Progressive MS treatment: where do we stand

Giancarlo Comi

Dept. of Neurology & Institute of Experimental Neurology

Università Vita Salute S. Raffaele, Milano
Disability Progression in Two Phases

This is one important factor in deciding to manage patients early to help slow progression, irrespective of initial clinical presentation.

Data from a retrospective, database review of the Rennes MS database showing the 718 MS patients who had reached both DSS 3 and 6; these were divided into five subgroups defined according to the duration of phase 1 (mean time from MS clinical onset to DSS 3).

DSS=disability status scale

Adapted from Leray E et al. Brain. 2010;133:1900-1913.
Relapsing Remitting MS

- Inflammatory Infiltrates
- White Matter Plaques
- Grey Matter Plaques
Progressive MS

White Matter Plaques
Cortical Plaques
Inflammation in Brain Tissue
Inflammation in Meninges
Pathological Differences between RRMS and Progressive MS (SPMS, PPMS)

RRMS

- New waves of inflammation entering the CNS from circulation
- Focal demyelinating lesions with variable axonal injury and blood brain barrier injury mainly in the white matter

RPMS

SPMS / PPMS

- Compartmentalized inflammation in the CNS
- Slow expansion of pre-existing white matter lesions
- Diffuse inflammation and axonal injury in NAWM
- Extensive cortical demyelination

Degeneration
Disability
Inflammation
Regeneration

EDSS 3

severity
time
Clinical Onset
MS disease progression

- Structural damage
- Functional reorganization
- Clinical disability

Schoonheim, Geurts, Barkhof. Neurology 2010
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
Jerry S. Wolinsky, MD
Laura J. Baker, MD, MSCE
Brenda Banwell, MD
Frederik Barkhof, MD, PhD
Bruce Bebo, Jr., PhD
Peter A. Calabresi, MD
Michel Clanet, MD
Giancarlo Comi, MD
Robert J. Fox, MD
Mark S. Freedman, MD

ABSTRACT
Accurate clinical course descriptions (phenotypes) of multiple sclerosis (MS) are important for communication, prognostication, design and recruitment of clinical trials, and treatment decision-making. Standardized descriptions published in 1996 based on a survey of international MS experts provided purely clinical phenotypes based on data and consensus at that time, but imaging and biological correlates were lacking. Increased understanding of MS and its pathology, coupled with general concern that the original descriptors may not adequately reflect more recently identified clinical aspects of the disease, prompted a re-examination of MS disease phenotypes by the International Advisory Committee on Clinical Trials of MS. While imaging and biological markers that might provide objective criteria for separating clinical phenotypes are lacking, we propose refined descriptors that include consideration of disease activity (based on clinical relapse rate and imaging findings) and disease progression. Strategies for future research to better define phenotypes are also outlined. Neurology® 2014;83:1-9

GLOSSARY
CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NMSS = National Multiple Sclerosis Society; OCT = optical coherence tomography; PP = primary progressive; PR = progressive relapsing; PRO = patient-reported outcomes; RIS = radiologically isolated syndrome; RR = relapsing-remitting; SP = secondary progressive.
1996 MS clinical description
Subtypes

Progressive disease → SP

Progressive accumulation of disability after initial relapsing course, with or without occasional relapses and minor remissions

Progressive disease → PR

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 (SP)

Progressive accumulation of disability after initial relapsing course

Not active and without progression (stable disease)
Progressive multiple sclerosis: The treatment gap

Courtney Humphries

_Nature_ 484, S10 (12 April 2012)  |  doi:10.1038/nature11108
Published online 11 April 2012

Most new treatments for multiple sclerosis are for patients with the relapsing–remitting form of the disease. Those with the more advanced, progressive type are being left behind.

When neurologist Robert Fox first diagnoses a patient with progressive multiple sclerosis (MS) — a form of the disease marked by a slow, gradual worsening of symptoms — he cannot offer much hope of a cure. “I’m very blunt with patients,” says Fox, who is medical director at the Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research in Ohio. “We don’t have a therapy to slow down this train.”
Table 2. Drugs tested in phase III clinical trials in progressive multiple sclerosis.

<table>
<thead>
<tr>
<th>SPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cladribine</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Dirucotide</td>
</tr>
<tr>
<td>Dronabinol</td>
</tr>
<tr>
<td>Interferon-beta 1a i.m.</td>
</tr>
<tr>
<td>Interferon-beta 1a s/c</td>
</tr>
<tr>
<td>Interferon-beta-1b s/c</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
</tr>
<tr>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Mitoxantrone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronabinol</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
</tr>
<tr>
<td>Interferon-beta 1a</td>
</tr>
<tr>
<td>Interferon-beta-1b</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>IFN1b (E)</td>
</tr>
<tr>
<td>IFN1b (NA)</td>
</tr>
<tr>
<td>IFN1a im</td>
</tr>
<tr>
<td>IFN1a sc</td>
</tr>
</tbody>
</table>

• (p<0.01)
ns  not improved
Placebo-Controlled Trials on Secondary Progressive Multiple Sclerosis

**EUSPMS**

Figure 2: *Time to confirmed progression, life-table estimate*  
*Month 36 visit for confirmation only.*

**NASPMS**

**SPECTRIMS**

**IMPACT**
Therapeutic issues in MS progressive forms

Secondary progressive multiple sclerosis: current knowledge and future challenges

Marco Rovaris, Christian Confavreux, Roberto Furlan, Ludwig Kappos, Giancarlo Comi, MassimoFilippi

Figure 5: Percentages of patients with secondary progressive MS who had relapses during treatment with interferon beta or placebo in EUSPMS, SPECTRIMS, NASPMS, and IMPACT trials.
Mitoxantrone

• Licenced in US

• Given 3 monthly 2-3 yrs or

5 doses over 8 months:
Mitoxantrone risks

- Cardiac: reduced LVEF, common, rare symptomatic, dose related
- Leukaemia
- Neutropenic infection
- Amenorrhea: age related
- Nausea /vomiting (common)
- Alopecia
Relative effects of mitoxantrone

Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial

55% SP MS

- Placebo
- Active
- Rebif 44

Relative effects of mitoxantrone

Relapse rate

Confirmed disability

Relapse free

Mean EDSS change

PROGRESSION-FREE PATIENTS AFTER MITOXANTRONE TREATMENT (394 pts)

Similar results from Buttinelli 2007
The window of therapeutic opportunity in multiple sclerosis
Evidence from monoclonal antibody therapy

J Neurol
DOI 10.1007/s00415-005-0934-5

SPMS

RRMS

Fig. 2 Comparison of the change in accumulation of disability between the secondary progressive (a) and relapsing-remitting (b) cohorts treated using Campath-1H. Gradients above the equator represent increasing disability and below represent reducing disability. Note the different time scale between a and b; the data are annualised to allow comparison between time epochs of different duration.
Failed or Inconclusive Placebo-Controlled Trials on Primary Progressive Multiple Sclerosis

- IFN beta 1a
- IFN beta 1b
- GA
- Rituximab

Failed or inconclusive trials with placebo controls for primary progressive multiple sclerosis.
Rituximab in Patients with Primary Progressive Multiple Sclerosis
Results of a Randomized Double-Blind Placebo-Controlled Multicenter Trial

Kathleen Hawker, MD,1 Paul O’Connor, MD,2 Mark S. Freedman, MD,3 Peter A. Calabresi, MD,4 Jack Antel, MD,5 Jack Simon, MD,6 Stephen Hauser, MD,7 Emmanuelle Waubant, MD,7 Timothy Vollmer, MD,8 Hillel Panitch, MD,9 Jiameng Zhang, PhD,10 Peter Chin, MD,10 and Craig H. Smith, MD,10 for the OLYMPUS trial group

Subgroup K-M plots

age<51; base GD lesion=0; n=143
HR= 0.70 (0.39,1.28)

age < 51; base GD lesion ≥1; n=72
HR= 0.37 (0.16, 0.86)
FTY720 has lipophilic nature and so enters the brain, where S1P receptors are widely expressed.

- Release of neurotrophic factors promoting survival of neurons/oligodendrocytes
- Reactive gliosis/scar formation
- Antigen presentation/amplification of immune response
- Modulation of BBB permeability
- Release of cytokines and chemokines

Astrocytes
(S1P3>1>2>5)

Oligodendrocyte
(S1P5>1=2>3)
Produce myelin sheaths that insulate axons, ensuring efficient signal transmission

Neuron
(S1P1=3>2=5)

Microglia

Activation of astrocytes and microglia can result in either neuroprotective or neurotoxic/detrimental effects, or both.
Oral fingolimod versus placebo in primary progressive multiple sclerosis: results of the phase III INFORMS trial

Fred Lublin¹ and David H Miller², Mark S Freedman³, Bruce Cree⁴, Jerry S Wolinsky⁵, Howard L Weiner⁶, Catherine Lubetzki,⁷ Hans-Peter Hartung,⁸ Xavier Montalban,⁹ Bernard MJ Uitdehaag,¹⁰ Martin Merschhemke,¹¹ Bingbing Li,¹² Norman Putzki,¹¹ Dieter A Häring,¹¹ Ludwig Kappos¹³

1. Icahn School of Medicine at Mount Sinai, New York, USA
2. Queen Square MS Centre, UCL Institute of Neurology, UK
3. The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada
4. Multiple Sclerosis Center, University of California San Francisco, USA
5. University of Texas Health Science Center at Houston, Houston, USA
6. Brigham and Women’s Hospital, Harvard Medical School, Boston, USA
7. Hôpital de la Salpêtrière, Paris, France
8. Heinrich-Heine University, Department of Neurology, Düsseldorf, Germany
9. Hospital Universitari Vall d’Hebron, Barcelona, Spain
10. VU University Medical Center, Amsterdam, The Netherlands
11. Novartis Pharma AG, Basel, Switzerland
12. Novartis Pharmaceuticals Corporation, East Hanover, USA
13. University Hospital, Neurology, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University of Basel, Switzerland
Study design, eligibility, and baseline characteristics

- Multicenter, double-blind, placebo-controlled, parallel-group study to evaluate the effects of fingolimod 0.5 mg versus placebo on disability progression in patients with PPMS treated for at least 3 years.

- Key eligibility criteria:
  - Age of 25–65 years and ≥1 year of disease progression plus two of the following three criteria: positive brain MRI; positive spinal cord MRI; positive cerebrospinal fluid
  - Duration of disease of 2–10 years prior to study entry and an increase in the EDSS score ≥0.5 points in the past 2 years.
  - Objective evidence of disability: EDSS score of 3.5–6, pyramidal functional system score ≥2 and a 25’TWT <30 seconds.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fingolimod 0.5 mg (N=336)</th>
<th>Placebo (N=487)</th>
<th>Total (N=823)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>173 (51.5)</td>
<td>252 (51.7)</td>
<td>425 (51.6)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>48.5 (8.6)</td>
<td>48.5 (8.3)</td>
<td>48.5 (8.4)</td>
</tr>
<tr>
<td>Disease duration*, years</td>
<td>5.8 (2.5)</td>
<td>5.9 (2.4)</td>
<td>5.8 (2.4)</td>
</tr>
<tr>
<td>EDSS score</td>
<td>4.70 (1.03)</td>
<td>4.66 (1.03)</td>
<td>4.67 (1.03)</td>
</tr>
<tr>
<td>n, (%) free of Gd+</td>
<td>290 (86.3)</td>
<td>423 (87.4)</td>
<td>713 (87.0)</td>
</tr>
<tr>
<td>Total volume of T2 lesions, mm³</td>
<td>9442.7 (10179.7)</td>
<td>10038.2 (13030.9)</td>
<td>9794.5 (11943.48)</td>
</tr>
</tbody>
</table>

All values are Mean (SD) unless otherwise stated; *since onset of symptoms; EDSS: expanded disability status scale; SD: standard deviation; Gd: gadolinium; PPMS: primary progressive multiple sclerosis.
3-month CDP and MRI outcomes

**Primary: composite endpoint**

- At least one of 3 criteria:
  1) Increase in EDSS by 1 point in patients with a baseline EDSS score ≤5.0 or by 0.5 points in patients with a baseline EDSS score ≥5.5;
  2) ≥20% increase from baseline in the time taken to complete the 25'-TWT; 3) ≥20% increase from baseline in time taken to complete the 9-HPT

**CDP, confirmed disability progression**

**Key secondary: EDSS**

*Mean number of new/newly enlarging T2 lesions per year from Month 0 to Month 36

†Number of Gd-enhancing T1 lesions at Month 36

‡Percent change from baseline to Month 36

PBVC, percent brain volume change
Overall conclusions

- A novel functional composite endpoint was introduced to assess disability progression comprehensively
- INFORMS succeeded in recruiting an adequate population of PPMS patients and was sufficiently powered
- Efficacy:
  - Fingolimod 0.5 mg had no treatment effect on the risk of disability progression nor on BVL in this patient population
  - Although overall inflammatory activity as depicted by MRI was low, the effects on Gd-enhancing and T2 lesions were consistent with fingolimod RMS studies
  - Safety:
    - Despite the inclusion of older-aged patients with more advanced disability, the safety and tolerability results for fingolimod 0.5 mg in INFORMS were generally consistent with results from RMS trials
- Different therapeutic strategies may be required to treat PPMS

BVL: brain volume loss; PPMS: primary progressive multiple sclerosis; RMS: relapsing multiple sclerosis;
Dirucotide: MAESTRO

Figure 2: Kaplan-Meier plot of time to first confirmed progression

A

Probability of remaining progression free (%)

Month

Treatment (N): Placebo (252) MBP8298 (261)

70 (27.8) 80 (30.7)

p-value: 0.527
The phase 2—perhaps how not to do it

Figure 2 Time to first confirmed disease progression in a retrospectively identified group of patients with HLA-DR2 and/or DR4 haplotypes at 84 months. Event times for MBP8298 treated patients are shown in open symbols and for placebo-treated patients in filled symbols (n = 20, P = 0.004). Data from 24 to 84 months is
Reasons why drugs fail in progressive MS

1.- Pathogenic mechanisms in the progressive phase are completely different from those in the relapsing phase of MS

2.- Patients populations included in trials are not appropriate

3.-Clinical outcomes are not sensitive enough to detect the worsening of disease over this period of time
Algorithm for SPMS treatment

SPMS

Clinical/MRI activity

yes

no

Therapy!

Contraindications for IFNβ Hyperactive disease

Mitoxantrone (Other ISs?)

IFNβ/GA

response

no

yes

Continue therapy

response

yes

Continue therapy

no

Rituximab?
<table>
<thead>
<tr>
<th>Interventions in ongoing/planned phase III clinical trials in progressive multiple sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Axon outgrowth inhibitors</td>
</tr>
<tr>
<td>- Anti-nogo-a antibody</td>
</tr>
<tr>
<td>- Anti-lingo antibody</td>
</tr>
<tr>
<td>- Fingolimod</td>
</tr>
<tr>
<td>- Fumarate</td>
</tr>
<tr>
<td>- Laquinimod</td>
</tr>
<tr>
<td>- Magnetic /electrical brain stimulation</td>
</tr>
<tr>
<td>- Mesenchymal stem cells</td>
</tr>
<tr>
<td>- Natalizumab</td>
</tr>
<tr>
<td>- Ocrelizumab</td>
</tr>
</tbody>
</table>
Rationale for Natalizumab as a Treatment for SPMS

- SPMS is the result of accumulation of intrathecal inflammation
- Blocking VLA4 can reduce disease progression by interfering with the intrathecal immune response responsible for neurodegeneration
- CXCL13 is elevated in the brain and CSF of patients with SPMS; natalizumab reduces intrathecal levels of CXCL13
- Preliminary data from SPMS (relapsing and nonrelapsing) clinical trials suggest TYSABRI has beneficial effects

Progressor Analysis in Phase 2b SPMS Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 26)</th>
<th>TYSABRI (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressor</td>
<td>8 (31%)</td>
<td>8 (19%)</td>
</tr>
</tbody>
</table>

Progressor: SPMS patients with confirmed progression from baseline in EDSS, T25FW or 9-HP at 3, 6, 9 months

EDSS=Expanded Disability Status Scale; T25FW=timed 25-foot walk; 9-HP=9-hole peg test.
ASCEND SPMS Study Overview (Ph 3)

- **STUDY DESIGN:** Ongoing, phase 3, randomized, double-blind, placebo-controlled
- **PRIMARY OBJECTIVE:** Investigate whether treatment with natalizumab slows the accumulation of disability **NOT** related to relapses in subjects with SPMS
- **PRIMARY ENDPOINT:** Proportion of subjects experiencing confirmed progression of disability as measured by a composite endpoint (EDSS / T25FW / 9HPT)
- **KEY INCLUSION CRITERIA:** SPMS ≥2 years with EDSS 3.0 to 6.5 (inclusive)
- **KEY EXCLUSION CRITERIA:** RRMS & PPMS

Natalizumab is not approved for SPMS
### Ocrelizumab in PPMS
#### PhIII Study - Oratorio: study design

| **Design** | • Global, randomised, double-blind, placebo-controlled |
| **Treatment** | • Ocrelizumab: 2 × 300 mg (600 mg) iv q24w  
• Placebo |
| **Target sample size** | • 630 patients (2:1 randomisation) |
| **Primary end point** | Time to sustained disability progression, with confirmation occurring at least 12 weeks after initial disease progression |
| **Secondary end points** | • Time to confirmed disease progression, with confirmation occurring at least 24 weeks after initial disease progression  
• Change from baseline to Week 120 in the Timed 25-foot Walk  
• Change from baseline to Week 120 in the total volume of T2 lesions |
| **Study duration** | • Minimum 120-week treatment period |
Evolving Understanding of Pathways Mediating Physiological Effects of DMF

DMF

Immune Modulation

Cytoprotection

Nrf2

HCA2

Nrf2=nuclear factor (erythroid-derived 2)-like 2; HCA2=hydroxycarboxylic acid receptor 2.

Dimethyl Fumarate May Impact Multiple Sclerosis Pathophysiology at Multiple Points

- Reduced microglial activation
- Protection from oxidative stress
- Reduced axonal transection
- Reduced infiltration of immune cells into CNS
- Reductions in pro-inflammatory cytokines
- Protection against oxidative stress

Many of these functional effects require Nrf2

Th=T helper; BBB=blood-brain barrier; CNS=central nervous system; Nrf2=nuclear factor (erythroid-derived 2)-like 2 factor 2.

Dimethylfumarate in SPMS

• A phase III clinical trial is under consideration
LAQUINIMOD
MECHANISM OF ACTION

CNS Resident Cells
Oligodendrocytes-
Astrocytes-
Microglia-

Peripheral
Immune Cells

REDUCED
Astrocyte Activation,
Demyelination & Neuronal Loss

Laquinimod Targets

References:
5. Data on file, Teva Pharmaceuticals, Inc.
Effect of Laquinimod on demyelination in the cuprizone model

Brück et al., in revision
Effect of Laquinimod on human astrocytes

Courtesy of Gareth John, Mount Sinai, USA
Confirmed Disability Progression (CDP) in ALLEGRO/BRAVO Pooled Analyses

Laquinimod effect on CDP is large, consistent, and maintained for increasingly rigorous confirmation durations.
Based on the efficacy profile a phase II study in PPMS has been initiated
48-week dose-ranging (LAQ 0.6mg; LAQ 1.5 mg) placebo-controlled study in patients with PPMS

Sample size: 375 patients (125 per arm)

**Primary endpoint:** Percentage brain volume change (PBVC)

**Secondary endpoint:** EDSS-based confirmed disability progression
Future therapies: Neuroprotection

- Erythropoietin
- Lamotrigine
- Simvastatin
- Riluzole
- Amiloride
- Ibudilast
- Dronabinol
- Stem cells
- Axon outgrowth inhibitors
  - Anti Nogo-A antibody (GSK 1223249)
  - Anti LINGO antibody
- Magnetic / Electrical brain stimulation
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

Figure 2: Primary outcome
Mean partial (central) cerebral volume by intention-to-treat comparison, including numbers of valid 6-monthly observations. Bars=SE.
Lamotrigine-pseudoatrophy

CCV linear over time with modelled pivot at 6months
by tablet compliant comparison

Monthly mean EDSS
by ITT comparison

Monthly mean TWT
by ITT comparison

Bars show standard error around mean
Numbers of valid monthly observations shown

Kapoor 2010 Lancet Neurology
Amiloride

Targeting ASIC1 in primary progressive multiple sclerosis: evidence of neuroprotection with amiloride

Tarunya Arun,1,2,1 Valentina Tomassini,1,2,1 Emilia Sbardella,3,4,5 Michiel B. de Ruiter,2,6 Lucy Matthews,1,2,6 Maria Isabel Leite,7 Rose Gelineau-Morel,5,6 Ana Cavey,1,7 Sandra Vergo,1,7 Matt Craner,1,7 Lars Fugger,1,7 Alex Rovira,8 Mark Jenkinson1 and Jacqueline Palace1
Phenitoin (sodium channel blocker) started <15 days from onset of Optic Neuritis-ON protects axons from neurodegeneration

81 pts randomized within 14 days from ON
- 39 Ph 4 mg/kg/day
- 42 placebo) 3 mo

OCT: significant difference vs placebo
- protective treatment effect 30% RNFL, 34% macula

VEPs: n.s.

Vision recovered well in both groups
- No significant difference between treatments
Riluzole

- Phase IIa: 16 patients with Progressive MS were studied 1 year before treatment, followed by riluzole 50mg bd for 1 year.
- Primary outcome was change in cervical spinal cord cross-sectional area that showed a reduction from -2% (yr 1) to -0.2% (yr 2).
- In addition the increase in T1 hypointense lesion load was reduced from 15% in year 1 to 6% in year 2
- and reduction in whole brain parenchymal/intracranial volume went from -1.0% (yr 1) to -0.7% (yr2).

Effects of Riluzole on spinal cord area

Kalkers 2002
Riluzole in early MS: Phase II Study

MRI:

Study Drug:

Months:

Screen (4 weeks)  Riluzole/placebo (1:1) treatment period (up to 36 months)

IM INFB-1a treatment period (up to 33 months)

Endpoint  Efficacy Outcome Measures

Primary

Percent brain volume change (SIENA) (n=43)

Secondary

Changes in nGMV and nNAWMV (SIENAX), MSFC, SDMT, RNFL

Tertiary

Changes in cortical thickness, MV, cognition, EDSS, MFIS, MSQLI, low contrast vision, mfVEP, tissue banking
Secondary and Primary pRrogressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis

• 96-week, 250-subject, randomized, placebo-controlled phase II trial of ibudilast (PDE- and MIF-inhibitor) 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
• Utilizing NeuroNEXT, a US-based, NIH-funded Phase II clinical trial network
  • Head-to-head comparison of imaging measures
    – Longitudinal validation to clinical outcomes
## Why Simvastatin and MS?

### Oral simvastatin treatment in relapsing-remitting multiple sclerosis

*Timothy Vollmer, Lyndon Key, Valerie Durkalski, William Tyor, John Corboy, Silva Markovic-Plese, Jana Preiningerova, Marco Rizzo, Inderjit Singh*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Treatment</th>
<th>Average mean difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Gd-enhancing lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.31 (1.39)</td>
<td>1.30 (0.99)</td>
<td>-1.01 (1.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of new Gd-enhancing lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.37 (1.53)</td>
<td>0.71 (0.68)</td>
<td>-0.679 (1.54)</td>
<td>0.0295</td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Volume of Gd-enhancing lesions (mm³)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>234 (262)</td>
<td>139 (235)</td>
<td>-98.3 (183.8)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Median</td>
<td>172.5</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T2 lesion volume (mm³)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27,019 (23,871)</td>
<td>27,994 (26,284)</td>
<td>862.5 (4605.5)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Median</td>
<td>21,398</td>
<td>20,831</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Brain parenchymal fraction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.87 (0.041)</td>
<td>0.86 (0.040)</td>
<td>-0.002 (0.005)</td>
<td>0.0467</td>
</tr>
<tr>
<td>Median</td>
<td>0.88</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EDSS (mean)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yearly relapse rate (mean)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EDSS=expanded disability status score. *Primary outcome (per-protocol, n=28).

**MRI and clinical outcomes of participants**

*Lancet* 2004; **363**: 1607–08
Mechanism

- Adhesion molecules (such as LFA1)
- Chemokine receptors (such as CXCR3 and CCR5)

Endothelial cell
- eNOS and NO production
- AKT
- NF-κB
- RHO
- ROCK
- ICAM1-RHO pathway supporting lymphocyte migration
- MMPs
- Leukocyte motility and directionality

Lymphocyte
- NF-κB
- P-selectin

Monocyte
- PPARγ
- MMP9
- RAB GTPases
- RHOA–ROCK

Macrophage
- Free radicals
- MMPs
- Phagocytosis

Cytokines (such as IFNγ)
Chemokines (such as CCL2)
Chemokine receptors (such as CXCR3 and CCR5)
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 in means (95% CI)*</th>
<th>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)
Change in EDSS 0 to 24 months

Placebo

Statin

% patients

0

20

40

60

80

100

-1.5

-1

-.5

0

.5

1

1.5

2.5
Results summary

• Simvastatin had a significantly beneficial effect on:
  – Rate of whole brain atrophy (mean difference) -0.254%/year [95% CI -0.423 to -0.085] p=0.003
  – EDSS -0.254 [-0.464 to -0.069] p<0.01
  – MSIS-29 -4.78 [-9.39 to -0.02] p<0.05

• No evidence was seen for an effect on:
  – MSFC 0.289 [-0.333 to 0.961] p>0.05
  – Rate of new and enlarging T2 lesions IRR 0.72 [0.45 to 1.16] p=0.176
  – Rate of relapse IRR 1.29 [0.64 to 2.60] p=0.473
Autologous Stem Cell Transplantation

• No convincing evidence of efficacy in purely progressive MS for any type of stem-cell therapy
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

Summary

Background More than half of patients with multiple sclerosis have progressive disease characterised by accumulating disability. The absence of treatments for progressive multiple sclerosis represents a major unmet clinical need. On the basis of evidence that mesenchymal stem cells have a beneficial effect in acute and chronic animal models of multiple sclerosis, we aimed to assess the safety and efficacy of these cells as a potential neuroprotective treatment for secondary progressive multiple sclerosis.

Methods Patients with secondary progressive multiple sclerosis involving the visual pathways (expanded disability status score 5·5–6·5) were recruited from the East Anglia and north London regions of the UK. Participants received intravenous infusion of autologous bone-marrow-derived mesenchymal stem cells in this open-label study. Our primary objective was to assess feasibility and safety; we compared adverse events from up to 20 months before treatment until up to 10 months after the infusion. As a secondary objective, we chose efficacy outcomes to assess the anterior visual pathway as a model of wider disease. Masked endpoint analyses was used for electrophysiological and selected imaging outcomes. We used piecewise linear mixed models to assess the change in gradients over time at the
LINGO-1: CNS-Specific Gene

Leucine Rich Repeat  Immunoglobulin-like domain

LINGO-1

1: Brain
2: Colon
3: Heart
4: Kidney
5: Liver
6: Lung
7: Muscle
8: Placenta
9: Small Intestine
10: Spleen
11: Stomach
12: Testis

Actin

4.4k
2.4k

CNS=central nervous system.

Anti-LINGO-1 is not approved.
Anti-LINGO-1 Antagonist Antibodies Promote Remyelination

Anti-LINGO-1 Phase II Clinical Development Plan

**RENIEW**

Acute Optic Neuritis
- Placebo-controlled proof of concept
- Subjects with recent first episode of acute optic neuritis
  - Dose: 100 mg/kg q4wks × 6
- Endpoints:
  - Visual evoked potential (VEP)/multifocal VEP (latency delay)
  - Optical coherence tomography (retinal nerve fiber and ganglion cell layer loss)
  - Visual function (low contrast letter acuity, visual quality of life)

**SYNERGY**

Relapsing Forms of MS
- Placebo-controlled proof of concept and dose ranging
- Subjects with RRMS and active SPMS receiving IM IFNβ-1a
  - Dose: 3, 10, 30, 100 mg/kg q4wks × 18
- Physical and cognitive endpoints:
  - EDSS/T25FW/9HPT/PASAT composite
    - Primary=improvement
    - Key secondary=delayed progression
    - MS-COG
  - MRI (MTR, DTI, black holes, atrophy)

q4wks=every 4 weeks; IM=intramuscular; IFNβ=interferon beta; EDSS=Expanded Disability Status Scale; T25FW=Timed 25-Foot Walking Test; 9HPT=9-Hole Peg Test; PASAT=Paced Auditory Serial Addition Test; MRI=magnetic resonance imaging; MTR=magnetization transfer ratio; DTI=diffusion tensor imaging.

ClinicalTrials.gov Identifiers: RENEW: NCT01721161; SYNERGY: NCT01864148.

BIIB033 (Anti-LINGO-1) is not approved for MS.
Change* in mfVEP latency (substudy) vs. FF-VEP latency (primary endpoint) at Week 24 in the affected eye compared with the unaffected fellow eye at Baseline

mfVEP substudy

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted Mean Change in mfVEP Latency, ms</th>
<th>CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>14.01 (n=15)</td>
<td>-24.28 to 0.73</td>
<td>0.06</td>
</tr>
<tr>
<td>Anti-LINGO-I</td>
<td>17.49 (n=21)</td>
<td>-16.03 to 6.09</td>
<td>0.37</td>
</tr>
</tbody>
</table>

FF-VEP (primary endpoint)

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted Mean Change in FF-VEP Latency, ms</th>
<th>CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>22.46 (n=18)</td>
<td>-15.12 to 0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Anti-LINGO-I</td>
<td>22.24 (n=36)</td>
<td>-10.61 to 3.65</td>
<td>0.33</td>
</tr>
</tbody>
</table>

CI = confidence interval. *Adjusted for the baseline latency of the unaffected fellow eye. (by ANCOVA)
Future

- We should consider other CNS cell types as primary targets for development of therapeutics in progressive MS
- Microglia, astrocytes or infiltrated myeloid APCs are valid and promising targets
- We should initiate protective treatments in MS patients when the disease is still relapsing remitting
New Perspectives

Setting a research agenda for progressive multiple sclerosis: The International Collaborative on Progressive MS

Robert J. Fox¹, Alan Thompson², David Baker³, Peer Baneke⁴, Doug Brown³, Paul Browne⁴, Dhia Chandraratna⁴, Olga Ciccarelli², Timothy Coetzee⁴, Giancarlo Comi⁷, Anthony Feinstein⁸, Raj Kapoor⁹, Karen Lee¹⁰, Marco Salvetti¹¹, Kersten Sharrock¹², Ahmed Toosy², Paola Zaratin¹³ and Kim Zuidwijk¹⁴