Clinical trials in secondary and primary progressive MS
Current challenges and future directions

Alan Thompson
UCL and MSIF
16th State of the Art Symposium
Lucerne January 2014
• Introduction

• Challenges

• Current activity

• Future directions
SPMS (and PPMS) represents a significant unmet clinical need.

Why such failure with Prog MS?

10 FDA-approved therapies

1 FDA-approved therapy (mitoxantrone - rarely used)
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.

**Figure 2** Aages at attainment of disability endpoints according to type of disease course.

<table>
<thead>
<tr>
<th>Age at</th>
<th>OPP</th>
<th>p</th>
<th>DSS 3</th>
<th>p</th>
<th>DSS 6</th>
<th>p</th>
<th>DSS 8</th>
<th>p</th>
<th>DSS 10</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR/SP</td>
<td>40.2 (39)</td>
<td>0.09</td>
<td>41.6 (41)</td>
<td>0.82</td>
<td>49.7 (48)</td>
<td>0.05</td>
<td>59.2 (58)</td>
<td>0.44</td>
<td>76.1 (78)</td>
<td>0.63</td>
</tr>
<tr>
<td>PP</td>
<td>38.6 (40)</td>
<td></td>
<td>42.3 (43)</td>
<td></td>
<td>48.0 (49)</td>
<td></td>
<td>58.4 (58)</td>
<td></td>
<td>73.8 (78)</td>
<td></td>
</tr>
</tbody>
</table>

Scalfari et al Neurology 2011
How the James Lind Alliance Works

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.
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?
1. Delayed Progression

2. Stabilised Progression

3. Improved Function

4. Recovered Function
WHAT ARE YOUR EXPECTATIONS OF A THERAPY FOR PROGRESSIVE MS?

- Recovery: 18%
- Improvement: 18%
- Stable: 44%
- Slowed: 20%

www.ms-res.org
Multiple Sclerosis: Prospects and Promise

Stephen L. Hauser, MD, Jonah R. Chan, PhD, and Jorge R. Oksenberg, PhD
Efforts Underway

2012 Global Progressive MS Portfolio

$85.5 M USD

Targets-Pathways: 117
Symptoms-Rehabilitation: 39
POC-Clinical Outcomes: 43
Experimental models: 4

Plus ~45 interventional clinical trials currently recruiting patients (www.clinicaltrials.gov)
• Introduction

• Challenges

• Current activity

• Future directions
Challenges

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

Progressive MS is defined differently from different perspectives

- **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
Multiple Sclerosis Phenotypes: Toward More Biologically-Relevant Definitions
New York City – 26/27 October 2012

A Project of the International Advisory Committee on Clinical Trials in MS

Sponsored by the National Multiple Sclerosis Society (NMSS) and the European Committee for Treatment and Research in MS (ECTRIMS)
Main conclusions

• Relapsing/Remitting, Primary Progressive, Secondary Progressive
• Active/in-active
• Progressing/non-progressing
• Terms
  => replace sustained with confirmed
  => selective use of term “Progressing”
Possible pathological correlates of progression

- Slowly expanding pre-existing lesions
- Persistent microglial activation
- Compartmentalized inflammation
- B cell/antibody involvement
- Remyelination failure
- Axonal/neuronal loss
- Cortical/gray matter involvement
- Changes in the NAWM
Key areas

- Inflammation
- White matter demyelination/remyelination
- Gray matter involvement
- Axonal loss
MRI in primary progressive MS

• 42% patients with early PPMS (< 5 years) had at least one enhancing lesion on their baseline scan

• Number of enhancing lesions associated with
  - younger age ($r=0.5$, $p=0.003$)
  - higher T2 load ($r=0.5$, $p=0.02$)
  - worse outcome!
Inflammation behind a closed (repaired) blood–brain barrier

Compartmentalized inflammation in progressive MS

Bradl and Lassmann, Semin Immunopathol 2009
Pathologic Mechanisms in Early vs. Late MS
Key areas

- Inflammation
- White matter demyelination/remyelination
- Gray matter involvement
- Axonal loss
More extensive spinal cord demyelination in SPMS compared to PPMS

Tallantyre et al., Brain 2009
Key areas

- Inflammation
- White matter demyelination/remyelination
- Gray matter involvement
- Axonal loss
Cortical demyelination is extensive in progressive MS

<table>
<thead>
<tr>
<th></th>
<th>Cortical lesion area forebrain (%)</th>
<th>White matter lesion area (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS</td>
<td>2.96</td>
<td>10.3</td>
</tr>
<tr>
<td>PPMS</td>
<td>12.54</td>
<td>6.54</td>
</tr>
<tr>
<td>SPMS</td>
<td>13.29</td>
<td>24.13</td>
</tr>
</tbody>
</table>

Kutzelnigg et al., Brain 2005
High cortical lesion load at baseline
High number of new CLs
High rate of GM atrophy progression
Characterize patients with disability progression after 5 yrs
Key areas

- Inflammation
- White matter demyelination/remyelination
- Gray matter involvement
- Axonal loss
Spinal cord axonal loss correlates with disease duration and disability

Schirmer et al., Brain Pathol 2011
Greater axonal loss in PPMS spinal cord

Tallantyre et al., Brain 2009
Neurodegeneration in MS

Inflammation

Trigger?

Microglia / Astroglia Activation

Oxidative Burst

ROS / RNI production

Liberation of Free Iron from Cellular Stores

Microglia activation due to pre-existing CNS damage

Mitochondrial Injury / Energy Deficiency

PARP / AIF

DNA Damage

Tissue Degeneration
  Oligodendrocytes > thin axons > neurons > others

Functional Disturbance
Outcomes/Biomarkers

- Clinical
- Imaging
- OCT
- CSF/Serum
MS Outcomes Assessments Consortium (MSOAC)

- Collaboration of academic, industry, regulatory, and patient-advocacy representatives
- Supported by the US National MS Society
- Coordinated by the C-Path - a nonprofit, public-private partnership with the Food and Drug Administration (FDA), created in 2005 under the auspices of FDA's Critical Path Initiative.
- Mission: to develop, gain regulatory approval, and support adoption of a new clinician-reported outcome measure for use in future MS clinical trials
Multiple Sclerosis Outcome Assessments Consortium: Genesis and initial project plan

Richard A Rudick¹, Nicholas LaRocca², Lynn D Hudson³ and MSOAC
Spinal fluid neurofilament levels

$r_s = 0.54$
$p < 0.01$

EDSS 3 year follow up

Natalizumab treatment of progressive multiple sclerosis reduces inflammation and tissue damage

- results of a phase 2A proof-of-concept study

J. Romme Christensen¹, R. Ratzer¹, L. Børnsen¹, E. Garde², M. Lyksborg², H.R. Siebner², T.B. Dyrby², P. Soelberg Sørensen¹ and F. Sellebjerg¹
Phase 2A study: CSF markers of axonal damage and demyelination (secondary endpoints)

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
The interim measure
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
• Introduction

• Challenges

• Current activity

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# Table 2A: 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); activities 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></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></td>
<td>2001</td>
</tr>
<tr>
<td>IMPACT</td>
<td>436</td>
<td>2</td>
<td>3.5-6.5</td>
<td>Avonex (60mcg/wk)</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 SMU/m2 alternate days</td>
<td>Time to confirmed EDSS worsening</td>
<td>-ve</td>
<td></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></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></td>
<td>2011</td>
</tr>
</tbody>
</table>

# Table 2B: 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>
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

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

HR: 0.77
(95% CI: 0.55 - 1.09)
p-value=0.1442

Time to Confirmed Disease Progression

Proportion of Patients

Rituximab
Placebo

Time to Confirmed Disease Progression (weeks)
**Proportion of Patients**

**Rituximab**

**Placebo**

**Time to Confirmed Disease Progression (weeks)**

**Subgroup Analysis**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Rituximab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
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<tr>
<td>48</td>
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<tr>
<td>60</td>
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<tr>
<td>72</td>
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</tr>
<tr>
<td>84</td>
<td></td>
<td></td>
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<tr>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>108</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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**

**Time to Confirmed Disease Progression (weeks)**
Phenytoin Optic Neuritis Study (Phase II)
PROXIMUS Trial - oxcarbazepine in SPMS (Phase II)
INFORMS – fingolimod in SPMS (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
| **Design** | • Global, randomised, double-blind, placebo-controlled of 120 weeks duration |
| **Treatment** | • Ocrelizumab: 2 × 300 mg (600 mg) iv q24w v Placebo |
| **Target sample size** | • 630 patients (2:1 randomisation) |
| **Primary end point** | Time to sustained disability progression, with confirmation at least 12 weeks after initial disease progression |
| **Secondary end points** | • Time to confirmed disease progression, with confirmation at least 24 weeks after initial disease progression  
• Change from baseline to Week 120 in 25-foot Walk  
• Change from baseline to Week 120 in the total volume of T2 lesions |
MS-STAT trial

High dose oral Simvastatin in Secondary Progressive Multiple Sclerosis

Jeremy Chataway

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

• EDSS 4.0 (500m) - 6.5 (20m/2 sticks)
  – Relapse free/no corticosteroids >3 months
  – DMT >6months
  – 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>Change WBV (%/year)</th>
<th>Mean (SD) placebo</th>
<th>Mean (SD) simvastatin</th>
<th>Difference means (95% CI)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></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 from Baseline to 24 months

**Placebo**
- 0 patients
- 5% patients
- 10% patients
- 15% patients
- 20% patients
- 25% patients
- 30% patients
- 35% patients
- 40% patients
- 45% patients
- 50% patients
- 55% patients
- 60% patients
- 65% patients
- 70% patients
- 75% patients
- 80% patients
- 85% patients
- 90% patients
- 95% patients
- 100% patients

**Statin**
- 0 patients
- 5% patients
- 10% patients
- 15% patients
- 20% patients
- 25% patients
- 30% patients
- 35% patients
- 40% patients
- 45% patients
- 50% patients
- 55% patients
- 60% patients
- 65% patients
- 70% patients
- 75% patients
- 80% patients
- 85% patients
- 90% patients
- 95% patients
- 100% patients

**Legend**:
- -1.5
- -1
- -.5
- 0
- .5
- 1
- 1.5
- 2.5
Cannabinoid trials

12 month follow-up (80%)

N=657 CAMS

Zajicek Lancet 2003; JNNP 2005
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

• assess the value of Δ⁹-THC in slowing progressive MS over 3 yrs
• assess the safety of Δ⁹-THC over the long-term.
• improve research methodology; using new, patient-orientated methods.
CUPID (THC): EDSS progression over 3 years

Zajicek J, et al. ECTRIMS 2012: Oral presentation 161X.
CUPID (THC): EDSS progression according to baseline EDSS score.

Baseline EDSS score:
- 4
- 4.5
- 5
- 5.5
- 6
- 6.5

P (EDSS progression)

Time to EDSS progression (days)

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

Log rank test $P = 0.01$

P (EDSS progression) vs. Time to EDSS progression (days)

Treatment group:
- Active
- Placebo

$n = 110$

• Introduction

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Neuroprotection

Repair/Remyelination

Lifestyle

Rehabilitation

Enhancing plasticity
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.
MS-STOP>>MS-SMART

4 arms [1 placebo + 3 active]
Multiplex Phase IIb trial

- 4*110=440
- allowing for drop-outs [10%+10%]
- Primary outcome = SIENA PBVC
- Gives 90% power for 35% treatment effect
<table>
<thead>
<tr>
<th>Repurposed Drug For MS</th>
<th>Approved in other clinical Indications</th>
<th>POC in MS Patients</th>
<th>POC in other Neurodegenerative Diseases</th>
<th>MS Animal Model Data</th>
<th>Putative Neuroprotective mechanism</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibudilast [MN-166; AV-411] (MediciNova Inc)</td>
<td>Used in asthma and post-stroke disorders in Japan for ~ 20 years</td>
<td>YES (Phase IIa Trial)</td>
<td></td>
<td></td>
<td>Suppresses TNFalpha production by glial cells functioning mainly as type III Phosphodiesterase inhibitor in CNS. Neuroprotective role on neuronal cell death induced by activated microglia</td>
<td>Barkhof F. Neurol 2010; 74,1033–1040</td>
</tr>
<tr>
<td>Riluzole [Rilutek] (Sanofi-Aventis)</td>
<td>Used for Amyotrophic lateral sclerosis (ALS), also referred to as Lou Gehrig's disease / motor neurone disease</td>
<td>YES</td>
<td>YES</td>
<td>Preferentially blocks TTX-sensitive sodium channels, which are associated with damaged neurons. This reduces influx of calcium ions and indirectly prevents stimulation of glutamate receptors.</td>
<td>Killestein J. J. Neurol Sci 2005</td>
<td></td>
</tr>
</tbody>
</table>
Amiloride blockade of the acid-sensing ion channel is myelo- and neuro-protective in CNS inflammation.

Acid-sensing ion channel 1 is involved in both axonal injury and demyelination in multiple sclerosis and its animal model.

Sandra Vergo, Matthew J. Craner, Ruth Etzensperger, Kathrine Altfield, Manuel A. Friese, Jia Newcombe, Margaret Esiri and Lars Fugger
Amiloride treatment in primary progressive MS

Atrophy rate reduced in amiloride treated (p = 0.018)

Amiloride reduced rate of white and grey matter damage (p < 0.01)

Slide courtesy of M Craner
• Phosphodiesterase and MIF inhibitor

• Placebo-controlled 2 year trial, mainly RRMS, 100 per arm

• No effect on new Gd, T2 lesions or relapses

• Significant decrease in
  – Brain atrophy (30%)
  – EDSS progression

Barkhof et al Neurology 2010
Secondary and Primary Progressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis

- 96-week, 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
- Utilize NeuroNEXT, an US-based, NIH-funded Phase II clinical trial network
Visual Outcomes in SPRINT-MS

- Primary OCT outcome: mean change in peripapillary RNFL
- Cirrus or Spectralis SD-OCT at all sites
  - 5 time points: Screening, W24, W48, W72, W96
  - Acquisitions: Peripapillary/Optic Disc and Macular
  - Central OCT Reading Center (R. Bermel, Cleveland Clinic)
- Exploratory outcomes:
  - ganglion cell layer thickness
  - total macular volume
  - macular RNFL
- Correlation with visual acuity
  - 100% and 2.5% contrast
An exploratory phase IIa study to evaluate phenytoin as neuroprotective strategy in acute optic neuritis

1. <14 days since symptom onset
2. Visual acuity worse than or equal to 6/9 in affected eye
3. No history of optic neuritis or disease in either eye; corrected VA in unaffected eye better than or equal to 6/6
4. If patients have MS EDSS 3.5 or less

Informed consent

Patients can be offered at the discretion of the treating physician treatment with a short course of steroids

PHENYTOIN
Randomised acutely (<14 days) to phenytoin* or placebo
*acute oral loading dose (15mg/kg rounded up to nearest 100mg) followed by maintenance dose 4mg/kg (rounded up to the nearest 50mg) or maximum 300mg/day for 14 weeks
Randomisation based on minimisation via web

Further investigations and baseline MRI brain within 28 days of symptom ONSET

Alternative diagnosis

Not part of ITT cohort

Primary outcome at 26 weeks
Retinal nerve fibre thickness in affected eye

Secondary outcomes at 48 weeks
Low contrast visual acuity
Visual evoked potential latency and amplitude
MRI outcomes
Blood and urine Biomarkers
Safety profile

Estimated power calculations*

<table>
<thead>
<tr>
<th>Clinical Classification</th>
<th>Placebo 1</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative diagnosis</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>ITT population</td>
<td>45</td>
<td>45</td>
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<td></td>
<td>45</td>
<td>45</td>
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</tbody>
</table>

* Data from a longitudinal study of OCT findings obtained in 12 patients with acute demyelinating optic neuritis who were followed serially from initial presentation for 10-18 months at Moorfields Eye Hospital and the Institute of Neurology (A Henderson, D Artioli, S Stanley-Whitmarsh and D Miller, unpublished) was used to calculate the sample size, based on the most efficient analysis of data on the primary outcome with a power of 80% to detect a treatment effect of 50% at 5% significance level, allowing for a combined loss to follow-up and non-adherence of 10%
## 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>
</tr>
<tr>
<td>Riordan 2009</td>
<td>Treatment-refractory MS</td>
<td>3</td>
<td>Autologous non-expanded adipose MSCs</td>
</tr>
<tr>
<td>Yamout 2010</td>
<td>SPMS</td>
<td>10</td>
<td>Autologous culture-expanded BM MSCs administered IT</td>
</tr>
</tbody>
</table>
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

Lancet Neurology Feb 2012

10 patients with secondary progressive MS
Studied visual system
• 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)

Autologous mesenchymal stem cells in secondary progressive MS

Connick et al Lancet Neurology 2012
• 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
Centralized protocol, inclusion / exclusion criteria and outcomes adopted by international clinical centers

Robust sample size (~160 subjects) to get conclusive data on the safety and efficacy of MSCT in MS.

Number of centers involved ( ≥10 )

Duration of the study: two years (including enrollment)

Contract Research Organization (CRO) for data collection

Clinical Research Associate (CRA) to support coordination

Centralized MRI reading

Blinded centralized data analysis
Disease-modifying treatments for progressive multiple sclerosis

Giancarlo Comi

Abstract
The last 20 years have seen major progress in the treatment of relapsing–remitting multiple sclerosis (RRMS) using a variety of drugs targeting immune dysfunction. In contrast, all clinical trials of such agents in primary progressive multiple sclerosis (PPMS) have failed and there is limited evidence of their efficacy in secondary progressive disease. Evolving concepts of the complex interplay between inflammatory and neurodegenerative processes across the course of multiple sclerosis (MS) may explain this discrepancy. This paper will provide an up-to-date overview of the rationale and results of the published clinical trials that have sought to alter the trajectory of both primary and secondary MS, considering studies involving drugs with a primary immune target and also those aiming for neuroprotection. Future areas of study will be discussed, building on these results combined with the experience of treating RRMS and new concepts emerging from laboratory science and animal models.
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 Chandraratna⁷, Olga Ciccarelli², Timothy Coetzee⁸, Giancarlo Comi⁷, Anthony Feinstein⁹, Raj Kapoor⁹, Karen Lee¹⁰, Marco Salvetti¹¹, Kersten Sharrock¹², Ahmed Toosy², Paola Zaratín¹³ and Kim Zuidwijk¹⁴
Initial discussions identified 5 priority areas:

- Experimental Models
- Target pathways and drug repurposing
- Proof of concept trials (phase II)
- Phase III clinical trials & outcome measures
- Symptom management and rehabilitation
Research community engagement – working groups to fill gaps, propose strategies and funding models

First International Scientific Conference on Progressive MS

Working groups present recommendations to Steering committee

First Request for Applications (RFA) by Alliance
Scientific Steering Committee

* Alan Thompson, UK, Chair
* Timothy Coetzee, USA
* Kathy Smith, USA
* Paola Zaratin, Italy
Peer Baneke, MSIF
* Ceri Angood, MSIF
* Susan Kolhaas, UK
Inga Huitinga, Netherlands
* Karen Lee, Canada
Giancarlo Comi, Italy, co-Chair
* Bruce Bebo, USA
Robert Fox, USA
Marco Salvetti, Italy
* Dhia Chandraratna, MSIF
Nick de Rijke, UK
Raj Kapoor, UK
Kim Zuitwijk, Netherlands
Anthony Feinstein, Canada
Countries actively involved in the Alliance
REQUEST FOR APPLICATIONS (RFA)

CHALLENGES IN PROGRESSIVE MS AWARDS - encourage scientific innovation in:

• Phenotype/Genotype and pathophysiological mechanisms

• Development of new and existing pre-clinical models for progressive disease based on community consensus building

• Discovery and validation of proof of concept biomarkers

• Innovative designs for proof of concept trials of therapeutic agents or therapeutic strategies
2. INFRASTRUCTURE AWARDS - to develop enabling technologies and infrastructure for data sharing to:

• promote and enhance data sharing and knowledge management

• encourage collaboration among researchers

• support one or more of the Alliance priority research areas

Awards - €75,000 for 12 months
REQUEST FOR APPLICATIONS (RFA)

APPLICATIONS DUE
31 January 2013

PRE-APPLICATIONS DUE
15 January 2013

ANNOUNCEMENT OF DECISIONS
May 2014

START
July 2014

http://www.endprogressivems.org
Long term commitment towards PMSA goal

2013 – 2021 PLAN

2013 – 2017 HORIZON 1

CHALLENGES AWARDS 2013 - 2016

COLLABORATIVE TEAM AWARDS 2014 - 2017

2017 – 2021 HORIZON 2/3

INNOVATIVE OPERATIVE FUNDING MODELS TO ACCELERATE RESEARCH

INTERNATIONAL PROGRESSIVE MS ALLIANCE
CONNECT TO END PROGRESSIVE MS

PROGRESSIVE MS ALLIANCE MANAGING MEMBERS

LONG TERM COMMITMENT TOWARDS PMSA GOAL
Challenges ahead

• Understand relevant aspects of human MS pathology
  – Validate a pre-clinical model that emulates human pathology
  – Develop high throughput screening tools
• Validate a Phase II outcome biomarker
  – Use trials to advance methodology
• Develop accepted clinical outcome measures
• Not forget about symptomatic treatments
• Expand international collaboration