Never stop trying to stop MS

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worldMSday
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Disclosures

PI of trials sponsored by Novartis, Roche, Teva, Medday.

Involved in trials sponsored by Biogen, Genzyme, BIAL, Cytokinetcs, Canbex.

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Disability accrual in MS: The EDSS

- Normal neurological examination
- No disability
- Minimal disability
- Moderate disability
- Relatively severe disability
- Disability precludes full daily activities
- Assistance required to walk
- Restricted to a wheelchair
- Restricted to bed or chair
- Confined to bed
- Death

- 0.0
- 1.0
- 2.0
- 3.0
- 4.0
- 5.0
- 6.0
- 7.0
- 8.0
- 9.0
- 10.0

- 8 y
- 20 y
- 30 y
Brain atrophy: across all stages

n= 963 pwMS

Exploring anatomical correlates of advanced MS

Schmierer-lab, Blizard Institute, QMUL
Giemsa

MBP

- 39%
Grey matter volume loss and disability

**Table 3. Correlations of Brain Volume Measurements with Clinical Features**

<table>
<thead>
<tr>
<th></th>
<th>EDSS (n = 73)(^a)</th>
<th>MSFC (n = 67)(^a)</th>
<th>Z-PEG (n = 70)(^a)</th>
<th>Z-WALK (n = 68)(^a)</th>
<th>Z-PASAT (n = 68)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMF(^a)</td>
<td>-0.48 (&lt;0.001)</td>
<td>0.56 (&lt;0.001)</td>
<td>0.59 (&lt;0.001)</td>
<td>-0.40 (0.001)</td>
<td>0.27 (0.026)</td>
</tr>
<tr>
<td>GMF(^b)</td>
<td>-0.41 (0.005)</td>
<td>0.55 (&lt;0.001)</td>
<td>0.44 (0.003)</td>
<td>-0.49 (0.001)</td>
<td>0.32 (0.038)</td>
</tr>
<tr>
<td>WMF(^a)</td>
<td>-0.20 (0.086)</td>
<td>0.03 (0.784)</td>
<td>0.16 (0.176)</td>
<td>-0.11 (0.337)</td>
<td>-0.07 (0.537)</td>
</tr>
<tr>
<td>WMF(^b)</td>
<td>-0.11 (0.443)</td>
<td>0.10 (0.526)</td>
<td>0.28 (0.071)</td>
<td>-0.09 (0.560)</td>
<td>-0.04 (0.761)</td>
</tr>
</tbody>
</table>

\(^a\)All patients.
\(^b\)Multiple sclerosis (MS) subgroup only.
rs = Spearman’s rank correlation coefficient; EDSS = expanded disability status scale; MSFC = multiple sclerosis functional composite score; GMF = gray matter fraction; WMF = white matter fraction.

n= 73 patients with initial diagnosis CIS, followed up for 20 years

1. Raise awareness of the global burden of MS
2. Speed up referral and diagnosis
3. Intervene early to maximize lifelong brain health
4. Monitor disease activity and treat to a target
5. Act swiftly on the evidence of disease activity
6. Take a comprehensive economic approach to evaluating treatment cost-effectiveness

7. Never stop trying to stabilize/improve brain health
Only one “window of therapeutic opportunity”?


Disease duration:
- SPMS: 11.2 years (6.1)
- EDSS: 5.8 (0.8)
- Relapsing MS: 2.7 years (2.9)
- EDSS: 4.8 (2)

n= 718 pwMS who reached both DSS 3 and DSS 6
Review article

Is multiple sclerosis a length-dependent central axonopathy? The case for therapeutic lag and the asynchronous progressive MS hypotheses

Gavin Giovannoni\textsuperscript{a,∗}, Gary Cutter\textsuperscript{b}, Maria Pia-Sormani\textsuperscript{c}, Shibeshih Belachew\textsuperscript{d}, Robert Hyde\textsuperscript{e}, Harold Koendgen\textsuperscript{e}, Volker Knappertz\textsuperscript{f}, Davorka Tomic\textsuperscript{g}, David Leppert\textsuperscript{g}, Robert Herndon\textsuperscript{h}, Claudia A.M. Wheeler-Kingshott\textsuperscript{i}, Olga Ciccarelli\textsuperscript{ij}, David Selwood\textsuperscript{k}, Elisabetta Verdun di Cantogno\textsuperscript{l}, Ali-Frederic Ben-Amor\textsuperscript{l}, Paul Matthews\textsuperscript{m}, Daniele Carassiti\textsuperscript{a}, David Baker\textsuperscript{a}, Klaus Schmieder\textsuperscript{a}
Length dependency and neuroanatomy

55% of cortico-spinal tract axons terminate at the cervical level.

An Exploratory Analysis of 12- and 24-Week Confirmed Composite Disability Progression in Patients With Primary Progressive Multiple Sclerosis in the ORATORIO Trial

Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis


Case study – treating progressive MS

- 38 years old woman of Afro-Caribbean extraction
- Diagnosed with primary progressive MS in 2009
- Enrolled in trial of fingolimod (INFORMS) in 2011
- Examination at baseline: brain stem signs (bilateral INO), hemiparesis on right, walking range 100-200m. EDSS = 5.5.

Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial

Fred Lublin*, David H Miller*, Mark S Freedman, Bruce A C Cree, Jerry S Wolinsky, Howard Weiner, Catherine Lubetzki, Hans-Peter Hartung, Xavier Montalban, Bernard MJ Uitdehaag, Martin Merschhemke, Bingbing Li, Norman Pützki, Fonda C Liu, Dieter A Häring, Ludwig Kappos, on behalf of the INFORMS study investigators†

Lancet 2016;387:1075-84.
Case study – treating progressive MS

EDSS

Case study – treating progressive MS

EDSS = 8

EDSS = 7

A highly significant association between inflammation and axonal injury was seen in the global multiple sclerosis population as well as in progressive multiple sclerosis alone... [suggesting] a close association between inflammation and neurodegeneration in all lesions and disease stages of multiple sclerosis.
Defining the clinical course of sclerosis
The 2013 revisions

Fred D. Lublin, MD
Stephen C. Reingold, PhD
Jeffrey A. Cohen, MD
Gary R. Curter, PhD
Per Soelberg Sorensen, MD, DMSc
Alan J. Thompson, MD
Jerry S. Wolinsky, MD
Laura J. Balcer, MD, MSCE
Brenda Banwell, MD
Frederik Barkhof, MD, PhD
Bruce Bebo, Jr., PhD

ABSTRACT
Accurate clinical course descriptions (phenotypes) of multiple sclerosis (MS) are essential for communication, prognostication, design and recruitment in clinical trials. Standardized descriptions published in the latest edition of the Expanded Disability Status Scale (EDSS) and other scales reflect more recently identified clinical subtypes as re-evaluation of MS disease phenotypes by the Internet Trials of MS. While imaging and biological markers that separate clinical phenotypes are lacking, we propose that the new World MS Order: MS clinical description Subtypes 1996 MS clinical description Subtypes

Progressive accumulation of disability from onset with or without temporary plateaus, minor remissions and improvements

PP 1996 MS clinical description Subtypes

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

SP 2013 MS disease modifiers Phenotypes

Progressive accumulation of disability from onset

Active* and with progression**

PP

Progressive accumulation of disability after initial relapsing course

Not active but with progression

SP

Progressive accumulation of disability from onset but clear acute clinical attacks with or without full recovery

PR

Progressive accumulation of disability after initial relapsing course

Not active and without progression (stable disease)
Start DMT as early as possible

1. Without intervention ~40% of cortical neurons are being lost over a lifetime with MS. The start of this loss from the earliest disease stages can be inferred from indices of brain volume, notably the cortical ribbon.

2. Gd⁺ lesions do not define primary progressive versus other phenotypes of MS.

3. Absence of new/Gd⁺ lesions does not necessarily mean there is no inflammation.

4. To establish efficacy in advanced MS, outcomes need to be used that are sensitive to functions which can be protected/recovered, such as upper limb dexterity, swallowing, speech, cognition.

5. Whilst “early” DMT promises a life relatively unaffected by MS over many years, evidence suggests DMT are effective in reducing disability accrual at more advanced stages of MS too.

6. When shifting the focus on “early DMT” a trade-off against people with more advanced disease, who may also benefit from DMT, needs to be avoided.
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