CONTROVERSIES IN MS

Carolyn Taylor, M.D.
Swedish Neuroscience Center
- When should disease modifying therapy be discontinued in MS?
- “Should we be using aggressive treatments earlier in the MS disease course and reserving the less aggressive treatments for later?”
- SPMS definitions play a key role in our decision making
MS patients and their treating physicians are routinely confronted with uncertainties regarding diagnosis, prognosis and disease modifying therapies.

We still have inadequate data to guide us.

More clinical data is needed particularly regarding progressive forms of disease.
A Need for More Precise Definition
Defining role of subtype characterization

When does RRMS become SPMS?

Establish better guidelines for treatment since most of our drugs are effective for relapsing subtypes

There are no adequate studies to guide us
MS is a complex neurologic disease characterized by inflammation and axonal loss.

Frequent inflammation, demyelination, axonal transection, plasticity, and remyelination.

Continuing inflammation, persistent demyelination.

Infrequent inflammation, chronic axonal degeneration, gliosis.

Clinical disability, brain volume, inflammation, axonal loss.

Relapsing-remitting, secondary progression.

Clinical threshold.
patients with RMS transition to a slow worsening of their condition independent of relapses

Some have periods of relative stability

Some have superimposed relapses

Often significantly delayed in patients treated with DMTs

Accounts for most of the disability
Disease course can vary significantly among patients making an individual’s course very difficult to predict.

Classification of MS subtypes has been historically by clinical progression and this has been further complicated by the advent of DMT.

Definitions of relapse, progression and subtype imprecise.

The definition that we choose can have far reaching impacts on treatment options in our current environment.
In 1996 the US National Multiple Sclerosis (NMSS) Advisory Committee on Clinical Trials in Multiple Sclerosis saw the need for more clarity and consistency in defining subtypes for natural history and demographic studies, to improve consistency in clinical trials, and to clarify communication among clinicians and patients with MS.

They sought to define the subtypes:
- Based on subjective views of MS experts
- MRI evidence and other markers for disease course were lacking

Lublin et al. Neurology. 2014 Jul 15; 83(3): 278-286
Clinically Isolated Syndrome (CIS)

First clinical presentation of disease that shows characteristics of inflammatory demyelination that could be MS but has not fulfilled criteria of dissemination in time and space

not considered a distinct MS phenotype

Lublin et al. Neurology. 2014 Jul 15; 83(3): 278-286
Radiologically Isolated Syndrome (RIS)

incidental imaging findings suggest inflammatory demyelination in the absence of clinical signs or symptoms

not considered a distinct MS phenotype

Lublin et al. Neurology. 2014 Jul 15; 83(3): 278-286
Diagnosed retrospectively by a history of gradual worsening after an initial relapsing course, with or without acute exacerbations during the progressive course.

No clear clinical, imaging, immunologic, or pathologic criteria to determine the transition point where RMMS converts to SPMS; the transition is usually gradual.

Lublin et al. Neurology. 2014 Jul 15; 83(3): 278-286
- Relatively poor prognosis
- DMT has limited effect
- No clear boundary between RRMS and SPMS
- The patient needs to accumulate a minimum of disability before diagnosis
- Irreversible disability progression independent of a relapse
Some evidence suggests that PPMS represents a distinct, noninflammatory pathologic form of MS.

Abundant clinical, imaging, and genetic data suggest that PPMS is part of a spectrum of progressive MS phenotypes.

Distinct clinical course from SPMS because of the absence exacerbations prior to the course of progression.

Lublin et al. Neurology. 2014 Jul 15; 83(3): 278-286
The definition of transition from RRMS to SPMS is still imprecise

There are still no adequate treatment options for SPMS

There is still much disagreement among clinicians regarding when to stop DMT that is meant for RR subtypes
RRMS treatment options

- Interferon B-1b
- Interferon beta-1a
- Glatiramer acetate
- Fingolimod
- Dimethyl fumarate
- Teriflunomide
- Daclizumab
- Natalizumab
- Ocrelizumab
SPMS treatment options

- Novantrone
  - Only FDA approved treatment for SPMS
  - Rarely if ever used due to risks of cardio- toxicity and leukemia
Ocrelizumab

recently approved for PPMS
Concensus that they are not distinct disease subtypes

Use of DMT has further blurred the distinction

Variable transition times
### Characteristics of RMS and SPMS

<table>
<thead>
<tr>
<th>RMS</th>
<th>SPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- intermittent relapses followed by improvement</td>
<td>- begins with RM course followed by clear worsening between relapses which become less frequent and ultimately cease</td>
</tr>
<tr>
<td>- new Gd+ and T2 FLAIR lesions</td>
<td>- new MRI lesions less frequent, Gd+ enhancement rare, high microscopic lesion burden, more T1 black holes</td>
</tr>
<tr>
<td>- gray matter involvement not as prominent on typical MRI sequences</td>
<td>- more extensive spinal cord involvement</td>
</tr>
<tr>
<td></td>
<td>- Prominent gray matter involvement and diffuse white matter injury</td>
</tr>
</tbody>
</table>
Pathogenesis

RMS

- mainly inflammatory
- typical demyelinating lesions in white matter

PROGRESSIVE MS

- mainly degenerative
- brain injury with neuronal damage
RMS
- acute demyelinating lesions, BBB injury, axonal injury not as marked
- evidence for remyelination repair
- inflammatory cortical lesions may correlate with cognitive disability
- microscopic injury is less marked

Progressive forms MS
- acute lesions and BBB injury less marked, slowly enlarging white matter lesions, progressive brain atrophy
- chronic demyelination leading to irreversible neuronal transection and neurological disability
- diffuse alterations in WM and GM, more severe axonal injury
Proposed a definition of SPMS based on MSBase pooled from 576 patients

Objective definition of MS was able to identify SPMS more than 3 years earlier in the disease course than the physicians’ diagnosis

Findings confirm that neurologists tend to wait until substantial disability has been accumulated before diagnosis of SPMS

Desire for patients to remain on DMT

Lorscheider et al. Brain 2016: 139; 2395-2405
SPMS Definition 2016

- EDSS ≥ 4
- Pyramidal FS ≥ 2
- 1-point worsening with EDSS ≤ 5.5 or 0.5-point worsening with EDSS ≥ 6.0
- Confirmed worsening ≥ 3 months within the same FS
- 89 % sensitivity and 86% specificity
- Allowed prediction of SPMS 3 years earlier than clinical observation

Lorschedier J et al. Brain 2016;139:2395-2405
More precise criteria for evaluating clinical trials

By identifying patient’s earlier, treatment options can be enhanced
Doctor, am I now secondary progressive?

Isn’t there anything else we can do?

Most MS specialists polled indicate that more often they continue DMT because they are just not sure. There are no good guidelines about when and if to stop DMT

The patient may relapse off DMT
CASE STUDY

Anna
55 yo woman presents with intermittent right leg weakness

She had been physically fit all her life and works as a Pilates instructor

MRI brain reveals numerous areas of abnormal T2 FLAIR signal without enhancement characteristic of MS

Spine MRI reveals an enhancing longitudinal lesion in thoracic cord

CSF positive for oligoclonal bands and elevated IgG index
Patient treated with IVSM and symptoms resolve
She is completely asymptomatic
Started on daily Copaxone therapy
She does well with no further symptoms or progression on MRI for 10 years
She develops fatigue and mild discomfort from leg spasticity and started on Provigil and Baclofen with improvement
2 years later she is again complaining of fatigue and struggling more to stay physically active.

- JCV negative – starts Tysabri

- Symptoms of fatigue markedly improve and she remains stable for 2 more years and then she develops Tysabri antibodies

- Switches to Tecfidera – tolerates this well and disease remains well controlled but develops lymphopenia

- She is now 70 and decides to discontinue treatment
One year later age 71 she develops a new spinal cord lesion associated with urinary retention and lower limb weakness.

This is her first new lesion since diagnosis age 55.

After careful consideration she resumes Copaxone 40 tiw and continues to remain stable, now age 74.
When should we stop DMT treatment?
We need to take the patient’s wishes into consideration.

Are they willing to risk a possible relapse off DMT under medical observation?

As our patient’s age they have less neurological reserve

Off DMT does a relapse represent return of inflammatory activity or rebound?
Recommendations

- Difficult to establish recommendations in the absence of evidence
- There are no studies in the literature that provide adequate data to make an evidence-based decision
- Some countries have disability eligibility rules to continue medication – i.e. EDSS ≥ 6.0 or 6.5
- The insurance industry is increasingly controlling our choice of treatment options
Part of the problem is that there is insufficient research on potential benefits of continuing medication other than for ambulation.

Too much emphasis on EDSS scores.

What about cognition, vision, bowel/bladder function, upper limb strength?

Risk of rebound if drug is discontinued.
REBOUND

- New and severe relapse with at least 1 contrast enhancing lesion within 3 months of stopping disease modifying therapy
- Natalizumab – well documented
- Fingolimod – increasingly recognized – pathophysiology unclear: part of immune reconstitution inflammatory syndrome of CNS (IRIS)
- Interferons – selected case reports
Less relapses over time
Relapses are less severe over time
Dissociation of Inflammatory effects and neurodegenerative effects
High cost of medication – burden on health care system
Higher co-morbidities as patients age
Increase risk of PML, shingles, etc.
Patients more debilitated – higher risk of complications
Disease Modifying Therapy Discontinuation in Patients with Multiple Sclerosis Over Age 60

Le H. Hua¹, Huijian Tracey Fan², Devon Conway³, Tyler G. Kinzy³, Nicholas Thompson³

¹Lou Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV ²Touro University School of Medicine, Las Vegas, NV ³Mellen Center for the Treatment and Research in MS, Cleveland Clinic, Cleveland, OH

Objective

To compare clinical and patient-reported outcomes in patients with multiple sclerosis (MS) over age 60 who stop or continue disease-modifying therapy (DMT) after at least 2 years of treatment.

Background

DMTs in MS have robust effects on inflammatory activity but less on disability. The immune system becomes less functional with age and it is unclear whether continued immunomodulation remains beneficial in older patients. Currently there is insufficient data regarding the necessary duration of DMT or impact of discontinuation to guide such decisions.

Methods

Retrospective cohort study comparing patients 60 years or older discontinuing DMT to those who have yet to discontinue. Data describing clinical and MRI history was merged with Patient-Reported Outcomes data. Data was collected from patients receiving treatment between 2010 and 2016. Patients were required to have received DMT at least two years before discontinuation to be included. Patient characteristics were described using frequencies, means and standard deviations. Differences between groups were assessed with univariate analyses (i.e., Student's t-test, Mann-Whitney U, Chi-squared and Fisher's exact tests). All analyses were calculated in R version 3.3.1.

Results

Table 1. Patient characteristics by DMT discontinuation status. All figures are presented as frequency (percentage) unless otherwise noted.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Continuers</th>
<th>Discontinuers</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>513 (70.9)</td>
<td>211 (29.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current Age, mean (SD)</td>
<td>66.7 (4.1)</td>
<td>66.8 (4.0)</td>
<td>0.800</td>
</tr>
<tr>
<td>Age At Diagnosis, mean (SD)</td>
<td>48.4 (9.5)</td>
<td>47.6 (9.3)</td>
<td>0.301</td>
</tr>
<tr>
<td>Male</td>
<td>145 (28.3)</td>
<td>59 (28.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>White</td>
<td>448 (87.6)</td>
<td>199 (90.0)</td>
<td>0.474</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (0.6)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Married</td>
<td>374 (73.6)</td>
<td>149 (72.1)</td>
<td>0.561</td>
</tr>
<tr>
<td>Disease Course at Baseline</td>
<td>5 (1.0)</td>
<td>3 (1.4)</td>
<td>0.645</td>
</tr>
<tr>
<td>PP</td>
<td>48 (9.4)</td>
<td>25 (11.8)</td>
<td>0.652</td>
</tr>
<tr>
<td>PR</td>
<td>15 (2.9)</td>
<td>5 (2.4)</td>
<td>0.652</td>
</tr>
<tr>
<td>RR</td>
<td>445 (88.7)</td>
<td>181 (85.5)</td>
<td>0.167</td>
</tr>
<tr>
<td>SP</td>
<td>4 (0.8)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Tumefactive</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td># of DMT Medications Used, mean (SD)</td>
<td>2.1 (1.3)</td>
<td>2.1 (1.3)</td>
<td>0.920</td>
</tr>
<tr>
<td>DMT Treatment Duration in years, mean (SD)</td>
<td>14.2 (5.5)</td>
<td>12.5 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease Duration in years, mean (SD)</td>
<td>18.4 (9.4)</td>
<td>21.0 (9.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deaths</td>
<td>16 (3.1)</td>
<td>12 (5.7)</td>
<td>0.157</td>
</tr>
</tbody>
</table>

Table 2. Description of those discontinuing DMT (n=211).

<table>
<thead>
<tr>
<th>Lesion Burden</th>
<th>Continuers (n=513)</th>
<th>Discontinuers (n=211)</th>
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<tr>
<td>None</td>
<td>2 (0.4)</td>
<td>2 (0.9)</td>
<td>0.301</td>
</tr>
<tr>
<td>Patchy</td>
<td>9 (1.8)</td>
<td>4 (1.9)</td>
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</tr>
<tr>
<td>Mid</td>
<td>224 (44.4)</td>
<td>103 (49.0)</td>
<td>0.301</td>
</tr>
<tr>
<td>Moderate</td>
<td>160 (31.2)</td>
<td>61 (28.9)</td>
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</tr>
<tr>
<td>Severe</td>
<td>43 (8.4)</td>
<td>23 (10.9)</td>
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</tr>
<tr>
<td>Cervical Spine</td>
<td>69 (24.9)</td>
<td>25 (11.8)</td>
<td>0.011</td>
</tr>
<tr>
<td>Pathy</td>
<td>20 (7.1)</td>
<td>6 (2.8)</td>
<td>0.011</td>
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<tr>
<td>Mid</td>
<td>114 (40.7)</td>
<td>59 (27.9)</td>
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<tr>
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<tr>
<td>Missing</td>
<td>233 (45.4)</td>
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Table 3. Brain and spine volume and lesion burden. All figures are presented as frequency (percentage).

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Conclusions

Most patients over age 60 who discontinued DMT after at least 2 years treatment, remained off DMT, with very low rates of MRI changes or clinical progression leading to reinitiation. This may help guide clinicians and patients considering DMT discontinuation.

References


Disclosures

LHH has received compensation for speaking activities from Teva, Biogen, Genzyme and consulting from Genzyme, Genentech, EMD Serono, and Novartis. DC and NT have received research support paid to their institution by Novartis pharmaceuticals. HTF and TDK have nothing to disclose.
Argument to Continue DMT

- Fewer relapses with age but less neurological reserve
- Patient’s may meet the criteria for SPMS in their 30’s or 40’s
- No adequate treatments available for SPMS
- Risk of rebound
There are no treatments that have shown efficacy for SPMS except Novantrone.

If we stop treatment we have no way of knowing if a relapse represents rebound inflammatory disease or natural history of secondary progression.

We have insufficient data to determine who these populations are and cannot tell them that they will not risk a relapse off treatment.

For this reason, many neurologists would continue treatment once a patient begins to progress into more disability.
MS specialists polled at 207 MS Centers

Case: patient with SPMS, on treatment, progression, no relapses, new MRI lesions

63% would change to more aggressive therapy

87% said that MRI disease should be treated the same in SPMS as RMMS

Majority picked natalizumab as the next treatment so they would continue to escalate

<table>
<thead>
<tr>
<th>Switch to:</th>
<th>Current therapy, n (%)</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>IM IFNβ-1a</td>
<td>SC IFNβ-1a</td>
<td>SC IFNβ-1b</td>
<td>GA</td>
<td></td>
</tr>
<tr>
<td>Different IFNβ</td>
<td>13 (18.3)</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td>20 (28.2)</td>
<td></td>
</tr>
<tr>
<td>GA</td>
<td>7 (9.9)</td>
<td>11 (15.4)</td>
<td>11 (15.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Natalizumab</td>
<td>40 (56.3)</td>
<td>45 (63.4)</td>
<td>45 (63.4)</td>
<td>39 (54.9)</td>
<td></td>
</tr>
<tr>
<td>Fingolimod</td>
<td>4 (5.6)</td>
<td>7 (9.9)</td>
<td>7 (9.9)</td>
<td>5 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (9.9)</td>
<td>7 (9.9)</td>
<td>7 (9.9)</td>
<td>7 (9.9)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GA = glatiramer acetate; IFNβ = interferon-β; IM = intramuscular; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis.
Escalation vs. Inductive Therapy
Start first line DMTs early

If first line therapy is ineffective or only partially effective, switch to second line DMTs

If second line therapy is partially ineffective then switch to more aggressive therapy
Induction Therapy

- Early use of immunosuppressive drugs
- Followed by long term maintenance treatment, generally with immunomodulatory agents
Alemtuzumab (Lemtrada)

HDIT/HCT – high dose immunosuppressant therapy after autologous hematopoietic stem cell transplant

These do not fulfill criteria for disease modulation, escalation or induction therapy
6 year extension data

Patient’s who received alemtuzumab in Care MS I and II showed a low rate of conversion from RRMS to SPMS in 6 years

Optimal definition of SPMS by Lorscheider et al

Care MS I – 4 (1.1%)

Care MS II - 16 (3.7%)
Alemtuzumab extension study

Figure 1. CARE-MS I and II Core and Extension Study Design

**Follow-up Year**
- Y1
- Y2
- Y3
- Y4
- Y5
- Y6

**Follow-up Month**
- 0
- 12
- 24
- 36
- 48
- 60
- 72

- Alemtuzumab 12 mg IV (CARE-MS I, n=376)
- (CARE-MS II, n=435*)

C1, C2

As-needed retreatment with alemtuzumab or other DMT

*As-treated population
C=course; Y=year
Figure 3. Sensitivity Analyses Show That Few Alemtuzumab-Treated Patients Converted to SPMS* Through 6 Years, Confirmed Over 6, 12, and 24 Months.

*Progression start date 6 months.
Most Patients Were Free of MRI Disease Activity in Each Year Through Year 6

*Defined as no new Gd-enhancing T1 lesions on current MRI or new/enlarging T2 hyperintense lesions since last MRI.*

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients Free of MRI Disease Activity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y2</td>
<td>77</td>
</tr>
<tr>
<td>Y3</td>
<td>72</td>
</tr>
<tr>
<td>Y4</td>
<td>70</td>
</tr>
<tr>
<td>Y5</td>
<td>70</td>
</tr>
<tr>
<td>Y6</td>
<td>66</td>
</tr>
</tbody>
</table>
Alemtuzumab brain volume loss

- Durably slows brain volume loss BLV in extension 6 year study of Care MS I (treatment naïve) and Care MS II (failed prior treatment) patients
- Slowed BVL 42% vs. SQ INB-1a in Care MS 1 study and the slowing was maintained over 6 years
24 patients RRMS
Primary end point “event-free survival” – 69.2%
Progression-free survival – 91.3%
Clinical relapse-free survival – 86.9%
MRI activity-free survival – 86.3%
Improvement in EDSS of 0.5
Progression-free and overall survival were greater in patients in younger age, relapsing MS, fewer prior disease modifying drugs and lower baseline EDSS scores
In view of available data indicating that all the drugs are most effective when used earlier in the course of MS, at a younger age, with a lower EDSS, why is the general consensus of treatment to reserve more aggressive therapy for later disease after the patient is at greater risk for disability???
This seems counterintuitive

MS is generally not life threatening but it can lead to significant disability at a young age

If we wait too long to treat aggressively, we may be missing opportunity to use the treatments when they are most effective

Other medical fields such as Rheumatology and Oncology treat differently
HERDING: A NEW PHENOMENON AFFECTING MEDICAL DECISION-MAKING IN MULTIPLE SCLEROSIS CARE?

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A behavioral phenomenon in which individuals follow others rather than behaving independently on the basis of their own information. A herding like phenomenon has been described in MS treatment when a neurologist follows a therapeutic recommendation by a colleague even though it does not follow best practice guidelines. As a result of this behavior a series of suboptimal decisions may arise that lead to worsening clinical consequences.
Study showed that nearly 8 out of 10 neurologists may exhibit negative herding by following an erroneous recommendation by an MS colleague.

High patient volume was the single most factor associated with herding.
Panel B: Prevalence of herding-like behavior by volume of MS patients seen per week (in terciles)

- Tercile 1 (n=1 to 10): 67.7%
- Tercile 2 (12 to 20): 78.2%
- Tercile 3 (21 to 140): 90%
Traditionally treatment is begun with platform or less aggressive treatment. It is safer. Neurologists are not as comfortable with aggressive treatments as some other specialties. Early on patients may have little or no disability so it is more difficult to justify exposure to drugs with more potential side effects.
DMT

- Reduce relapses, MRI lesions and brain atrophy
- Slow progression in young patients
- They do not protect neuronal death independent of inflammation, repair or replace cells
- They are not known for prevention of progressing into SPMS phase
We know that if we wait long enough our patients will progress. Evidence suggests that the longer we wait to treat aggressively, the less responsive our patients will be to these treatments. What if we were to treat more aggressively in the early years when our patients have less disability and revert to the safer disease modifying therapies later when our patients have less inflammation and fewer co-morbidities?
Is it possible in some cases that we could better prevent conversion to SPMS if we treated our patients more aggressively earlier in the course of disease than waiting until they were already progressing into disability?
Edan and LaPage proposed criteria to help identify risk of early disability at an early phase of disease:

- Purely RMMS
- Age < 40 years
- Highly active disease with a least 2 relapses within previous 12 months
- EDSS > 4.0
- Worsening EDSS due to relapses
- At least 2 additional enhancing lesions on MRI
There still remains an urgent need for treatments that protect against demyelination and axonal loss and that promote remyelination/regeneration.

Saponimod
Laquinimod
Statins
Alpha lipoic acid
Treatment Choice

- Efficacy
- Safety
- Side effect profile

Hauser et al.:

“ The best medication is the safest that completely arrests the disease.”