Grand Rounds: Exploring Current Therapeutic Agents in Multiple Sclerosis Management

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Multiple Sclerosis Grand Rounds
Clinical Case Presentation #1

- 36 y/o female with a four week history of intermittent numbness in both arms and legs and a 1 week history of weakness in right arm and leg.
- Examination finds 4/5 strength of the right deltoid and iliopsoas with an extensor plantar response on the right
- Labs:
  - Hepatitis B & C, Lyme are all negative
  - ANA ESR negative
  - Normal thyroid function, B12
- CSF + oligoclonal bands
- MRI presented two 4-5 cm lesions, one which is a right juxtacortical which enhances and one left periventricular non enhancing. MRI of spine is negative
The Philosophical Principles Behind Understanding and Treating the Entity We Call Multiple Sclerosis

- A progressive inflammatory disease
- Punctuated by acute relapses in the majority of patients
Poser and McDonald Criteria for Diagnosing MS

- Both require dissemination in space and time for a diagnosis of MS to be made
- McDonald criteria revision in 2011 was simplified
- Very useful in ruling out monophasic illnesses or symptoms that do not meet the criteria for MS

DIS can be demonstrated by ≥1 T2 Lesion\(^a\) in at least 2 of 4 areas of the CNS:
- Periventricular
- Juxtacortical
- Intratentorial
- Spinal Cord\(^b\)

\(^a\) Gadolinium enhancement of lesions is not required DIS
\(^b\) If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count

2010 McDonald MRI Criteria for Demonstration of DIT

DIT can be demonstrated by:

1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan irrespective of the timing of the baseline MRI

2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
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<tbody>
<tr>
<td>≥2 attacks; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack</td>
<td>None</td>
</tr>
<tr>
<td>≥2 attacks; objective clinical evidence of 1 lesion</td>
<td>Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or Await a further clinical attack implicating a different CNS site</td>
</tr>
<tr>
<td>1 attack; objective clinical evidence of ≥2 lesions</td>
<td>Dissemination in time demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time, or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack</td>
</tr>
<tr>
<td>1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)</td>
<td>Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or Await a further clinical attack implicating a different CNS site; and For DIT: A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack</td>
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Back to Our Case

Clinical having relapse with objective evidence of at least one lesion by exam MRI meets revised McDonald criteria for dissemination in time and space

2 lesions

= dissemination in space

Enhancement of one lesion

= dissemination in time
Prognostic Risk Factors in MS

Six risk factors
- Completeness of recovery from initial attacks
- Attack frequency in first 2 years (relapse rate)
- Interval between first and second attack
- MRI status
- Symptoms at onset
- Age at onset

Patient risk groups
- Low – 0 to 1 risk factor
- Medium – 2 to 3 risk factors
- High – 4 to 6 risk factors

An 8 yr retrospective chart review study of 98 MS patients

Role of CSF in Diagnosis

- Presence of oligoclonal bands or an elevated IgG/albumin index is evidence of intrathecal antibody production, presumably from resident plasma cells with the CNS.

- Has a very important role in the diagnostic criteria for PPMS.

- Interestingly, in patients with MRIs that are consistent with demyelination disseminated in time and space, only 16% of directors of MS centers would examine the CSF.

Treatment of the Newly Diagnosed MS Patient

All of the immunomodulatory agents have a potential role in the treatment of the newly diagnosed MS patient.
Interferons and Glatiramer

Phase III data from pivotal trials for all 3 interferons and glatiramer have been standard of care for the past 2 decades in newly diagnosed MS patients

Natalizumab in Newly Diagnosed MS Patients

- Role in early disease supported by Phase III data
- In the newly diagnosed, should be reserved for those patients who are JCV antibody negative given risk of PML

Fingolimod in Newly Diagnosed MS Patients

• Role in early disease supported by Phase III data

• Exclusion criteria should include those patients with a known cardiovascular disease history

Panel Discussion
Multiple Sclerosis Grand Rounds
Clinical Case Presentation #1
Continuation

- Pt. remained on glatiramer acetate for 2 years
- Continued to have relapses over the last 2 years and has been compliant
- Current neurological exam demonstrates bilateral lower extremity weakness 4 out of 5 strength, some left upper extremity dysmetria, and nystagmus
- Follow-up MRI demonstrates new enhancing lesions
Adequate Response to Treatment?
Socratic Method Applied to this Decision

• Same course as when therapy-naïve
• Better, but not perfect
  - Progression, Relapses, MRI, cognition, fatigue
• Minimal clinical symptoms
• MRI signs only
  - One, two, three -- new lesion threshold
• Perfect control. But, there some drugs are statistically better on relapse rate, or oral
Mark Freedman’s MS Dashboard

Response to Therapy

Frequency of Relapses

Severity of Relapses

Benign MS  R  Bad MS

Great response  R  Poor response

Pre-Rx

Post-Rx

Black and white
All or none

T Reder
Response to Therapy

Frequency of Relapses

Benign MS ← Great response ← Bad MS

Severity of Relapses

Post-Rx

Gray zone

Corollary—Is one attack bad?

“Poor” response
Switch Studies vs. Direct Comparison

Glatiramer switches

• Switchers were worse, do worse, switched in past, use combo Rx;
• Remove confounders: same statistical trends

% Relapse-free

• IFN-beta 42% → glatiramer 53%
• Glatiramer 12% → interferon 87%
• IM IFN-β-1a 41% → SQ IFN-β 67%

Clinical vs. MRI predictors

• 0-2 T2+ on IM IFN-β-1a → no progression
• 3+ T2+ → 0.8 progression, similar to PL, & 2+ Gd+
• 2 Clinical attacks = 1.0 progression in IFN and PL

Rudick RA. *J Neuroimaging*. 2004.;4(3) Suppl 54S - 64S.
Switch Studies vs. Direct Comparison

- All drugs are **partially effective**, but
  - some may be more effective than others, and
  - individual responses will vary
- Change will be to a partially effective DMD
- Side effects vary, and affect compliance
- Mode of administration – patients differ
  - Lipoatrophy, IPIR
  - Needle fatigue, high LFT
  - Plethora of safety tests
  - PML

GA
IFN-β
FTY
Natalizumab
DMD Effects on Relapses -- % better

<table>
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<tr>
<th></th>
<th>CIS</th>
<th>Early RR MS</th>
<th>Late RR MS</th>
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<tbody>
<tr>
<td>IFN-b-1a IM</td>
<td>30-44 3y</td>
<td>29-32</td>
<td>-</td>
</tr>
<tr>
<td>IFN-b-1a SQ</td>
<td>52 (35 w/ R22) 2y</td>
<td>33 (27 R22;38 prog)</td>
<td>-</td>
</tr>
<tr>
<td>IFN-b-1b SQ</td>
<td>54</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>Glatiramer</td>
<td>45</td>
<td>33</td>
<td>-</td>
</tr>
<tr>
<td>FTY720</td>
<td>-</td>
<td>54</td>
<td>-</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>-</td>
<td>65 (42 progr)</td>
<td>-</td>
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# DMD in RRMS – Effects on Progression

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<tr>
<th></th>
<th>CIS</th>
<th>RR MS (in trial)</th>
<th>RR Long-term FU</th>
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<tr>
<td>IFN-b-1a IM</td>
<td>-</td>
<td>37</td>
<td>Prog: 1y delay@ 13y 12% less EDSS Δ 16y 25% less death 16y [79% of 172 2y-Rx’d]</td>
</tr>
<tr>
<td>IFN-b-1a SQ</td>
<td>-</td>
<td>48</td>
<td>Prog: 3y delay w/hi Rx @ 7-8y (IFN44) [68% of total]</td>
</tr>
<tr>
<td>IFN-b-1b SQ</td>
<td>No progr. in either group over 8 y, with all on Rx as of year 2</td>
<td>29 NS (31 unconf, signif)</td>
<td>Prog: 8y delay w/hi Rx @ 16y 47% less death @21y [98% of total]</td>
</tr>
<tr>
<td>Glatiramer</td>
<td>-</td>
<td>More with improved EDSS</td>
<td>Fewer attacks in GA users (high dropout rate by active pts) [40% of Piv; 43% of GA]</td>
</tr>
<tr>
<td>FTY720</td>
<td>-</td>
<td>30-37</td>
<td>-</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>-</td>
<td>42</td>
<td>-</td>
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## DMD Effects on Progressive MS -- % better

<table>
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<th>SPMS</th>
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<tr>
<td><strong>IFN-b-1a IM 60 ug/wk</strong></td>
<td>40 MSFC</td>
</tr>
<tr>
<td><strong>IFN-b-1a SQ 44</strong></td>
<td>17-22 NS; 30 Relapse</td>
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<tr>
<td><strong>IFN-b-1a SQ 22</strong></td>
<td>12 NS; 30 Relapse</td>
</tr>
<tr>
<td><strong>IFN-b-1a SQ 22/wk</strong></td>
<td>-13 NS; 10 Relapse</td>
</tr>
<tr>
<td><strong>IFN-b-1b SQ Euro</strong></td>
<td>22% (9-mo delay)</td>
</tr>
<tr>
<td><strong>IFN-b-1b SQ N Amer</strong></td>
<td>30% relapses</td>
</tr>
<tr>
<td>Glatiramer</td>
<td>PROMISE: Trend in men with PPMS</td>
</tr>
<tr>
<td><strong>FTY720</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>Natalizumab</strong></td>
<td>-</td>
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Switch to Non-IFN

Fingolimod

• Minimal risk of significant cardiac, liver abnormality
• Hint of pulmonary, derm effect
• Long-term concerns – no evidence (ongoing)
  - Infections, cancer, persistent lymphopenia

Natalizumab

• Minimal risk if JCV negative, in 50% of pts
• JCV+: 1/1000 after 1st year. 1/250 p chemoRx
  - Risk is per year, so 1/1000 becomes 1/100 p 10 y

Panel Discussion
52 year old white female with a 15 yr h/o MS and has developed secondary progressive multiple sclerosis. She is treated with:

- IFN Beta-1b, Amantidine, Nortriptyline

This patient has received some benefit from aggressive physical therapy, neuromuscular electronic stimulation treatments, and adherence to a diet designed to reduce oxidative stress

The patient remains fatigued, depressed, and disabled
What does it mean to develop SPMS?

- Vast majority of MS patients begin as relapsing-remitting (RRMS) ~85%
- In past, it was estimated that 50% of those with RRMS transition to SPMS
- 2 forms of SPMS
  - With relapses
  - Without relapses
RRMS

PRMS

SPMS

PPMS
The Dual Face of MS Progression

Clinical

• Incomplete recovery from relapses (step-wise worsening)
• Gradual, progressive worsening, independent of relapses

Pathological

• Inflammatory Disease – increasing burden
• Degeneration – loss of brain tissue
The Dual Face of MS Progression
The Dual Face of MS Progression

What is Progressive Disease

- Wave or particle
- Axonal loss
- Neuronal loss
- Failure of repair mechanisms

Is it definable early?

Is there a transition?

How inevitable is progression?
SPMS Disease Modification?

With relapses

- Other DMDs used for “relapsing forms of MS”
  - Beta Interferon-1b
    - European study
    - North American study
  - Mitoxantrone
    - Other chemotherapeutic agents

Without relapses

- Same as with relapses
Emerging SPMS Disease Modification

• Daclizumab
  - Anti CD 25 monoclonal antibody

• Emerging therapies being developed for PPMS
  - Fingolimod
  - Ocrelizumab
  - Other treatments
Improving Quality of Life

• Education
  - Patient
  - Carepartner

• Addressing side effects from DMDs / other meds

• Symptom treatment / management

• NeuroFunctional Enhancer (NFE)
NeuroFunctional Enhancer (NFE)

• Treatment that enhances the functioning of people with neurological diagnoses

• We cannot predict who will respond to various DMDs, but we know early on who responds to NFEs

• Enhances patients’ lives by allowing them to judge whether their neurological function is improving
Time to Stop Medications?

• Does MS “burn out?”
• Futility of Treatment?
  - Individual
    - Patient
    - Neurologist
  - General philosophy
Personalized Medicine

• No lab biomarker
  - MRI
  - History
  - Physical Examination
    - Neurologist
      - Neurological exam
    - Scales
    - Patient perspective
• Treat each person as an individual → personalized medicine
Panel Discussion