Disclosures

• Natalie Parks has received compensation from Biogen, EMD Serono, Roche, and Sanofi Genzyme
Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

Alan J Thompson, Brenda L Banwell, Frederik Barkhof, William M Carroll, Timothy Coetzee, Giancarlo Comi, Jorge Correale, Franz Fazekas, Massimo Filippi, Mark S Freedman, Kazuo Fujihara, Steven L Galetta, Hans Peter Hartung, Ludwig Kappos, Fred D Lublin, Ruth Ann Marrie, Aaron E Miller, David H Miller, Xavier Montalban, Ellen M Mowry, Per Soelberg Sorensen, Mar Tintoré, Anthony L Traboulsee, Maria Trojano, Bernard M J Uttinghaag, Sandra Vukusic, Emmanuelle Waubant, Brian G Weinshenker, Stephen C Reingold, Jeffrey A Cohen

The 2010 McDonald criteria for the diagnosis of multiple sclerosis are widely used in research and clinical practice. Scientific advances in the past 7 years suggest that they might no longer provide the most up-to-date guidance for clinicians and researchers. The International Panel on Diagnosis of Multiple Sclerosis reviewed the 2010 McDonald criteria and recommended revisions. The 2017 McDonald criteria continue to apply primarily to patients experiencing a typical clinically isolated syndrome, define what is needed to fulfil dissemination in time and space of lesions in the CNS, and stress the need for no better explanation for the presentation. The following changes were made: in patients with a typical clinically isolated syndrome and clinical or MRI demonstration of dissemination in space, the presence of CSF-specific oligodendroglial bands allows a diagnosis of multiple sclerosis; symptomatic lesions can be used to demonstrate dissemination in space or time in patients with supratentorial, infratentorial, or spinal cord syndrome; and cortical lesions can be used to demonstrate dissemination in space. Research to further refine the criteria should focus on optic nerve involvement, validation in diverse populations, and incorporation of advanced imaging, neurophysiological, and body fluid markers.
Question

• 24 year old woman with partial sensory myelitis causing sensory alteration distal to T4. MRI brain demonstrates multiple periventricular lesions. MRI cervical/thoracic spine demonstrates a single enhancing lesion at T2. Can relapsing remitting multiple sclerosis be diagnosed at this point?
  • Yes
  • No
Clinical Presentation

Radiologically isolated syndrome
Asymptomatic

Clinically isolated syndrome
Single demyelinating event

Multiple sclerosis
Relapsing remitting
Primary progressive
### Diagnostic Criteria - Relapse Remitting

- **McDonald Criteria**
  - Identify multiple sclerosis in patient with high likelihood of multiple sclerosis

<table>
<thead>
<tr>
<th>Number of lesions with objective clinical evidence</th>
<th>Additional data needed for a diagnosis of multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 clinical attacks</td>
<td>None*</td>
</tr>
<tr>
<td>≥2 clinical attacks</td>
<td>None*</td>
</tr>
<tr>
<td>≥2 clinical attacks</td>
<td><strong>Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡</strong></td>
</tr>
<tr>
<td>1 clinical attack</td>
<td>Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of <strong>CSF-specific oligoclonal bands††</strong></td>
</tr>
<tr>
<td>≥2 clinical attacks</td>
<td>Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of <strong>CSF-specific oligoclonal bands††</strong></td>
</tr>
</tbody>
</table>
Diagnostic Criteria - Relapse Remitting

- MRI dissemination in space (≥2 regions):
  - Periventricular
  - Juxtacortical AND cortical
  - Infratentorial
  - Spinal cord

Panel 5: 2017 McDonald criteria for demonstration of dissemination in space and time by MRI in a patient with a clinically isolated syndrome

- Dissemination in space can be demonstrated by one or more T2-hyperintense lesions* that are characteristic of multiple sclerosis in two or more of four areas of the CNS: periventricular, cortical or juxtacortical and infratentorial brain regions, and the spinal cord
- Dissemination in time can be demonstrated by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions* at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required. †For some patients—eg, individuals older than 50 years or those with vascular risk factors—it might be prudent for the clinician to seek a higher number of periventricular lesions.
Diagnostic Criteria - Relapse Remitting

• MRI dissemination in time:
  • Simultaneous non-enhancing and **ANY enhancing** demyelinating lesion
  • New demyelinating lesions on follow-up imaging (regardless of timing)

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**Panel 5: 2017 McDonald criteria for demonstration of dissemination in space and time by MRI in a patient with a clinically isolated syndrome**

- Dissemination in space can be demonstrated by one or more T2-hyperintense lesions* that are characteristic of multiple sclerosis in two or more of four areas of the CNS: periventricular, †cortical or juxtacortical, and infratentorial brain regions, and the spinal cord
- Dissemination in time can be demonstrated by the simultaneous presence of **gadolinium-enhancing and non-enhancing lesions* at any time** or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required. †For some patients—e.g., individuals older than 50 years or those with vascular risk factors—it might be prudent for the clinician to seek a higher number of periventricular lesions.
Diagnostic Criteria - Relapse Remitting

- RRMS criteria have been updated
  - Dissemination in space
    - Now includes juxtacortical AND cortical lesions
  - Dissemination in time
    - Simplification of gadolinium-enhancing vs non-enhancing lesions
    - Oligoclonal banding
  - Enable earlier diagnosis of RRMS
Primary Progressive Multiple Sclerosis Evolving From Radiologically Isolated Syndrome

Orhun H. Kantarci, MD,1 Christine Lebrun, MD, PhD,2 Aksel Siva, MD,3
Mark B. Keegan, MD,1 Christina J. Azevedo, MD, MPH,4 Matilde Inglese, MD,5
Mar Tintoré, MD,6 Braedon D. Newton, BS,7 Francoise Durand-Dubief, MD,8
Maria Pia Amato, PhD,9 Nicola De Stefano, MD,10 Maria Pia Sormani, PhD,11
Daniel Pelletier, MD,6 and Darin T. Okuda, MD7

Objective: The aim of this work was to evaluate the preprogressive phase in subjects with radiologically isolated syndrome (RIS) who evolve to primary progressive multiple sclerosis (PPMS).

Methods: A multicenter RIS cohort was previously established. Demographic, clinical, and radiological characteristics of subjects with RIS that evolved directly to PPMS were compared to those that developed a relapsing disease course from onset (clinically isolated syndrome (CIS) or relapsing-remitting MS) and were also compared to two other population- and clinic-based PPMS cohorts.

Results: Of the 453 subjects with RIS, 128 evolved to symptomatic MS during the follow-up (113 developed a first acute clinical event consistent with CIS/MS, 15 evolved to PPMS). PPMS prevalence (11.7%) and onset age (mean ± standard deviation: 49.1 ± 12.1) in the RIS group were comparable to other PPMS populations (p > 0.05). Median time to PPMS was 3.5 years (range, 1.6–5.4). RIS evolved to PPMS more commonly in men (p = 0.005) and at an older age (p < 0.001) when compared to CIS/MS, independent of follow-up duration. Subjects who evolved to PPMS had more spinal cord lesions (100%) before symptomatic evolution than those that developed CIS/MS (64%) and those that remained asymptomatic (23%) within the follow-up period (P = 0.005). Other MRI characteristics in the preprogressive phase of PPMS were indistinguishable from CIS/MS.

Interpretation: Subjects with RIS evolve to PPMS at the same frequency as expected from general MS populations in an age-dependent manner. Besides age, unequivocal presence of spinal cord lesions and being male predicted evolution to PPMS. Our findings further suggest that RIS is biologically part of the MS spectrum.

ANN NEUROL 2016;79:288–294
Clinical Presentation

Radiologically isolated syndrome
Asymptomatic

Clinically isolated syndrome
Single demyelinating event

Multiple sclerosis
Relapsing remitting
Primary progressive
Radiologically Isolated Syndrome (RIS)

• Definition RIS
  • Incidental CNS white matter lesions
    • Ovoid, well-circumscribed, homogeneous foci with or without involvement of corpus callosum
    • T2 hyperintensities >3 mm fulfilling Barkhoff criteria (3/4) for dissemination in space
      • ≥1 Gd-lesion or ≥9 T2 hyperintense lesions in brain or cord
      • ≥1 infratentorial or cord
      • ≥1 juxtacortical lesion
      • ≥3 periventricular lesions
    • Not consistent with vascular pattern
  • No clinical symptoms consist with demyelination
  • Not better accounted for by another disease process

Okuda et al., 2009
Radiologically Isolated Syndrome (RIS)

- Follow-up (median): 5.8 years
  - Symptomatic MS 28.3%
  - PPMS 11.7% among those developing symptomatic demyelinating disease
    - Greater risk of PPMS vs RRMS:
      - Male
      - Older age
      - Spinal cord lesions
Radiologically Isolated Syndrome (RIS)

- Diagnosis of PPMS after RIS is proportionate to MS cohorts
- Asymptomatic phase with similar active demyelinating lesions in both PPMS and RRMS
Question

• In the past year have you treat RIS?
  • Yes
  • No
  • I don’t see patients with demyelinating disease
Radiologically Isolated Syndrome (RIS)

• Ongoing randomized clinical trials to determine RIS best practices
  • Terflunomide in Radiologically Isolated Syndrome (TERIS)
    • Expected completion 2021
  • Assessment of Tecfidera in Radiologically Isolated Syndrome (ARISE)
    • Expected completion 2022
3. Clinically Isolated Syndrome: Minocycline

Trial of Minocycline in a Clinically Isolated Syndrome of Multiple Sclerosis


ABSTRACT

BACKGROUND
On the basis of encouraging preliminary results, we conducted a randomized, controlled trial to determine whether minocycline reduces the risk of conversion from a first demyelinating event (also known as a clinically isolated syndrome) to multiple sclerosis.

METHODS
During the period from January 2009 through July 2013, we randomly assigned participants who had had their first demyelinating symptoms within the previous 180 days to receive either 100 mg of minocycline, administered orally twice daily, or placebo. Administration of minocycline or placebo was continued until a diagnosis of multiple sclerosis was established or until 24 months after randomization, whichever came first. The primary outcome was conversion to multiple sclerosis (diagnosed on the basis of the 2005 McDonald criteria) within 6 months after randomization. Secondary outcomes included conversion to multiple sclerosis within 24 months after randomization.
Clinically Isolated Syndrome: Minocycline

• Inclusion Criteria
  • Age 18-60 years
  • Demyelinating event
    • <180 days ago
  • MRI brain
    • ≥2 lesions

• Exclusion Criteria
  • Diagnosis RRMS
    • McDonald 2005 criteria
  • Alternative diagnosis

• Primary Outcome
  • Conversion to RRMS at 6 months
    • McDonald 2005 criteria
Clinically Isolated Syndrome: Minocycline

- Minocycline 100 mg PO bid vs placebo x 2 years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants (N = 142)</th>
<th>Minocycline (N = 72)</th>
<th>Placebo (N = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of clinically isolated syndrome — yr</td>
<td>35.8±9.2</td>
<td>35.9±9.3</td>
<td>35.7±9.2</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>97 (68.3)</td>
<td>54 (75.0)</td>
<td>43 (61.4)</td>
</tr>
<tr>
<td>White race — no. (%)†</td>
<td>120 (84.5)</td>
<td>61 (84.7)</td>
<td>59 (84.3)</td>
</tr>
<tr>
<td>EDSS score‡</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Range</td>
<td>0–4.5</td>
<td>0–3.0</td>
<td>0–4.5</td>
</tr>
<tr>
<td>Location of symptom onset — no. (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal cord</td>
<td>61 (43.0)</td>
<td>25 (34.7)</td>
<td>36 (51.4)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>49 (34.5)</td>
<td>22 (30.6)</td>
<td>27 (38.6)</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>45 (31.7)</td>
<td>24 (33.3)</td>
<td>21 (30.0)</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>19 (13.4)</td>
<td>11 (15.3)</td>
<td>8 (11.4)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>11 (7.7)</td>
<td>4 (5.6)</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>Multifocal symptoms — no. (%)</td>
<td>33 (23.2)</td>
<td>12 (16.7)</td>
<td>21 (30.0)</td>
</tr>
<tr>
<td>Duration of clinically isolated syndrome — days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>83.5</td>
<td>81.5</td>
<td>86.0</td>
</tr>
<tr>
<td>Range</td>
<td>21–190</td>
<td>21–190</td>
<td>25–174</td>
</tr>
<tr>
<td>Glucocorticoid treatment for clinically isolated syndrome — no./total no. (%)¶</td>
<td>51/136 (37.5)</td>
<td>27/69 (39.1)</td>
<td>24/67 (35.8)</td>
</tr>
</tbody>
</table>
Clinically Isolated Syndrome: Minocycline

- Minocycline delayed onset RRMS
  - 6 months (adjusted risk)
    - 61.5% placebo
    - 43.0% minocycline
    - Risk difference = 18.5% (p=0.01)
  - 24 months
    - No difference
Clinically Isolated Syndrome: Minocycline

- Side Effects in CIS Trial
  - Dizziness
  - Skin/dental discolouration
  - Sun sensitivity/rash

- Effect minocycline in delaying RRMS diagnosis among CIS patients similar to other DMTs (interferon-B, glatiramer acetate, teriflunomide, cladribine)
How do you treat CIS with demyelinating lesions not meeting criteria for RRMS?

- No treatment
- Minocycline
- Injectables
- Other DMT
MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study

Ayman Tourbah, Christine Lebrun-Frenay, Gilles Edan, Michel Clanet, Caroline Papex, Sandra Vukusic, Jerome De Sèze, Marc Debouverie, Olivier Gout, Pierre Clavelou, Gilles Defer, David-Axel Laplau, Thibault Moreau, Pierre Labauge, Bruno Brochet, Frédéric Sedel and Jean Pelletier; on behalf of the MS-SPI study group

Abstract
Background: Treatment with MD1003 (high-dose biotin) showed promising results in progressive multiple sclerosis (MS) in a pilot open-label study.
Objective: To confirm the efficacy and safety of MD1003 in progressive MS in a double-blind, placebo-controlled study.
Methods: Patients (n=154) with a baseline Expanded Disability Status Scale (EDSS) score of 4.5–7 and evidence of disease worsening within the previous 2 years were randomised to 12-month MD1003 (100 mg biotin) or placebo thrice daily, followed by 12-month MD1003 for all patients. The primary endpoint was the proportion of patients with disability reversal at month 9, confirmed at month 12, defined as an EDSS decrease of ≥1 point (≥0.5 for EDSS 6–7) or a ≥20% decrease in timed 25-foot walk time compared with the best baseline among screening or randomisation visits.
Progressive Multiple Sclerosis: Biotin

Oligodendrocyte
Acetyl-CoA
Biotin-dependent carboxylase
Fatty acid

Myelinated Axon
Neuron
Progressive Multiple Sclerosis: Biotin

• Inclusion criteria
  • Age 18-75 years
  • PPMS or SPMS
  • EDSS 4.5-7
    • Evidence of progression ≥2 years

• Exclusion criteria
  • Clinical or radiological inflammatory activity <1 year

• Primary Outcome
  • Improvement in MS-related disability at month 9 confirmed at month 12
    • EDSS decrease ≥0.5 for EDSS 6-7 or ≥1 for EDSS 4.5-5.5
    • Timed 25 foot walk ≥20% decrease in time
Progressive Multiple Sclerosis: Biotin

Biotin 100 mg PO tid vs placebo x 1 year

Extension phase with biotin 100 mg PO tid x 1 year

Table 1. Baseline demographic characteristics of the intention-to-treat population.

<table>
<thead>
<tr>
<th></th>
<th>MD1003 (n = 103)</th>
<th>Placebo (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, n (%)</td>
<td>53 (51.5)</td>
<td>30 (58.8)</td>
</tr>
<tr>
<td>Age, mean (SD) (years)</td>
<td>51.8 (9.1)</td>
<td>50.7 (8.4)</td>
</tr>
<tr>
<td>Disease phenotype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPMS</td>
<td>42 (40.8)</td>
<td>13 (25.5)</td>
</tr>
<tr>
<td>SPMS</td>
<td>61 (59.2)</td>
<td>38 (74.5)</td>
</tr>
<tr>
<td>Duration of MS, mean (SD) (years)</td>
<td>14.8 (8.9)</td>
<td>17.4 (10.3)</td>
</tr>
<tr>
<td>EDSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.98 (0.75)</td>
<td>6.20 (0.52)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>6.0 (4.5–7.0)</td>
<td>6.0 (5.0–7.0)</td>
</tr>
<tr>
<td>EDSS 4.5–5.5, n (%)</td>
<td>28 (27.2)</td>
<td>7 (13.7)</td>
</tr>
<tr>
<td>EDSS 6–7, n (%)</td>
<td>75 (72.8)</td>
<td>44 (86.2)</td>
</tr>
<tr>
<td>TW25 (seconds)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>21.8 (27.0)</td>
<td>30.6 (39.4)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>13.0 (4.0–180.0)</td>
<td>14.5 (4.8–180.0)</td>
</tr>
<tr>
<td>Physical therapy programme in the 3 months prior to inclusion, n (%)</td>
<td>19 (18.4)</td>
<td>10 (19.6)</td>
</tr>
<tr>
<td>Concomitant DMT, n (%)</td>
<td>42 (40.8)</td>
<td>20 (39.2)</td>
</tr>
</tbody>
</table>
Progressive Multiple Sclerosis: Biotin

Double-blind phase

<table>
<thead>
<tr>
<th></th>
<th>Patients with improvement at month 9, confirmed at month 12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD1003 (n = 103)</td>
<td>12.6%</td>
</tr>
<tr>
<td>Placebo (n = 51)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Extension phase

<table>
<thead>
<tr>
<th></th>
<th>Patients with improvement at month 18, confirmed at month 24 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD1003 (n = 91)</td>
<td>13.2%</td>
</tr>
<tr>
<td>Placebo (n = 42)</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

Extension phase

<table>
<thead>
<tr>
<th></th>
<th>Patients with improvement at month 24 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD1003 (n = 91)</td>
<td>15.4%</td>
</tr>
<tr>
<td>Placebo (n = 42)</td>
<td>11.9%</td>
</tr>
</tbody>
</table>
Progressive Multiple Sclerosis: Biotin

• Side Effects in Trial
  • No trends or significant adverse events
  • Interference with biotin-based lab assays
    • Thyroid assays
Question

• Are you using biotin?
  • No
  • PPMS
  • SPMS
  • PPMS/SPMS
  • I don’t see patients with demyelinating disease
Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis


The authors’ full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Montalban at the Neurology—Neuroimmunology Department and Neurorehabilitation Unit, Centre d’Esclerosi Múltiple de Catalunya, Hospital Universitari Vall d’Hebron, Passeig de la Vall d’Hebron 119–129, 08035 Barcelona, Spain, or at xavier.montalban@cemcat.org; or to Dr. Wolinsky at the McGovern Medical School, University of Texas Health Science Center.
Primary Progressive MS: Ocrelizumab

B Cell

Ocrelizumab: CD20 antibody

CD20
Primary Progressive MS: Ocrelizumab

• Inclusion Criteria
  • Age 18-55 years
  • PPMS
  • EDSS 3-6.5
  • Duration
    • <15 years if EDSS >5
    • <10 years if EDSS ≤5

• Exclusion Criteria
  • Relapsing disease

• Primary Outcome
  • Confirmed 12-week disability progression
    • Increase EDSS ≥1 for EDSS ≤5.5 or increase EDSS ≥0.5 for EDSS >5.5

• Relapsing disease
Primary Progressive MS: Ocrelizumab

Ocrelizumab 600 mg IV q6 months vs placebo

Duration treatment was minimum 5 doses (120 weeks) although event driven until 253 12-week confirmed disability progression events

---

**Table 1. Baseline Demographic and Disease Characteristics (Intention-to-Treat Population).**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ocrelizumab (N=488)</th>
<th>Placebo (N=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age — yr</strong></td>
<td>Mean 44.7±7.9</td>
<td>Mean 44.4±8.3</td>
</tr>
<tr>
<td></td>
<td>Median (range) 46.0 (20–56)</td>
<td>Median (range) 46.0 (18–56)</td>
</tr>
<tr>
<td><strong>Female sex — no. (%)</strong></td>
<td>237 (48.6)</td>
<td>124 (50.8)</td>
</tr>
<tr>
<td><strong>Time since onset of MS symptoms — yr†</strong></td>
<td>Mean 6.7±4.0</td>
<td>Mean 6.1±3.6</td>
</tr>
<tr>
<td></td>
<td>Median (range) 6.0 (1.1–32.9)</td>
<td>Median (range) 5.5 (0.9–23.8)</td>
</tr>
<tr>
<td><strong>Time since diagnosis of PPMS — yr‡</strong></td>
<td>Mean 2.9±3.2</td>
<td>Mean 2.8±3.3</td>
</tr>
<tr>
<td></td>
<td>Median (range) 1.6 (0.1–16.8)</td>
<td>Median (range) 1.3 (0.1–23.8)</td>
</tr>
<tr>
<td><strong>No previous use of disease-modifying therapy — no. (%)§</strong></td>
<td>433 (88.7)</td>
<td>214 (87.7)</td>
</tr>
<tr>
<td><strong>Score on EDSS¶</strong></td>
<td>Mean 4.7±1.2</td>
<td>Mean 4.7±1.2</td>
</tr>
<tr>
<td></td>
<td>Median (range) 4.5 (2.5–7.0)</td>
<td>Median (range) 4.5 (2.5–6.5)</td>
</tr>
<tr>
<td><strong>Gadolinium-enhancing lesions on T1-weighted images — no./total no. (%)</strong></td>
<td>Yes 133/484 (27.5)</td>
<td>No 60/243 (24.7)</td>
</tr>
<tr>
<td></td>
<td>351/484 (72.5)</td>
<td>183/243 (75.3)</td>
</tr>
<tr>
<td><strong>No. of lesions on T2-weighted images</strong></td>
<td>Mean 48.7±38.2</td>
<td>Mean 48.2±39.3</td>
</tr>
<tr>
<td></td>
<td>Median (range) 42.0 (0–249.0)</td>
<td>Median (range) 43.0 (0–208.0)</td>
</tr>
</tbody>
</table>
Primary Progressive MS: Ocrelizumab

A 12-Wk Confirmed Disability Progression

Hazard ratio, 0.76 (95% CI, 0.59–0.98)
P=0.03

Cumulative Probability of Confirmed Progression (%)

Placebo  Ocrelizumab

No. at Risk
Placebo: 244 232 212 199 189 180 172 162 153 145 136 120 85 66 46 30 20 7 2
Ocrelizumab: 487 462 450 431 414 391 376 355 338 319 304 281 207 166 136 80 47 20 7

39.3%
32.9%
Primary Progressive MS: Ocrelizumab

• Side Effects
  • Allergic reaction/anaphylaxis
  • Increased risk infection
  • Theoretical PML risk
    • Rituximab 1/25,000
  • Signal of increased risk of cancer particularly breast cancer
Question

• In what proportion of your PPMS patients are you recommending ocrelizumab?
  • <25%
  • 25-50%
  • 51-75%
  • >75%
  • I don’t see patients with demyelinating disease
6. Secondary Progressive MS: Siponimod

Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study

Ludwig Kappos, Amit Bar-Or, Bruce A C Cree, Robert J Fox, Gavin Giovannoni, Ralf Gold, Patrick Vermersch, Douglas L Arnold, Sophie Arnould, Tatiana Scherz, Christian Wolf, Erik Wallström, Frank Dahlke, for the EXPAND Clinical Investigators*

Summary
Background No treatment has consistently shown efficacy in slowing disability progression in patients with secondary progressive multiple sclerosis (SPMS). We assessed the effect of siponimod, a selective sphingosine 1-phosphate (S1P) receptor₃ modulator, on disability progression in patients with SPMS.

Methods This event-driven and exposure-driven, double-blind, phase 3 trial was done at 292 hospital clinics and specialised multiple sclerosis centres in 31 countries. Using interactive response technology to assign numbers linked to treatment arms, patients (age 18–60 years) with SPMS and an Expanded Disability Status Scale score of 3·0–6·5 were randomly assigned (2:1) to once daily oral siponimod 2 mg or placebo for up to 3 years or until the occurrence of a prespecified number of confirmed disability progression (CDP) events. The primary endpoint was time to 3-month CDP. Efficacy was assessed for the full analysis set (ie, all randomly assigned and treated patients); safety was assessed for the safety set. This trial is registered with ClinicalTrials.gov, number NCT01665144.

Findings 1651 patients were randomly assigned between Feb 5, 2013, and June 2, 2015 (1105 to the siponimod group, and 546 to the placebo group). One patient did not use the consent form, and five patients did not receive study treatment. Siponimod significantly delayed the time to the primary endpoint (hazard ratio 0·76, 95% CI 0·62–0·94; p=0·011). There were 2·6 CDP events per 100 patient-years in the siponimod group and 3·5 in the placebo group (p=0·03). The most common adverse events were upper respiratory tract infection (31·0% vs 21·0%), nasopharyngitis (19·9% vs 15·0%), and headache (11·4% vs 9·8%).

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*Members listed in the appendix
Neurologic Clinic and Polyclinic,
Departments of Medicine,
Clinical Research, Biomedicine,
and Biomedical Engineering,
University Hospital, University
of Basel, Basel, Switzerland
(Prof L Kappos MD); Center for
Neuroinflammation and
Secondary Progressive MS: Siponimod

Lymph Node

Lymphocytes

Siponimod

Sphingosine-1-phosphate receptor
Secondary Progressive MS: Siponimod

- Inclusion Criteria:
  - 18-60 years
  - SPMS
  - EDSS 3.0-6.5
    - EDSS progression in 2 years prior to study
  - >3 months no relapse

- Primary Endpoint: Time to 3-month confirmed disability progression for 374 individuals
Secondary Progressive MS: Siponimod

- Siponimod 2 mg PO daily vs placebo (2:1)
- Event driven
  - 21 months median time on study
  - 18 months median time on study drug

<table>
<thead>
<tr>
<th></th>
<th>Siponimod (n=1105)</th>
<th>Placebo (n=546)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>48.0 (7.8)</td>
<td>48.1 (7.9)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>49.0 (22-61)</td>
<td>49.0 (21-61)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-40 years</td>
<td>188 (17%)</td>
<td>103 (19%)</td>
</tr>
<tr>
<td>&gt;41 years</td>
<td>917 (83%)</td>
<td>443 (81%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>669 (61%)</td>
<td>323 (59%)</td>
</tr>
<tr>
<td>Men</td>
<td>436 (39%)</td>
<td>223 (41%)</td>
</tr>
<tr>
<td>Time since diagnosis of multiple sclerosis (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>12.9 (7.9)</td>
<td>12.1 (7.5)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>12.0 (0-1-44.4)</td>
<td>11.2 (0-4-39.4)</td>
</tr>
<tr>
<td>Time since onset of multiple sclerosis symptoms (years)</td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>17.1 (8.4)</td>
<td>16.2 (8.2)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>16.4 (1-4-45.0)</td>
<td>15.4 (1-3-43.0)</td>
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<tr>
<td>Time since conversion to SPMS (years)</td>
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<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.9 (3.6)</td>
<td>3.6 (3.3)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.6 (0-1-24.2)</td>
<td>2.5 (0-1-21.7)</td>
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<tr>
<td>No previous use of disease-modifying therapy</td>
<td>245 (22%)</td>
<td>114 (21%)</td>
</tr>
<tr>
<td>No relapses in the year before screening</td>
<td>878 (79%)</td>
<td>416 (76%)</td>
</tr>
<tr>
<td>No relapses in the 2 years before screening*</td>
<td>712 (64%)</td>
<td>343 (63%)</td>
</tr>
<tr>
<td>Number of relapses in the year before screening</td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>0.2 (0.5)</td>
<td>0.3 (0.6)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0 (0-4)</td>
<td>0 (0-4)</td>
</tr>
<tr>
<td>Number of relapses in the 2 years before screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.7 (1.2)</td>
<td>0.7 (1.2)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0 (0-12)</td>
<td>0 (0-8)</td>
</tr>
<tr>
<td>EDSS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.4 (1.1)</td>
<td>5.4 (1.0)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>6.0 (2.0-7.0)</td>
<td>6.0 (2.5-7.0)</td>
</tr>
</tbody>
</table>
Secondary Progressive MS: Siponimod

- Confirmed disability progression 3 months
  - Siponimod 288/1096 (26%)
  - Placebo 173/545 (32%)
  - HR 0.79 (95% CI 0.65-0.95), p=0.01

- Side effect profile similar to fingolimod
  - Lymphopenia, elevated liver enzymes, bradycardia, macular edema, varicella zoster activation, convulsions
7 and 8. Neurofilament

Serum Neurofilament Light: A Biomarker of Neuronal Damage in Multiple Sclerosis

Giulio Disanto, MD, PhD,1 Christian Barro, MD,2 Pascal Benkert, PhD,3 Yvonne Naegelin, MD,2 Sabine Schädelin, MSc,3 Antonella Giardiello, MD,1 Chiara Zecca, MD,11 Kaj Blennow, PhD,4 Henrik Zetterberg, PhD,4,5 David Leppert, MD,2 Ludwig Kappos, MD,2 Claudio Gobbi, MD,1 Jens Kuhle, MD, PhD,2 and the Swiss Multiple Sclerosis Cohort Study Group

Objective: Neurofilament light chains (NFL) are unique to neuronal cells, are shed to the cerebrospinal fluid (CSF), and are detectable at low concentrations in peripheral blood. Various diseases causing neuronal damage have resulted in elevated CSF concentrations. We explored the value of an ultrasensitive single-molecule array (Simoa) serum NFL (sNFL) assay in multiple sclerosis (MS).

Methods: sNFL levels were measured in healthy controls (HC, n = 254) and two independent MS cohorts: (1) cross-sectional with paired serum and CSF samples (n = 142), and (2) longitudinal with repeated serum sampling (n = 246, median follow-up = 3.1 years, interquartile range [IQR] = 2.0–4.0). We assessed their relation to concurrent clinical, imaging, and treatment parameters and to future clinical outcomes.

Results: sNFL levels were higher in both MS cohorts than in HC (p < 0.001). We found a strong association between CSF NFL and sNFL (β = 0.589, p < 0.001). Patients with either brain or spinal (43.4pg/ml, IQR = 25.2–65.3) or both brain and spinal gadolinium-enhancing lesions (62.5pg/ml, IQR = 42.7–71.4) had higher sNFL than those without (29.6pg/ml, IQR = 20.9–41.8, β = 1.461, p = 0.005 and β = 1.902, p = 0.002, respectively). sNFL was independently associated with Expanded Disability Status Scale (EDSS) assessments (β = 1.105, p < 0.001) and presence of relapses (β = 1.430, p < 0.001). sNFL levels were lower under disease-modifying treatment (β = 0.818, p = 0.003). Patients with sNFL levels above the 80th, 90th, 95th, 97.5th, and 99th HC-based percentiles had higher risk of relapses (97.5th percentile: incidence rate ratio = 1.94, 95% confidence interval [CI] = 1.21–3.10, p = 0.006) and EDSS worsening (97.5th percentile: OR = 2.41, 95% CI = 1.07–5.42, p = 0.034).

Interpretation: These results support the value of sNFL as a sensitive and clinically meaningful blood biomarker to monitor tissue damage and the effects of therapies in MS.

ANN NEUROL 2017;81:857–870
Neurofilament

• Neurofilament scaffolding protein released from neuron following axonal damage
  • Increased in many CNS diseases (MS, ALS, dementia, etc)
Neurofilament

- 142 individuals with RIS, CIS, RRMS, PPMS, or SPMS from Lugano, Switzerland
- Median serum level 42-fold lower than CSF
  - Strong positive correlation (Pearson r=0.77)
- Neurofilament light chain (NfL) can be reliably measured in serum
Neurofilament

- 246 individuals with CIS, RRMS, PPMS, or SPMS from Basel, Switzerland.
- Median sNfL significantly different
  - PPMS/SPMS>CIS/RRMS>HC
Neurofilament

• 246 individuals with CIS, RRMS, PPMS, or SPMS from Basel, Switzerland.

• sNfL decreased following initiation of DMT
Serum neurofilament is associated with progression of brain atrophy and disability in early MS

ABSTRACT

Objective: To investigate a potential effect of riluzole on serum neurofilaments (Nf) compared to placebo and the relationship between longitudinal clinical and MRI outcomes and serum Nf levels.

Methods: Serum samples were obtained from participants enrolled in a randomized double-blind trial of neuroprotection with riluzole vs placebo as an add-on to weekly interferon-β (IFN-β)-1a IM initiated 3 months after randomization. Nf measurements were performed by ELISA and electrochemiluminescence immunoassay.

Results: Longitudinal serum samples were available from 22 riluzole and 20 placebo participants over 24 months. There was no observed treatment effect with riluzole. Nf light chain (NFL) levels decreased over time (p = 0.007 at 24 months), whereas the Nf heavy chain was unchanged (p = 0.997). Changes in NFL were correlated with EDSS change (p = 0.009) and neuropsychological outcomes. Brain volume decreased more rapidly in patients with high baseline NFL (p = 0.05 at 12 months and p = 0.008 at 24 months) and this relationship became stronger at 24 months (p = 0.024 for interaction). Higher and increasing NFL predicted higher number of gadolinium-enhancing lesions (p < 0.001 for both).
Neurofilament

• Phase 2 Study
  • RRMS diagnosed <12 months
    • Interferon-alpha
    • Riluzole vs placebo
  • No benefit to adding riluzole
  • Measured sNfL
Neurofilament

• sNfL positively correlated with EDSS

• sNfL negatively correlated with brain volume
Question

• Are you currently using neurofilament light chain in clinical practice?
  • Yes
  • No
  • I don’t see patients with demyelinating disease
9. No Evident disease activity: NEDA

Topical Review

“No evident disease activity”: The use of combined assessments in the management of patients with multiple sclerosis

Gavin Giovannoni, Davorka Tomic, Jeremy R Bright and Eva Havrdová

Abstract: Using combined endpoints to define no evident disease activity (NEDA) is becoming increasingly common when setting targets for treatment outcomes in multiple sclerosis (MS). Historically, NEDA has taken account of the occurrence of relapses, brain magnetic resonance imaging (MRI) lesions and disability worsening, but this approach places emphasis on inflammatory activity in the brain and mostly overlooks ongoing neurodegenerative damage. Combined assessments of NEDA which take account of changes in brain volume or neuropsychological outcomes such as cognitive function may begin to address this imbalance, and such assessments may also consider blood or spinal-fluid neurofilament levels or patient-reported outcomes and quality of life measures. If a combined NEDA assessment can be validated in prospective studies as indicative of long-term disease remission at the individual patient level, treating to achieve NEDA could become the goal of clinical practice and achieving NEDA may become the “new normal” state of disease control for patients with MS.
NEDA

NEDA-4

Relapses
Progression
MRI Activity
Brain Atrophy ≥0.4%/yr
NEDA

- Relapses
- Progression
- MRI Activity
- Brain Atrophy $\geq 0.4\%/yr$
- Biomarkers
Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial

Ari J Green, Jeffrey M Gelfand, Bruce A Cree, Carolyn Bevan, W John Boscardin, Feng Mei, Justin Inman, Sam Arnow, Michael Devereux, Aya AbuAnsar, Hirono Nohata, Alyssa Zhu, Matt Friessen, Roy Gerona, Hans Christian von Büdingen, Roland G Henry, Stephen L Hauser, Jonah R Chan

Summary
Background Multiple sclerosis is a degenerative inflammatory disease of the CNS characterised by immune-mediated destruction of myelin and progressive neuroaxonal loss. Myelin in the CNS is a specialised extension of the oligodendrocyte plasma membrane and clemastine fumarate can stimulate differentiation of oligodendrocyte precursor cells in vitro, in animal models, and in human cells. We aimed to assess the efficacy and safety of clemastine fumarate as a treatment for patients with multiple sclerosis.

Methods We did this single-centre, 150-day, double-blind, randomised, placebo-controlled, crossover trial (ReBUILD) in patients with relapsing multiple sclerosis with chronic demyelinating optic neuropathy on stable immunomodulatory therapy. Patients who fulfilled international panel criteria for diagnosis with disease duration of less than 15 years were eligible. Patients were randomly assigned (1:1) via block randomisation using a random number generator to receive either clemastine fumarate (5-36 mg orally twice daily) for 90 days followed by placebo for 60 days (group 1), or placebo for 90 days followed by clemastine fumarate (5-36 mg orally twice daily) for 60 days (group 2). The primary outcome was shortening of P100 latency delay on full-field, pattern-reversal, visual-evoked potentials. We analysed by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT02040298.

Findings Between Jan 1, 2014, and April 11, 2015, we randomly assigned 50 patients to group 1 (n=25) or group 2 (n=25). All patients completed the study. The primary efficacy endpoint was met with clemastine fumarate treatment, which reduced the latency delay by 1.7 ms/eye (95% CI 0.5–2.9; p=0·0048) when analysing the trial as a crossover. Clemastine fumarate treatment was associated with fatigue, but no serious adverse events were reported.

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See Comment page 2421
Department of Neurology
(A J Green MD, J M Gelfand MD, B A Cree MD, C Bevan MD, F Mei PhD, J Inman BS, S Arnow BS, M Devereux BS, A AbuAnsar BS, A Zhu BS, H C von Büdingen MD, R G Henry MD, S L Hauser MD, J R Chan MD), Department of Ophthalmology (A J Green), Department of Epidemiology and Biostatistics (W J Boscardin PhD), Program in Neuroscience (F Mei, S L Hauser, J R Chan), Department of Obstetrics and Gynecology
Remyelination

- **Inclusion Criteria:**
  - RRMS
  - Duration RRMS <15 years
  - No optic neuritis either eye <6 months and <5 years in qualifying eye
  - VEP P100 latency >=118 ms in at least 1 eye
  - OCT RNFL >70 um in qualifying eye

- **Primary Outcome:** Change in VEP P100 latency during treatment phase
Remyelination

- Clemastine 5.36 mg PO bid vs placebo x 90 days followed by cross-over x 60 days
- Clemastine
  - Antihistamine
  - Screening method detected ability to induce oligodendrocyte differentiation

<table>
<thead>
<tr>
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<th>Group 1 (n=25)</th>
<th>Group 2 (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40.2 (10.8)</td>
<td>40.0 (10.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (76%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (24%)</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>5.7 (6.5)</td>
<td>4.4 (3.6)</td>
</tr>
<tr>
<td>EDSS</td>
<td>2.2 (1.0)</td>
<td>2.1 (1.2)</td>
</tr>
<tr>
<td>History of ON</td>
<td>15 (60%)</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Time since ON (years)</td>
<td>3.7 (3.4)</td>
<td>4.9 (4.6)</td>
</tr>
<tr>
<td>VEP P100 latency (ms)</td>
<td>128.6 (11.6)</td>
<td>126.8 (9.4)</td>
</tr>
<tr>
<td>OCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNFL, μm</td>
<td>90.2 (12.0)</td>
<td>85.1 (7.9)</td>
</tr>
<tr>
<td>Macular volume (mm²)</td>
<td>3.05 (0.14)</td>
<td>3.01 (0.11)</td>
</tr>
</tbody>
</table>
Remyelination

- Significant improvement in P100 latency during 3 month treatment phase
- Sustained during 2-month cross-over phase
Multiple Sclerosis: Top 10 papers