MS Treatments

Current and Emerging

Focus on Progressive MS

Neurological Information Day

September 2015
In the past year, Alan Thompson has received honoraria and support for travel for consultancy from Biogen Idec and MedDay, honorarium for consultancy from Eisai, and honoraria and support for travel for lecturing from Serono Symposia International Foundation and Novartis.

He received support for travel from the MS International Federation as Chair of their Medical and Scientific Advisory Board, from the International Progressive MS Alliance, as chair of their Scientific Steering Committee and from the National MS Society (USA) as member of their Research Programs Advisory Committee. He receives an honorarium from SAGE Publishers as Editor-in-Chief for Multiple Sclerosis Journal.

September 2015
Outline

• Introduction/Context

• MS Management

• The challenge of Progressive MS
MS Is a Disabling Condition

QOL
EDSS and utility\textsuperscript{a} have shown a significant inverse relationship\textsuperscript{1}

Mortality
Mortality ratio of MS exceeds CV disease,\textsuperscript{2,}\textsuperscript{b} stroke,\textsuperscript{3,}\textsuperscript{c} and early breast cancer\textsuperscript{4}

Employment
50% of patients with MS are unemployed 10 years after diagnosis\textsuperscript{5}

Relationships
Compared with general population, patients with MS have a higher probability of separating/divorcing and doing so sooner\textsuperscript{5}

Healthcare costs
Bulk of cost attributed to services (29%) and long-term sick leave and early retirement (30%)\textsuperscript{6,}\textsuperscript{d}

MS has a negative impact on...

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\textsuperscript{CV=cardiovascular; EQ-5D=EuroQol 5-Dimension questionnaire.}


\textsuperscript{a. Utility measures derived from EQ-5D}
\textsuperscript{b. In patients with type 2 diabetes}
\textsuperscript{c. In patients with valvular heart disease in Olmsted County, Minnesota}
\textsuperscript{d. MS patients with EDSS ≥6.0}
Natural History of MS

- **Preclinical**
- **Relapsing**
- **Secondary Progressive**

- relapses and impairment
- MRI activity
- brain volume
- MRI burden of disease
Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis

W. Ian McDonald, FRCP, Alistair Compston, FRCP, Gilles Edan, MD, Donald Goodkin, Hans-Peter Hartung, MD, Fred D. Lublin, MD, Henry F. McFarland, MD, Donald W. Paty, MD, Chris H. Polman, MD, Stephen C. Reingold, PhD, Magnhild Sandberg-Wollheim, MD, William Sibley, MD, Alan Thompson, MD, Stanley van den Noort, MD, Brian Y. Weinshenker, MD, and Jerry S. Wolinsky, MD

Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the “McDonald Criteria”

Chris H. Polman, MD, PhD, Stephen C. Reingold, PhD, Gilles Edan, MD, Massimo Filippi, MD, Hans-Peter Hartung, MD, Ludwig Kappos, MD, Fred D. Lublin, MD, Luanne M. Metz, MD, Henry F. McFarland, MD, Paul W. O’Connor, MD, Magnhild Sandberg-Wollheim, MD, Alan J. Thompson, MD, Brian G. Weinshenker, MD, and Jerry S. Wolinsky, MD
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 Clanet, 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
## 2010 Revised McDonald MS Diagnostic Criteria

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in space (DIS) and time (DIT)*

<table>
<thead>
<tr>
<th>Clinical (Attacks)</th>
<th>Lesions</th>
<th>Additional Criteria to Make DX</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more</td>
<td>Objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack</td>
<td>None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS</td>
</tr>
<tr>
<td>2 or more</td>
<td>Objective clinical evidence of 1 lesion</td>
<td>DIS; OR await further clinical attack implicating a different CNS site</td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of ≥2 lesions</td>
<td>DIT; OR await a second clinical attack</td>
</tr>
<tr>
<td>1</td>
<td>Objective clinical evidence of 1 lesion</td>
<td>DIS OR await further clinical attack implicating a different CNS site AND DIT; OR await a second clinical attack</td>
</tr>
<tr>
<td>0 (progression from onset)</td>
<td></td>
<td>One year of disease progression (retrospective or prospective) AND at least two of: DIS in the brain based on ≥1 T2 lesion in periventricular, juxtacortical or infratentorial regions; DIS in the spinal cord based on ≥2 T2 lesions; or positive CSF</td>
</tr>
</tbody>
</table>

# Paraclinical Evidence in MS Diagnosis

<table>
<thead>
<tr>
<th>Evidence for Dissemination of Lesions in Space (DIS)²</th>
<th>Evidence for Dissemination of Lesions in Time (DIT)³</th>
</tr>
</thead>
</table>
| ≥ 1 T2 lesion in at least two out of four areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord  
  - Gadolinium enhancement of lesions is not required for DIS  
  - If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to lesion count |  
  - 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  
  - Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time |

<table>
<thead>
<tr>
<th>Evidence for Positive CSF</th>
<th></th>
</tr>
</thead>
</table>

These diagnostic criteria were developed through the consensus of the International Panel on the Diagnosis of MS. See cited articles for details. Funding through National Multiple Sclerosis Society (USA) and European Committee for Treatment and Research in MS; additional support from the Multiple Sclerosis International Federation and MS Ireland.

National Multiple Sclerosis Society (USA) Professional Resource Center. 733 Third Avenue. New York, NY 10017-3288  
http://www.nationalMSsociety.org/PRC. MD_info@nmss.org  
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MS Survey of 1,500 people with MS in 2015

- 1 in 4 people with MS misdiagnosed with having a trapped nerve
- 1 in 10 people with MS told they’d had a stroke
- 39% of people with MS waited over a year for diagnosis
The unmet need is massive

Disease modification

MRI, relapse reduction, delayed onset of CDMS, delayed disease progression, disease activity free, delayed onset of SPMS, prevention of SPMS

Anti-inflammatory strategies

Neuroprotective strategies

Neurorestorative strategies

Symptomatic therapies

Cognition

Fatigue

Spasticity

Bladder/Bowel

Mobility

Mood

MS prevention

Vitamin D

Smoking

EBV
An holistic approach to MS
Oh My God!
The MS Nurse Was Right About Everything!
Guidelines in MS

NICE guidelines
NHS England
Association of British Neurologists

2014-2015
Management

Education

Treatment & monitoring
• Disease-modifying treatments (DMD)
  • Treatment of relapses
  • Symptomatic treatment

Multidisciplinary approach

Self-management
Management: Education

Education should **aim** at:

- Improving the **understanding of the disease**
- Increasing the knowledge about **healthy lifestyles** and their consequences
- Increasing awareness of **noxious factors** such as smoking
- Promoting **patients’ empowerment**
Management: Multidisciplinary approach

• Comprehensive annual assessments

• Focused on:
  • Mobility, balance, and falls
  • Mobility aids including wheelchair assessments
  • Use of arms and hands
  • Muscle spams and stiffness

• Healthcare professionals involved
  • Consultant neurologists
  • MS nurses
  • Physiotherapists, occupational therapists, speech and language therapists, and continent nurses
  • Psychologists and social care specialists
  • Dieticians
Management: Self-management

- Patients are aware of their condition and their symptoms

- Patients can adopt self-management strategies to solve day-to-day issues and gain independence

- Patients are at the centre of all decision-making processes

- Important decisions include
  - Healthy lifestyle
  - Start of treatment and compliance
  - Stop of treatment
  - Pregnancy and other family-related decisions
HEALTHCARE WITHOUT WALLS

NeuroDirect

NeuroView

NeuroMail
National MS Society Wellness Initiative

Wellness

Life-long personalized process through which people make informed choices about their lifestyle behaviors and activities across multiple, inter-related dimensions with the aim of leading their best lives.
Wellness and Multiple Sclerosis

• Wellness is attainable for everyone. It is achieved by each person living with MS within the context of his or her priorities, abilities and limitations.

• The National MS Society is committed to connecting people to the information and resources they need to pursue their personal wellness goals.
The dimensions of wellness act and interact in ways that contribute to well-being. They are influenced by health and other factors and involve lifestyle behaviors and activities.
Therapeutic era of Multiple Sclerosis

- 1993 - First positive trial of therapeutic agent
- 1998 - Four agents available - reduce relapse rate
- 2004 - Second line agent licensed for more aggressive MS
- 2005 - Withdrawn because of serious side-effect
- 2006 - Reintroduced
- 2010 - First oral agent licensed
- 2015 – 12 treatments
Early treatment seems to be desirable

Figure: http://multiple-sclerosis-research.blogspot.co.uk/2012/06/research-dmt-slow-onset-of-progression.html
Early treatment seems to be desirable

![Chart showing the relationship between time, disability, and treatment. The chart illustrates the natural history, delayed intervention, and early intervention scenarios. The text indicates that earlier treatment seems to be desirable.](http://multiple-sclerosis-research.blogspot.co.uk/2012/06/research-dmt-slow-onset-of-progression.html)

Figure: http://multiple-sclerosis-research.blogspot.co.uk/2012/06/research-dmt-slow-onset-of-progression.html

Brain health

Time matters in multiple sclerosis

Gavin Giovannoni
Helmut Butzkueven
Suhayl Dhib-Jalbut
Jeremy Hobart
Gisela Kobelt
George Pepper
Maria Pia Sormani
Christoph Thalheim
Anthony Traboulsee
Timothy Vollmer

Preparation of these recommendations was funded by an educational grant from F. Hoffmann-La Roche, who had no editorial influence on the content.
EFFECTIVE DRUGS ARE AVAILABLE
DRUGS LICENCED TO TREAT RELAPSING MS

- Interferon beta 1a s.c.
- Interferon beta 1b s.c.
- Interferon beta 1a i.m.
- Glatiramer acetate
- Mitoxantrone
- Natalizumab
- Fingolimod
- Teriflunomide
- DMF
- Alemtuzumab
Interferon beta 1a s.c.
Interferon beta 1a pegylated
Interferon beta 1b s.c.
Interferon beta 1a i.m.
Glatiramer acetate 40 tiw
Mitoxantrone
Natalizumab
Fingolimod
Teriflunomide
DMF
Alemtuzumab
Daclizumab

OTHER MOLECULES ARE COMING, SOME VERY SOON
Timeline of MS Treatment Approvals

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS</td>
<td>554</td>
<td>3 trials</td>
</tr>
<tr>
<td>RRMS</td>
<td>32405</td>
<td>65 trials</td>
</tr>
<tr>
<td>PPMS</td>
<td>2574</td>
<td>5 trials</td>
</tr>
<tr>
<td>SPMS</td>
<td>2856</td>
<td>7 trials</td>
</tr>
<tr>
<td>Mixed</td>
<td>17369</td>
<td>62 trials</td>
</tr>
</tbody>
</table>

**Overview**
- Alemtuzumab
- Dalfampridine
- Dimethyl Fumarate
- Fingolimod
- Glatiramer Acetate
- IFNB-1b

**Detailed Timeline**
- IFNB-1a (Rebif)
- IFNB-1a (Plegridy)
- IFNB-1a (Avonex)
- Mitoxantrone
- Natalizumab
- Teriflunomide

**FDA Approval**
- 1988: IFNB-1b (Betaseron)
- 1990: IFNB-1a (Avonex)
- 1994: GA (Copaxone)
- 1998: Mitoxantrone (Novantrone)
- 2002: IFNB-1a (Rebif)
- 2003: Natalizumab (Tysabri)
- 2004: Teriflunomide (Aubagio)
- 2005: Alemtuzumab (Lemtrada)
- 2006: Dalfampridine (Ampyra)
- 2010: Fingolimod (Gilenya)
- 2012: Dimethyl Fumarate (Tecfidera)
- 2013: IFNB-1a (Plegridy)

**EMA Approval**
- 1990: IFNB-1a (Plegridy)
- 2006: Fingolimod (Gilenya)
- 2013: IFNB-1a (Plegridy)
# Treatment

## Treatment & monitoring – DMD: First-line treatments

<table>
<thead>
<tr>
<th>Drug, administration route</th>
<th>Reduction (%) in clinical activity (relapses) in clinical trials</th>
<th>Main side effects</th>
<th>Recommended safety monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vs. placebo</td>
<td>Vs. first-line DMD</td>
<td></td>
</tr>
<tr>
<td>Beta-interferon, SC or IM</td>
<td>30%</td>
<td>NA</td>
<td>-Flu-like symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Mild-moderate lymphopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Elevated liver enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate, SC</td>
<td>30%</td>
<td>NA</td>
<td>-Immediate post-injection reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Local injection-site skin reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Hypersensitivity</td>
</tr>
<tr>
<td>Dimethyl fumarate, oral</td>
<td>45-50%</td>
<td>22%</td>
<td>-Flushing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Gastrointestinal events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Lymphopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Elevated liver enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriflunomide, oral</td>
<td>40-50%</td>
<td>No proved superiority of teriflunomide vs. SC beta-interferon</td>
<td>-Hair loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Elevated liver enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Leukopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Elevated blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment

Treatment & monitoring – DMD: First-line treatments

Indications
• RRMS: At least 2 relapses over the past 2 years (all first-line drugs)
• CIS: Within the first 2 years if high risk of 2nd relapse (beta-interferons)
Oral fingolimod modulates S1P receptors on lymphocytes and neural cells.

It targets MS via actions in both the immune system and CNS.

Neural cells express S1P receptors known to modulate neuropathological processes relevant to MS.

Autoaggressive lymphocytes remain in the lymph nodes, away from the CNS → reversible REDISTRIBUTION, not depletion.
Natalizumab: A Humanized, Monoclonal Antibody (mAb) Against $\alpha_4$ Integrins

Complementarity-Determining Regions

- CDR grafted from murine Ab
- Human IgG4 framework
- Retains full potency

Framework
Natalizumab is a humanized ab against subunit alfa 4 of the integrins $\alpha_4\beta_1$ y $\alpha_4\beta_7$
NATALIZUMAB

A

Lymphocyte

$\alpha_4$ integrin

Lumen

VCAM1

Endothelial cell

Parenchyma

B

Natalizumab

...
Alemtuzumab
Target of activity

- Alemtuzumab is a CD52-directed immunomodulator
- CD52 is a surface protein expressed on adaptive and innate cells of the immune system to varying degrees

**Innate immune system:** Primary defense against pathogens including bacteria, viruses, and parasites
- Neutrophils
- NK cells
- Eosinophils
- Macrophage

**Adaptive immune system:** Second line of defense against antigens
- T lymphocytes
- B lymphocytes

**Low CD52 expression**
- Innate immune cells are largely spared and preserve functionality to fight infections

**Alemtuzumab administration**
- Alemtuzumab binding causes lysis and subsequent reduction of circulating T and B lymphocytes, resulting in decreased inflammation in the CNS

**High CD52 expression**
# Treatment

## Treatment & monitoring – DMD: Second-line treatments

<table>
<thead>
<tr>
<th>Drug, administration route</th>
<th>Reduction (%) in clinical activity (relapses) in clinical trials</th>
<th>Main side effects</th>
<th>Recommended safety monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vs. placebo</td>
<td>Vs. first-line DMD</td>
<td></td>
</tr>
<tr>
<td>Fingolimod, oral</td>
<td>55-60%</td>
<td>51-52%</td>
<td>-Bradycardia and other heart conduction abnormalities -Lymphopenia -Macular oedema -Elevated liver enzymes -Elevated blood pressure</td>
</tr>
<tr>
<td>Natalizumab, IV</td>
<td>68%</td>
<td>NA</td>
<td>-Perfusion reaction (nausea, vomiting, generally mild) -Hypersensitivity -Immunogenicity (antibodies against natalizumab) -Infections, including PML -Elevated lymphocyte count in peripheral blood</td>
</tr>
<tr>
<td>Alemtuzumab, IV</td>
<td>NA</td>
<td>55%</td>
<td>-Perfusion reaction (marked) -Marked lymphopenia -Infections -Secondary autoimmunity</td>
</tr>
</tbody>
</table>
Treatment

Treatment & monitoring – DMD: Second-line treatments

Indications

- At least 2 relapses over the previous year together with MRI evidence of inflammatory activity while on first-line DMD

Exceptionally, in highly active MS, all three can be used as first-line drugs
PML in association with Natalizumab

Cells with inclusions have positive nuclear signal for JC virus
Disease modifying drugs
a guide to treatments for relapsing MS

Multiple Sclerosis Trust
MS

MS Decisions
Visual Map of MS Clinical Trials

142 ongoing clinical trials in MS with a targeted total sample size of 55,758 patients.
MS Trials by Patient Population

CIS
N=554, 3 trials

RRMS
N=32405, 65 trials

PPMS
N=2574, 5 trials

SPMS
N=2856, 7 trials

Mixed
N=17369, 62 trials

Despite the identified need for more clinical trials in PPMS and SPMS, RRMS remains the main focus for the Pharma industry.
Urgent need to find solutions for people with Progressive MS

- Large worldwide impact: at least half of all (2.3 million) MS patients
- Currently no effective treatment for progressive MS
- Onset of progression is the main determinant of disability
- Finding treatments for progressive MS is one of the top priorities for patients
- Every time another therapy is approved for RRMS, a large proportion of our constituents feel left out
Development of secondary progression is the dominant determinant of long-term prognosis, independent of disease duration and early relapse frequency.
Onset of progressive phase determines disability

Scalfari et al Neurology 2011
The JLA facilitates Priority Setting Partnerships. These bring patients, carers and clinicians together to identify and prioritise for research the treatment uncertainties which they agree are the most important. The JLA believes that:

- Addressing uncertainties about the effects of treatments should become accepted as a much more routine part of clinical practice

- Patients, carers and clinicians should work together to agree which, among those uncertainties, matter most and thus deserve priority attention

- Prioritise the top 10 uncertainties… that they agree are most important.
The Top 10

1. Which treatments are effective to slow, stop or reverse the accumulation of disability associated with MS? i.e. TREAT PROGRESSION

2. How can MS be prevented?

3. Which treatments are effective for fatigue in people with MS?

4. How can people with MS be best supported to self-manage their condition?

5. Does early treatment with aggressive disease modifying drugs improve prognosis?

6. Is Vitamin D supplementation an effective disease modifying treatment for MS?

7. Which treatments are effective to improve mobility for people with MS?

8. Which treatments are effective to improve cognition in people with MS?

9. Which treatments are effective for pain in people with MS?

10. Is physiotherapy effective in reducing disability in people with MS?
Challenges

- Defining phenotype
- Clarifying pathological mechanisms underpinning progression
- Identifying treatment targets
- Outcomes/Biomarkers
- Trial design
Defining Progressive MS

- Neurologist
  - accumulation of disability,
  - gradual change over time (Progressive myelopathy)

- Imager:
  - Progressive atrophy, expanding lesions
  - Reduced MTR, NAA, fractional anisotropy

- Pathologist:
  - Axonal pathology
  - Oligodendrocyte pathology

- Patient:
  - Loss of independence
  - Inability to work, worsening symptoms

Progressive MS is defined differently from different perspectives.
Defining the clinical course of multiple sclerosis
The 2013 revisions

Fred D. Lublin, MD
Stephen C. Reingold, PhD
Jeffrey A. Cohen, MD
Gary R. Cutter, PhD
Per Soelberg Sørensen, MD, DMSc
Alan J. Thompson, MD

Neurology® 2014;83:278-286
The 2013 Revisions (1)

Core Phenotypes and Modifiers

- The core MS phenotypes (relapsing and progressive disease) should be retained with some modification.

- Assessment of disease **activity**, measured by clinical relapses or CNS lesion activity is an important modifier of the core phenotypes.

- Assessment of ongoing **progression** of disability is an important modifier of the core phenotypes.
Active Disease

Clinical: relapses, acute or sub-acute episodes of new or increasing neurological dysfunction followed by full or partial recovery \((\text{in the absence of fever or infection})\)

Imaging (MRI): occurrence of contrast enhancing T1 hyperintense or new or unequivocally enlarging T2 hyperintense lesions
Definitions (2)

Progressive Disease

**Clinical**: steadily increasing objectively documented neurological dysfunction/disability without unequivocal recovery (fluctuations and phases of stability may occur)

**Imaging (MRI)**: no standardized imaging measures of disease progression are established. Increasing number and volume of T1 hypo-intense lesions, brain volume loss and changes in MTI and DTI are being explored.
MS Clinical Forms: revised classification

Figure 2  The 1996 vs 2013 multiple sclerosis phenotype descriptions for progressive disease

1996 MS clinical description
Subtypes

- Progressive accumulation of disability from onset with or without temporary plateaus, minor remissions and improvements
- Progressive accumulation of disability after initial relapsing course, with or without occasional relapses and minor remissions
- Progressive accumulation of disability from onset but clear acute clinical attacks with or without full recovery

2013 MS disease modifiers
Phenotypes

- Progressive accumulation of disability from onset
  - Active* and with progression**
    - (PP)
  - Active but without progression
  - Not active but with progression
  - Not active and without progression (stable disease)

*Activity determined by clinical relapses assessed at least annually and/or MRI activity (contrast-enhancing lesions; new and unequivocally enlarging T2 lesions). **Progression measured by clinical evaluation, assessed at least annually. If assessments are not available, activity and progression are “indeterminate.” MS = multiple sclerosis; PP = primary progressive; PR = progressive relapsing; SP = secondary progressive.

Pathologic Mechanisms in Early vs. Late MS

Inflammation

Degeneration
Will the real multiple sclerosis please stand up?

Peter K. Stys, Gerald W. Zamponi, Jan van Minnen and Jeroen J. G. Geurts

Nat Rev Neurosci 2012

host’s immune reaction to it (orange). Thus, MS requires these two intertwined ingredients, one uniformly progressive, the other intermittent and highly variable, which establish the type of disease in any one patient. We propose that the ‘real’ MS is the underlying cytodegeneration, which is most faithfully reflected by primary progressive disease. SPMS, secondary progressive MS
Clinical Trials

Conventional trial design

Large numbers, lengthy, very expensive

Targeting inflammation (largely)

=> Need to consider new trial designs

=> Need to focus on neuroprotection/repair?
Moving to adaptive trials

- Treatment A: Placebo
- Treatment B: Placebo
- Treatment C: Placebo

Stage 1:

- Control: \( n_1 \) to \( n_2 \)
- A: \( n_1 \) to \( n_2 \)
- B: \( n_1 \) to \( n_2 \)
- C: \( n_1 \) to \( n_2 \)
- D: \( n_1 \) to \( n_2 \)

Stage 2:

- Patients to extension study: Randomised to treatments A and C (To be decided)

Interim Analysis:
- Based on early outcome(s); e.g. MRI and/or disability
- Purpose:
  - Treatment selection
  - Futility stopping
  - No early stopping for rejection of \( H_0 \)

Final Analysis:
- Including data from stages 1 & 2
- Disability outcome; e.g. EDSS
The interim measure

Δ MRI

Δ EDSS
A novel adaptive design strategy increases the efficiency of clinical trials in secondary progressive multiple sclerosis

Jeremy Chataway¹,², Richard Nicholas², Susan Todd³, David H Miller¹,⁴, Nicholas Parsons⁵, Elsa Valdés-Márquez³, Nigel Stallard⁵ and Tim Friede⁵
### Table 2 A: Trials in MS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Follow Up in Yrs</th>
<th>Entry EDSS</th>
<th>Active Treatment</th>
<th>Primary outcome measure</th>
<th>Primary Result</th>
<th>Comments</th>
<th>Publication Yr &amp; Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine- MSSG</td>
<td>547</td>
<td>1.5</td>
<td>3.0-7.0</td>
<td>Cyclosporine</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td>Two other co-primary endpoints were also used: time to wheelchair bound (+ve); activites of daily living (-ve)</td>
<td>1990</td>
</tr>
<tr>
<td>CCMSSG</td>
<td>168</td>
<td>2 (mean)</td>
<td>4.0-6.5</td>
<td>Cyclophosphamide or plasma exchange</td>
<td>Comparison of rates of EDSS worsening</td>
<td>-ve</td>
<td>Enrollment allowed if pre-study deterioration due to incomplete relapse recovery (more of RRMS cohort)</td>
<td>1991</td>
</tr>
<tr>
<td>EUSPMS</td>
<td>718</td>
<td>3</td>
<td>3.0-6.5</td>
<td>Betaseron 8MU/alternate days vs placebo</td>
<td>Time to confirmed EDSS worsening</td>
<td>-/+ve</td>
<td>Enrollment allowed if pre-study deterioration due to incomplete relapse recovery (more of RRMS cohort)</td>
<td>1998</td>
</tr>
<tr>
<td>SPECTRIMS</td>
<td>618</td>
<td>3</td>
<td>3.0-6.5</td>
<td>Rebif (22 or 44mcg 3/week)</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td>Enrollment allowed if pre-study deterioration due to incomplete relapse recovery (more of RRMS cohort)</td>
<td>2001</td>
</tr>
<tr>
<td>IMPACT</td>
<td>436</td>
<td>2</td>
<td>3.5-6.5</td>
<td>Avonex (60mcg/week)</td>
<td>MSFC</td>
<td>-/+ve</td>
<td>Positive outcome on MSFC (upper limb but not walking component), but not EDSS</td>
<td>2002</td>
</tr>
<tr>
<td>MIMS</td>
<td>188</td>
<td>2</td>
<td>3.0-6.0</td>
<td>Mitoxantrone 5 or 12 mg/m2 every 3 months</td>
<td>Composite measure (EDSS/ambulation index/relapses)</td>
<td>-/+ve</td>
<td>50% of cohort RRMS; 5 domain outcome measure not validated; cardiotoxicity/leukaemia risk</td>
<td>2002</td>
</tr>
<tr>
<td>NASG</td>
<td>939</td>
<td>3</td>
<td>3.0-6.5</td>
<td>Betaseron 8MU or 5MU/m2 alternate days</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td>Enrollment allowed if pre-study deterioration due to incomplete relapse recovery (more of RRMS cohort)</td>
<td>2004</td>
</tr>
<tr>
<td>ESIMS</td>
<td>318</td>
<td>2</td>
<td>3.0-6.5</td>
<td>Immunoglobulin 1g/kg/month (27 months)</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td>Enrollment allowed if pre-study deterioration due to incomplete relapse recovery (more of RRMS cohort)</td>
<td>2004</td>
</tr>
<tr>
<td>MAESTRO</td>
<td>612</td>
<td>2</td>
<td>3.0-6.5</td>
<td>MBP8298</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td>Enrollment allowed if pre-study deterioration due to incomplete relapse recovery (more of RRMS cohort)</td>
<td>2011</td>
</tr>
</tbody>
</table>

### Table 2 B: Current UK Trials in SPMS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Follow up Yrs</th>
<th>Entry EDSS</th>
<th>Active Treatment</th>
<th>Primary outcome measure</th>
<th>Reporting Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUPID (Phase III)</td>
<td>493</td>
<td>3</td>
<td>4.0-6.5</td>
<td>Tetrahydrocannabinol</td>
<td>Time to confirmed EDSS worsening; MSIS29 mean change</td>
<td>2012</td>
</tr>
<tr>
<td>MS-STAT (Phase IIb)</td>
<td>140</td>
<td>2</td>
<td>4.0-6.5</td>
<td>Simvastatin</td>
<td>MRI brain atrophy</td>
<td>2012</td>
</tr>
</tbody>
</table>
Trials in Progressive MS

- Phenytoin Optic Neuritis Study (Phase II)
- PROXIMUS Trial - oxcarbazepine in SPMS (Phase II)
- **INFORMS** – fingolimod in PPMS (Phase III)
- ASCEND – natalizumab in SPMS (Phase III)
- ORATORIO – ocrelizumab (rituximab cousin) in PPMS (Phase III)
- EXPAND – siponimod (fingolimod cousin) in SPMS (Phase III)

- **MS Smart Trial** – riluzole, amiloride, ibudilast in SPMS (Phase II)
- **SPRINT-MS** – ibudilast in PPMS/SPMS (Phase II)
- **MS – STAT** – high dose simvastatin
- **CUPID** – cannabinoids

- rituximab, mesenchymal stem cells, mastitinib, lipoic acid, erythropoietin, hydroxyurea, idebenone
Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial

• High-dose simvastatin (80mg) in SPMS
• Established secondary progression (narrative/EDSS) for ≥ 2 years

• EDSS 4.0 (500m) - 6.5 (20m/2 sticks)
  – Relapse free/no corticosteroids >3 months
  – DMT >6 months
  – Mitoxantrone >12 months
  – Never alemtuzumab/natalizumab
Outcomes

• Primary
  – Volumetric MRI BBSI

• Secondary
  – Disability (EDSS/MSIS-29v2/MSFC)
  – New and enlarging lesions T2 MRI
  – Relapses
  – Safety

• Other*
  – Neuropsychology
  – Immunology/Proteomics
Screening showing BBSI colour overlay
Primary outcome: BBSI change in whole brain volume (%/year)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) placebo</th>
<th>Mean (SD) simvastatin</th>
<th>Difference means (95% CI)*</th>
<th>in p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change WBV (%/year)</td>
<td>0.589 (0.528)</td>
<td>0.298 (0.562)</td>
<td>-0.254 (-0.423 to -0.085)</td>
<td>0.003</td>
</tr>
<tr>
<td>Number patients evaluated</td>
<td>64</td>
<td>66</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusting for minimisation variables and MRI site
Change whole brain volume (%/yr)

![Graph showing change in whole brain volume over time]

- Change WBV %/year:
  - 0 to 12 months
  - 12 to 25 months
  - 0 to 25 months

- Mean and Individual values shown for each time period.
Change in EDSS 0 to 24 months

Change in EDSS from Baseline to 24 months
Aims of CUPID study
• assess the value of $\Delta^9$-THC in slowing progressive MS over 3 yrs
• assess the safety of $\Delta^9$-THC over the long-term.
• improve research methodology; using new, patient-orientated methods.

Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial

John Zajicek, Susan Ball, David Wright, Jane Vickery, Andrew Nunn, David Miller, Mayam Gomez Cano, David McManus, Sharukh Mallik, Jeremy Hobart, on behalf of the CUPID investigator group
CUPID (THC): EDSS progression over 3 years

Time to EDSS progression (days)

P (EDSS progression)

Treatment group

Active

Placebo
CUPID (THC): EDSS progression in patients with baseline EDSS <6 (post-hoc analysis)

Log rank test $P = 0.01$

$n = 110$

Time to EDSS progression (days)
Key PPMS clinical trials

Completed, ongoing and planned trials in primary progressive MS (PPMS)

- PROMiSE (N=943) and OLYMPUS (N=439) are the two largest randomized trials in PPMS patients completed to date

- **Glatiramer acetate**
  - Phase 3 PROMiSE Trial
  - April 2004

- **Rituximab**
  - Phase 2/3 OLYMPUS Trial
  - April 2009

- **Masitinib**
  - Phase 2/3 PPMS and SPMS
  - Data expected 2015

- **Fingolimod**
  - Phase 3 INFORMS Trial
  - Data release: Q2 2015

- **Ocrelizumab**
  - Phase 3 ORATORIO Trial
  - Data expected Q4 2015

- **Laquinimod**
  - Phase 2/3 PPMS and SPMS
  - Data expected 2018

- **Glatiramer acetate**

- **Rituximab**

- **Masitinib**

- **Fingolimod**

- **Ocrelizumab**

- **Laquinimod**
Rituximab
Anti-CD20 Monoclonal Antibody

- Rituximab is a genetically engineered chimeric (mouse-human) monoclonal antibody that targets CD20-positive B lymphocytes

- CD20 is present on B and pre-B lymphocytes but not on stem cells or plasma cells

- Long duration of action

Time to Confirmed Disease Progression

All Intent-to-Treat Patients (N=439)

HR: 0.77
(95% CI: 0.55 –1.09)
p-value=0.1442
Proportion of Patients

Rituximab
Placebo

Time to Confirmed Disease Progression (weeks)

Subgroup Analysis

Gd (-) at Baseline
n=143
HR: 0.63
(95% CI: 0.34–1.18)
p=0.1427

Gd (+) at Baseline
n=72
HR: 0.33
(95% CI: 0.14–0.79)
p=0.0088

Rituximab
Placebo

Time to Confirmed Disease Progression (weeks)
Randomised, multicentre, double-blind, placebo-controlled, parallel-group study in ~940 patients with PPMS

<table>
<thead>
<tr>
<th>Screening (Day -45 to Day -1)</th>
<th>Baseline (Day -14 to Day -1)</th>
<th>Double-blind treatment period*</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI Visit</td>
<td>Randomisation (1:1)</td>
<td>Placebo</td>
<td>n=487</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fingolimod 0.5 mg</td>
<td>n=336</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td></td>
<td>End of treatment (Month 36)</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Double-blind treatment period will last until the last patient randomised in the study completes treatment (Month 36, if not discontinued earlier) or a patient completes the 5-year maximum duration of treatment. Following implementation of Amendment 5 in 2010, patients who were randomised to receive fingolimod 1.25 mg or matching placebo were switched in a blinded manner to fingolimod 0.5 mg or continued on placebo. Patients who were enrolled in the study following implementation of Amendment 5 were randomised to receive fingolimod 0.5 mg or matching placebo. Miller D et al. Poster P07.116 presented at AAN 2013
Primary endpoint, a novel approach

- The primary endpoint is time to sustained disability progression (SDP)
- SDP is defined based on any of three types of event:
  - 3-month sustained increase of ≥20% from Baseline in the timed 25-foot walk test (25’TWT) OR
  - 3-month sustained increase from Baseline in the EDSS score defined as:
    - 1 point in patients with Baseline EDSS 3.5-5.0
    - 0.5 point in patients with Baseline EDSS 5.5-6.0
  OR
  - 3-month sustained increase of ≥20% from Baseline in the 9-hole peg test (9-HPT)

*Defined as an increase of ≥20% from baseline in 25’TWT or increase from Baseline in EDSS score (1 point in patients with Baseline of 3.5 to 5.0; 0.5 points in patients with Baseline of 5.5 to 6.0) or increase of ≥20% from Baseline in 9-HPT
Abstract AAN April 2015:

- The composite primary endpoint in INFORMS was not met: Fingolimod demonstrated **no difference** compared to placebo in the time to the composite 3M-CDP versus placebo.

- EDSS: Fingolimod did **not** delay the time to 3M-CDP as measured by the EDSS as single outcome compared to placebo.

- BVL: Percent brain volume change (PBVC) measured using SIENA (Structural Image Evaluation, using Normalization, of Atrophy) was **not** different in patients treated with fingolimod 0.5 mg when compared to patients treated with placebo.
Neuroprotection

Repair/Remyelination

Lifestyle

Rehabilitation

Enhancing plasticity
Treatment target
Neuroprotection: sodium channel blockers

Partial sodium channel blockade has been shown to be neuroprotective in experimental models of inflammatory axonal injury.
Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial

Raju Kapoor, Julian Furby, Thomas Hayton, Kenneth J Smith, Daniel R Altmann, Robert Brenner, Jeremy Chataway, Richard A C Hughes, David H Miller

Summary

Background Partial blockade of voltage-gated sodium channels is neuroprotective in experimental models of inflammatory demyelinating disease. In this phase 2 trial, we aimed to assess whether the sodium-channel blocker lamotrigine is also neuroprotective in patients with secondary progressive multiple sclerosis.

Methods Patients with secondary progressive multiple sclerosis who attended the National Hospital for Neurology and Neurosurgery or the Royal Free Hospital, London, UK, were eligible for inclusion in this double-blind, parallel-group trial. Patients were randomly assigned via a website by minimisation to receive lamotrigine (target dose 400 mg/day) or placebo for 2 years. Treating physicians, evaluating physicians, and patients were masked to treatment allocation. The primary outcome was the rate of change of partial (central) cerebral volume over 24 months. All patients who were randomly assigned were included in the primary analysis. This trial is registered with ClinicalTrials.gov, NCT00257855.

Findings 120 patients were randomly assigned to treatment (87 women and 33 men): 61 to lamotrigine and 59 to placebo. 108 patients were analysed for the primary endpoint: 52 in the lamotrigine group and 56 in the placebo group. The mean change in partial (central) cerebral volume per year was −3.18 mL (SD −1.25) in the lamotrigine group and −2.48 mL (−0.97) in the placebo group (difference −0.71 mL, 95% CI −2.56 to 1.15; p=0.40). However, in an exploratory modelling analysis, lamotrigine treatment seemed to be associated with greater partial (central) cerebral volume loss than placebo in the first year (p=0.04), and volume increased partially after treatment stopped (p=0.04). Lamotrigine treatment reduced the deterioration of the timed 25-foot walk (p=0.02) but did not affect other secondary clinical outcome measures. Rash and dose-related deterioration of gait and balance were experienced more by patients in the lamotrigine group than the placebo group.

Interpretation The effect of lamotrigine on cerebral volume of patients with secondary progressive multiple sclerosis did not differ from that of placebo over 24 months, but lamotrigine seemed to cause early volume loss that reversed partially on discontinuation of treatment. Future trials of neuroprotection in multiple sclerosis should include investigation of complex early volume changes in different compartments of the CNS, effects unrelated to neurodegeneration, and targeting of earlier and more inflammatory disease.

Funding Multiple Sclerosis Society of Great Britain and Northern Ireland.
Figure 2: Primary outcome
Mean partial (central) cerebral volume by intention-to-treat comparison, including numbers of valid 6-monthly observations. Bars=SE.

Acute neuroprotection
Phenytoin is neuroprotective in acute optic neuritis: Results of a phase 2 randomized controlled trial

R Kapoor¹, ², R Raftopoulos¹, ², S Hickman⁴, A Toosy¹, ², B Sharrack⁴, S Mallik¹, ², D Altmann², P Malladi¹, M Koltzenburg¹, ², C Wheeler-Kingshott², K Schmierer³, G Giovannoni³, and DH Miller²

National Hospital for Neurology and Neurosurgery¹, UCL Institute of Neurology², and Queen Mary University of London³, London UK, and Royal Hallamshire Hospital, Sheffield UK⁴
Trial design

Primary outcome measure: RNFL thickness

- Direct, noninvasive measurement of degeneration in retinal ‘white & gray matter’
- Correlates with visual loss and brain volume
- Sensitive, semiautomated measurement
- Longitudinal natural history data enables sample sizes to be calculated

- Numbers per arm ($\alpha=0.05$, $\beta=0.8$)
- Placebo-controlled, parallel group design, measurements at 0, 6 months
- Method: 6 month affected eye RNFL adjusted for fellow eye at baseline
- Allow 20% dropout/nonadherence

Sample size vs treatment effect

<table>
<thead>
<tr>
<th>Treatment Effect</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>55</td>
<td>35</td>
<td>25</td>
</tr>
</tbody>
</table>
Primary outcome: RNFL

- Active-placebo adjusted difference 7.15 µm (95% CI 1.08, 13.22 p=0.02)
- 30% reduction of atrophy in active group

- PP comparison: Active-placebo adjusted difference 7.40 µm (95% CI 0.76, 14.04 p=0.03)

Bars are standard errors around the unadjusted group means
Lamotrigine in SPMS

Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial

Raj-Kumar, Thyme, Staunton, Smith, Duffield, Nunn, Robert Storey, Jeremy Chataway, Richard A. Hughes, David Miller

Summary

Background: Partial blockade of voltage-gated sodium channels in neuroprotective experimental models of inflammatory demyelinating disease. In this phase II trial, we aimed to assess whether the sodium-channel blocker lamotrigine is also neuroprotective in patients with secondary progressive multiple sclerosis.

Methods: Patients with secondary progressive multiple sclerosis who attended the National Hospital for Neurology and Neurosurgery or the Royal Free Hospital, London, UK, were eligible for inclusion in this double-blind, parallel-group trial. Patients were randomly assigned via a website by minimisation to receive lamotrigine targeted dose 400 mg daily or placebo for 2 years. Trained physicians, excluding physicians, and patients were masked to treatment allocation. The primary outcome was the rate of change of partial (mild) cerebral volume over 18 months. All patients who were randomised were included in the primary analysis. This trial is registered with ClinicalTrials.gov, NCT01835583.

Findings: 120 patients were randomly assigned to treatment (57 women and 33 men aged 59 to 70 years) and 121 to placebo. 108 patients were analysed for the primary endpoint: 52 in the lamotrigine group and 56 in the placebo group. The total change in partial (mild) cerebral volume per year was −1.16 ml (95% CI −2.25 to −0.07) in the lamotrigine group and −2.43 ml (95% CI −3.97 to −0.89) in the placebo group (p=0.43). However, in an exploratory modelling analysis, lamotrigine treatment seemed to be associated with greater partial cerebral volume loss than placebo in the first year (p=0.04), and volume increased slightly after treatment stopped (p=0.04). Lamotrigine treatment halved the deterioration of the timed 25-foot walk (p=0.02) but did not affect other secondary clinical outcome measures. Risk and dose-related differences of gastrointestinal and balance were experienced more in patients in the lamotrigine group than in the placebo group.

Interpretation: The effect of lamotrigine on cerebral volume in patients with secondary progressive multiple sclerosis did not differ from that of placebo over 2 years, but lamotrigine seemed to cause cerebral volume loss that occurred partially on discontinuation of treatment. Future trials of neuroprotection in multiple sclerosis should include investigation of complex multifactorial volume changes in different compartments of the CNS, effects unrelated to neuroimmunology, and targeting of earlier and more inflammatory disease.

Funding: Multiple Sclerosis Society of Great Britain and Northern Ireland

<table>
<thead>
<tr>
<th>Rate of change of speed (1/T25FW) (%/mo $\times 10^3$)</th>
<th>active</th>
<th>placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT comparison</td>
<td>-0.38</td>
<td>-0.88</td>
<td>0.02</td>
</tr>
<tr>
<td>PP comparison</td>
<td>-0.20</td>
<td>-0.88</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Suggestions of slower volume loss in year 2

Slower deterioration of timed walk

Positive NfH response in adherent group

Biomarker Report from the Phase II Lamotrigine Trial in Secondary Progressive MS – Neurofilament as a Surrogate of Disease Progression

Sharmilee Gnanapavan1, Donna Grant1, Steve Morant1, Julian Furdy1, Tom Hayton1, Charlotte E. Teunissen1, Valerio Leoni1, Monica Marta1, Robert Brenner1, Jacqueline Palace1, David H. Miller1, Raj Kapoor1, Gavin Giovannoni2

1Department of Neuroimmunology, UCL Institute of Neurology, London, United Kingdom. 2Independent Statistician, Haddenham, Bucks, United Kingdom.

001Department of Clinical Chemistry, VU University Medical Center Amsterdam, Amsterdam, The Netherlands. 4Laboratory of Clinical Pathology and Medical Genetics, Foundation Rijks Neurology Institute “Carlo Besta”, Milano, Italy. 5Rizzoli Institute, Queen Mary University London, London, United Kingdom. 8Department of Clinical Neuroscience, Royal Free Hospital, London, United Kingdom. 7Department of Clinical Neurology, Radcliffe Infirmary, Oxford, United Kingdom.
Effect of MD1003 (High Doses of Biotin) in Progressive Multiple Sclerosis: Results of a pivotal phase III Randomized Double Blind Placebo Controlled Study

A. Tourbah, C. Lebrun-Frenay, G. Edan,
M. Clanet, C. Papeix, S. Vukusic, J. de Sèze, M. Debouverie,
O. Gout, P. Clavelou, G. Defer, D. Laplaud, T. Moreau,
P. Labauge, B. Brochet, F. Sedel, J. Pelletier

CHU Reims, CHU Nice, CHU Rennes,
CHU Toulouse, GH Pitié-Salpêtrière Paris, CHU Lyon, CHU Strasbourg, CHU Nancy,
FOAR Paris, CHU Clermont-Ferrand, CHU Caen, CHU Nantes, CHU Dijon,
CHU Montpellier, CHU Bordeaux, Medday Pharmaceuticals, CHU Marseille
Biotin targets two mechanisms that may underpin progressive MS

ACC: acetyl CoA carboxylase
## Baseline Characteristics (154 patients)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MD1003 n=103</th>
<th>Placebo n=51</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>51.5</td>
<td>58.8</td>
<td>NS</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>51.8 (9.1)</td>
<td>50.7 (8.4)</td>
<td>NS</td>
</tr>
<tr>
<td>PPMS (%)</td>
<td>40.8</td>
<td>25.5</td>
<td>NS</td>
</tr>
<tr>
<td>SPMS (%)</td>
<td>59.2</td>
<td>74.5</td>
<td>NS</td>
</tr>
<tr>
<td>MS duration, years, mean (SD)</td>
<td>14.8 (8.9)</td>
<td>17.4 (10.3)</td>
<td>NS</td>
</tr>
<tr>
<td>EDSS, mean (SD)</td>
<td>5.98 (0.8)</td>
<td>6.2 (0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Concomitant DMT (%)</td>
<td>40.8</td>
<td>41.2</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment with fampridine (%)</td>
<td>41</td>
<td>54.9</td>
<td>NS</td>
</tr>
</tbody>
</table>
Primary endpoint: Proportion of patients with improvement at M9 confirmed at M12

- Definition of improvement:
  
  EDSS decrease by at least by 1 point if baseline EDSS 4.5-5.5 and 0.5 point if baseline EDSS 6-7 or Timed 25-Foot Walk (TW25) decrease 20% compared to baseline

- Baseline values: best EDSS and TW25 between M-1 and M0
### Primary Endpoint results

<table>
<thead>
<tr>
<th></th>
<th>MD1003 n(%)</th>
<th>Placebo n(%)</th>
<th>p-value $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT population</strong></td>
<td>N=103</td>
<td>N=51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (12.62%)</td>
<td>0 (0.0%)</td>
<td>0.0051</td>
</tr>
<tr>
<td><strong>Per protocol</strong></td>
<td>N=87</td>
<td>N=42</td>
<td></td>
</tr>
<tr>
<td>population</td>
<td>13 (14.9%)</td>
<td>0 (0.0%)</td>
<td>0.0093</td>
</tr>
</tbody>
</table>

(1) Fisher's Exact test

- Primary endpoint met with EDSS: 76.9%
- Primary endpoint met with TW25: 38.5%
Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial

MS-SMART Trialists

Dr Jeremy Chataway
"This report is independent research funded by the Medical Research Council (MRC) and Multiple Sclerosis Society (MS Society) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership."
MULTI-ARM trials: an effective way of speeding up the therapy evaluation process!

STANDARD TRIALS

50%

Treatment A

VS

Placebo

Treatment B

VS

Placebo

Treatment C

VS

Placebo

25%

Treatment A

25%

Treatment B

25%

Treatment C

25%

Placebo

25%
Interventions

- Amiloride 5 mg bd
- Riluzole 50mg bd
- Fluoxetine 20mg bd
Secondary and Primary Progressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis

- 96-week, randomized, placebo-controlled phase II trial of ibudilast in SPMS/PPMS (Concurrent treatment with IFN-β1 or GA is allowed)
- Primary Outcome: whole brain atrophy (BPF)
  - Secondary Outcomes:
    - DTI (descending pyramidal tracts)
    - MTR (whole brain), OCT (retinal nerve fiber layer)
    - Cortical atrophy (CLADA)
- Standardized 3T imaging at all sites
- EDSS, MSFC-4, PROs

- Utilize NeuroNEXT, NIH-funded, Phase II clinical trial network
  - Head-to-head comparison of imaging measures
    - Longitudinal validation to clinical outcomes
## MSC Treatment of Multiple Sclerosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Indication</th>
<th>Patients</th>
<th>MSC Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connick 2012</td>
<td>SPMS</td>
<td>10</td>
<td>Autologous culture-expanded BM MSCs administered IV</td>
</tr>
<tr>
<td>Karussis 2010</td>
<td>RR, SP, PP MS</td>
<td>15</td>
<td>Autologous culture-expanded BM MSCs administered IV and IT</td>
</tr>
<tr>
<td>Liang 2009</td>
<td>PP MS</td>
<td>1</td>
<td>Allogeneic umbilical cord MSCs administered IV and IT after CTX</td>
</tr>
<tr>
<td>Mohyeddin Bonad 2007</td>
<td>Treatment-refractory MS</td>
<td>10</td>
<td>Autologous culture-expanded BM MSCs administered IT</td>
</tr>
<tr>
<td>Rice 2010</td>
<td>Chronic MS</td>
<td>6</td>
<td>Fresh BM cells enriched for MSCs</td>
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<tr>
<td>Riordan 2009</td>
<td>Treatment-refractory MS</td>
<td>3</td>
<td>Autologous non-expanded adipose MSCs</td>
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<tr>
<td>Yamout 2010</td>
<td>SPMS</td>
<td>10</td>
<td>Autologous culture-expanded BM MSCs administered IT</td>
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Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study

Peter Connick, Madhan Kolappan, Charles Crawley, Daniel J Webber, Rickie Patani, Andrew W Michell, Ming-Qing Du, Shi-Lu Luan, Daniel R Altmann, Alan J Thompson, Alastair Compston, Michael A Scott, David H Miller, Siddharthan Chandran

10 patients with secondary progressive MS Studied visual system
Autologous mesenchymal stem cells in secondary progressive MS

- 10 SPMS patients with previous optic neuritis
- Studied pre- and post stem cell Rx
- Significant improvement of visual acuity (unblinded)
- Laboratory evidence for remyelination (blinded)
  - ↓VEP latency ($p=0.016$) & ↑optic nerve area ($p=0.006$)
Constitution of IMSCT Study Group (Paris, March 2009) supported by CMSC, Canadian MS Society and ECTRIMS

Consensus paper on the utilization of MSCs for the treatment of MS published in Mult. Scler. 2010

Consensus paper set the guidelines for phase I/II clinical trials of MSCT in MS
Progressive MS Alliance

Mission

To expedite the development of effective disease modifying and symptom management therapies for progressive forms of multiple sclerosis
Setting a research agenda for progressive multiple sclerosis: The International Collaborative on Progressive MS

Robert J. Fox¹, Alan Thompson², David Baker³, Peer Baneke⁴, Doug Brown⁵, Paul Browne⁶, Dhia Chandraaratna⁷, Olga Ciccarelli², Timothy Coetzee⁴, Giancarlo Comi⁷, Anthony Feinstein⁸, Raj Kapoor⁹, Karen Lee¹⁰, Marco Salvetti¹¹, Kersten Sharrock¹², Ahmed Toosy², Paola Zaratin¹³ and Kim Zuidwijk¹⁴
Countries actively involved in the Alliance
<table>
<thead>
<tr>
<th>Scientific Steering Committee</th>
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<tbody>
<tr>
<td>Alan Thompson, UK, Chair</td>
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<tr>
<td>Timothy Coetzee, USA</td>
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<tr>
<td>Kathy Smith, USA</td>
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<td>Paola Zaratin, Italy</td>
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<tr>
<td>Dhia Chandraratna, MSIF</td>
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<td>Ceri Angood, MSIF</td>
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<td>Susan Kolhaas, UK</td>
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<td>Jeroen Geurts, Netherlands</td>
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<tr>
<td>Karen Lee, Canada</td>
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<tr>
<td>Giancarlo Comi, Italy, Vice-Chair</td>
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<tr>
<td>Bruce Bebo, USA</td>
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<tr>
<td>Robert Fox, USA</td>
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<td>Marco Salvetti, Italy</td>
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<td>Xavier Montalban, Spain</td>
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<td>Nick de Rijke, UK</td>
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<td>Raj Kapoor, UK</td>
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<tr>
<td>Per Soelberg Sorensen, Den</td>
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<tr>
<td>Anthony Feinstein, Canada</td>
</tr>
<tr>
<td>Reinhard Hohlfeld, Germany</td>
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</tbody>
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Priority areas:

- Underlying Mechanism/Experimental Models
- Target pathways and drug repurposing
- Proof of concept trials (phase II)
- Phase III clinical trials & outcome measures
- Symptom management and rehabilitation
Current Progressive MS Research Initiatives

1. Over 100 investigator initiated research projects
2. MS Outcomes Assessment Consortium
3. Clinical Trials- MS SMART, SPRINT MS
4. SUMMIT natural history and risk factors study
5. Revision of Lublin-Reingold Clinical Course Descriptor
6. International Progressive MS Alliance
Global Research Funders

- Government
  - NIH, CDMRP, Medical Research Council (UK), CIHR (Canada)
- MS Societies
- Private foundations
  - Hilton Foundation, Wellcome Trust
- Pharmaceutical companies
Global Progressive MS Projects - Pushgraph™ Analytics

- 405 projects (out of 707) identified as relevant to progressive MS

- Total Multi-Year Commitment = $132,608,598
Progressive MS Map

Purple = Progressive
Orange = Non-Progressive
Global Progressive MS Portfolio

Distribution of Projects by Alliance Priority

- Understanding Progression: 103, 26%
- Clinical Trial Design/Tools and Outcomes: 236, 58%
- Development/Testing of New Treatments: 36, 9%
- Symptom Management/Rehab: 30, 7%
Global Progressive MS Portfolio

Distribution of Projects by Priority/Stage

- **Discovery**
  - Understanding Progression: 213 projects
  - Clin. Trial Designs/Outcomes: 6 projects
  - Dev./Testing of New Agents: 18 projects
  - Sympt. Mgmt/Rehab: 3 projects

- **Clinical Trials**
  - Clinical Research: 23 projects
  - Clinical Trials: 30 projects
  - Dev./Testing of New Agents: 6 projects
  - Sympt. Mgmt/Rehab: 16 projects
Symptoms/Rehab Priority
Projects by Area of Focus

No of Projects

Bladder | Cognition/Memory | Exercise | Exercise/Cognition | General Rehab | Mindfulness | Mobility | Pain | QoL | Spasticity
Long term commitment towards PMSA goal

2013 – 2021 PLAN

2013 – 2017
HORIZON 1

2017 – 2021
HORIZON 2/3

CHALLENGES AWARDS 2013 - 2016

COLLABORATIVE TEAM AWARDS 2014 - 2017

INNOVATIVE OPERATIVE FUNDING MODELS TO ACCELERATE RESEARCH
Scientific Strategy Timeline

- **Sept 2013**
  - Science Strategy Meeting

- **Sept 2014**
  - RFA 1 – Challenge & Infrastructure
  - Rehab Meeting

- **Sept 2015**
  - RFA 2 – Collaborative Networks
  - Industry stakeholders engagement
  - Alliance Scientific Meeting

- **Sept 2016**
  - Industry stakeholders meeting
Progressive MS: from pathophysiology to drug discovery

Marco Salvetti, Douglas Landsman, Peter Schwarz-Lam, Giancarlo Comi, Alan J Thompson and Robert J Fox
Benefits from the PMSA

• Providing multiple avenues for experts (MS organisations, academia, industry etc.) from around the world to meet and discuss the most urgent issues in Progressive MS research

• Growing global commitment to Progressive MS research to €22 million over the next 5 years

• For the first time ever, MS Societies are funding research together without considering geography – funding the best science anywhere in the world

• Raising profile and underlining need
Progressive multiple sclerosis 1

Pathological mechanisms in progressive multiple sclerosis

Progressive multiple sclerosis 2

Treatment of progressive multiple sclerosis: what works, what does not, and what is needed

Anthony Feinstein, Jenny Freeman, Albert C Lo

Progressive multiple sclerosis 3

Clinical trials in progressive multiple sclerosis: lessons learned and future perspectives

Daniel Ontaneda, Robert J Fox, Jeremy Chataway
Challenges ahead

• Understand relevant aspects of human MS pathology
  – Validate a pre-clinical model that emulates human pathology
  – Develop high through-put screening tools

• Validate a Phase II outcome biomarker
  – Use trials to advance methodology

• Develop accepted clinical outcome measures

• Drive symptomatic treatments and rehabilitation

www.endprogressivems.org
Take home messages

• Although we can diagnose better, there is an urgent need to raise awareness in community

• Great progress in treatments for relapsing/remitting MS. Now focus on risk-benefit analysis

• Needs to be replicated in progressive MS

• More work on models of care which provide greater continuity and encourage self-management.