Multiple Sclerosis – A Review

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Declaration of Conflicts of Interests

- Have served on advisory boards, received honoraria, conducted clinical trials with and received research funding from:
  - Allergan
  - Biogen Canada
  - Serono Canada
  - Teva Neurosciences
  - Schering (Berlex)
  - BioMS
  - Bayer Canada
  - Novartis, Canada
  - Sanofi-Aventis
  - Genzyme, Canada
Learning Objectives

- Recognize the clinical features of multiple sclerosis
- Review the evolving treatment options in multiple sclerosis
- Recognize medical complications of MS and how to treat
- Review community resources available for MS patients

MS

- The most common seriously disabling disease
- 35,000 Canadians
- Prevalence rates of 1 in 1000 in North America
Sex, age and ethnicity susceptibility to MS

**Sex**
- Sex ratio: 2F/1M

**Age of onset**
- 30 - 40 years

**Ethnicity**
- High risk: Northern Europeans, US Caucasians, Canadians
- Low risk: Australians, South African whites, Southern Europeans, African blacks, Orientals

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Potential Triggers for Multiple Sclerosis

- Infectious agent
- Genetic predisposition
- Abnormal immunologic response
- Environmental factors

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Disease Course in MS

Demographics

(N = 3019)

Relapsing-remitting MS

Primary progressive MS

Secondary progressive MS

Progressive-relapsing MS

Multiple Sclerosis - Signs

- Optic nerve
  - decreased visual acuity
  - colour desaturation
  - RAPD
  - pale disc

- Brainstem
  - INO; dysconjugate EOM’s
  - nystagmus
  - pseudo-bulbar (dysarthria)
Multiple Sclerosis - Signs

- Motor Findings (UMN)
  - spasticity
  - weakness
  - hyperreflexia
  - extensor plantars
  - absent abdominal reflexes

- Sensory
  - increased vibration sense (esp. legs)
  - pseudo-athetosis
  - sensory level (transverse myelitis)

- Coordination
  - dysmetria
  - cerebellar tremor/rubral tremor
Multiple Sclerosis - Signs

- Gait
  - spastic
  - wide-based (difficulty with tandem)
- Cognition
  - dementia
  - pathological crying
  - depression

Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,1 Stephen C. Reingold, PhD,2 Brenda Banwell, MD,3 Michel Clenet, MD,4 Jeffrey A. Cohen, MD,5 Massimo Filippi, MD,6 Kazuo Fujihara, MD,7 Eva Havrdova, MD, PhD,8 Michael Hutchinson, MD,9 Ludwig Kappos, MD,10 Fred D. Lublin, MD,11 Xavier Montalban, MD,12 Paul O’Connor, MD,13 Magnhild Sandberg-Wollheim, MD, PhD,14 Alan J. Thompson, MD,15 Emmanuelle Waubant, MD, PhD,16 Brian Weinshenker, MD,17 and Jerry S. Wolinsky, MD18

New evidence and consensus has led to further revision of the McDonald Criteria for diagnosis of multiple sclerosis. The use of imaging for demonstration of dissemination of central nervous system lesions in space and time has been simplified, and in some circumstances dissemination in space and time can be established by a single scan. These revisions simplify the Criteria, preserve their diagnostic sensitivity and specificity, address their applicability across populations, and may allow earlier diagnosis and more uniform and widespread use.

ANN NEUROL 2011;69:292-302
### TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS

| DIS Can Be Demonstrated by $\geq 1$ T2 Lesion$^*$ in at Least 2 of 4 Areas of the CNS: |
|---------------------------------|---------------------------------|
| Pons/Periventricular             | Juxtacortical                    |
| Infratentorial                   | Spinal cord                     |

Based on Swanton et al 2006, 2009.$^{27,28}$

$^*$Gadolinium enhancement of lesions is not required for DIS.

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.

MRI = magnetic resonance imaging; DIS = lesion dissemination in space; CNS = central nervous system.

### TABLE 2: 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

Based on Montalban et al 2010.$^{29}$

MRI = magnetic resonance imaging; DIT = lesion dissemination in time.

### TABLE 3: 2010 McDonald Criteria for Diagnosis of MS in Disease with Progression from Onset

PPMS May Be Diagnosed in Subjects With:

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$^*$

   B. Evidence for DIT in the spinal cord based on $\geq 2$ T2$^*$

   C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

$^*$If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the Criteria.

Gadolinium enhancement of lesions is not required.

MS = multiple sclerosis; PPMS = primary progressive MS; DIS = lesion dissemination in space; CNS = central nervous system; IgG = immunoglobulin G.
Implications

- Ability to make diagnosis of clinically definite multiple sclerosis in a patient with one relapse

- NB: needs to have MRI brain with Gad completed +/- MRI spine

Multiple Sclerosis - Natural History

- 50% of patients develop secondary progression after 10 years
- 90% of patients develop secondary progression after 25 years
- 50% of patients become dependent on an assistive device after 15 years
- Only 10% patients accumulate minimal disability or in “benign state”

Weinshenker BG, Brain, 1989
Phase III trials in R-R MS

- Beta-interferon 1-b (Betaseron) – 1993
- Beta-interferon 1-a (Avonex) – 1996
- Beta-interferon 1-a (Rebif) – 1998
- Glatiramer Acetate (Copaxone) – 1995
- Natalizumab (Tysabri) – 2007
- Fingolimod (Gilenya) = 2011
- BG-12 (Tecfidera) – 2012
- Teriflunomide (Aubagio) – 2013
- Alemtuzumab (Lemtrada) - 2014

34% reduced attack frequency
p<0.0001

Interferon beta-1a—time to increased disability by 1.0 EDSS steps


![Graph showing the time to sustained progression in weeks for Placebo and Interferon beta-1a.](image1)

- Placebo
- Interferon beta-1a

\[ p = 0.02 \]

37% reduction

Burden of Disease with MRI

![Graph showing the burden of disease with MRI over time for Placebo, 6 MIU, and 12 MIU.](image2)

- 12 MIU
- 6 MIU
- Placebo

Glatiramer Acetate

- Local skin reactions
- Idiosyncratic chest tightness sensations
- Blood work not required

- Costs about $17000-20000/year
SAM Inhibitors: Implications for MS Therapy

Leukocyte
\( \alpha 4\text{-integrin} \)

Blood-Brain Barrier
Endothelial Cells

VCAM-1

Tissue

\( \text{Natalizumab} \)
Annualized Relapse Rate
Pre-specified Primary Endpoint

Placebo
n=315
0.81
P<0.0001

Natalizumab
n=627
0.26

68%

American Academy of Neurology, April 2005

Natalizumab PML Incidence Estimates by Treatment Duration

Incidence per 1000 patients

Clinical Trials*  Post Marketing
≥12 infusions ≥18 infusions ≥24 infusions ≥30 infusions ≥36 infusions ≥42 infusions

Observed clinical trial rate in patients who received a mean of 17.9 monthly doses of natalizumab. The post-marketing rate is calculated as the number of PML cases since reintroduction in patients that have had at least 1 dose of natalizumab.

Incidence estimates by treatment duration are calculated as the number of PML cases divided by the number of patients exposed to TYSABRI (e.g., for ≥24 infusions all PML cases diagnosed with exposure of 24 infusions or more divided by the total number of patients exposed to at least 24 infusions). Biogen Idec, data on file.
**Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis**

Jeffrey A. Cohen, M.D., Frederik Barkhof, M.D., Giancarlo Comi, M.D., Hans-Peter Hartung, M.D., Bhupendra O. Khatri, M.D., Xavier Montalban, M.D., Jean Pelletier, M.D., Ruggero Capra, M.D., Paolo Gallo, M.D., Guillermo Izquierdo, M.D., Klaus Tiel-Wilck, M.D., Ana de Vera, M.D., James Jin, Ph.D., Tracy Sipes, Ph.D., Stacy Wu, M.D., Shreeram Aradhye, M.D., and Ludwig Kappos, M.D., for the TRANSFORMS Study Group.

**Primary endpoint: annualized relapse rate**

- **IFNβ-1a IM** (n = 431) - 0.33
- **Fingolimod 0.5 mg** (n = 429) - 0.16
- **Fingolimod 1.25 mg** (n = 420) - 0.20

-52% vs IFNβ-1a, p < 0.001
-38% vs IFNβ-1a, p < 0.001

Modified intention-to-treat population: all patients who underwent randomization and received at least one dose of a study drug.

Negative binomial regression model adjusted for study group, country, baseline number of relapses in previous 2 years and baseline disability score. p = 0.16 for fingolimod 0.5 mg vs 1.25 mg.
Table 3. (Continued.)

<table>
<thead>
<tr>
<th>Event</th>
<th>Fingolimod 1.25 mg (N=420)</th>
<th>Fingolimod 0.5 mg (N=420)</th>
<th>Interferon Beta-1a (N=431)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>no. of patients (%)</td>
<td>no. of patients (%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any serious event</td>
<td>45 (10.7)</td>
<td>10 (7.0)</td>
<td>23 (5.8)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia or sinus bradycardia</td>
<td>10 (2.4)</td>
<td>2 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Atioventricular block</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second degree</td>
<td>3 (0.7)</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>First degree</td>
<td>2 (0.5)</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicitis</td>
<td>2 (0.5)</td>
<td>0</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Herpesvirus infection</td>
<td>3 (0.7)</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal-cell carcinoma</td>
<td>2 (0.5)</td>
<td>3 (0.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Melanoma (including in situ)</td>
<td>0</td>
<td>3 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Breast cancer (including in situ)</td>
<td>2 (0.5)</td>
<td>2 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (0.5)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Listed are all adverse events that occurred in more than 5% of patients in any study group (with the exception of lymphopenia), in decreasing order of total frequency. Listed serious adverse events occurred in at least two patients in any study group. 
† The two deaths in the group that received fingolimod at a dose of 1.25 mg were caused by disseminated primary variant cells, central infection and herpes simplex encephalitis.

Overview of current situation with regards to mortality in MS patients on fingolimod

More than 30,000 MS patients treated since 2003 (trials and post-marketing)

11 deaths of potential interest
- 3 complications of advanced MS
- 3 myocardial infarctions
- 2 drownings
- 2 sudden unexplained deaths during sleep
- 1 hypertensive cardiovascular disease

20 other cases
- 6 suicides
- 6 off drug at time of death
- 4 progression of MS
- 2 infections
- 1 traffic accident, 2 others

Controlled trials show no increased rate of death compared to placebo

Rates of overall death in line with background rates in a comparable population

* Status as of December 13, 2011
† Off fingolimod for between 3 months and 2 years
‡ 1 off fingolimod for 1 month
§ 2 disseminated primary variant cells, 1 herpes simplex encephalitis
BG-12 (Tecfidera)

Annualized Relapse Rate at 2 Years

DEFINe

CONFIRM

*Annualized relapse rate (ARR) calculated with negative binomial regression, with pre-specified adjustment for baseline EDSS score (≤ 2.0 vs > 2.0), baseline age (< 40 vs ≥ 40 years), region, and number of relapses in the 1 year prior to study entry; data after switch to alternative MS therapy were excluded. Confidence interval.

**Duration of Flushing and GI Events**

A. Flushing events as measured by Global Flushing Severity Scale (GFSS: 0-10)
   All groups, n=6

B. Duration of abdominal pain, nausea/vomiting and diarrhea events reported in the first 3 months of DMF BID treatment

- Diarrhea (n=73)
- Nausea/vomiting (n=108)
- Abdominal pain (n=113)

Median duration:
- Diarrhea = 8 days
- Nausea/vomiting = 8 days
- Abdominal pain = 9.5 days

**Teriflunomide: Introduction**

Teriflunomide is the active metabolite of leflunomide and is responsible for the activity of leflunomide in vivo.

Leflunomide is indicated for the treatment of active rheumatoid arthritis (RA) in adults.

Once daily, oral administration
May be taken with or without food

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TEMSO: Hair Thinning

In most cases, hair thinning occurred early in treatment (within 6 months), was mild to moderate, transient, and recovered without sequelae.

The probability of onset of hair thinning reduces over time.

0.5% of patients in the teriflunomide 7-mg group and 1.4% in the teriflunomide 14-mg group discontinued treatment due to hair thinning.

AE=adverse event
Data on file – CONFIDENTIAL.

Outcomes of patients who developed hair thinning during the TEMSO study (Week 108)

- Placebo (n=360)
- Teriflunomide 7 mg (n=368)
- Teriflunomide 14 mg (n=358)

Time course of probability of hair thinning

- Highest probability
- Lessened risk over time

Third line treatment

- Alemtuzumab (Lemtrada)
Alemtuzumab’s exact mechanism of action is not fully elucidated


Alemtuzumab a monoclonal antibody is Thought to Rebalance the Immune System in RRMS

- Alemtuzumab selectively targets CD52 to deplete circulating B and T lymphocytes\(^1\)\(^3\)
  - Minimal impact on innate immune cells, which represent the first line of defense against infection due to little or no expression of CD52
- Repopulation potentially leads to a rebalanced the immune system\(^4\)
  - A shift in T cell cytokines toward a less inflammatory pattern and a relative increase in the proportion of regulatory T lymphocytes potentially leads to long-term control of disease

### Laboratory Monitoring

<table>
<thead>
<tr>
<th>Lab Measurement</th>
<th>Rationale</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>ITP</td>
<td>Prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion</td>
</tr>
<tr>
<td>Thyroid function tests, such as TSH level</td>
<td>Thyroid disorders</td>
<td>Prior to initiation of treatment and at quarterly intervals thereafter until 48 months after the last infusion</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Nephropathies*</td>
<td>Prior to initiation of treatment and at monthly intervals thereafter until 48 months after the last infusion</td>
</tr>
<tr>
<td>Urinalysis with urine cell counts</td>
<td>Nephropathies*</td>
<td>Quarterly intervals until 48 months after the last infusion</td>
</tr>
</tbody>
</table>

*Including anti-GBM disease.
What would I do….Escalation

**First Line**
- Interferon
- Glatiramer Acetate
- Teriflunomide
- BG-12

**Second Line**
- Fingolimod
- Natalizumab

**Third Line**
- Alemtuzumab
- Clinical Trial/chemotherapy
- Stem cell
New Developments

- Minocycline 100mg BID (Clinically Isolated Syndrome)
  - 6 month conversion to MS – absolute risk reduction by 27.4% (NNT of 4)
  - Early or concomitant treatment?

- Ocrelizumab (Primary Progressive MS)

Symptomatic management

- Fatigue – amantadine, modafinil; Fampyra

- Spasticity – benzodiazepine, baclofen; tizanidine, dantrolene, Botulinum toxin

- Bladder frequency – oxybutynin, tolterodine, flavoxate, vasopressin, mirabegron
Symptomatic management

- Paroxysmal Dystonia – anti-convulsants
- Tremor – primidone, propranolol, DBS
- Depression – anti-depressants
- Chronic Pain/Neuropathic Pain – gabapentin, tricyclic, Cymbalta, cannabinoids

For acute relapses

- Solumedrol 1.0g IV for 3-5 days, followed by oral taper…
- Prednisone 500mg po BID for 3-5 days – no taper…..
- Rule out underlying infection first (ie UTI)…
Resources for the family physician

- CCAC…http://healthcareathome.ca (OT, PT, SW, PSW)
- Toronto Rehab Institute…www.uhn.ca/torontorehab…416 597-3422
- West Park Health Care Centre: http://www.westpark.org/
- MS Society: www.mssociety.ca (support groups, education, local resources) 416 922-6065

Conclusions

- Our understanding of the pathophysiology of MS has evolved…
- Expanding treatment options of MS – potentially progressive types as well?
- Improved symptomatic management options