>NewT2 lesions=4</td>
<td>2.26 (1.29-3.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NewT2 lesions=5</td>
<td>1.77 (0.76-4.11)</td>
<td>0.18</td>
</tr>
<tr>
<td>NewT2 lesions=6+</td>
<td>2.39 (1.43-4.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relapse=0</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Relapse=1</td>
<td>1.68 (1.27-2.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relapse=2+</td>
<td>2.70 (1.85-3.94)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
MAGNIMS Score

- Score 0: 0 Relapses and 0-2 New T2 Lesions
- Score 1: 0 Relapses and 3+ New T2 Lesions, or 1 Relapse and 0-2 New T2 Lesions
- Score 2: 2+ Relapses or 1 Relapse and 3+ New T2 Lesions
### Table 5: MAGNIMS score

<table>
<thead>
<tr>
<th>Risk groups</th>
<th>(%)</th>
<th>Risk of progression after 2 years (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapses=0 and new T2 lesions&lt;3</td>
<td>65.5</td>
<td>19% (1% )</td>
</tr>
<tr>
<td><strong>Intermediate risk:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse=0 and new T2 lesions&gt;=3</td>
<td>24.1</td>
<td>28% ( 3%)</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td>HR= 1.6 (1.2-2.1)</td>
</tr>
<tr>
<td>Relapses=1 and new T2 lesions&lt;3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapses=1 and new T2 lesions&gt;=3</td>
<td>10.4</td>
<td>48% ( 5%)</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td>HR= 3.4 (2.5-4.6)</td>
</tr>
<tr>
<td>Relapses&gt;=2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary

• With a suboptimal response on first-line drugs, a change in management strategy needs to be considered

• Combination of both clinical and MRI measures is the best way to assess treatment response

• Integrated scoring systems incorporating clinical and MRI measures of disease activity could be useful for a personalized approach to treatment
Thank you for your kind attention !!!
Relevance of lesion location

Figure 1. Survival curves on effect of presence of spinal cord lesions on time to conversion to clinically definite multiple sclerosis.

Sombekke et al. Neurology 2013

Figure 1. Infratentorial lesions and disability progression.

Tintore et al. Neurology 2010