Prognosis of MS
How to communicate it to people with MS
Gavin Giovannoni
Disclosures

I have 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, Almirall, Bayer-Schering Healthcare, Biogen-Idec, Canbex, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, GW Pharma, Ironwood, Merck-Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthom BV, Teva, UCB Pharma and Vertex Pharmaceuticals.
Reasoning by analogy
ESRF
end-stage renal failure

Images courtesy of Professor Gavin Giovannoni
Rheumatoid arthritis
End-stage joint disease

Images  http://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-symptoms/
The treatment target in MS is an evolving and moving target.
Early effective treatment
Stroke or brain attack: ‘time really is brain’

Passive ————> Active
Early intervention and long-term prognosis

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

Potential range of outcomes

Increasing disability

Time

www.msbrainhealth.org

International policy initiative

Brain health
Time matters in multiple sclerosis

www.msbrainhealth.org

Goal: maximize lifelong brain health

Early referral and diagnosis → Early treatment

Shared decision-making

Use

Comprehensive economic approach

Access to DMTs

Consult

Lifestyle and other factors

Real-world evidence

DMT, disease-modifying therapy.

MS Brain Health vision and aim*

Our vision is to create a better future for people with MS and their families

Our overarching **aim** is to encourage the widespread adoption of a therapeutic strategy that aims to **maximize the lifelong brain health** of every person with MS

*Defined by MS Brain Health Steering Committee in 2015*
Expert patient
Expert Patient

‘When acute disease was the primary cause of illness, patients were generally inexperienced and passive recipients of medical care. Now that chronic illness has become the principle medical problem, the patient must become a co-partner in the process’

(Holman & Lorig 2000)
Moving from compliance to concordance requires a culture change

Compliance model

- Neurologist decides diagnosis and treatment
- Neurologist’s task is to explain and instruct
- Neurologist’s task is to comprehend
- Successful outcome is compliance

Concordance model

- Neurologist and patient negotiate diagnosis and treatment
- Neurologist elicits, explains, persuades and accommodates
- Patient explains, considers and accommodates
- Successful outcome is a negotiated agreement

Source: From Compliance to Concordance, 1997
Infographics
Telling it how it is

What is the risk of you not being treated?

www.ms-res.org
Impact of disability on employment

European burden of illness study:
Cross sectional study of 16,808 participants, 52% with RRMS, across 16 countries.
Prognostic factors
Prognostic factors

1. Older age of onset (>40 years)
2. Male sex
3. Multifocal onset
4. Efferent system affected
   a. Motor/weakness
   b. Cerebellar
   c. Bladder
5. Relapses
   a. Partial or no recovery from initial relapses
   b. High relapse rate in the first 2-yrs (>2 relapses)
6. Disability after 5 years (EDSS > 3.0)
7. Abnormal MRI
   a. High lesion load (>9 lesions on MRI)
   b. Gd-enhancing lesions
   c. Posterior fossa lesions
   d. Spinal cord lesions
   e. Brain atrophy
8. Abnormal evoked potentials
9. Abnormal spinal fluid
   a. Oligoclonal IgG bands
   b. Raised neurofilament levels
10. Low vitamin D levels
11. Comorbidities
    a. Smoker
    b. Diabetes
    c. Hypertension
    d. Obesity
Relapses and EDSS

Time from disease onset to EDSS 6*

Number of relapses 1st and 2nd year

Percentage of patients

Time (yrs)

Predictors of Long-Term Outcome in Multiple Sclerosis Patients Treated with Interferon Beta

Robert A. Bermel, MD,1 Xiaojun You, PhD,2 Pamela Foulds, MD,2 Robert Hyde, PhD,2 Jack H. Simon, MD,3 Elizabeth Fisher, PhD,4 and Richard A. Rudick, MD1

EDSS, Expanded Disability Status Scale; Gd, gadolinium; IFN, interferon; IM, intramuscular; OR, odds ratio

CIS patients: n=40

Healthy controls: n=30

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

Patients failing ≥2 cognitive tests

CIS, clinically isolated syndrome

Brain atrophy occurs across all stages of the disease

n= 963 MSers

De Stefano, et al. Neurology 2010
Poor cognitive function in untreated patients predicts clinically meaningful disability progression over 2 years

Best baseline factor predicting confirmed progression:
Data from placebo arms of four Biogen Phase 3 RRMS trials (AFFIRM, DEFINE, CONFIRM, ADVANCE*)

*AFFIRM, natalizumab vs placebo; DEFINE and CONFIRM, dimethyl fumarate vs placebo; ADVANCE, peginterferon beta-1a vs placebo.
†Progression confirmed at 6 months on any of EDSS (≥1 point increase), T25FW, 9HPT, PASAT-3 (≥20% worsening), or visual function (≥10 letter worsening on 2.5% contrast Sloan letter chart). BL, baseline; 9HPT, 9-hole peg test; PASAT, paced auditory serial addition test; T25FW, timed 25-foot walk; VFT, visual function test.
Cognitive impairment can have a major impact on patients‘ lives

Rates of employment versus number of tests in the BICAMS cognitive assessment battery failed, in a cohort of MS patients (n=62)

Even mild cognitive impairment, i.e. failing one of the battery of tests, results in significant functional loss, seen here as a 50% decrease in patients’ employment.
Cognitive impairment in newly-diagnosed RRMS patients predicts MS progression over 10 years

Results of a retrospective, 10-year study of 155 RRMS patients, comparing presence and absence of cognitive impairment on the Rao BRB, assessed within 6 months of diagnosis:

- First relapse: HR=0.793; p=0.209
- Disability: HR=3.183; p<0.001
- Progression to SPMS: HR=2.535; p=0.008

NB: Hazard ratios (HR) are based on outcome probability for patients with cognitive impairment relative to those without.

Example of serum NfL profile in an MS patient: NfL tracked with disease activity

- Year 1 to Year 2: high NfL, high disease activity and brain atrophy
- Year 2 to Year 4: low NfL levels, stabilized MRI and brain atrophy

Data from ADVANCE study.
Prognostic score
Prognostic factors

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? / 22 factors

Prognostic factors

1. Older age of onset (>40 years) ✓
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Aim of treatment

- Good
- Indeterminate
- Poor

As time progresses, the aim of treatment moves from poor to good.
Predicting a DMT response
100 MSers
Who will be the DMT responders?
Hypothetical responder rates on a low efficacy DMT

EDA = evidence of disease activity (clinical); MEDA = minimal evidence of disease activity (MRI); NEDA = no evidence of disease activity (no clinical and MRI activity)
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Hypothetical responder rates on a moderate efficacy DMT

40:60
EDA = evidence of disease activity (clinical); MEDA = minimal evidence of disease activity (MRI); NEDA = no evidence of disease activity (no clinical and MRI activity)

Hypothetical responder rates on a very high efficacy DMT

80:20
At present it is not possible to predict who will respond to a particular DMT.

You simply increase your odds of being a responder with more efficacious DMTs.

- **20:80** Low efficacy DMT
- **40:60** Moderate efficacy DMT
- **80:20** Very high efficacy DMT
Treatment ladder vs. flipping the pyramid
Alem, alemtuzumab; Clad, cladribine tablets; DMF, dimethyl fumarate; Fingo, fingolimod; HDA, high disease activity; GA, glatiramer acetate; *HSCT, hematopoietic stem cell transplantation; IFN beta, interferon-beta; Mitox, Mitoxantrone; Nz, natalizumab; Ocre, ocrelizumab; RES, rapidly-evolving severe; Teri, teriflunomide
Different therapeutic approaches to the use of disease-modifying therapies in the treatment of relapsing forms of MS

**Therapeutic targets**

- **NEDA - 1 & 2**
  - Clinical activity
  - Conventional step-care
    - ‘Treatment Ladder’
  - Watchful waiting
  - Nz/Az/Ocr
  - IFN-β/GA/Teri/DMF

- **NEDA-3**
  - Focal MRI activity
  - Rapid escalation
    - ‘Treatment Escalator’
  - Fingo/Clad
  - IFN-β/GA/Teri/DMF

- **NEDA-4/5**
  - Brain atrophy / CSF-NFL levels
  - Early top-down
    - ‘Flipping the Pyramid’
  - Nz/Az/Ocr/Fingo/Clad

**Therapeutic approaches**

NEDA = no evident disease activity; NEDA-2 = clinical only (relapse-free and progression free); NEDA-3 = clinical and focal MRI activity; NEDA-4/5 = clinical and focal MRI activity free and normalising brain atrophy loss & normalisation of CSF neurofilament levels. IFN-β = interferon-beta; GA = glatiramer acetate; Teri = teriflunomide; DMF = dimethyl fumarate; Fingo = fingolimod; Nz = natalizumab; Az = alemtuzumab; Dac = daclizumab; Clad = oral cladribine; Ocr = ocrelizumab.

Benefits vs. Risks
Benefits of treatment

Risks of treatment
Infection (PML) complicating treatment with natalizumab
Benefits of treatment

Risks of untreated or undertreated MS

Derisking DMTs

Risks of treatment
Conclusions
Conclusions

- Educate your patients; help them become experts
- MS is a bad disease and given time it will cause disability in the majority of patients
  - It is very important to communicate this to patients
- Cognitive impairment is common and occurs early
- Treat early and effectively to preserve brain
- Treat to a target
  - NEDA and beyond
- Rapid escalation and flipping the pyramid
- Important to understand how to de-risk DMTs
Thank you