Update on Multiple Sclerosis

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Baylor College of Medicine
February 2016
Objectives

1. Provide an update on MS diagnostic criteria
2. Discuss prognosis of MS
3. Discuss longevity and survival in MS
4. Discuss the risk of PML associated with certain MS medications
Idiopathic Inflammatory Demyelinating Diseases of the CNS

• Optic Neuritis
• Transverse Myelitis

• Multiple sclerosis
  – Relapsing-remitting
  – Primary progressive
  – Secondary Progressive

• Acute Disseminated Encephalomyelitis (ADEM)

• Neuromyelitis Optica Spectrum Disorder (NMOSD)
Clinically Isolated Syndrome

- Acute or subacute episode of neurologic disturbance of the sort seen in multiple sclerosis
- Due to a single white matter lesion
- Up to 85% of MS starts with CIS
- Most commonly:
  - Optic Neuritis
  - Partial myelitis
  - Brainstem/cerebellar syndrome
Multiple Sclerosis

• An idiopathic inflammatory demyelinating disease of the CNS (brain and spinal cord).
• Episodes of neurologic dysfunction “disseminated in time and space”.
• Most common cause of non-traumatic neurologic disability in young adults.
• Autoimmune disorder.
Epidemiology of MS

- Affects 2.5 million worldwide
- Over 450,000 cases in the US.
- Rare in black Africans and Asians.
- Female:male ratio of 3:1
- Age of onset varies.
The Evolution of MS

- Pre-clinical
- CIS
- RRMS
- SPMS

Clinical Threshold
Atrophy and Axonal Degeneration

Total lesion load (T2 lesion volume)
MRI lesion activity
Number of lesions

McDonald MS
Poser CDMS
Natural History of MS

- MRI studies reveal that the early course of MS is primarily subclinical.
- 50% of patients with relapsing-remitting MS (RRMS) develop secondary progressive MS within 10 years.
- 90% of patients with RRMS will eventually develop progressive MS.
Median times from MS onset to disability levels

- **London, Ontario, Canada Cohort**
  - EDSS 3: 7.7 years
  - EDSS 6: 15 years
  - EDSS 8: 46.4 years

- **Lyon, France cohort**
  - EDSS 4: 8.4 years
  - EDSS 6: 20.1 years
  - EDSS 7: 29.9 years
Prognostic factors

- Clinical factors at onset and during early course of disease would be most helpful
- Efforts being made to supplement this with
  - Imaging data
  - Biomarkers
  - Genetic factors
  - Environmental factors
Prognostic factors

- Race: several studies support more aggressive disease in African Americans
- Sex: some studies suggest worse prognosis for males.
  - Not supported in multi-variate analysis
- Age at onset: Younger age at onset associated with longer time to disability landmarks.
Prognostic factors

• Unfavorable
  – Progressive onset (vs. relapse onset)
  – Incomplete recovery from initial attack
  – Shorter interval to second attack
  – Higher number of relapses during early years
  – Initial symptoms: cerebellar, motor or sphincter
Exposure factors

• Smoking
  – MS disability progressed more quickly in smokers
  – Difference was also noted in MRI measures of disease activity
  – Smokers had greater amounts of tissue damage observed on imaging, a greater volume of tissue damage; and more brain atrophy.

Zivadinov, Neurology 2009; Ascherio, Ann Neurol 2007
Effect of smoking cessation on MS prognosis

- Used Swedish MS Registry including 728 MS patients who smoked at time of MS diagnosis
  - Each additional year of smoking after MS diagnosis accelerated time to conversion to SPMS by 4.7%
  - Those who continued to smoke after diagnosis converted to SPMS faster than those who quit smoking
- Reached SPMS at 48 and 56 years, respectively

Ramanujam, JAMA Neurol, 2015
From: **Effect of Smoking Cessation on Multiple Sclerosis Prognosis**


**Figure Legend:**

Kaplan-Meier Plot of Quitters and Continuers

A Kaplan-Meier plot with the age at conversion to secondary progressive (SP) disease for smokers at diagnosis who quit smoking completely (n = 118) and smokers at diagnosis who smoked continuously (n = 332).
Role of Vitamin D in MS

• Geographic distribution of MS
  – Higher MS incidence in areas farther from the equator, limited sunlight exposure
• Sun/UVR exposure early in life is inversely proportional to risk of MS development
• MS patients have relatively low vitamin D levels
• Vitamin D has multiple immunological effects which are anti-inflammatory and decreases disease activity in EAE mice (MS model).

Hewer, J Clin Neurosci, 2013
Revised Diagnostic Criteria
2010 McDonald Criteria

MRI Criteria for dissemination in space:
≥1 T2 lesion in ≥2 of the 4 locations:
  • Periventricular
  • Juxtacortical
  • Infratentorial
  • Spinal cord

Polman, Ann Neurol 2011
Revised Diagnostic Criteria
2010 McDonald Criteria

Dissemination in time by MRI

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

Polman, Ann Neurol 2011
Primary Progressive MS

1. One year of disease progression (retrospectively or prospectively determined)

2. Plus 2 of the 3 following criteria:
   A. Evidence for DIS in the brain based on $\geq 1$ T2 lesion in $\geq 1$ area characteristic for MS (periventricular, juxtacortical, or infratentorial)
   B. Evidence for DIS in the spinal cord based on $\geq 2$ T2 lesions in the cord
   C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Polman, Ann Neurol 2011
<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 attacks</td>
<td>None</td>
</tr>
<tr>
<td>Objective clinical evidence of &gt;2 lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 attacks</td>
<td>Dissemination in space</td>
</tr>
<tr>
<td>1 objective clinical lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>or await further attack implicating</td>
</tr>
<tr>
<td></td>
<td>a different site</td>
</tr>
<tr>
<td>1 attack</td>
<td>Dissemination in time</td>
</tr>
<tr>
<td>2 objective clinical lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>or second clinical attack</td>
</tr>
</tbody>
</table>

Polman, Ann Neurol 2011
### MS Diagnostic Criteria: McDonald

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Additional Data Needed for MS Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 attack</td>
<td>Dissemination in space MRI</td>
</tr>
<tr>
<td>1 objective clinical lesion (monosymptomatic presentation)</td>
<td>AND dissemination in time MRI</td>
</tr>
<tr>
<td></td>
<td>or second clinical attack</td>
</tr>
</tbody>
</table>

Polman, Ann Neurol 2011
Spinal Cord MRI: MS

FSE-T2  
T1-Gd  
Axial-T2

Mortality in MS

- Median survival times from MS clinical onset have ranged from 25 to 45 years
  - Longer durations in more recent studies
- Excess mortality (1.3-3x)
- Reduced life expectancy (6-14 years)
Mortality in MS
French study

• Large study across 15 French MS Centers (up to 1/3 of all French MS patients)
• Study population of over 29,000 MS patients
• Mean follow-up 15.2 (±10.3) years from clinical disease onset
• 5.7% had died (3.7 per 1000 PY)
• Standardized mortality ratio (SMR) 1.48
  – Increased considerably after 20 years (SMR 2.20)

Leray, PLOS One, 2015
Fig 2. Comparison of the survival in MS patients with the survival of the French general population.

doi:10.1371/journal.pone.0132033
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0132033
Table 2. Characteristics of the 1569 deaths categorized by underlying cause of death.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number of deaths (/1569) (%)</th>
<th>F/M sex ratio</th>
<th>Median age in years at MS clinical onset (range)</th>
<th>Median age in years at death (range)</th>
<th>Median disease duration in years at death (range)</th>
<th>Number (%) of patients with relapsing onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1569 (100%)</td>
<td>884/685/129</td>
<td>34.3 (6-72)</td>
<td>56.0 (19-96)</td>
<td>19.7 (1-88)</td>
<td>1.137 (72.5%)</td>
</tr>
<tr>
<td>MS</td>
<td>700 (44.6%)</td>
<td>380/320/1.19</td>
<td>32.2 (10-72)</td>
<td>54.5 (22-88)</td>
<td>19.7 (1-63)</td>
<td>509 (72.8%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>187 (11.8%)</td>
<td>120/67/1.79</td>
<td>38.0 (6-63)</td>
<td>58.8 (21-85)</td>
<td>19.2 (1-55)</td>
<td>152 (81.3%)</td>
</tr>
<tr>
<td>Cardiovascular disease / stroke</td>
<td>126 (8.1%)</td>
<td>60/66/0.91</td>
<td>38.1 (7-70)</td>
<td>61.0 (34-88)</td>
<td>22.2 (2-58)</td>
<td>89 (70.6%)</td>
</tr>
<tr>
<td>Infections</td>
<td>67 (3.0%)</td>
<td>41/26/1.58</td>
<td>33.3 (17-58)</td>
<td>63.9 (35-92)</td>
<td>24.6 (2-57)</td>
<td>39 (58.2%)</td>
</tr>
<tr>
<td>Suicide</td>
<td>47 (3.0%)</td>
<td>24/23/1.04</td>
<td>32.2 (14-54)</td>
<td>46.4 (19-69)</td>
<td>12.3 (2-45)</td>
<td>35 (74.5%)</td>
</tr>
<tr>
<td>Other causes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>211 (13.4%)</td>
<td>126/85/1.48</td>
<td>36.0 (11-72)</td>
<td>59.0 (20-96)</td>
<td>21.5 (1-59)</td>
<td>140 (66.3%)</td>
</tr>
<tr>
<td>Unknown&lt;sup&gt;b&lt;/sup&gt;</td>
<td>231 (14.7%)</td>
<td>133/98/1.36</td>
<td>34.3 (11-72)</td>
<td>54.2 (19-88)</td>
<td>19.2 (1-53)</td>
<td>173 (74.9%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Accidents, digestive diseases, respiratory diseases, neurological diseases other than MS, unspecified, and other causes.

<sup>b</sup> Unavailable death certificates.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0132033
Table 3. Mortality rates and survival probabilities 25 years after MS clinical onset.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Number of deaths (%)</th>
<th>Death rate (per 1000 patient-years) [95% CI]</th>
<th>Probability of being alive 25 years after MS clinical onset (%) [95% CI]</th>
<th>Adjusted odds ratio [95% CI]</th>
<th>p-value (Logrank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1,569 (5.7%)</td>
<td>3.73 [3.55–3.92]</td>
<td>89.6 [88.9–90.2]</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>685 (8.6%)</td>
<td>5.53 [5.13–5.96]</td>
<td>84.9 [83.4–86.2]</td>
<td>1.67 [1.51–1.85]</td>
<td>$10^{-4}$</td>
</tr>
<tr>
<td>Female</td>
<td>884 (4.5%)</td>
<td>2.98 [2.79–3.18]</td>
<td>91.7 [91.0–92.4]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age at MS onset (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;20</td>
<td>134 (4.9%)</td>
<td>2.45 [2.07–2.90]</td>
<td>95.1 [93.8–96.2]</td>
<td>1</td>
<td>$10^{-4}$</td>
</tr>
<tr>
<td>20–40</td>
<td>925 (5.1%)</td>
<td>3.23 [3.03–3.45]</td>
<td>91.4 [90.6–92.1]</td>
<td>1.81 [1.50–2.18]</td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td>510 (7.5%)</td>
<td>6.38 [5.85–6.96]</td>
<td>76.1 [73.3–78.6]</td>
<td>4.84 [3.94–5.94]</td>
<td>$10^{-4}$</td>
</tr>
<tr>
<td>Initial course</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Relapsing</td>
<td>1,137 (4.9%)</td>
<td>3.16 [2.98–3.34]</td>
<td>91.6 [90.9–92.2]</td>
<td>1</td>
<td>$10^{-4}$</td>
</tr>
<tr>
<td>Progressive</td>
<td>430 (10.8%)</td>
<td>7.33 [6.67–8.06]</td>
<td>73.3 [74.7–79.6]</td>
<td>1.73 [1.53–1.95]</td>
<td></td>
</tr>
<tr>
<td>Year of onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1980</td>
<td>327 (18.2%)</td>
<td>5.44 [5.04–5.89]</td>
<td>93.7 [92.8–94.5]</td>
<td>Not included</td>
<td>$10^{-4}$</td>
</tr>
<tr>
<td>1980–1989</td>
<td>485 (9.1%)</td>
<td>4.05 [3.70–4.42]</td>
<td>88.2 [87.0–89.3]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990–1999</td>
<td>380 (3.7%)</td>
<td>2.78 [2.51–3.07]</td>
<td>n.a.</td>
<td>1.52 [1.21–1.91]</td>
<td></td>
</tr>
<tr>
<td>2000–2009</td>
<td>73 (0.8%)</td>
<td>1.52 [1.21–1.91]</td>
<td>n.a.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS duration (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–10</td>
<td>257 (2.6%)</td>
<td>1.11 [0.98–1.26]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–20</td>
<td>543 (5.4%)</td>
<td>4.46 [4.10–4.85]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–30</td>
<td>447 (8.9%)</td>
<td>9.27 [8.45–10.17]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–40</td>
<td>216 (11.0%)</td>
<td>14.11 [12.35–16.12]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>106 (15.1%)</td>
<td>26.48 [21.89–32.03]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MS = multiple sclerosis; CI = confidence interval; n.a. = not applicable


http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0132033
Mortality in MS: NARCOMS

• Of over 32,000 MS patients, 2927 had died

• Causes of death

  - MS: 41.4%
  - Other: 20.7%
  - Major CV Disease: 16.8%
  - Cancer: 11.4%
  - Pneumonia: 4.2%
  - Septicemia: 2.3%
  - Suicide: 1.6%
  - Accident: 1.6%

Cutter, Mult Scler Rel Dis, 2015
MS Prognosis in the Era of DMT

• Clinical trials with MS DMTs include disability measures
  – Trials are usually 2-3 years
  – Some decrease in sustained accumulation of disability (20-40% decrease)
  – Limited data on long-term survival
  – Long-term outcomes after initial enrollment in IFN registry trials
PRISMS-15

• PRISMS study of SC IFN-beta 1a (Rebif) 1998
• 560 RRMS patients randomized to placebo, or one of two doses of IFN
• After 2 years, all placebo patients re-randomized to one of two doses of IFN
• All invited back for 15 year visit
  – Clinical exam and retrospective review of history and medications

Kappos, J Neurol Neurosurg Psychiatry, 2015
PRISMS-15

- 291 patients returned for PRISMS-15 (52.0%)
- 118 still receiving IFN-beta 1a
- 168 still receiving any DMT

Kappos, J Neurol Neurosurg Psychiatry, 2015
PRISMS-15

• Compared MIN (lowest quartile of cumulative IFN exposure) vs MAX (highest quartile)
  – MAX group had:
    • Lower ARR
    • Lower proportion with 3-month confirmed disability progression
    • Smaller mean increase in EDSS
    • Lower proportion with EDSS>4, EDSS>6
    • Lower proportion converted to SPMS (20.8% vs 52.1%)

Kappos, J Neurol Neurosurg Psychiatry, 2015
21 year follow-up
IFN-beta 1b

• Original IFN-beta 1b (Betaseron) trial, 1993
• 372 RRMS patients randomized to placebo, or one of two doses of IFN
• Long-term FU visit at median of 21.1 years
• 366 ascertained (98.4%)!
• 81 had died (22.1%)
  – MS patients originally randomized to IFN had reduced HR for “all cause” mortality (by 46%)

Goodin, Neurology, 2012
# 21 year follow-up IFN-beta 1b

Decision algorithm for determining the relationship of death to MS

<table>
<thead>
<tr>
<th>Always MS related</th>
<th>Probably MS related</th>
<th>Probably not MS related</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Suicide</td>
<td>1. Brainstem dysfunction</td>
<td>1. CV disease and stroke</td>
</tr>
<tr>
<td>2. EDSS $\geq 7.0$ prior to death</td>
<td>2. Pulmonary infections</td>
<td>2. All cancers</td>
</tr>
<tr>
<td>3. MS the only listed COD</td>
<td>3. Aspiration pneumonia</td>
<td>3. Other infections</td>
</tr>
<tr>
<td>5. Death from MS treatment</td>
<td>5. Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Sepsis (especially urosepsis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Death due to trauma</td>
<td></td>
</tr>
</tbody>
</table>

Goodin, BMJ Open, 2012
21 year follow-up
IFN-beta 1b

- Average age at death was 51.7 (±8.7) years
- Relationship of COD to MS could be established in 85.2%
  - Death due to MS in 31.3%
  - 54 of the deaths were adjudicated to be MS related (78.3%)
  - Excess mortality in original placebo group was largely from MS-related causes

Goodin, Neurology, 2012
Self-injection

– 5 Beta-interferons
  • IFN beta 1-b SC every other day (two brands)
  • IFN beta 1-a IM weekly
  • IFN beta 1-a (pegylated) SC every 14 days
  • IFN beta 1-a SC three times per week

– Glatiramer acetate 20 mg SC daily or 40 mg SC TIW
Treatment overview: MS

Oral

Fingolimod 0.5 mg daily

Dimethyl fumarate 240 mg BID

Teriflunomide 7 or 14 mg daily
Treatment overview: MS

Intravenous

Natalizumab 300 mg every 28 days

Alemtuzumab 12 mg daily for 5 days; repeat 3 day cycle after 1 year

Mitoxantrone (rarely used)
Goals of Disease Modifying Therapy in RRMS

**Standard treatment outcomes in MS**

1. Reduce relapses; extend time between relapses
2. Reduce severity of relapses
3. Prevent or extend time to disability milestones
4. Prevent or extend time to onset of secondary progressive MS
5. Prevent or reduce the number and size of new & enhancing lesions on MRI
6. Limit overall MRI lesion burden in the central nervous system (CNS)
Progressive multifocal leukoencephalopathy (PML)

- Subacute infection by JC Virus of oligodendrocytes and astrocytes of the CNS
- Opportunistic infection associated with immunosuppression
  - HIV/AIDS
  - Malignancies
  - Organ transplant
  - Rheumatic diseases
  - Sarcoidosis
  - Biological treatments
PML in MS

- PML reported with natalizumab use as early as 2005
- PML with fingolimod (5 patients without previous natalizumab exposure)
- PML with dimethyl fumarate (4 patients, all with prolonger lymphopenia <600)
PML

- Caused by mutating, neurotropic strain of JCV
- About 60% of the population has been affected by JCV
- JCV is typically benign and resides in gut, kidneys, bone marrow and lymphoreticular system
- Not clear what drives drugs to convert the virus to pathogenic strain
JCV Ab testing

• STRATIFY JCV test commercially available for the past few years

• Two step assay resulted as positive or negative
  – Results have included an index value for the past 2 years

• Index is the sample optical density (OD) value normalized to an assay calibrator. Index is a corollary to antibody titer, which is derived by serially diluting the sample.
Approximate Incidence of PML, Stratified According to Risk Factors

## Current US Risk estimates

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Negative</th>
<th>TYSABRI Exposure†</th>
<th>Anti-JCV Antibody Positive</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No Prior Immunosuppressant Use</td>
<td>Prior Immunosuppressant Use</td>
</tr>
<tr>
<td>&lt;1/1,000</td>
<td>1-24 months</td>
<td>&lt;1/1,000</td>
<td>1/1,000</td>
</tr>
<tr>
<td></td>
<td>25-48 months</td>
<td>3/1,000</td>
<td>12/1,000</td>
</tr>
<tr>
<td></td>
<td>49-72 months</td>
<td>6/1,000</td>
<td>13/1,000</td>
</tr>
</tbody>
</table>

Notes: The risk estimates are based on postmarketing data in the United States from approximately 69,000 TYSABRI exposed patients.
†Data beyond 6 years of treatment are limited.
The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%.
PML with natalizumab

- As of 10/31/2015, over 146,000 patients received postmarket NTZ worldwide
- Overall incidence of PML with NTZ use is 4.11 per 1000
- 86% had >24 doses at time of diagnosis of PML
- 8% asymptomatic at time of diagnosis of PML
- 23% of PML patients died from PML
NTZ-associated PML

• Factors associated with improved survival after PML
  – Younger age at diagnosis
  – Less functional disability prior to diagnosis
  – Lower JC viral load at diagnosis
  – More localized brain involvement by MRI at time of diagnosis

Dong-Si, presented at ECTRIMS 2013
<table>
<thead>
<tr>
<th>Anti-JCV antibody index</th>
<th>1–24 months (99% CI)</th>
<th>25–48 months (99% CI)</th>
<th>49–72 months (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.9</td>
<td>0.06 (0–0.19)</td>
<td>0.51 (0–1.57)</td>
<td>0.58 (0–1.75)</td>
</tr>
<tr>
<td>≤1.1</td>
<td>0.11 (0–0.26)</td>
<td>0.76 (0–1.76)</td>
<td>0.98 (0–2.00)</td>
</tr>
<tr>
<td>≤1.3</td>
<td>0.14 (0–0.29)</td>
<td>1.06 (0.19–2.15)</td>
<td>1.30 (0.21–2.45)</td>
</tr>
<tr>
<td>≤1.5</td>
<td>0.17 (0.04–0.30)</td>
<td>1.13 (0.26–2.36)</td>
<td>1.37 (0.20–2.73)</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>1.17 (1.04–1.29)</td>
<td>8.83 (7.75–9.62)</td>
<td>10.12 (8.90–11.11)</td>
</tr>
</tbody>
</table>
New patient:
- Recommend baseline index test
- No additional safety monitoring in initial 12-months

Existing patients / At 12-months:
- Monitoring adapted based on JCV status
- If anti-JCV antibody-positive, monitor based on index value

Anti-JCV antibody-negative
PML risk 1 in 10,000

Test anti-JCV antibody index 6-monthly

- Anti-JCV antibody negative
  - MRI scan 12-monthly
    - Index ≤1.5
      - Manage as per index ≤1.5
    - Index >1.5
      - Manage as per index >1.5

- Anti-JCV antibody positive
  - Index ≤1.5
  - Index >1.5

Anti-JCV antibody-positive, index ≤1.5
PML risk 1 in 5,882

Test anti-JCV antibody index 6-monthly

- Index ≤1.5
  - Manage as per index ≤1.5
- Index >1.5
  - Manage as per index >1.5

Anti-JCV antibody-positive, index >1.5
PML risk 1 in 855

Further anti-JCV antibody index testing not mandatory

If patient chooses to remain on therapy

Anti-JCV antibody-positive, index >1.5
PML risk 1 in 113 during months 25-48 of therapy

After 18-months from natalizumab commencement, increase frequency of MRI scanning to minimum 6-monthly PML risk 1 in 885 during months 25-48 of therapy

McGuigan, BMJ Open, 2015
Monitoring on NTZ

• Serum JCV Ab testing every 3-6 months (for those who remain negative)
  – Risk re-evaluation in those who convert to positive
  – Conversion of 1-2% of patients per year

• Clinical evaluation every 3-6 months and at first report of any new neurologic symptoms

• Brain MRI every 6-12 months
Stopping natalizumab

- Rapid discontinuation of natalizumab in setting of JCV infection almost universally associated with immune reconstitution inflammatory syndrome (IRIS).
  - Paradoxical neurologic worsening during immune recovery
  - Worsening clinical symptoms and enlargement of lesions on MRI, often with corresponding contrast enhancement
  - IRIS is treated with IV corticosteroids
Stopping natalizumab

• Personalized decision with patient and physician
  
  – Safety, anxiety and natalizumab continuation in JC virus-seropositive MS patients.
    • van Rossum et al. Mult Scler 2013

• Plasma Tysabri levels detectable for several months
  
  – ? Washout before next drug
Stopping natalizumab

• Debate regarding whether natalizumab cessation causes increased MS activity apart from IRIS.
• Aggressive MS relapses leading to fulminant neurologic deterioration have been reported.
• MS disease activity returns shortly after natalizumab discontinuation and peaked at 4-7 months post-discontinuation.
Italian study of NTZ discontinuation

- Included RRMS with at least 6 infusions of NTZ
- Followed for > one year after stopping NTZ
- Clinical data collected for 2 years before NTZ treatment and intervals after stopping
- 132 enrolled, median of 25 NTZ infusions

Lo Re, Neurol Ther, 2015
Italian study of NTZ discontinuation

- Rebound defined as:
  - ARR increase
  - ≥1 severe relapse with sustained disability progression
  - ≥3 new large T2 lesions and/or Gd-enhancing lesions on MRI
  - New tumor-like demyelinating lesions on MRI

Lo Re, Neurol Ther, 2015
Italian study of NTZ discontinuation

- 95 patients (72%) switched to other therapies after median washout period of 5 months
  - 57 switched to fingolimod
  - 16 switched to IFN or GA
- 72 patients (54.5%) had clinical reactivation
- 60 patients (48%) had radiological reactivation
- 28 patients (21.2%) had rebound
- Higher risk for increased activity related to lower number of NTZ infusions and longer washout

Lo Re, Neurol Ther, 2015
Questions?