For HCPs

Brain Health: Time Matters

Gavin Giovannoni
Barts and The London
Disclosures

Professor Giovannoni has received personal compensation for participating on Advisory Boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from: Abbvie, Bayer-Schering Healthcare, Biogen-Idec, Canbex, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, GW Pharma, Ironwood, Merck-Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB Pharma and Vertex Pharmaceuticals.

Regarding www.ms-res.org survey results in this presentation: please note that no personal identifiers were collected as part of these surveys and that by completing the surveys participants consented for their anonymous data to be analysed and presented by Professor Giovannoni.

Professor Giovannoni would like to acknowledge several companies and colleagues for making available data slides for this presentation.
Who should take responsibility?

- The person with MS?
- The HCP or neurologist?
- The healthcare system?
- The regulators?
- Society?

HCP, healthcare practitioner; MS, multiple sclerosis.
Brain reserve and cognitive reserve in MS

**Brain reserve protects against disease-related cognitive decline**

**Cognitive reserve independently protects against disease-related cognitive decline over and above brain reserve**

MS, multiple sclerosis; T2LL, T2 lesion load.
Consequences of increasing EDSS scores: loss of employment

The proportion of MSers employed or on long-term sick leave is calculated as a percentage of MSers aged 65 or younger.

Impact of MS: cognitive functioning in the CIS stage

Deficits were found mainly in memory, speed of information processing, attention and executive functioning

Patients failing ≥ 2 cognitive tests

CIS Patients: n = 40

Healthy Controls: n = 30

57% of CIS Patients fail 2 or more cognitive tests

7% of Healthy Controls fail 2 or more cognitive tests

p < 0.0001
IFN-beta long term follow up: Time from Study Randomization to Death

Early treatment with IFNB1b: associated with 46.8% reduction in the hazard rate for mortality - NNT 8

HR=0.532 (95% CI: 0.314–0.902) 46.8% reduction in hazard ratio
Log rank, P=0.0173

Pathological substrate for brain atrophy: 11,000 to 1

<table>
<thead>
<tr>
<th>Tissue (no. of patients)</th>
<th>No. of Lesions Analyzed</th>
<th>No. of Transected Axons/mm²*</th>
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<tr>
<td>Active lesions (3)</td>
<td>5</td>
<td>11,236±2775</td>
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<tr>
<td>Chronic active lesions (4)</td>
<td>13</td>
<td>3138±688</td>
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<tr>
<td>Chronic active lesions Core</td>
<td></td>
<td>875±246</td>
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<tr>
<td>Nonlesion white matter (5)</td>
<td>11</td>
<td>17±2.8</td>
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<tr>
<td>Control white matter (4)</td>
<td>5</td>
<td>0.7±0.7</td>
</tr>
</tbody>
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Trapp, et al. NEJM 1998;338:278-85
Brain atrophy occurs across all stages of the disease

n= 963 MSers
Treatment effect on disability predicted by effect on T2-lesion load and brain atrophy

Meta-analysis of treatment effect on EDSS worsening (y) vs effects on MRI lesions and brain atrophy, individually or combined, in 13 placebo-controlled RRMS trials (13,500 patients)

No evident disease activity: NEDA

What is NEDA?

- No relapses
- No sustained disability progression (EDSS)
- No MRI activity
  - No new or enlarging T2 lesions
  - No Gd-enhancing lesions

What about MEDA (minimal evident disease activity)?

Gd, gadolinium.
Relapses

Unreported relapses

Clinical disease progression

Subclinical relapses: focal MRI activity

Focal gray and white matter lesions not detected by MRI

Brain atrophy

Spinal fluid neurofilament levels

END-ORGAN DAMAGE

NEDA

Biomarkers

MS Iceberg

Clinical activity

Focal MRI activity

Hidden focal and diffuse MRI activity

Microscopic or biochemical pathology
Fingolimod and CSF neurofilament light chain levels in relapsing-remitting multiple sclerosis

Clinical and MRI outcomes at baseline and Month-12 for outlier patients:
Patient W: EDSS decreased from 2 to 1.5; reduction in Gd-lesions from 5 to 0; decrease in T2 lesion volume (12309 mm³ to 11828 mm³) and no relapses.
Patient X: stable EDSS score of 1.5; no Gd+ lesions (both timepoints); stable T2 lesion volume (5153 mm³ to 5159 mm³) and no relapses.
Patient Y: EDSS from 1.5 to 4.5; reduction in Gd+ lesions from 1 to 0; increase in T2 lesion volume (6512 mm³ to 23794 mm³); two relapses.
Patient Z: increase in EDSS (3 to 4.5); increase in Gd+ lesions from 1 to 7; increase in T2 lesion volume (5888 mm³ to 6568 mm³); two relapses.

Fingolimod → PPMS (INFORMS STUDY)
ClinicalTrials.gov ID: NCT00731692

Siponimod → SPMS (EXPAND STUDY)
ClinicalTrials.gov ID: NCT01665144
BARTS-MS T2T-NEDA ALGORITHM

T2T = treating-to-target; NEDA = no evident disease activity

Define the individual’s MS

Choose a therapeutic strategy

Maintenance-escalation

Choose therapy

Initiate or Switch or Escalate Rx

Rebaseline

Monitoring

Treatment failure?

No

Complete course / Re-treat

Rebaseline

Monitoring

Breakthrough disease

Yes

Induction

Choose therapy

Choose therapy

Patient’s preferences?

Your choice?

Rebaselining:

- ifn-β, natalizumab, fingolimod, teriflunomide, dimethyl-fumarate=3-6 months
- glatiramer acetate=9 months
- alemtuzumab=24 months

Individual measures:

- Evidence of disease activity?
- Tolerability/safety?
- Adherence?
- Drug or inhibitory markers, e.g. NABs?

No

Yes

Only one licensed induction therapy at present

Disclaimer: data presented on this slide reflects the algorithm at Barts-MS and is not a Merck recommendation

Ifn-β = interferon-beta; NABs = neutralizing antibodies; Rx = treatment
Relapse reporting

Patients who have ever experienced an MS relapse and not contacted a healthcare professional

- Yes, 4
- No, 5

N = 102

Patients reporting most recent relapse to a specialist MS team

- Yes, 7
- No, 2

N = 101

Most common reasons for not reporting their most recent relapse to a specialist MS team were:
- ‘Mild relapse so not felt necessary’ 5/28 (18%)
- ‘Saw or spoke to their GP’ 4/28 (14%)

Most common reasons for not seeking healthcare support were:
- ‘Felt I could manage’/mild relapse 18/42 (43%)
- ‘Nothing that they can do to help’ 8/42 (19%)
EDSS

Survey of UK MSologists

Clinical – In your routine MS clinical practice, do you use the EDSS?

- Yes – I do an EDSS whenever I see a patient: 14 (25%)
- Yes – I do an EDSS annually: 10 (18%)
- Yes – I occasionally do an EDSS: 20 (36%)
- No – I never do an EDSS: 3 (5%)
- Other: 9 (16%)

Clinical – If you do an EDSS in your routine clinical practice, do you walk the patients to assess their walking distance?

- Yes: 9 (16%)
- No: 20 (36%)
- Sometimes: 22 (39%)
- Other: 5 (9%)

Validating a novel web-based method to capture disease progression outcomes in MS

The midpoint of the diamonds is the mean difference between the two EDSS scores, the upper and lower lines within the diamonds are the 95% CI. The width of the diamond indicates the sample size, the dots the actual values. The horizontal line at 0.46 indicates the mean difference between the two scores. The graph indicates the greater variation at lower EDSS scores, with greater agreement at scores > 5.

P-EDSS, physician or actual EDSS.

9 hole peg test

The 9 hole peg test is the gold standard for monitoring arm and hand function in clinical trials. This cardboard version gives you independence from your neurologist, empowering you to test and monitor your own disease progression.

🔗 2 minute instructional video

EDSS online assessment

Calculate, track and understand your MS disease status.

This is version 1 of the system and will be updated once we have new tools for assessing the neurological systems and walking distance more accurately.

🔗 5-10 minute online assessment
What is the 9 hole peg test?

The 9 hole peg test is the gold standard for monitoring arm and hand function in clinical trials. This cardboard version gives you independence from your neurologist, empowering you to test and monitor your own disease progression.

Why is the 9 hole peg test important?

Preserving arm and hand function is critical for people with MS to remain independent and to preserve their quality of life. Over 90% of people with Multiple Sclerosis valued arm and hand function as being more important to them than leg function.

Although disease-modifying therapies (DMTs) may not be able to preserve lower limb function in people with MS who already have pre-existing walking problems, we hypothesise that some DMTs may be able to preserve arm and hand function.

Therefore, we are striving for future trials of new and existing DMTs to focus on arm and hand function.

How do I use the 9 hole peg test?
Disability Accumulation in MS Has a Negative Impact on Multiple Aspects of Life

20:50:80

Employment

1. Approximately **20%** of MSers with MS for <5 years are unemployed

2. More than **50%** of MSers are unemployed 10 years after diagnosis

3. Approximately **80%** of MSers with an EDSS of 6.0 are unemployed

MS disability impacts life roles and reduces quality of life

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EVALUATION OF SCHOOL PERFORMANCE AS AN INDIRECT MARKER OF COGNITIVE DECLINE PRIOR TO DIAGNOSIS OF MULTIPLE SCLEROSIS

Perez Akly, M.1; Zanga, G.1; Ciardli, C.1; Racosta, J.2,3; Sinay, V.2,3.
1 Hospital Dr. César Milstein, 2 Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina / 3 Institute of Neurosciences at Favalaro Foundation

AAN 2013
Association of MRI metrics and cognitive impairment in radiologically isolated syndromes

Figure: Magnetic resonance data expressed in cm³ in radiologically isolated syndrome (RIS), relapsing-remitting multiple sclerosis (RRMS), and healthy control subjects (HCs).

- T2LV
- T1LV
- NCV
- NBV

NBV = normalized brain volume; NCV = normalized cortical volume; T1/LV = T1 lesion volume; T2/LV = T2 lesion volume.

Reduced head and brain size for age and disproportionately smaller thalami in child-onset MS

Why Grey Matter matters

Brain atrophy in MS: what are its consequences?

**BRAIN ATROPHY**
Brain atrophy, or shrinkage, occurs in the majority of MSers at all stages. Grey matter atrophy accelerates over time and with disease progression.

**DIVORCE**
Compared with the general population, MSers are 40% more likely to separate, or divorce, and do so sooner.

**JOBS**
10 years after diagnosis 50% of MSers are unemployed. By the time you need a wheelchair, over 80% of MSers are unemployed.

**MEMORY**
At the time of the first clinical attack over 50% of CISers have cognitive impairment in at least two cognitive areas.

**SUICIDE**
MSers have a 2-7x higher chance of committing suicide.

**EMOTIONAL**

**PHYSICAL**

**DISABILITY**
The average time from MS onset to needing a walking stick is 20 years, and for a wheelchair 30 years.

**QUALITY OF LIFE**
Society rates the quality of life of someone with MS who is bed bound as being worse than death.

**SURVIVAL**
MS reduces life expectancy by approximately 8 years and half of MSers die of MS-related complications.

**OPTIC NEURITIS**
After a single attack of optic neuritis approximately 20% of the nerve fibres are lost in the optic nerve.

**INFLAMMATION**
In each cubic millimetre of an acute MS lesion there are over 11,000 transected axons, or nerve fibres, compared to less than one in normal brains.

**GREY MATTER**
In MS there is extensive demyelination, neuronal transection and death, and loss of neurons, in the cerebral cortex or grey matter.

**ATROPHY**
The brains of MSers shrinks at a rate of 0.5-1.0% per year compared to a rate of between 0.1-0.4% in normal brains.

**BRAIN VOLUME**
Brain atrophy, or brain shrinkage, in MS, as measured by MRI, is associated with disability and cognitive impairment.

Save your Grey Matter it really does matter.
Early treatment
Theoretical model: treat early and effectively

- Treatment at diagnosis
- Later treatment
- Natural course of disease
- Later intervention
- Intervention at diagnosis

Time is brain

Disability

Disease Onset

Time
The Traditional Approach to MS Treatment

• Heterogeneity of disease course across different MSers and over time can affect treatment response\textsuperscript{1-3}

• Depending on the definition used, up to 49\% of MSers treated with a first-line injectable therapy (IFNB) still have clinical disease activity\textsuperscript{1}

Treating beyond symptoms with a view to improving IBDer outcomes in inflammatory bowel diseases

“FLIPPING THE PYRAMID”

The cost of delayed access to highly active treatment

**20 month vs. 32 month delay or 2 relapses**

EDSS = 3.5: unable to run, play tennis or walk down stairs quickly without the use of a handrail

EDSS = 0.0: fully functional
Making a difference

BMJ Case Reports 2015; doi:10.1136/bcr-2014-208960

CASE REPORT

Timing is everything in the treatment of multiple sclerosis

Claire Louise McCarthy¹, Gavin Giovannoni², Alasdair John Coles³

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Published 15 April 2015

Summary

We present two similar cases of relapsing–remitting multiple sclerosis, both of whom received treatment with the monoclonal antibody alemtuzumab, but had significantly different long-term outcomes. Patient A is 12 years into his illness and was treated early in his disease course, he has no disability and continues to perform at a high level as a professional golfer. Patient B was initially started on interferon-β1a therapy and went on to have two disabling relapses on this treatment which resulted in a degree of fixed disability prior to the start of alemtuzumab. 10 years into his disease course he has moderate disability and daily symptoms of spasticity in his legs which impair his quality of life. These two contrasting cases highlight the difficult decision of when to start potent immune modulating therapies for multiple sclerosis in young adults who appear well early in their disease but have the potential to rapidly accrue irreversible disability from future relapses.
Case 3

Case scenario: 25-year-old woman with RRMS

2011
Optic neuritis
MRI+ve

April 2015
Brain stem
INO

May 2015
Spinal cord
triparesis

IV methylprednisolone

IV methylprednisolone

EDSS = 5.0

Natalizumab
or
Alemtuzumab?

Patient case scenario provided by Professor Gavin Giovannoni.
INO=internuclear ophthalmoplegia; IV=intravenous.
Case 3

Case scenario: 25-year-old woman with RRMS

2011
- Optic neuritis
- MRI+ve

April 2015
- Brain stem
- INO

May 2015
- Spinal cord
- Triparesis

June 2015
- JCV+ve
  (index = 1.6)

IV methylprednisolone

EDSS = 5.0

Natalizumab
or
Alemtuzumab?

Patient case scenario provided by Professor Gavin Giovannoni.
Case 3

Case scenario: 25-year-old woman with RRMS

Patient case scenario provided by Professor Gavin Giovannoni.
Case 3

Case scenario: 25-year-old woman with RRMS

2011
- Optic neuritis
- MRI+ve

April 2015
- Brain stem INO
- IV methylprednisolone
- IV methylprednisolone

May 2015
- Spinal cord triaparesis
- IV methylprednisolone

June 2015
- JCV+ve (index = 1.6)
- Severe spinal cord relapse, paraparesis, loss B&B, pressure sore
- Anti-AQ4 -ve
- IV methylprednisolone x2

EDSS = 5.0

Natalizumab or Alemtuzumab?

July 2015

EDSS = 7.0 → 6.5

Natalizumab or Alemtuzumab?

Sept 2015

May 2016
- Brain stem
- INO
- IV methylprednisolone

EDSS = 6.0

Feb 2016
- Natalizumab
- Alemtuzumab

April 2016
- Natalizumab
- Alemtuzumab

EDSS = 6.0

Patient case scenario provided by Professor Gavin Giovannoni.

AQ4=Aquaporin-4

Stroke or brain attack: ‘time really is brain’
Therapeutic hierarchy

Therapeutic pyramid

- Neuro-restoration
- Remyelination
- Neuroprotection
- Anti-inflammatory

Brain Health Initiative
- Smoking
- Exercise
- Diet
- Sleep
- Co-morbidities
- Infections
- Concomitant medications
Rapid adoption of innovations has the potential to improve MS care

Slow adoption of innovations results in healthcare inequity.
Large disparities exist in access to disease-modifying therapies

International policy initiative
Early intervention and long-term prognosis

- **Intervention at diagnosis**
- **Intervention later**
- **No treatment**
- **Later intervention**

Increasing disability over time with potential range of outcomes.

Barts-MS: 2016 Brain Health Challenge
Barts-MS: 2016 Brain Health Challenge

- Prognosis
- Active MS
- Treatment
- Re-baselining
- Monitoring
- NEDA
Barts-MS: 2016 Brain Health Challenge

Treat-2-Target

Lifestyle

Comorbidities

Wellness

- Diet & supplements
- Exercise
- Smoking
- Alcohol
- Sleep
- Stress
Barts-MS: 2016 Brain Health Challenge

Treat-2-Target

- Obesity
- Hypertension
- Glucose
- Cholesterol
- Smoking
- Sleep disorders
- Infections
- Falls

Lifestyle

- Depression & anxiety
- Concomitant medications

Comorbidities

Wellness
Barts-MS: 2016 Brain Health Challenge

- Treat-2-Target
- Lifestyle
- Comorbidities
- Wellness

- Intellectual
- Emotional
- Physical
- Social
- Spiritual
- Occupational
- Environmental
ESRF
end-stage renal failure

Images courtesy of Professor Gavin Giovannoni
Rheumatoid arthritis
End-stage joint disease
From initial impact to lasting improvement – the logical next step!

The MS Brain Health report has united the global MS community in support of its messages and recommendations. This unity is a precious resource and one to be nurtured.

We need to look for ways to describe the collective aims that recognize and allow for the variation or diversity between systems.

Representative from a major patient organization that has endorsed and promoted the report
A quality improvement approach to measure local adoption of the recommendations

Aim: maximize lifelong brain health in people with MS and improve outcomes

Agree on the **overall aim**, aspirations and scope

Agree on **factors that contribute** to the aim

**Interventions** are changes made to achieve the aim

Measure concept, are we seeing improvement in a process/outcome?

Cause/effect arrow

Engage with a wide range of stakeholders to gain buy-in and to agree on an overall aim, desired outcomes and measure concepts

**Action effect methodology** is iterative; the diagram develops as different stakeholders are engaged

The diagram acts as a ‘road map’ – a starting point for pilot projects in specific healthcare systems
1. What is multiple sclerosis?
2. Are you sure that you have MS?
3. What type of MS do you have?
4. What prognostic group do you fall into?
5. What is the risk of you not being treated with a DMT?
6. Do you have active MS?
7. Am I eligible for treatment with a DMT?
8. Do you understand the difference between the treatment strategies of maintenance-and-escalation and induction therapy?
9. Do you understand the concept of treat-2-target of no evident disease activity (NEDA)?
MS Brain Health – a potential ‘tripadvisor’ for MS …

tripadvisor®  

msAdvisor®
<table>
<thead>
<tr>
<th></th>
<th>Rating</th>
<th>Number</th>
<th>Average Time</th>
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<tr>
<td>Overall</td>
<td></td>
<td>62</td>
<td>38.6 days</td>
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<td>Diagnosis</td>
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Our vision is to create a better future for people with MS and their families

Your voice will help to effect this change

Be an early adopter

Pledge your support of the report’s recommendations at www.msbrainhealth.org
Summary

1. Disability accumulation and health status deterioration occur early in MS, suggesting an **early therapeutic window** of opportunity.

2. Heterogeneity of treatment response supports that **treatment decision-making should be individualised**, rather than taking a step-wise “treatment ladder” approach for all MSers.

3. Evaluation of the **benefits and risks** of treatment vs the risk of MS disease progression requires consideration of both the physician’s and MSers’ perspectives.

4. **Optimising therapy** requires ongoing assessment to identify MSers who are experiencing suboptimal response to current therapy.

5. **Treatment adherence** is an important consideration both at treatment initiation and in the face of **suboptimal treatment response**.
Questions?