- Introduction
- Challenges
- Current activity
- Future directions

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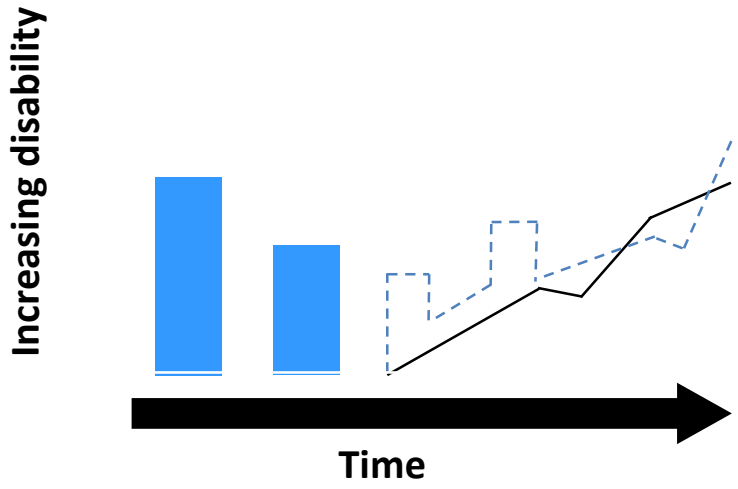
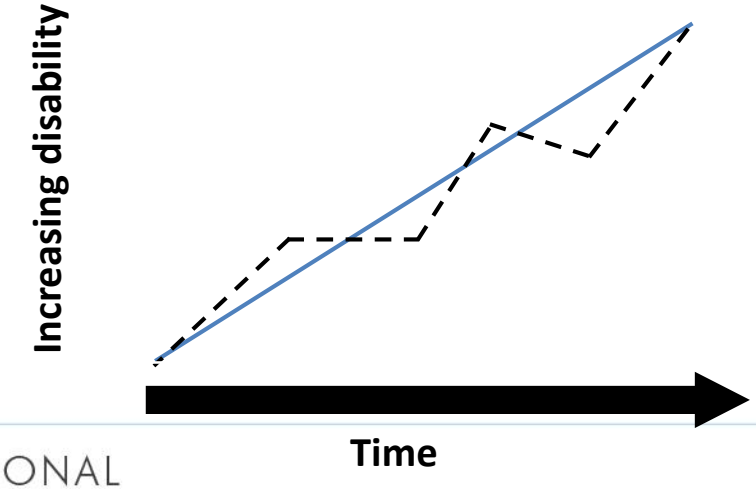
Progressive Forms of MS





- Many MS patients begin with a relapsing form and convert to a progressive form
- A small percentage of MS patients have nearly continuous progression of disability with no distinct relapses

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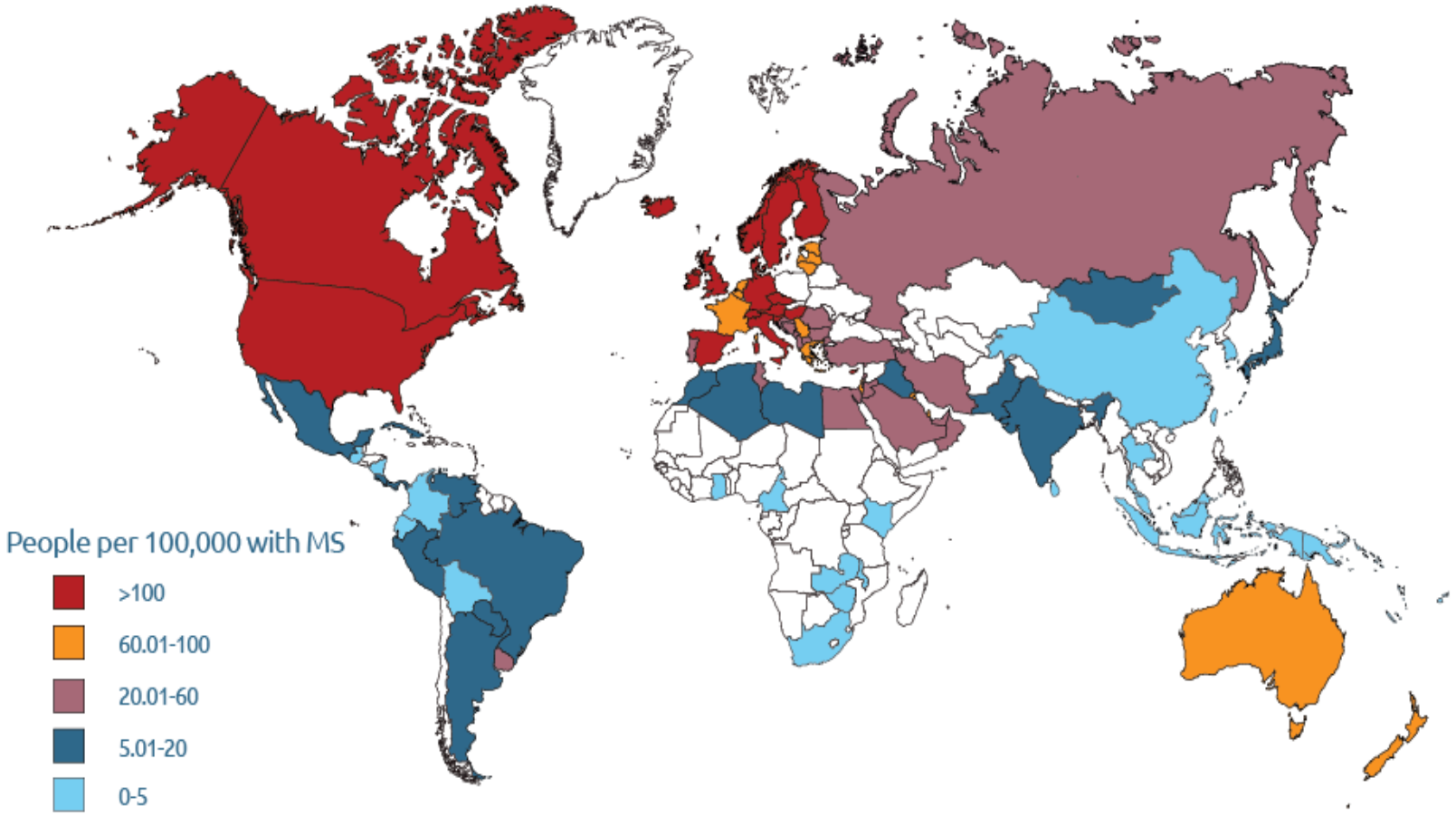
Urgent need to find solutions for people with Progressive MS

- Large worldwide impact: at least half of all (2.3million) MS patients
- Currently no effective treatment for progressive forms of MS
- Onset of progression is the main determimant of disability
- Finding treatments for progressive MS is one of the top priorities for patients
- Every time another therapy is approved for RRMS, a large proportion of our constituents feel left out

Prevalence of MS

2013 : 2.3 million



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ms international federation

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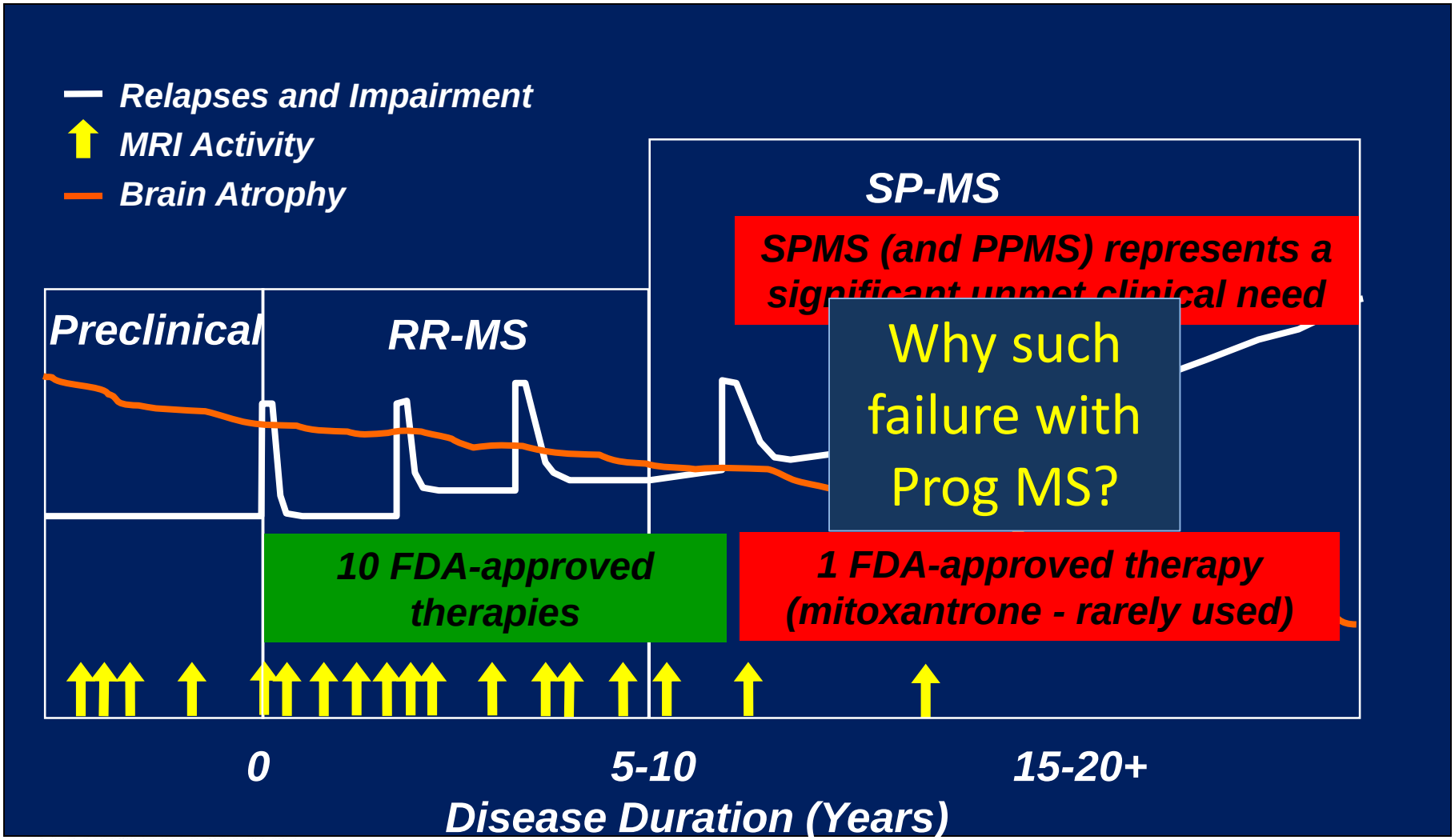
Natural History



PROGRESSIVE MS ALLIANCE

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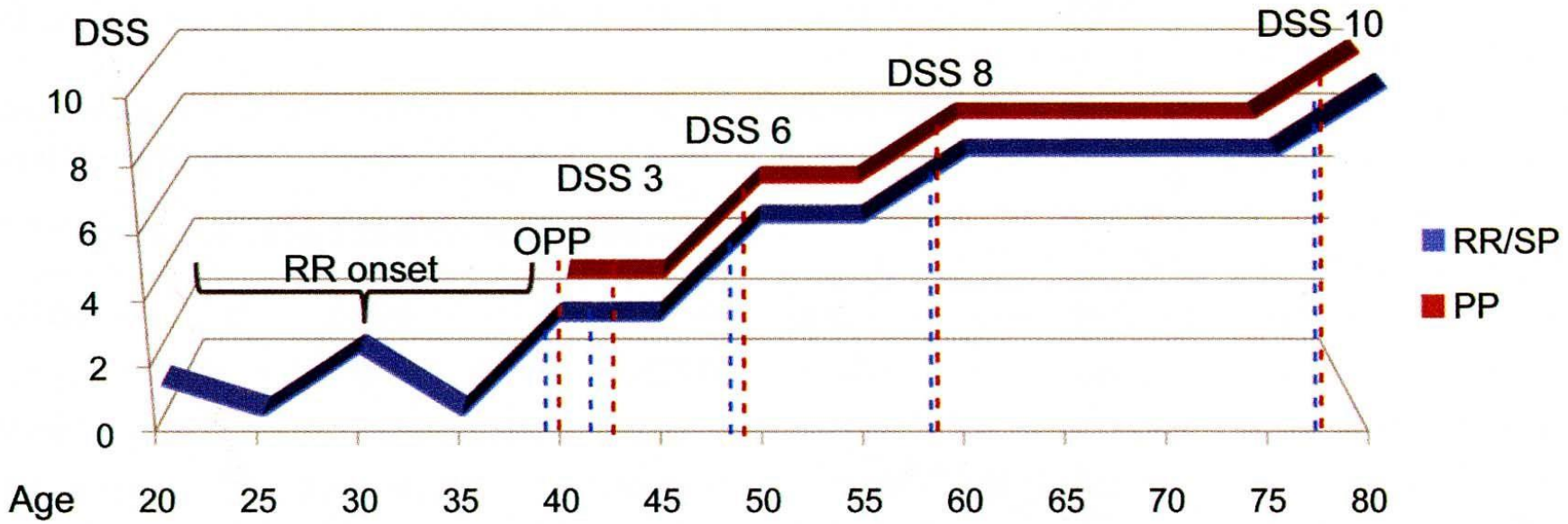
Age and disability accumulation in multiple sclerosis

Development of secondary progression is the dominant determinant of long-term prognosis, independent of disease duration and early relapse frequency

Scalfari et al Neurology 2011

Onset of progressive phase determines disability

Figure 2 Ages at attainment of disability endpoints according to type of disease course



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

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Scalfari et al Neurology 2011

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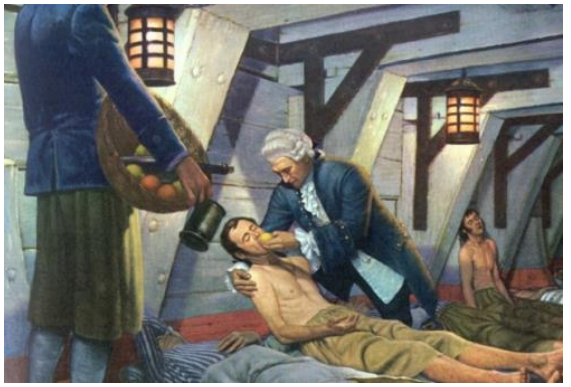
The James Lind Alliance

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.

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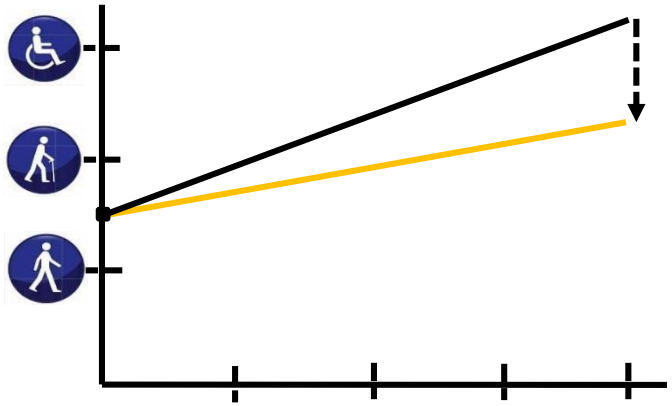
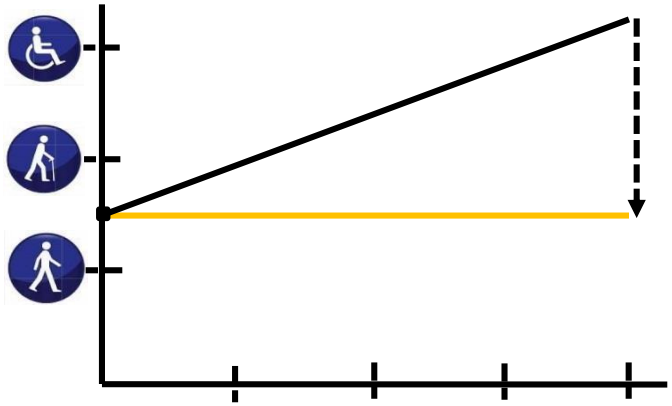
The Top 10

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?

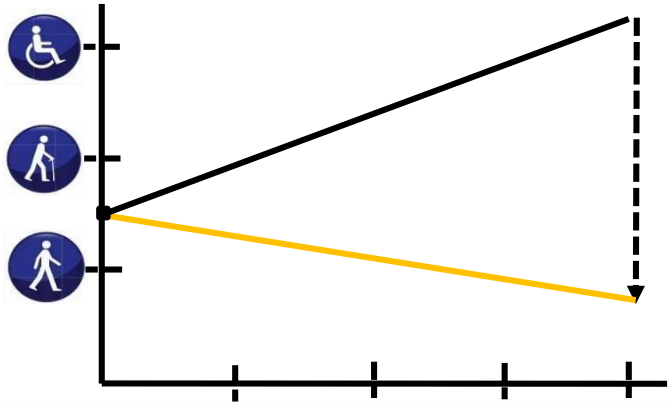
1. Delayed Progression



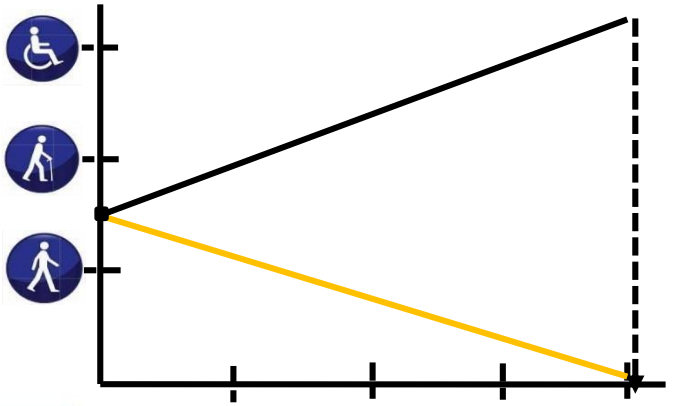
2. Stabilised Progression



3. Improved Function



4. Recovered Function



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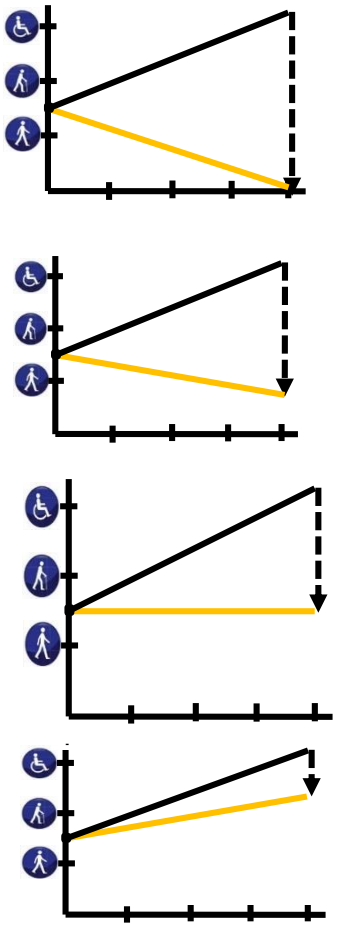
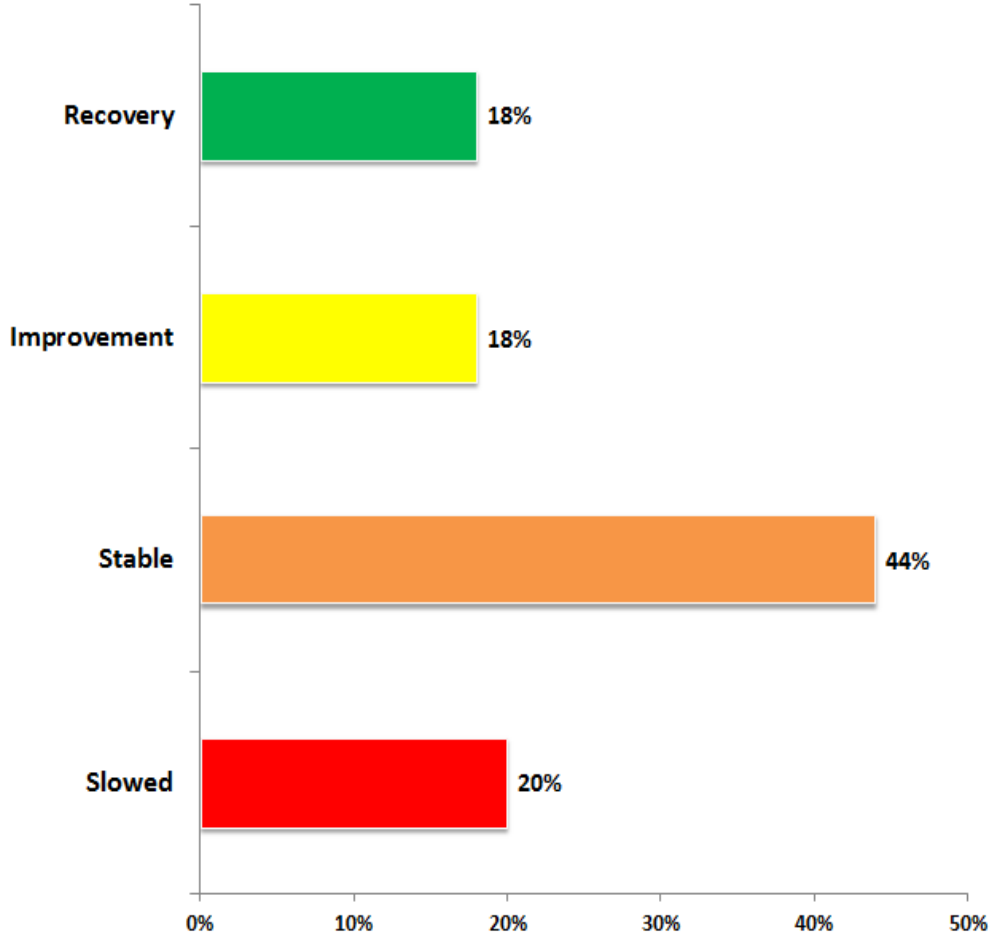
WHAT ARE YOUR EXPECTATIONS OF A THERAPY FOR PROGRESSIVE MS?





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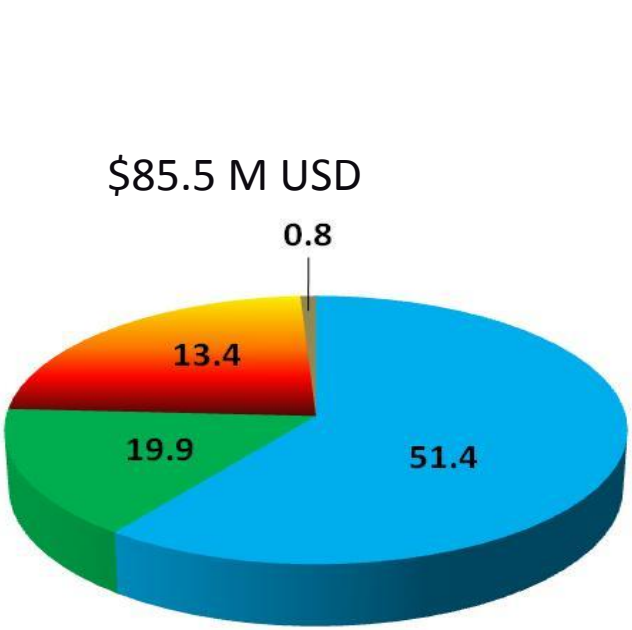
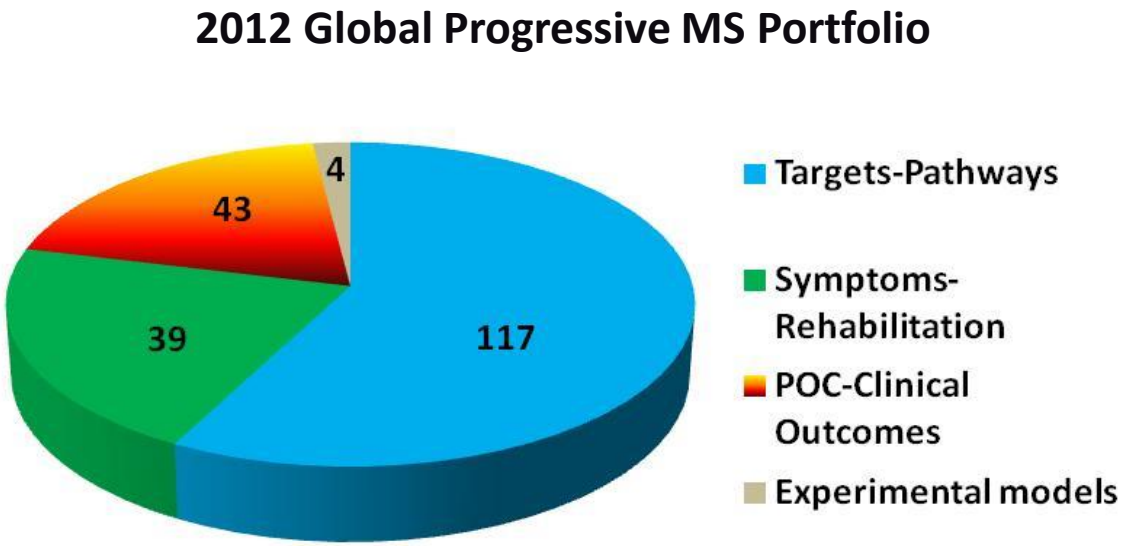
Efforts Underway





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 so we can identify targets for treatment
- Outcomes/Biomarkers that will tell us when we have something with potential
- Trial design which is faster and more efficient

Defining Progressive MS

- 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

Progressive MS is defined differently from different perspectives

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Defining the clinical course of multiple sclerosis

The 2013 revisions

OPEN

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

Neurology® 2014;83:278-286

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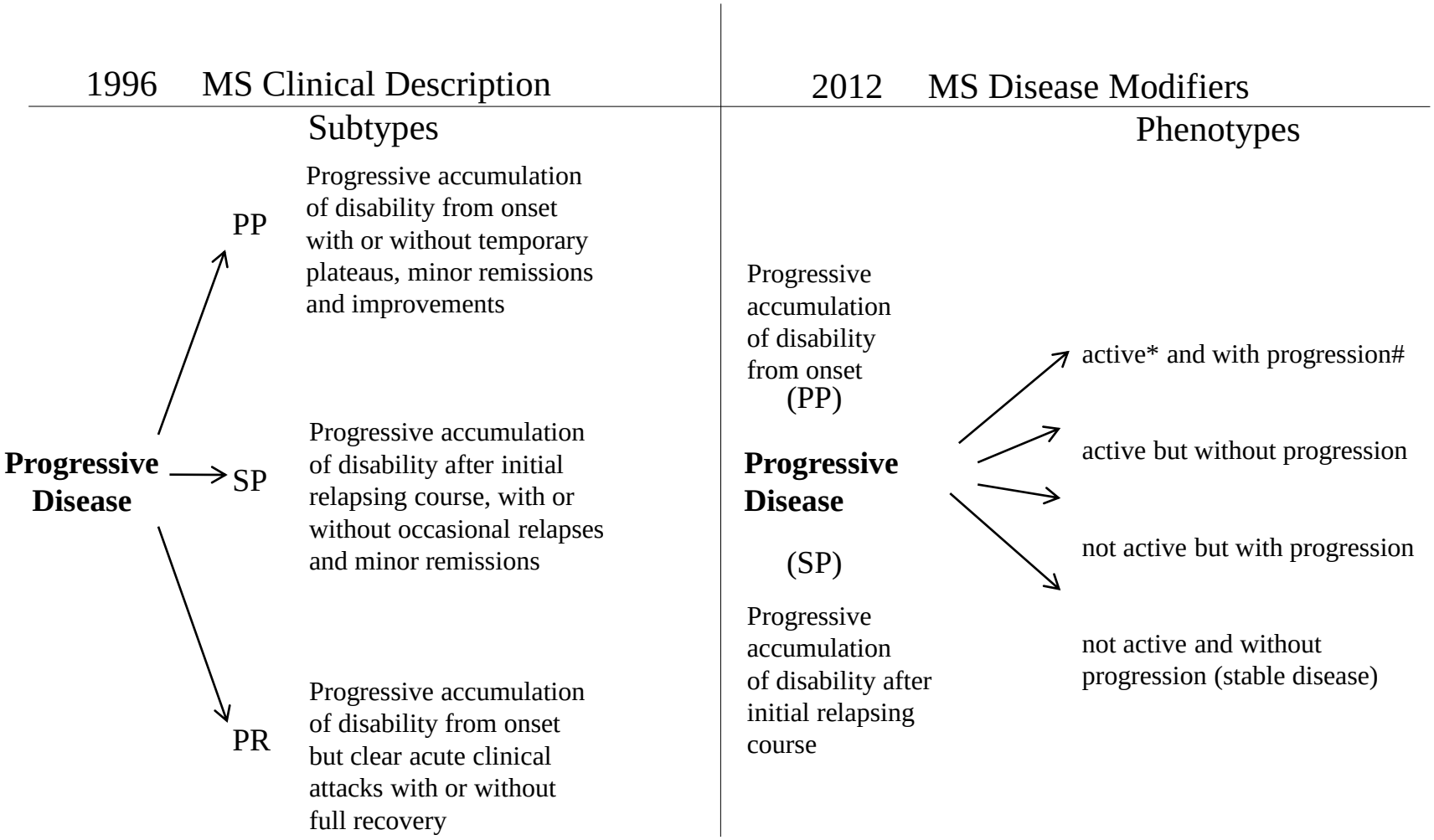

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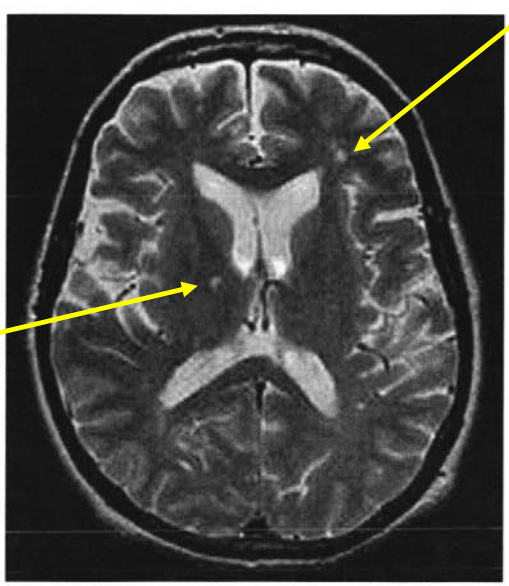
Possible pathological correlates of progression

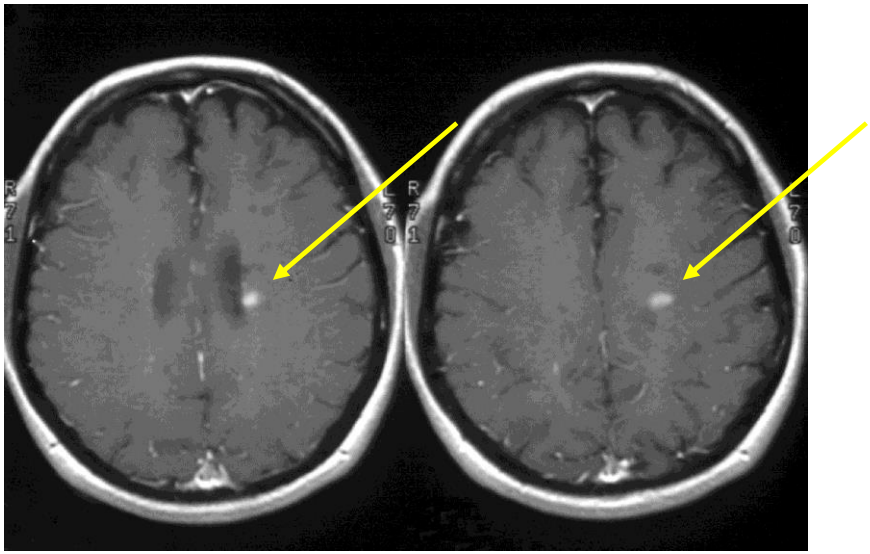
- Slowly expanding pre-existing lesions
- Persistent microglial activation
- Compartmentalized inflammation
- B cell/antibody involvement
- Remyelination failure
- Axonal/neuronal loss
- Cortical/gray matter involvement
- Changes in the NAWM

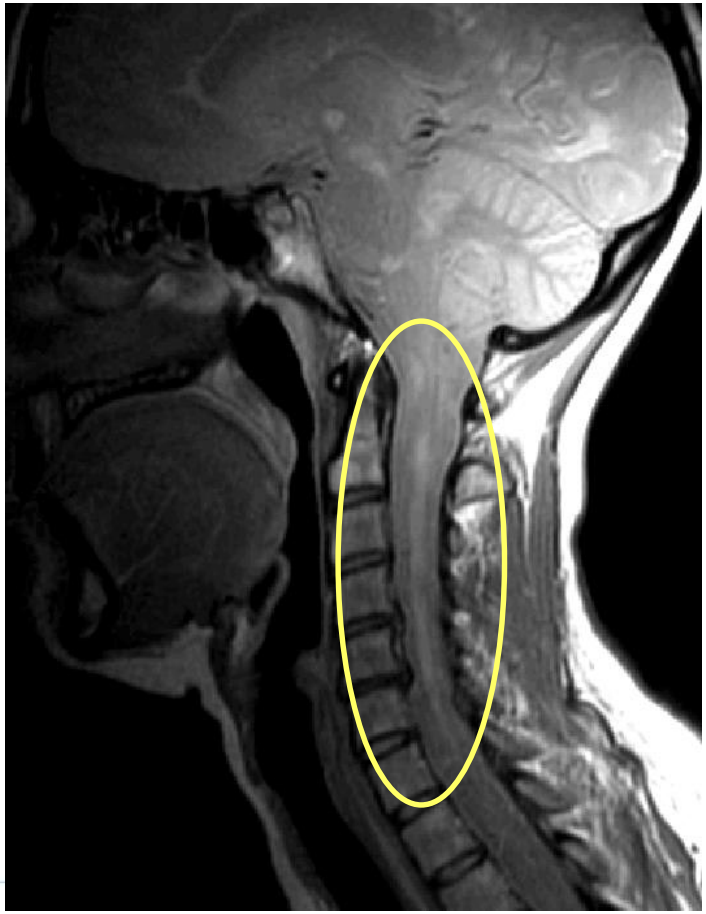
Key areas

- Inflammation
- Gray matter involvement
- Axonal loss

MRI in primary progressive MS







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Thompson et al. Ann Neurol 1991

Brain Enhancement

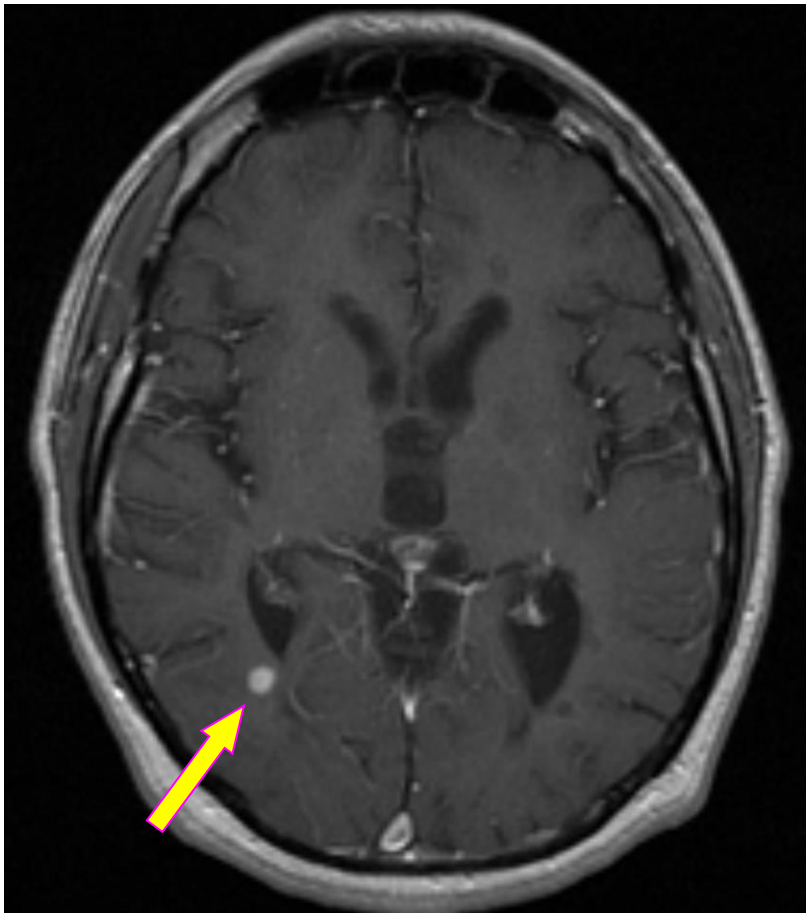
- 42% patients with early PPMS (< 5 years) had at least one enhancing lesion on their baseline scan

- Number of enhancing lesions associated with

  - younger age ($r=0.5$, $p= 0.003$)

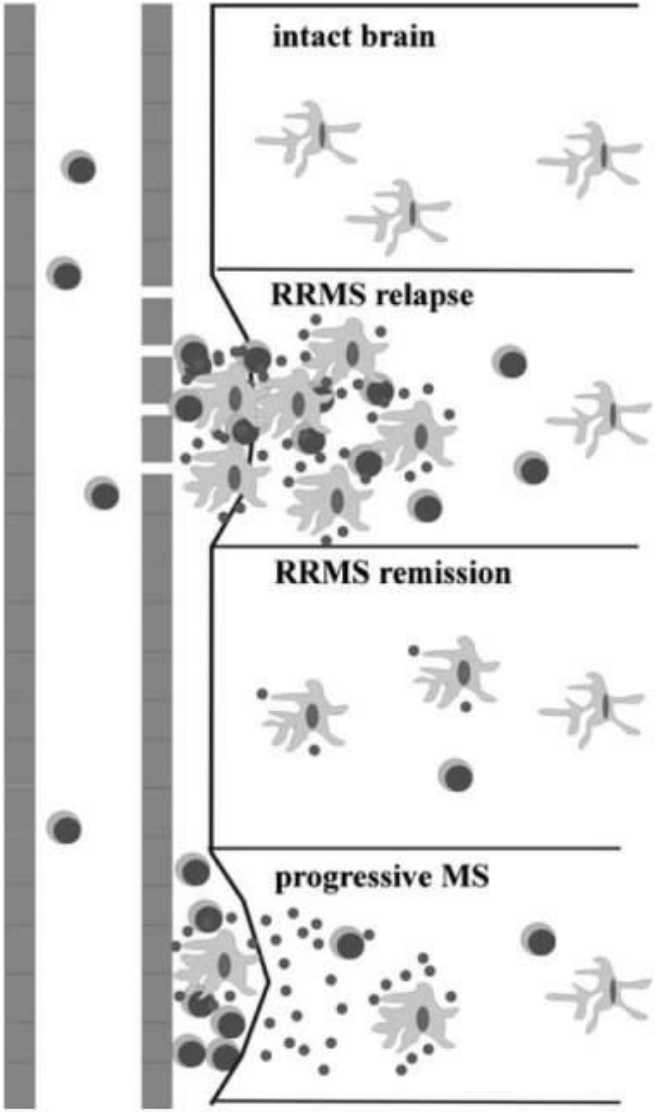
  - higher T2 load ($r= 0.5$, $p=0.02$)

  - worse outcome!



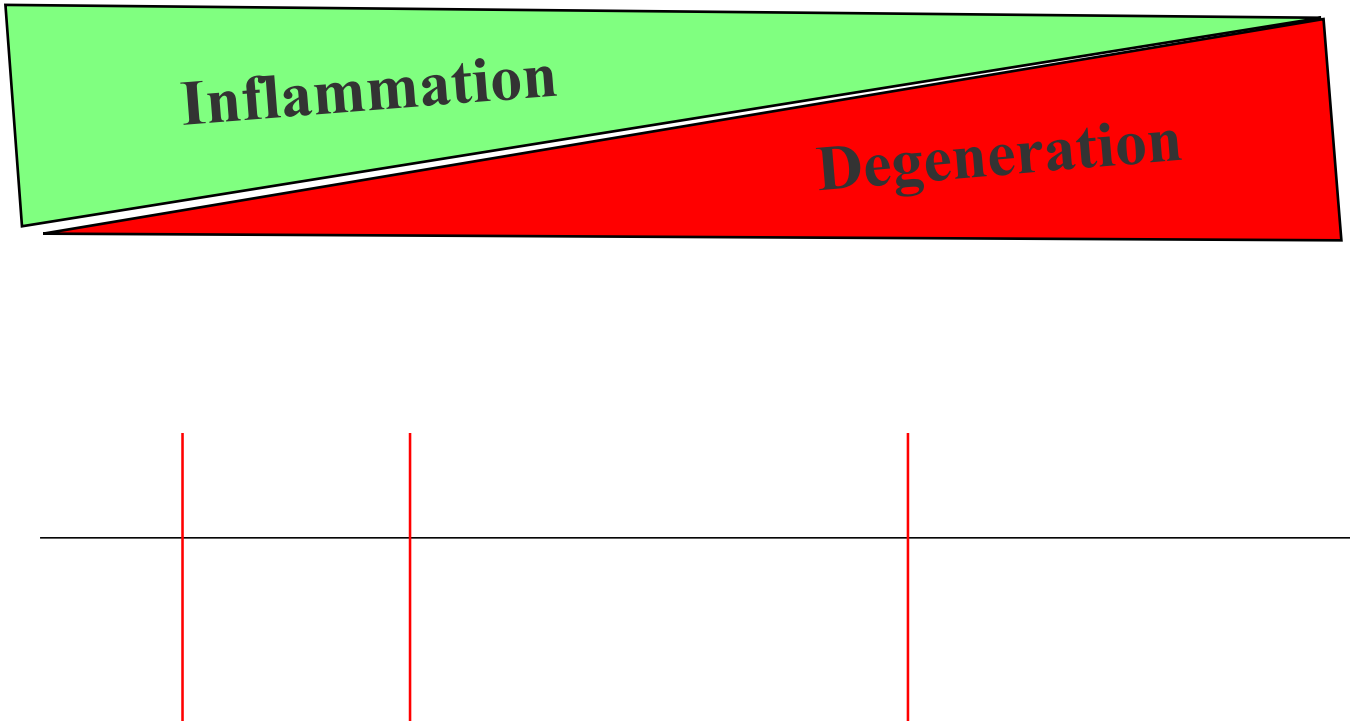
Compartmentalized inflammation in progressive MS

Inflammation behind a closed (repaired) blood–brain barrier



Bradl and Lassmann, Semin Immunopathol 2009

Pathologic Mechanisms in Early vs. Late MS

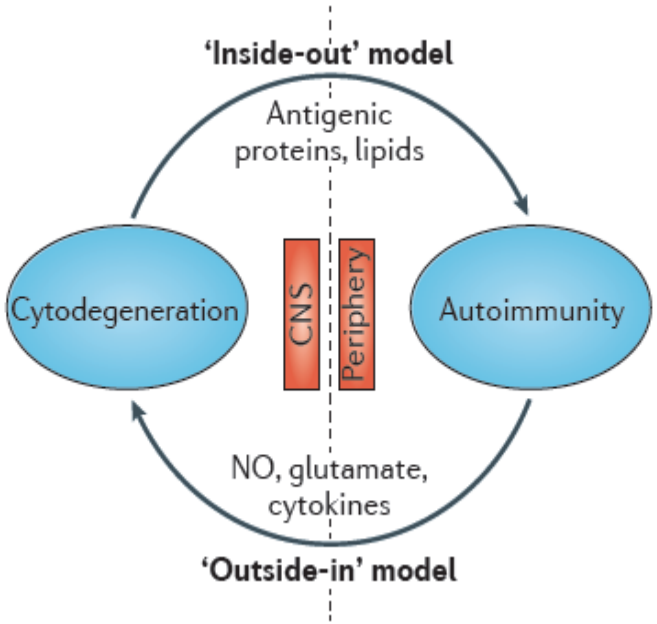


OPINION

Will the real multiple sclerosis please stand up?

Peter K. Stys, Gerald W. Zamponi, Jan van Minnen and Jeroen J. G. Geurts

Nat Rev Neurosci 2012



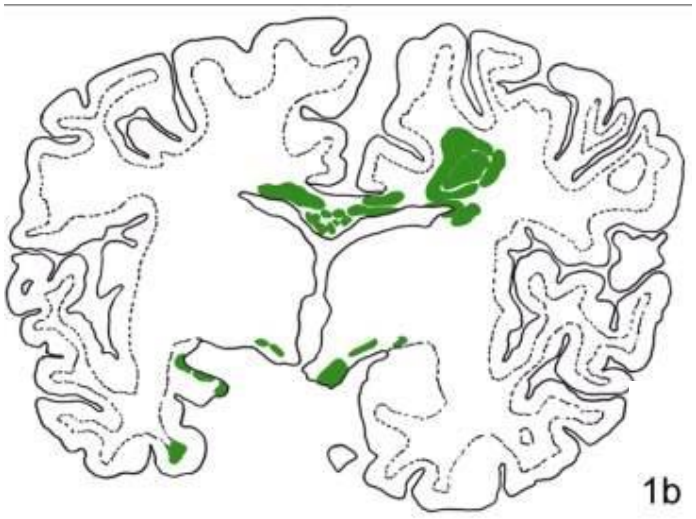
host's immune reaction to it (orange). Thus, MS requires these two intertwined ingredients, one uniformly progressive, the other intermittent and highly variable, which establish the type of disease in any one patient. We propose that the 'real' MS is the underlying cytodegeneration, which is most faithfully reflected by primary progressive disease. SPMS, secondary progressive MS

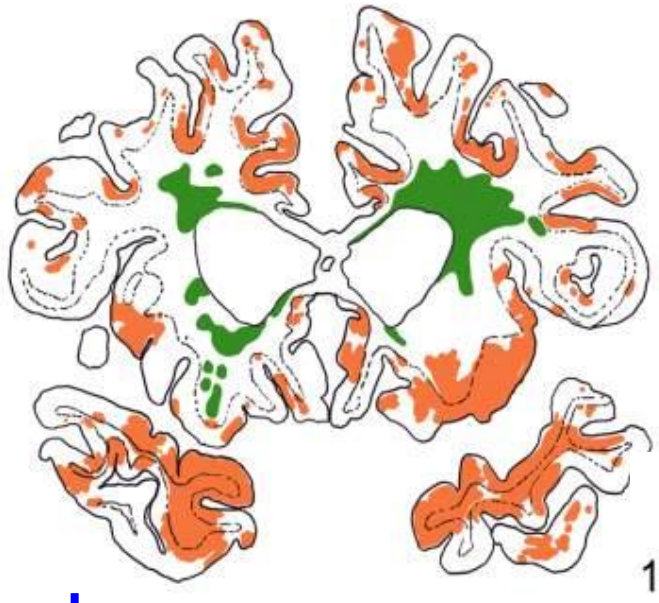
Key areas

- Inflammation
- **Gray matter involvement**
- Axonal loss

Cortical demyelination is extensive in progressive MS

RRMS





SPMS/
PPMS

	Cortical lesion area forebrain (%)	White matter lesion area (%)
RRMS	2.96	10.3
PPMS	12.54	6.54
SPMS	13.29	24.13

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Kutzelnigg et al., Brain 2005

BRAIN
A JOURNAL OF NEUROLOGY

Cortical lesion load associates with progression of disability in multiple sclerosis

Massimiliano Calabrese,[1] Valentina Poretto,[1] Alice Favaretto,[1] Sara Alessio,[1] Valentina Bernardi,[1] Chiara Romualdi,[2] Francesca Rinaldi,[1] Paola Perini[1] and Paolo Gallo[1]

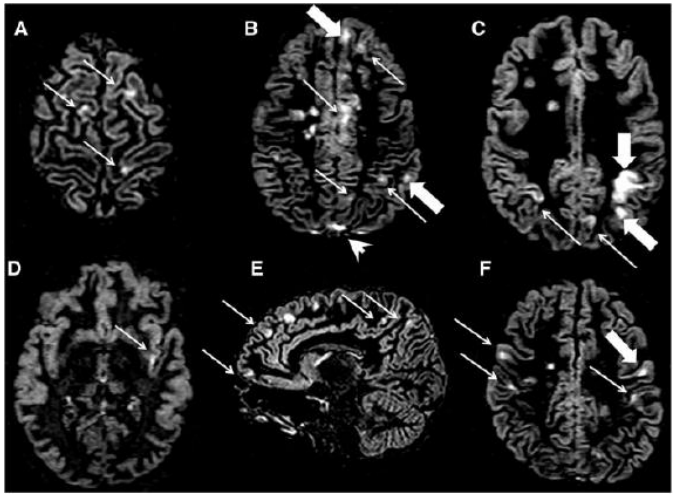

Table 2 MRI characteristics at study entry (T0) and after 5 years (T5) of patients showing disability progression compared with clinically stable patients

Parameter	Clinically stable ($n = 170$)	With disability progression ($n = 101$)
T0		
Patients with cortical lesions	113 (66.4%)	90 (89.1%)**
Cortical lesion number	2.7 ± 3.5 (0–20)	4.5 ± 5.5 (0–24)**
Cortical lesion volume	0.7 ± 0.5 (0–2.1)	1.2 ± 0.7 (0–3.8)**
WMLV (cm^3)	5.9 ± 4.1 (0.4–4)	6.5 ± 5.3 (0.3–20.6)
T5		
Patients with cortical lesions	122 (71.8%)	91 (90.0%)*
Patients with new cortical lesions	118 (69.4%)	85 (84.2%)*
New cortical lesions	1.3 ± 1.8 (0–8)	4.8 ± 2.9 (0–12)**
Cortical lesion volume change	0.4 ± 0.3 (0–0.8)	0.9 ± 0.5 (0–0.9)**
New white matter lesions	3.8 ± 1.6 (0–11)	4.0 ± 3.0 (0–14)
Patients with new white matter lesions	92 (54.1%)	65 (64.4%)
WMLV change	1.4 ± 1.0 (0.2–3.9)	1.6 ± 0.9 (0.4–5.9)
Grey matter fraction % change	1.6 ± 1.5 (0.6–3.6)	2.3 ± 1.8 (0.9–4.9)*

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

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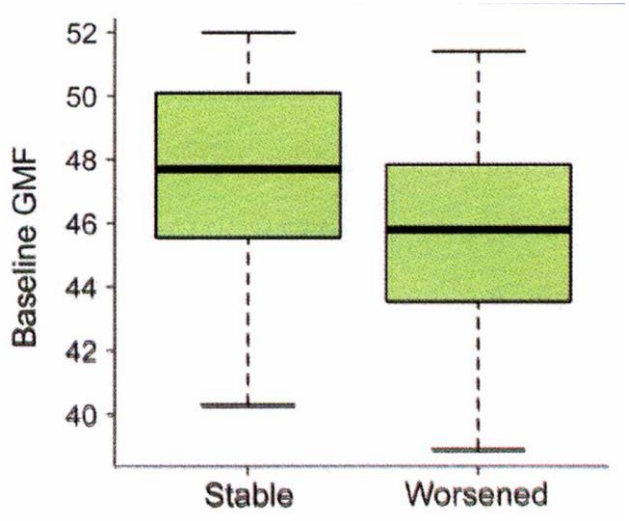
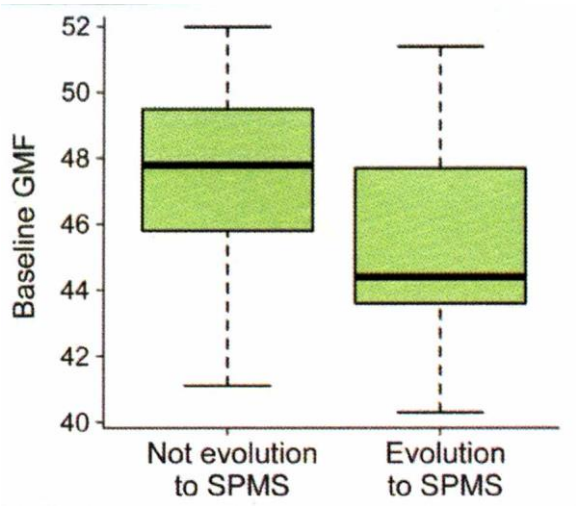
Neurology® 2013;81:1759-1767

Gray matter damage predicts the accumulation of disability 13 years later in MS

Massimo Filippi, MD
Paolo Preziosa, MD
Massimiliano Copetti, PhD
Gianna Riccitelli, PhD
Mark A. Horsfield, PhD
Vittorio Martinelli, MD
Giancarlo Comi, MD
Maria A. Rocca, MD





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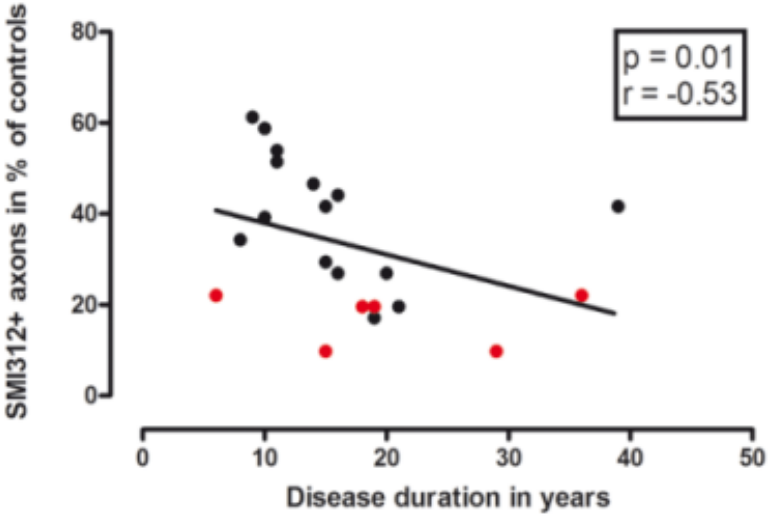
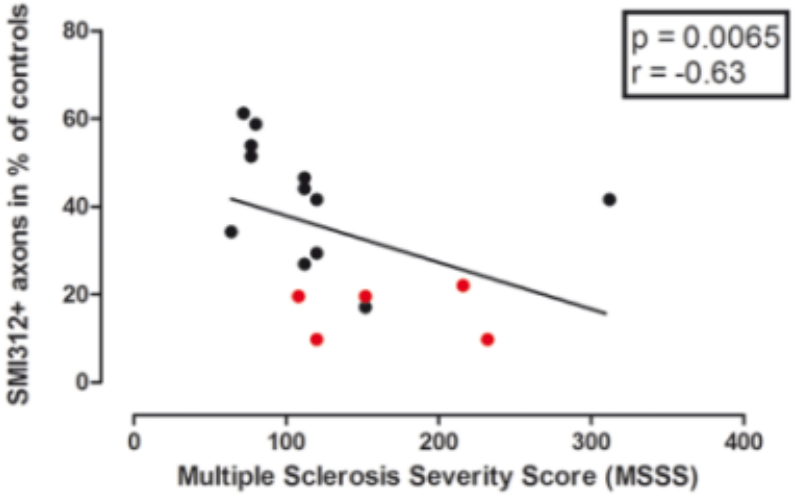
Key areas

- Inflammation
- Gray matter involvement
- Axonal loss

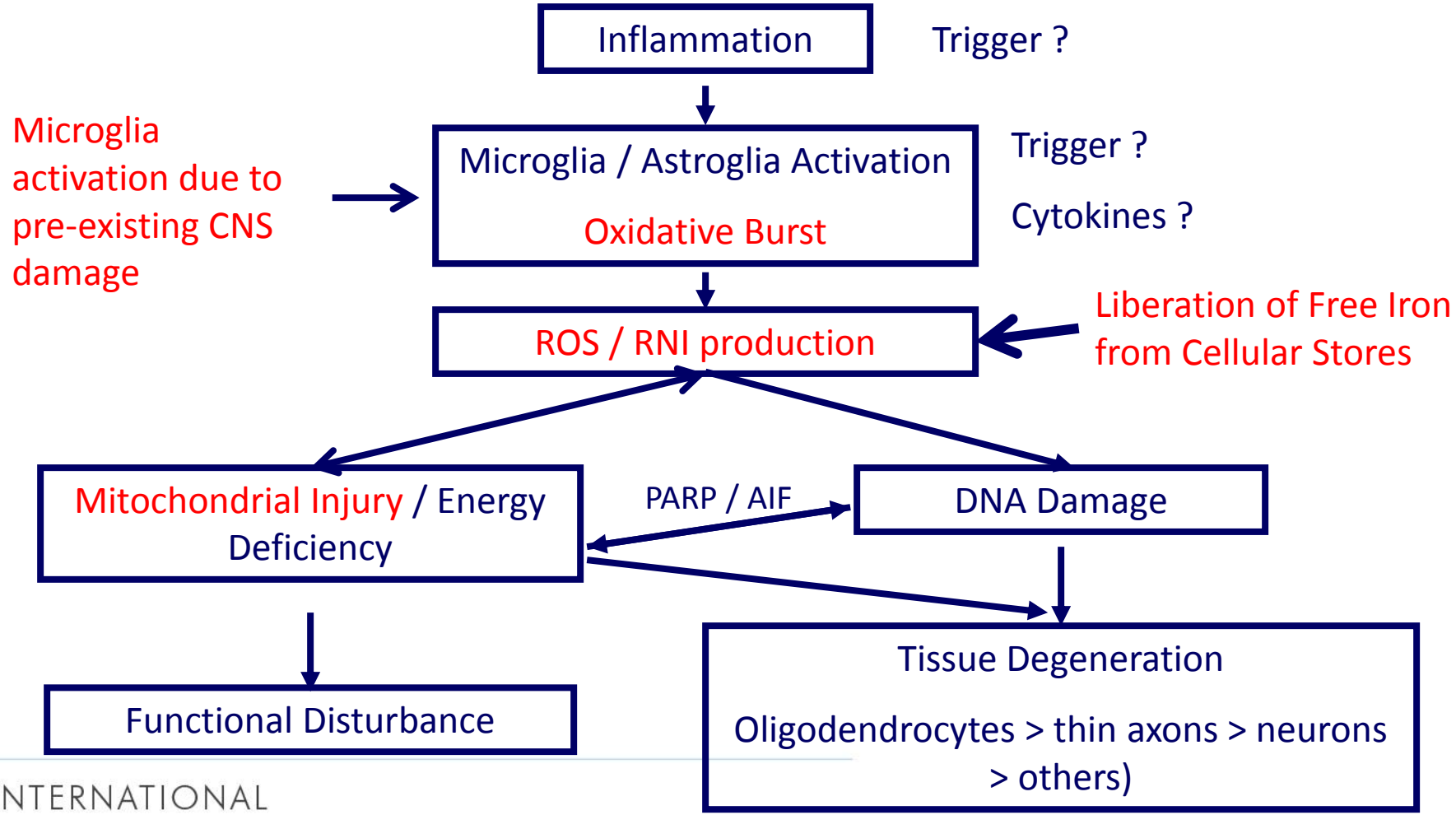
Spinal cord axonal loss correlates with disease duration and disability



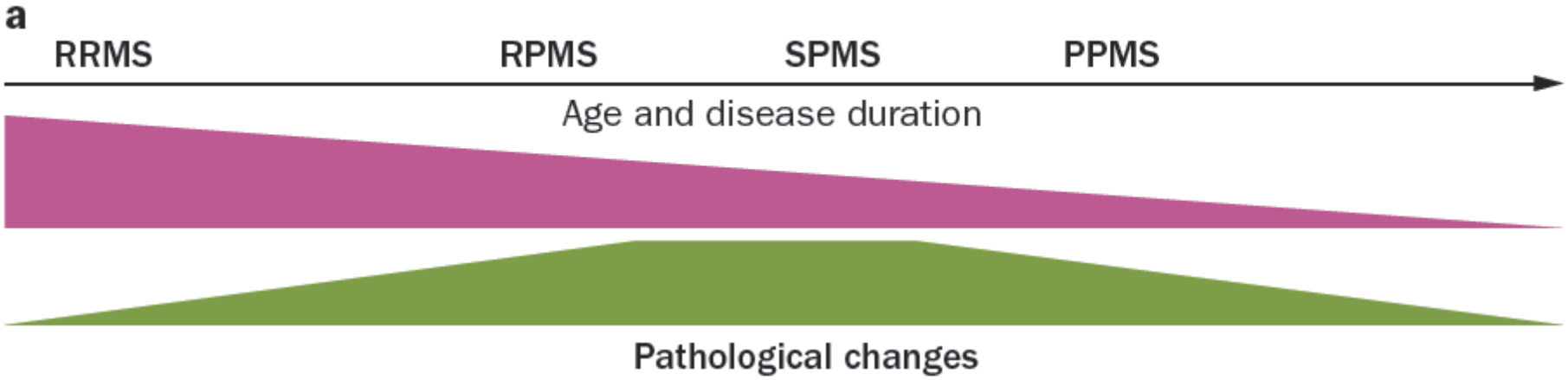


Schirmer et al., Brain Pathol 2011

Neurodegeneration in MS



Summary



- Inflammation
- New waves of lymphocytes entering the CNS
- Blood–brain barrier disturbance
- New active CNS lesions
- Initial remyelination in active lesions

- Trapped inflammation
- Meningeal inflammatory aggregates
- Slow expansion of pre-existing lesions
- Subpial cortical demyelination
- Diffuse white matter injury
- Brain atrophy

Lassmann et al., Nat. Rev. Neurol. 2012

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Outcomes/Biomarkers

- Clinical
- Imaging
- 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
JOURNAL

Meeting Review

Multiple Sclerosis Outcome Assessments Consortium: Genesis and initial project plan

Multiple Sclerosis Journal
2014, Vol 20(1) 12–17

DOI: 10.1177/1352458513503392
msj.sagepub.com
SAGE

Richard A Rudick[1], Nicholas LaRocca[2], Lynn D Hudson[3] and MSOAC

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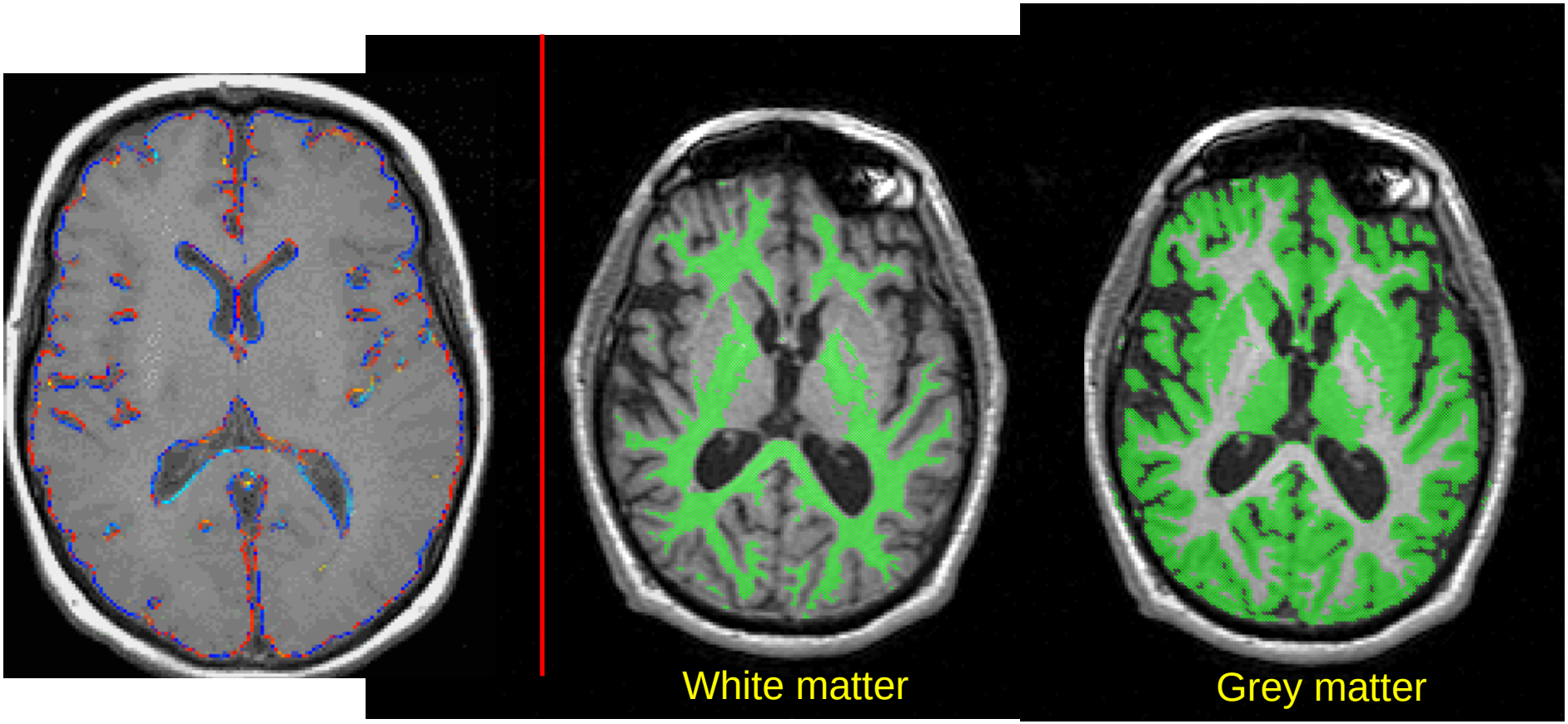
MRI measures for Progressive MS trials

- Recommend T2 lesion load and brain atrophy

- Emerging MRI measures
  - Grey matter atrophy and spinal cord atrophy
  - Diffusion-MRI measures of axonal density/diameter
  - Sodium imaging

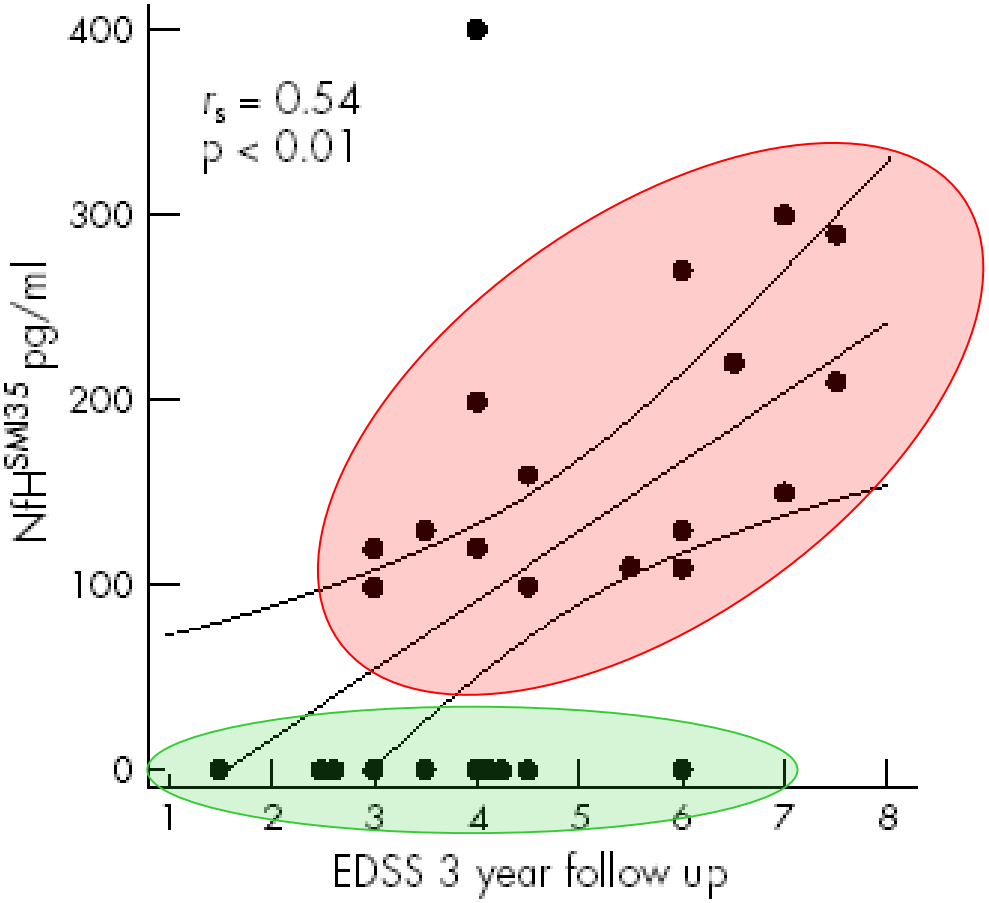
Brain atrophy



Changes in 1 year in normal control: 0.2-0.4%

Changes in 1 year in MS patients: 0.5-1%

Spinal fluid neurofilament levels



Petzold et al. J Neurol Neurosurg Psychiatry. 2005 Feb;76(2):206-11.

Danish Multiple Sclerosis Center

UNIVERSITY OF COPENHAGEN

Natalizumab treatment of progressive multiple sclerosis reduces inflammation and tissue damage

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

J. Romme Christensen[1], R. Ratzer[1], L. Börnsen[1], E. Garde[2], M. Lyksborg[2], H.R. Siebner[2], T.B. Dyrby[2], P. Soelberg Sørensen[1] and F. Sellebjerg[1]

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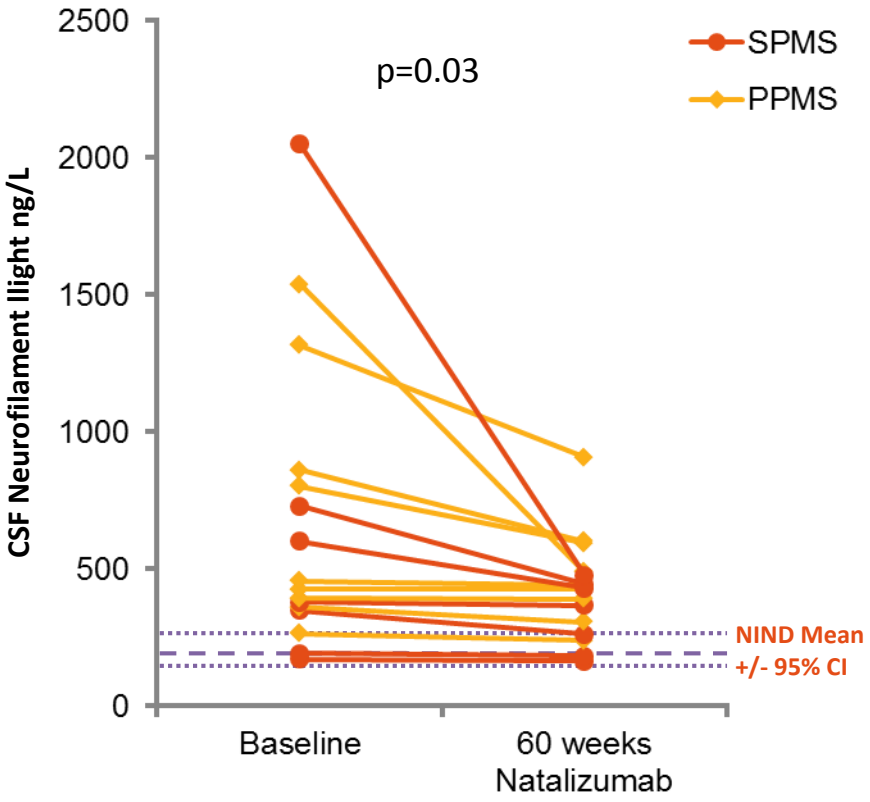
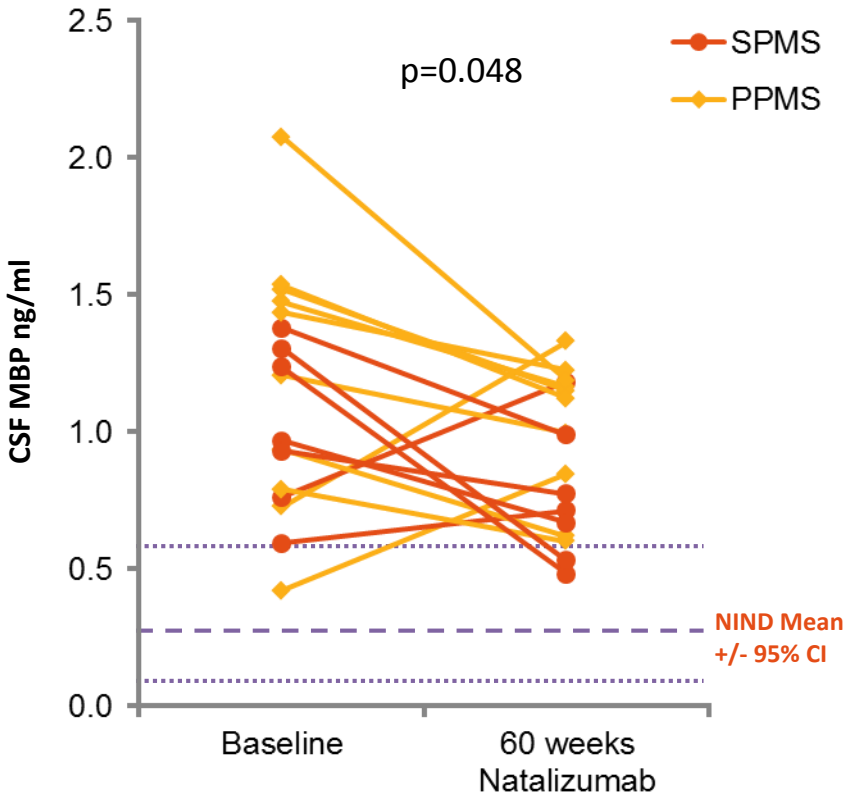
ClinicalTrials.gov Identifier: NCT01077466

Phase 2A study: CSF markers of axonal damage and demyelination (secondary endpoints)





Romme Christensen J, *et al*..

INTERNATIONAL
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Clinical Trials

Conventional trial design

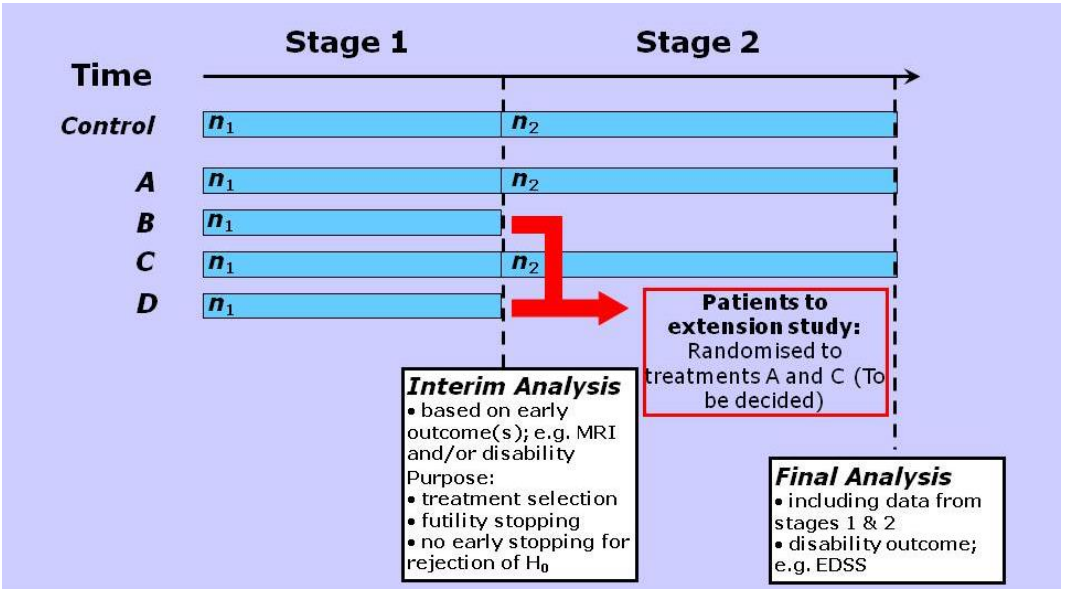
Large numbers, lengthy, very expensive

Targeting inflammation (largely)

=> Need to consider new trial designs

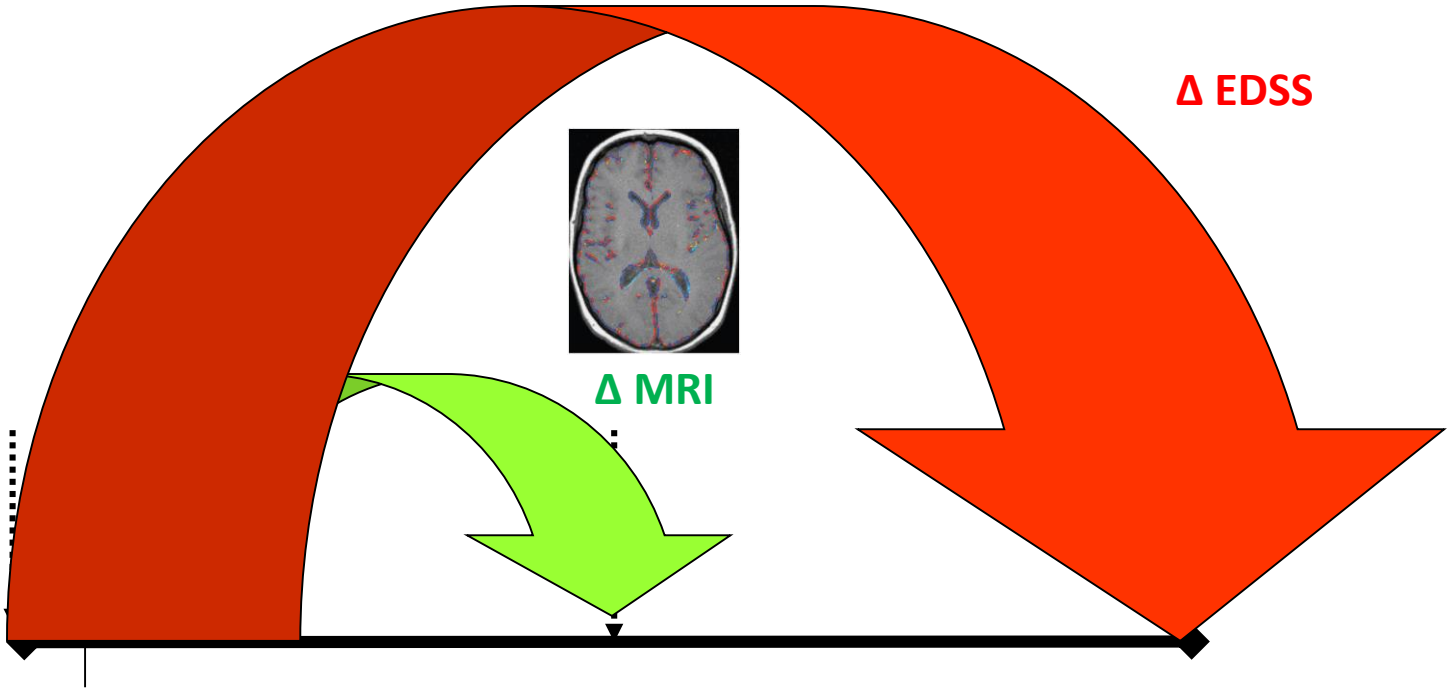
=> Need to focus on neuroprotection/repair?

Moving to adaptive trials



INTERNATIONAL
PROGRESSIVE MS ALLIANCE

The interim measure



Research Paper

MULTIPLE SCLEROSIS JOURNAL

Multiple Sclerosis Journal
17(1) 81–88

DOI: 10.1177/1352458510382129
msj.sagepub.com
SAGE

A novel adaptive design strategy increases the efficiency of clinical trials in secondary progressive multiple sclerosis

Jeremy Chataway[1,2], Richard Nicholas[2], Susan Todd[3], David H Miller[1,4], Nicholas Parsons[5], Elsa Valdés-Márquez[3], Nigel Stallard[5] and Tim Friede[5]

INTERNATIONAL
PROGRESSIVE MS ALLIANCE

- Introduction
- Challenges
- Current activity
- Future directions

INTERNATIONAL
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Previous trials

Table 2 A: Trials in MS								
Trial	**N**	**Follow Up in Yrs**	**Entry EDSS**	**Active Treatment**	**Primary outcome measure**	**Primary Result**	**Comments**	**Publication Yr & Ref**
Cyclosporine-MSSG	547	1.5	3.0-7.0	Cyclosporine	Time to confirmed EDSS worsening	-ve	Two other co-primary endpoints were also used: time to wheelchair bound (+ve); activites of daily living (-ve)	**1990**
CCMSSG	168	2 (mean)	4.0-6.5	Cyclo-phosphamide or plasma exchange	Comparison of rates of EDSS worsening	-ve		**1991**
EUSPMS	718	3	3.0-6.5	Betaseron 8MU/alternate days vs placebo	Time to confirmed EDSS worsening	-/+ve	Enrollment allowed if pre-study deterioration due to incomplete relapse recovery (more of RRMS cohort)	**1998**
SPECTRIMS	618	3	3.0-6.5	Rebif (22 or 44mcg 3/week)	Time to confirmed EDSS worsening	-ve		**2001**
IMPACT	436	2	3.5-6.5	Avonex (60mcg/week)	MSFC	-/+ve	Positive outcome on MSFC (upper limb but not walking component), but not EDSS	**2002**
MIMS	188	2	3.0.-6.0	Mitoxantrone 5 or 12 mg/m2 every 3 months	Composite measure (EDSS/ ambulation index/relapses)	-/+ve	50% of cohort RRMS; 5 domain outcome measure not validated; cardiotoxicity/leukaemia risk	**2002**
NASG	939	3	3.0-6.5	Betaseron 8MU or 5MU/m2 alternate days	Time to confirmed EDSS worsening	-ve		**2004**
ESIMS	318	2	3.0-6.5	Immunoglobulin 1g/kg/month (27 months)	Time to confirmed EDSS worsening	-ve		**2004**
MAESTRO	612	2	3.0-6.5	MBP8298	Time to confirmed EDSS worsening	-ve		**2011**

Table 2 B: Current UK Trials in SPMS						
Trial	**N**	**Follow up Yrs**	**Entry EDSS**	**Active Treatment**	Primary outcome measure	**Reporting Date**
CUPID (Phase III)	493	3	4.0-6.5	Tetra-hydrocannabinol	Time to confirmed EDSS worsening; MSIS29 mean change	**2012**
MS-STAT (Phase IIb)	140	2	4.0-6.5	Simvastatin	MRI brain atrophy	**2012**

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

Ann Neurol 2009;66:460–471

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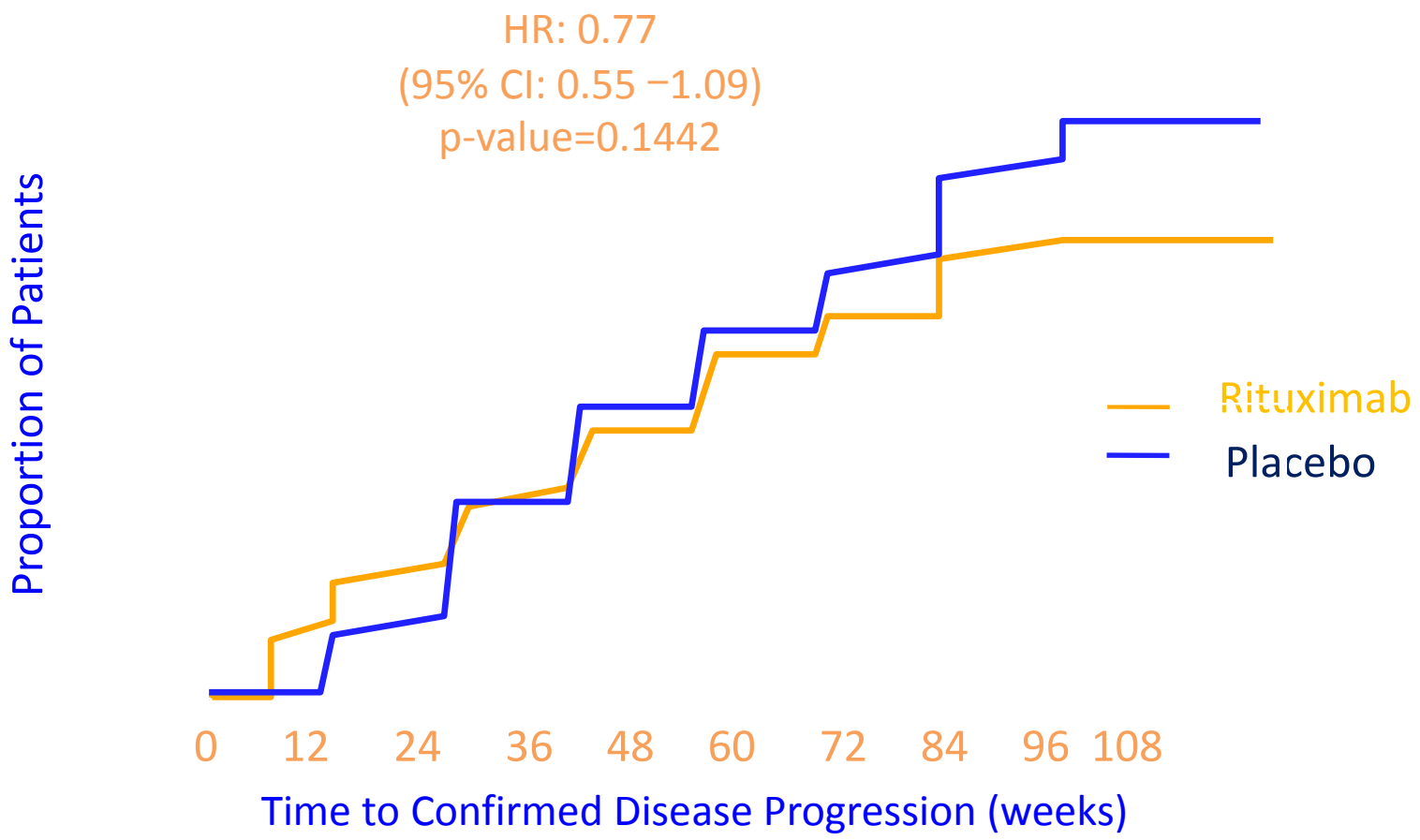
Time to Confirmed Disease Progression

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



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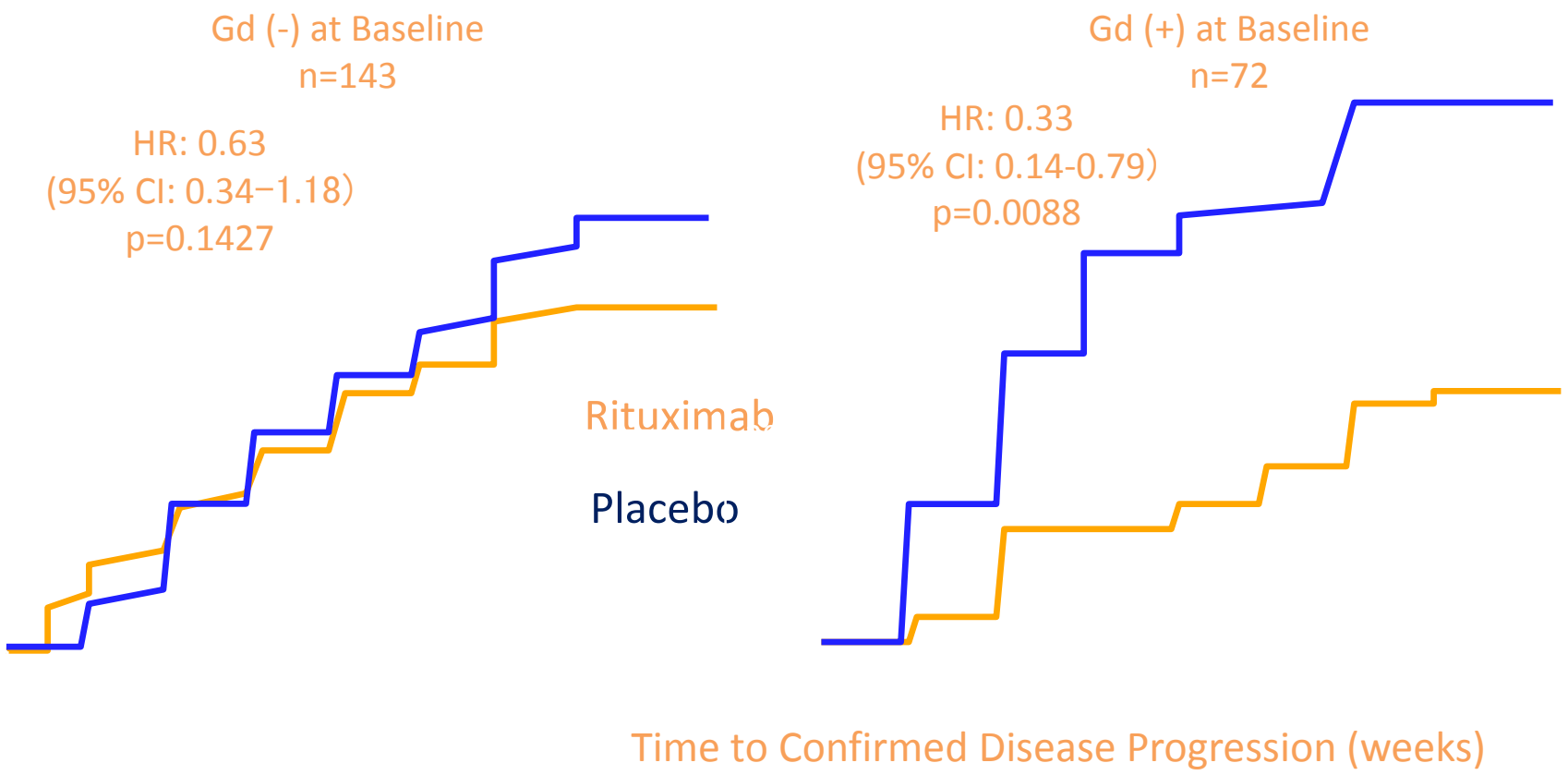
Time to Confirmed Disease Progression

Subgroup Analysis



Trials in Progressive MS

- Phenytoin Optic Neuritis Study (Phase II)
- PROXIMUS Trial - oxcarbazepine in SPMS (Phase II)
- **INFORMS – fingolimod in PPMS (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

Lancet 2014; 383: 2213–21

Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial

Jeremy Chataway, Nadine Schuerer, Ali Alsanousi, Dennis Chan, David MacManus, Kelvin Hunter, Val Anderson, Charles R M Bangham, Shona Clegg, Casper Nielsen, Nick C Fox, David Wilkie, Jennifer M Nicholas, Virginia L Calder, John Greenwood, Chris Frost, Richard Nicholas

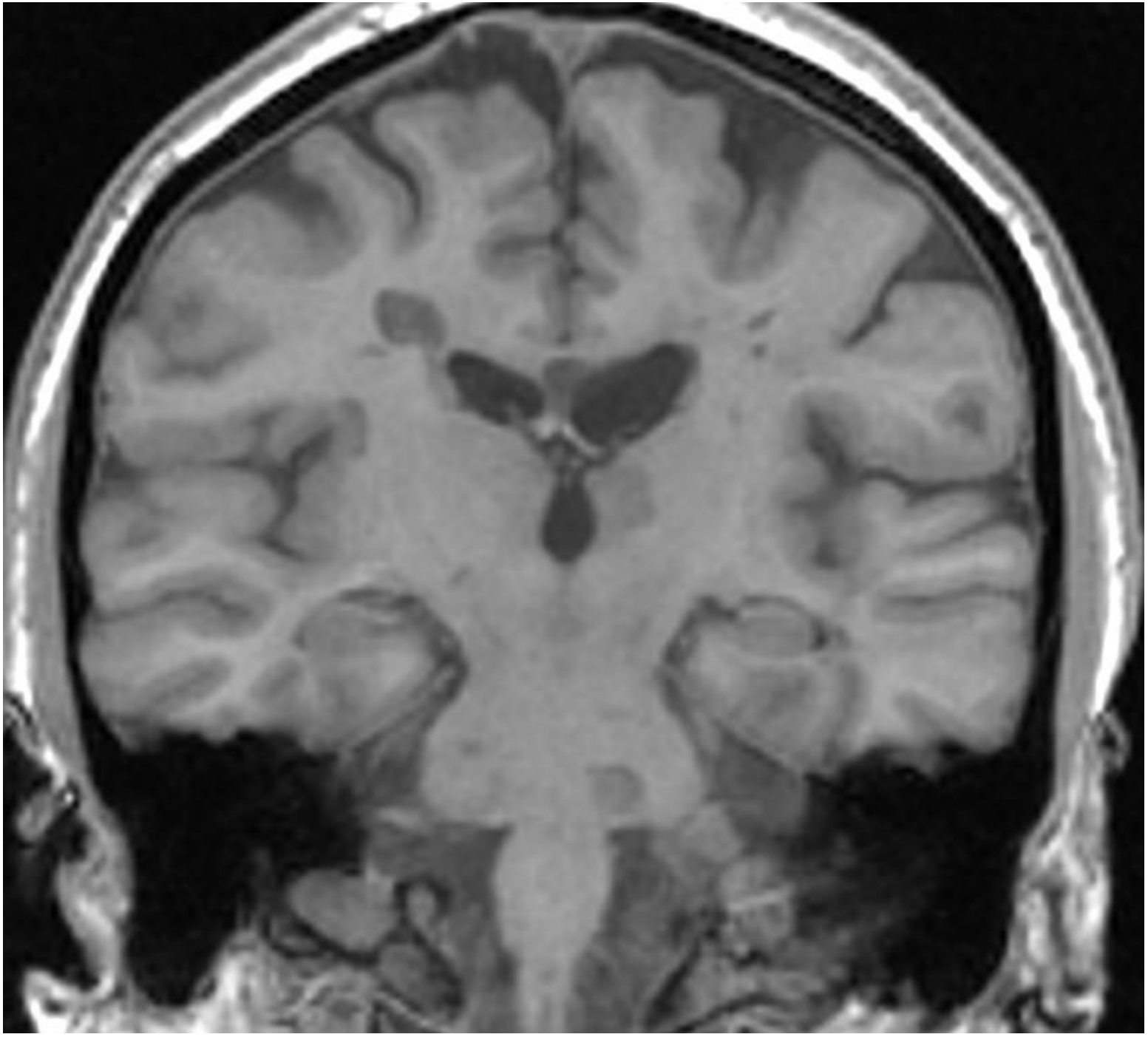
INTERNATIONAL
PROGRESSIVE MS ALLIANCE

- High-dose simvastatin (80mg) in SPMS
- Established secondary progression (narrative/EDSS) for ≥ 2years

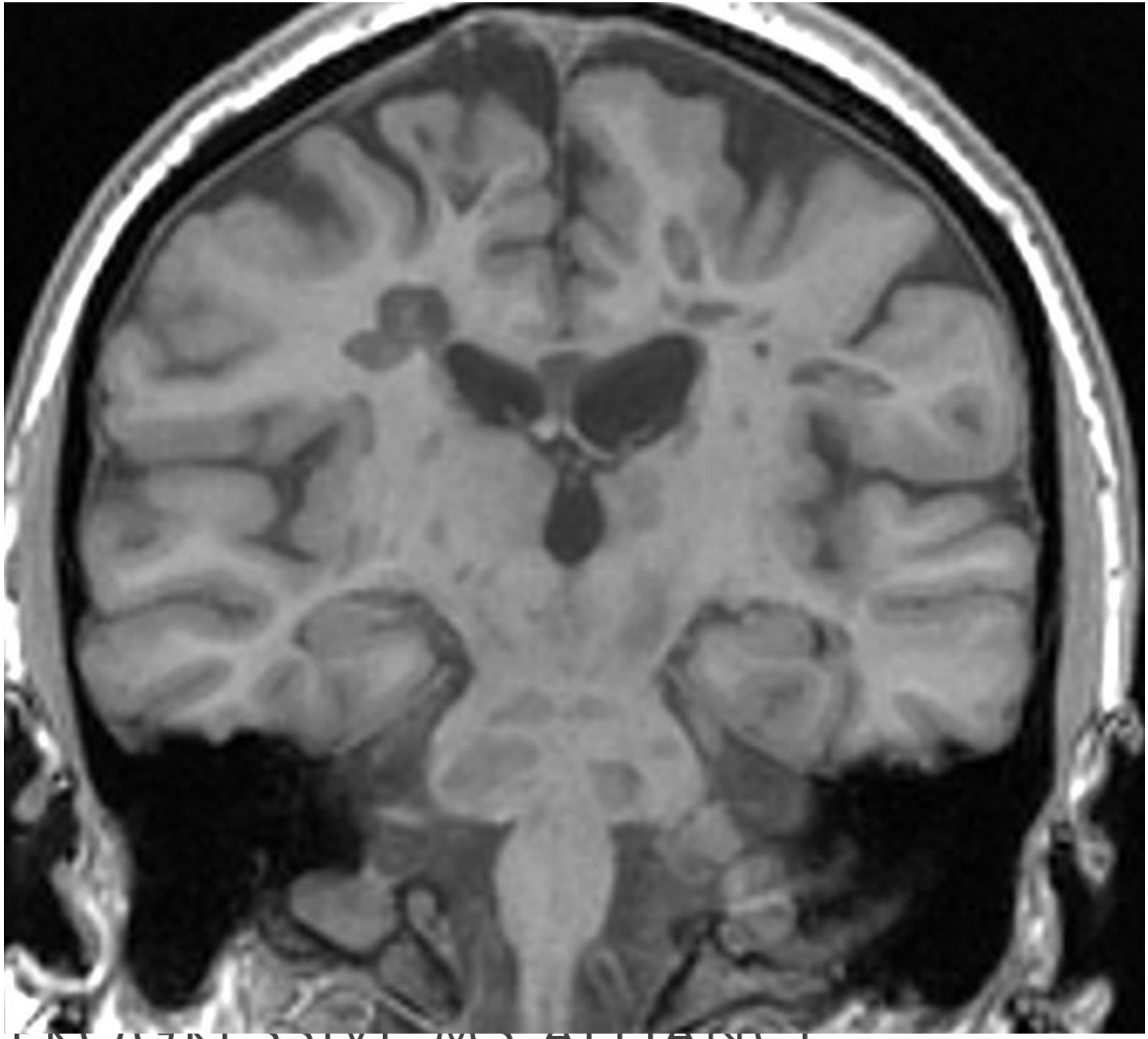
- EDSS 4.0 (500m) - 6.5 (20m/2 sticks)
  - Relapse free/no corticosteroids >3 months
  - DMT >6months
  - Mitoxantrone >12 months
  - Never alemtuzumab/natalizumab

Outcomes

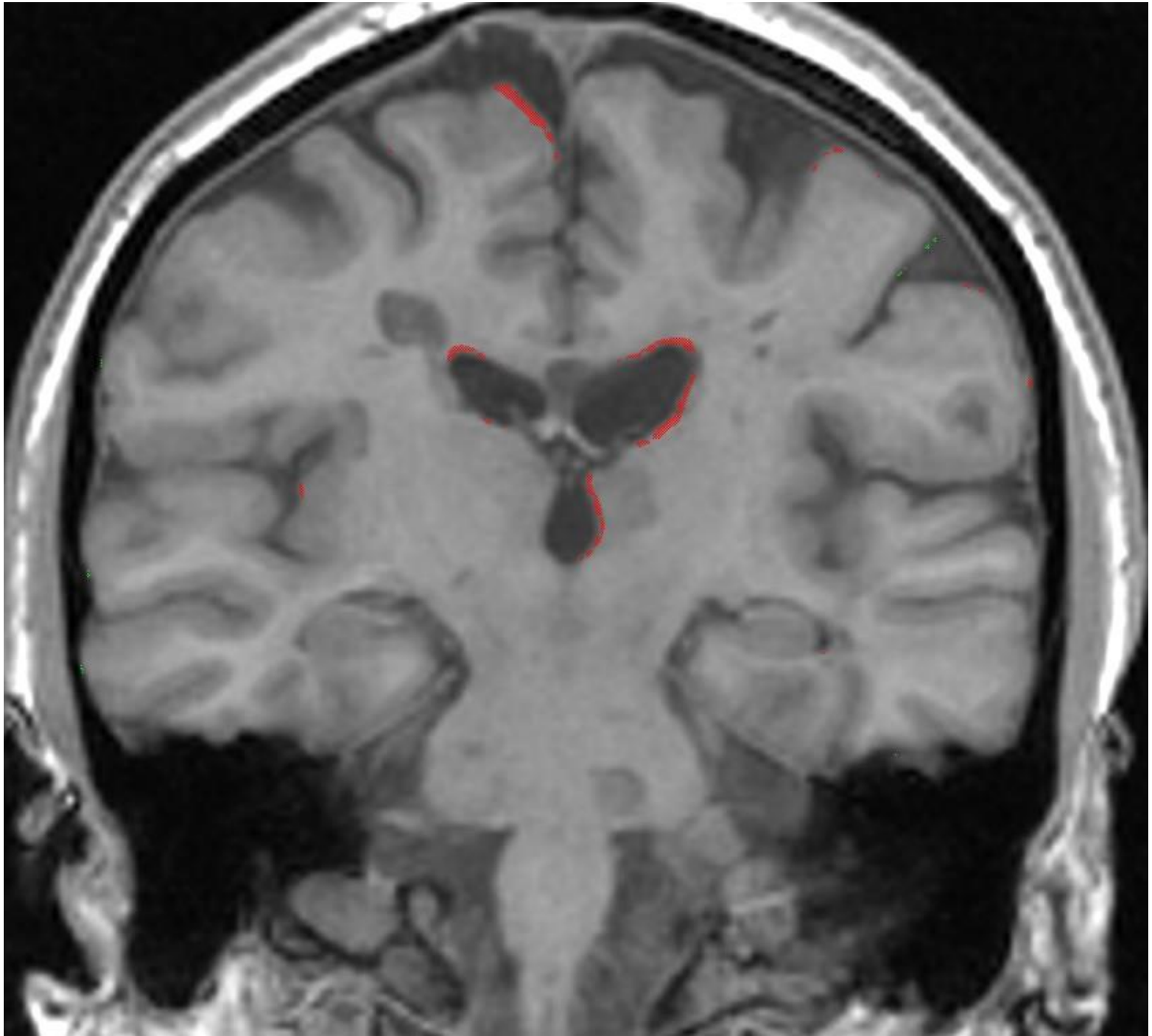
- Primary
  - Volumetric MRI BBSI
- Secondary
  - Disability (EDSS/MSIS-29v2/MSFC)
  - New and enlarging lesions T2 MRI
  - Relapses
  - Safety
- Other*
  - Neuropsychology
  - Immunology/Proteomics



Baseline



Registered
Year 2



Screening showing BBSI colour overlay

Primary outcome: BBSI change in whole brain volume (%/year)

	Mean (SD) placebo	**Mean (SD) simvastatin**	**Difference in means (95% CI)***	**p-value**
Change WBV (%/year)	0.589 (0.528)	0.298 (0.562)	-0.254 (-0.423 to -0.085)	0.003
Number patients evaluated	**64**	**66**		

*Adjusting for minimisation variables and MRI site

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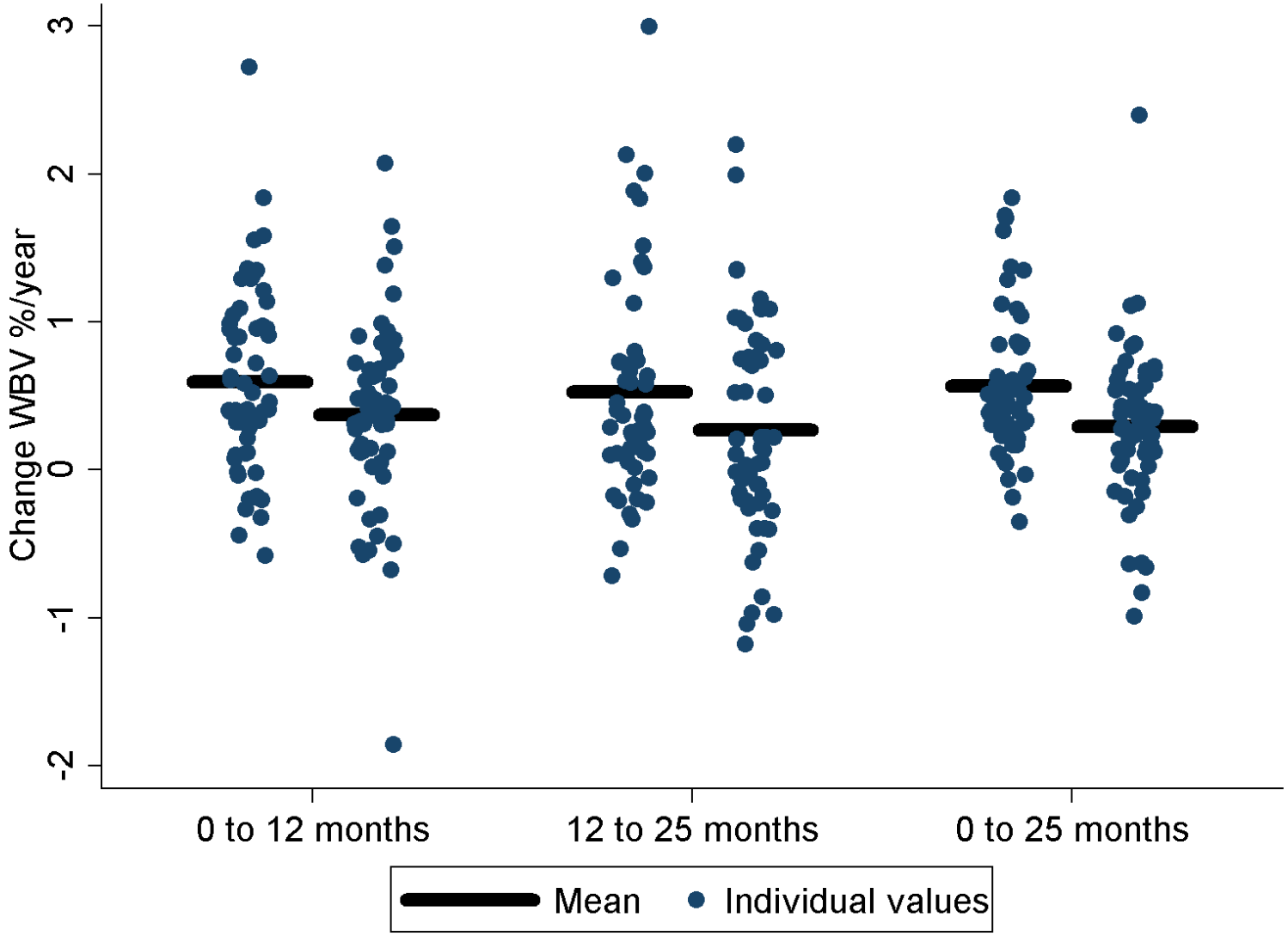
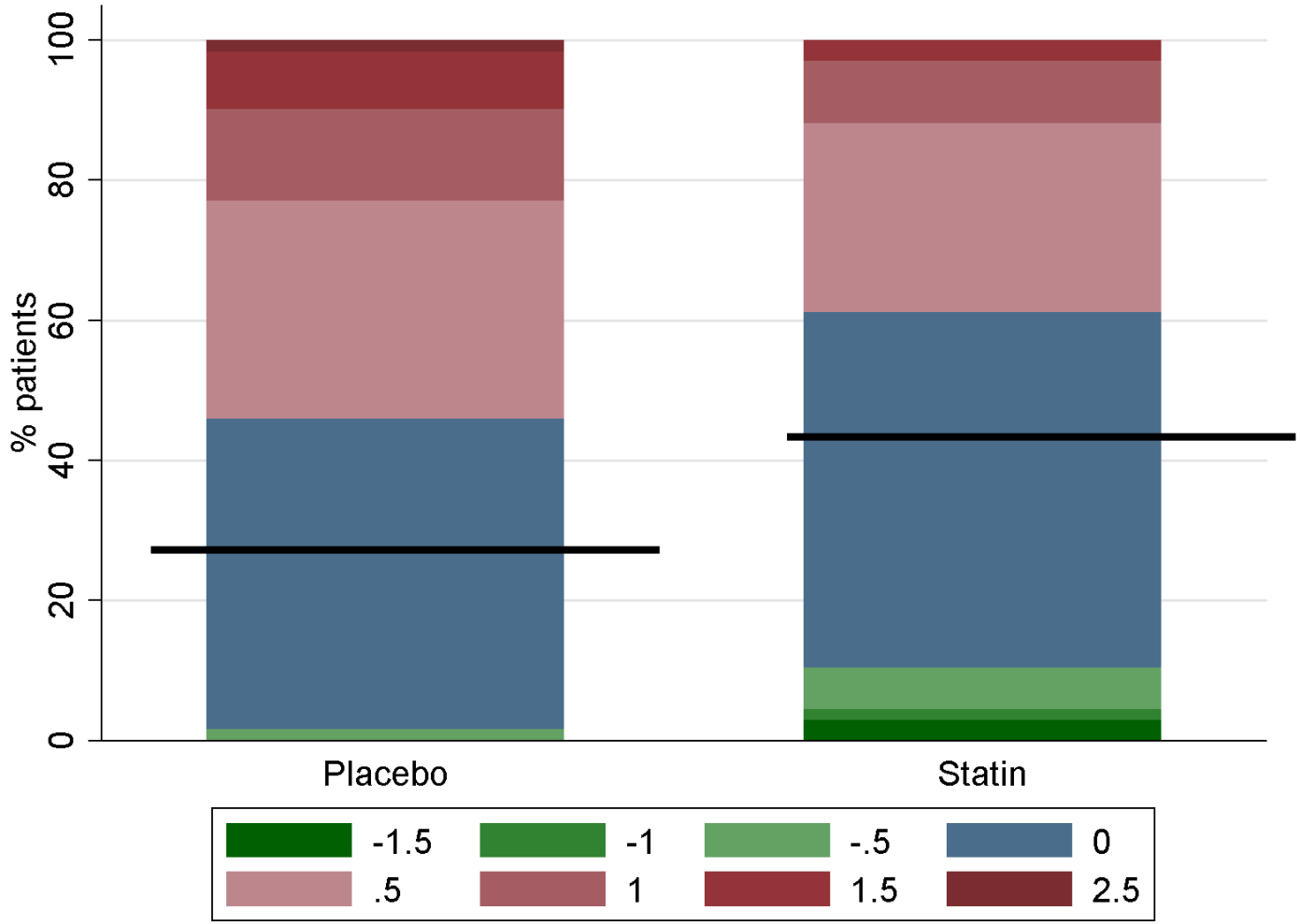
Change whole brain volume (%/yr)



Change in EDSS 0 to 24 months



Change in EDSS from Baseline to 24 months

- Introduction
- Challenges
- Current activity
- Future directions

INTERNATIONAL
PROGRESSIVE MS ALLIANCE

Neuroprotection

Repair/Remyelination

Lifestyle

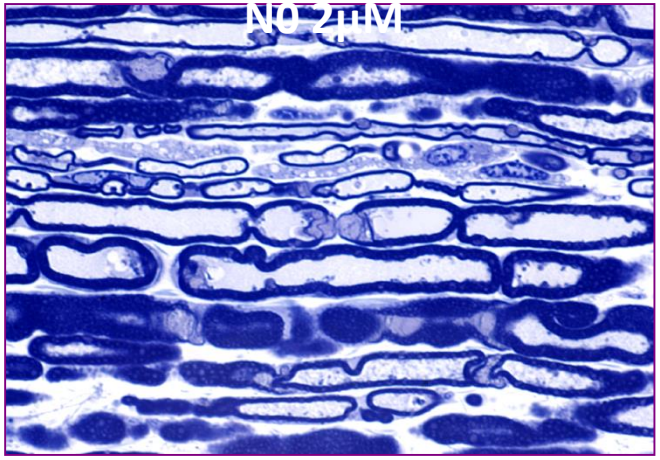
Rehabilitation

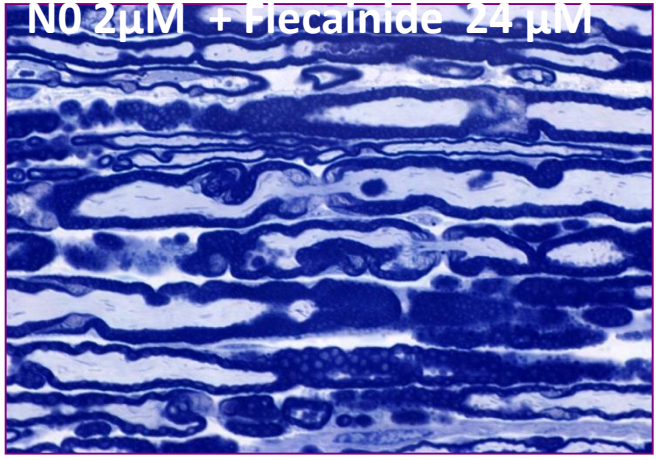
Enhancing plasticity

Neuroprotection: sodium channel blockers

Partial sodium channel blockade has been shown to be neuroprotective in experimental models of inflammatory axonal injury

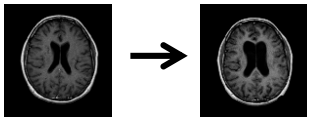
Flecainide, lamotrigine, oxcarbazepine, phenytoin





Kapoor et al 2003, Loh et al 2003, Craner et al 2005

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 was 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.

Lancet Neurol 2010; 9: 681–88

Published Online
June 7, 2010
DOI:10.1016/S1474-4422(10)70131-9

See Reflection and Reaction page 647

Department of Neuroinflammation, National Hospital for Neurology and Neurosurgery and the Institute of Neurology, Queen Square, London, UK (R Kapoor FRCP, J Furby MRCP, T Hayton MRCP, Prof K J Smith PhD, D R Altmann PhD, J Chataway FRCP, Prof R A C Hughes FRCP, Prof D H Miller FRCP); **Medical Statistics Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK** (D R Altmann); **and Department of Neurology, Royal Free Hospital, Pond Street, London, UK** (R Brenner FRCP)

Correspondence to:
Raju Kapoor, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK
raj.kapoor@uclh.nhs.uk

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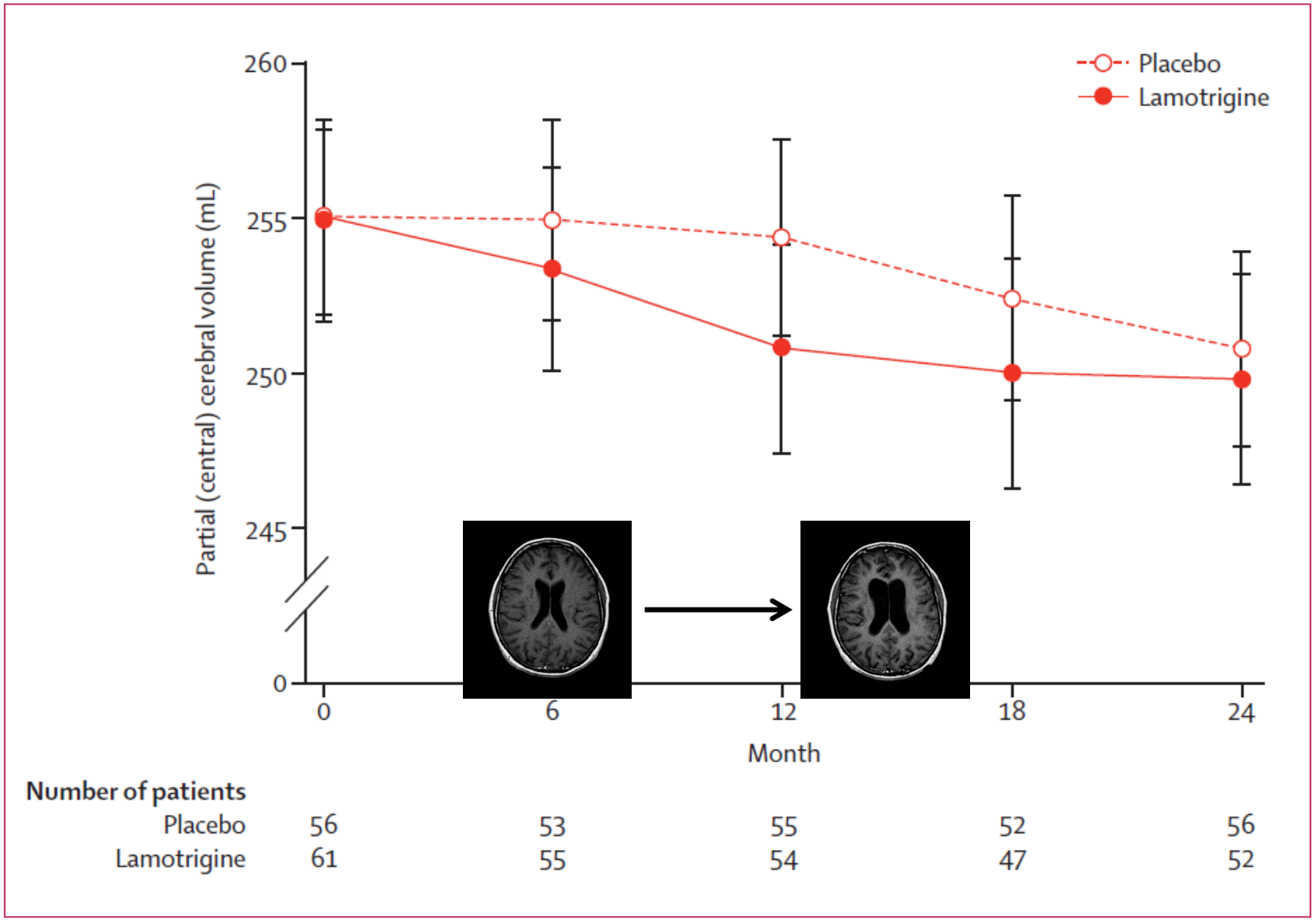

Figure 2: **Primary outcome**
Mean partial (central) cerebral volume by intention-to-treat comparison, including numbers of valid 6-monthly observations. Bars=SE.

Kapoor et al. Lancet Neurol 2010; 9: 681–88.

INTERNATIONAL
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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 3: Putative Neuroprotective Repurposed Drugs Selected for Phase IIb Trial Evaluation						
Repurposed Drug For MS	**Approved in other clinical Indications**	**POC in MS Patients**	**POC in other Neurodegenerative Diseases**	**MS Animal Model Data**	**Putative Neuroprotective mechanism**	**Refs**
Ibudilast [MN-166; AV-411] (MediciNova Inc)	Used in asthma and post-stroke disorders in Japan for ~ 20 years	YES (Phase IIa Trial)			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	Barkhof F. Neurol 2010; 74,1033–1040
Amiloride [MK 870]	Used in UK for Hypertension & congestive heart failure	YES		YES	Acid sensing ion channel blocker	de Ruiter MB. Late breaking trial news: ECTRIMS Amsterdam 19-22 Oct 2011.
Riluzole [Rilutek] (Sanofi-Aventis)	Used for Amyotrophic lateral sclerosis (ALS), also referred to as Lou Gehrig's disease / motor neurone disease	YES	YES	YES	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.	Killestein J. J. Neurol Sci 2005

Amiloride blockade of the acid-sensing ion channel is myelo- and neuro-protective in CNS inflammation

nature medicine

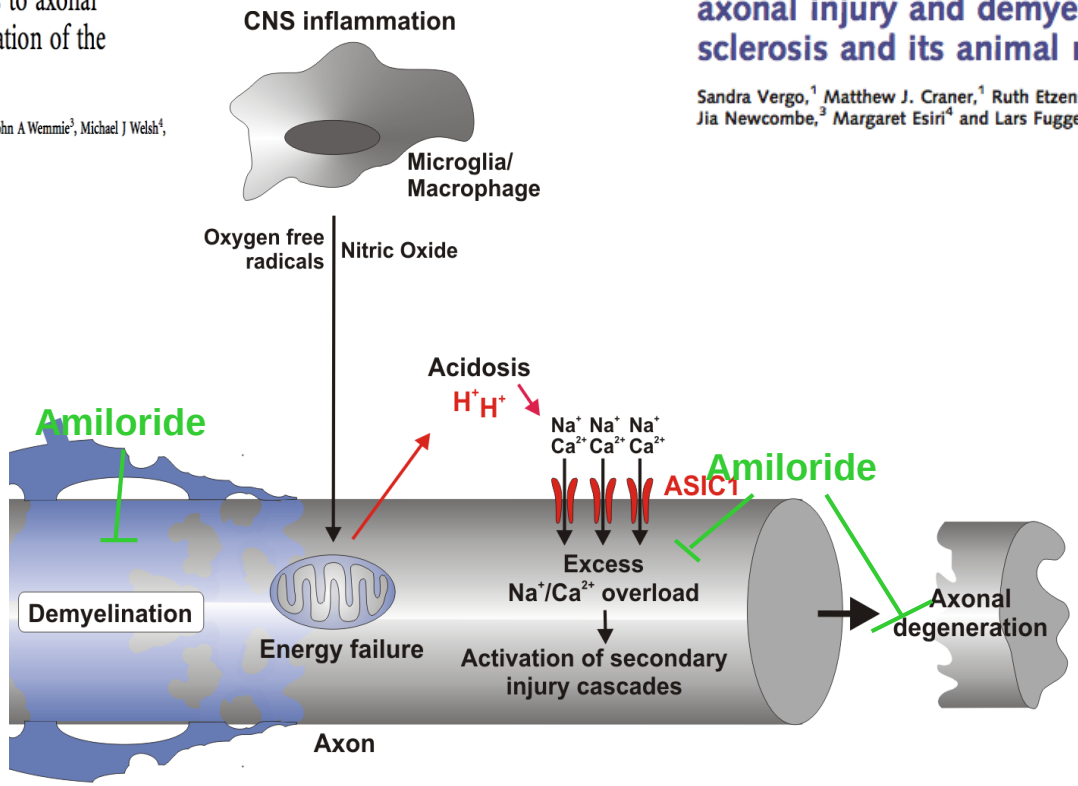
Acid-sensing ion channel-1 contributes to axonal degeneration in autoimmune inflammation of the central nervous system

Manuel A Friese[1], Matthew J Craner[2], Ruth Etzensperger[1], Sandra Vergo[1], John A Wemmie[3], Michael J Welsh[4], Angela Vincent[2] & Lars Fugger[1,5]

doi:10.1093/brain/awq337 Brain 2011: 134; 571–584 | 571
BRAIN
A JOURNAL OF NEUROLOGY

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

Sandra Vergo,[1] Matthew J. Craner,[1] Ruth Etzensperger,[1] Kathrine Attfield,[1] Manuel A. Friese,[1,2] Jia Newcombe,[3] Margaret Esiri[4] and Lars Fugger[1]



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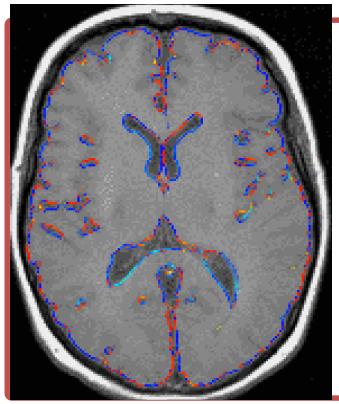
Slide courtesy of M Craner

doi:10.1093/brain/aws325 Brain 2013: 136; 106–115 | 106
BRAIN
A JOURNAL OF NEUROLOGY

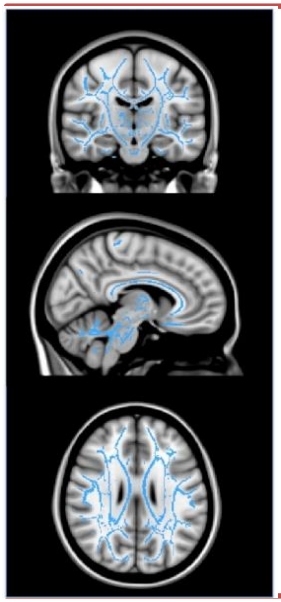
Targeting ASIC1 in primary progressive multiple sclerosis: evidence of neuroprotection with amiloride

Tarunya Arun,[1,2,*] Valentina Tomassini,[1,2,3,*] Emilia Sbardella,[1,2,4] Michiel B. de Ruiter,[2,5] Lucy Matthews,[1,2] Maria Isabel Leite,[1] Rose Gelineau-Morel,[6] Ana Cavey,[1] Sandra Vergo,[1,7] Matt Craner,[1,7] Lars Fugger,[1,7] Alex Rovira,[8] Mark Jenkinson[2] and Jacqueline Palace[1]

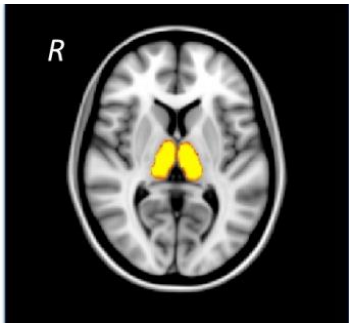
Amiloride treatment in primary progressive MS



Atrophy rate reduced in amiloride treated ($p = 0.018$)



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



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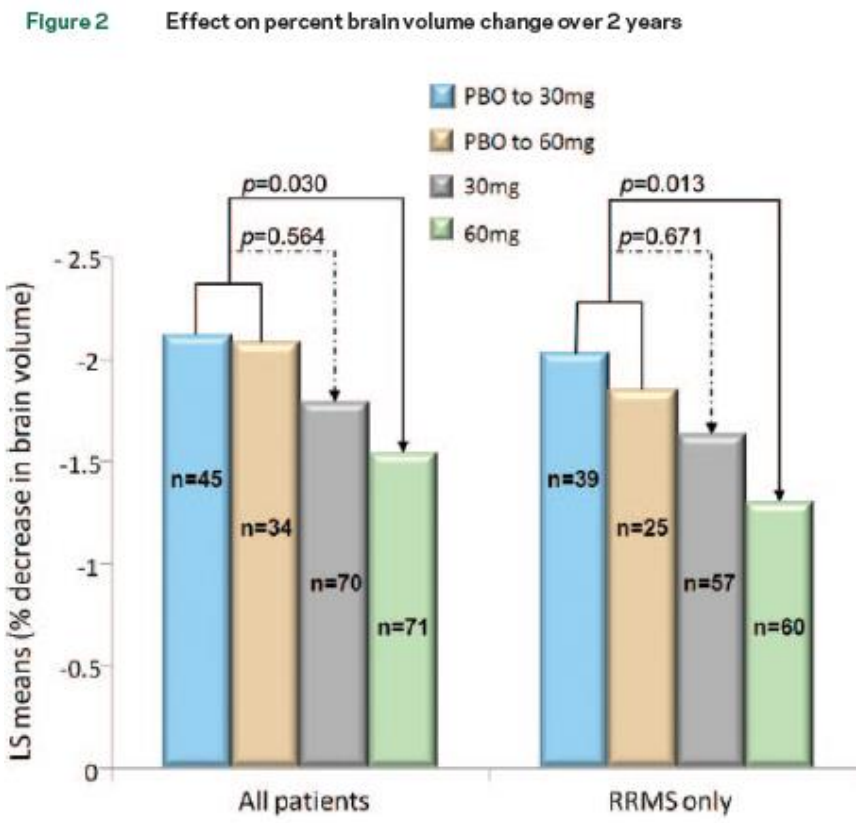
Slide courtesy of M Craner

Ibudilast trial (relapsing remitting MS)

- Phosphodiesterase 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 **P**rimary p**R**rogressive **I**budilast **N**euroNEXT **T**rial in **M**ultiple **S**clerosis

- 96-week, randomized, placebo-controlled phase II trial of ibudilast 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, NIH-funded, Phase II clinical trial network

Head-to-head comparison of imaging measures

– Longitudinal validation to clinical outcomes

INTERNATIONAL
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Acute neuroprotection

An exploratory phase IIa study to evaluate phenytoin as neuroprotective strategy in acute optic neuritis

Acute unilateral optic neuritis (OS or MS)

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 has MS EDSS 5.5 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 50 mg) or maximum 300mg/day for 14 weeks
Randomisation based on minimization via web

↓

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

↓

Alternative diagnosis → yes → **Not part of ITT cohort**

↓ no

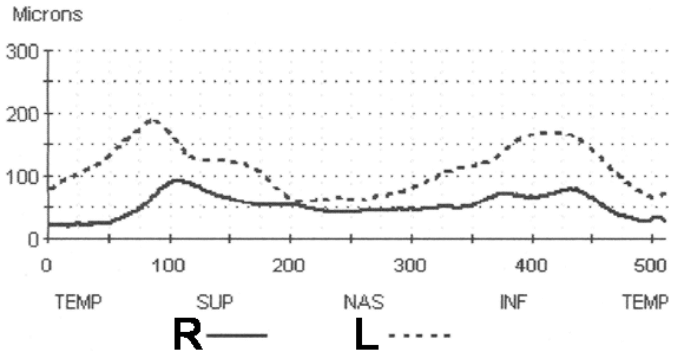
Primary outcome at 26 weeks
Retinal nerve fibre thickness in affected eye

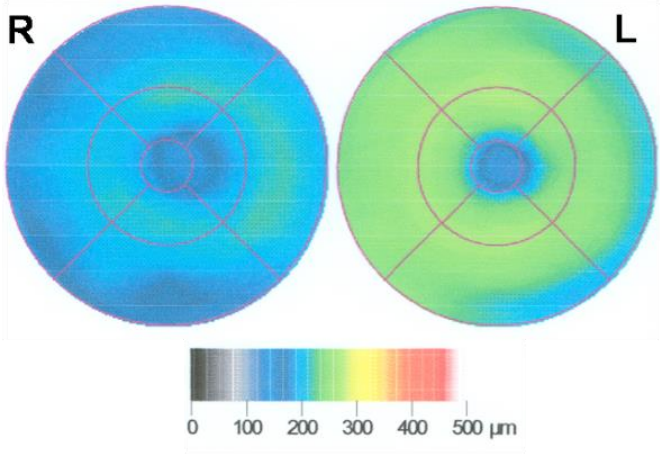
Secondary outcomes at 48 weeks
Low contrast visual acuity
Visual evoked potential latency and amplitude
MRI outcomes
Blood and urine Biomarkers
Safety profile

Estimated power calculations*

Clinical Classification		Placebo 1	Phenytoin	
Alternative diagnosis		?	?	?
ITT population		45	45	90
		45	45	?

*Data from a longitudinal study of OCT findings obtained in 22 patients with acute demyelinating optic neuritis who were followed serially from initial presentation for 12-18 months at Moorfields Eye Hospital and the Institute of Neurology (A Henderson, D Altmann, D Garway-Heath and CH Miller, unpublished) was used to calculate the sample size, based on the most efficient analysis of data on the primary outcome, and a power of 90% to detect a treatment effect of 50% at 5% significance level, allowing for a combined loss to follow-up and non-adherence of 20%.





PROMISE 2010

MSC Treatment of Multiple Sclerosis

Reference	Indication	Patients	MSC Source
Connick 2012	SPMS	10	Autologous culture-expanded BM MSCs administered IV
Karussis 2010	RR, SP, PP MS	15	Autologous culture-expanded BM MSCs administered IV and IT
Liang 2009	PP MS	1	Allogeneic umbilical cord MSCs administered IV and IT after CTX
Mohyeddin Bonad 2007	Treatment-refractory MS	10	Autologous culture-expanded BM MSCs administered IT
Rice 2010	Chronic MS	6	Fresh BM cells enriched for MSCs
Riordan 2009	Treatment-refractory MS	3	Autologous non-expanded adipose MSCs
Yamout 2010	SPMS	10	Autologous culture-expanded BM MSCs administered IT

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

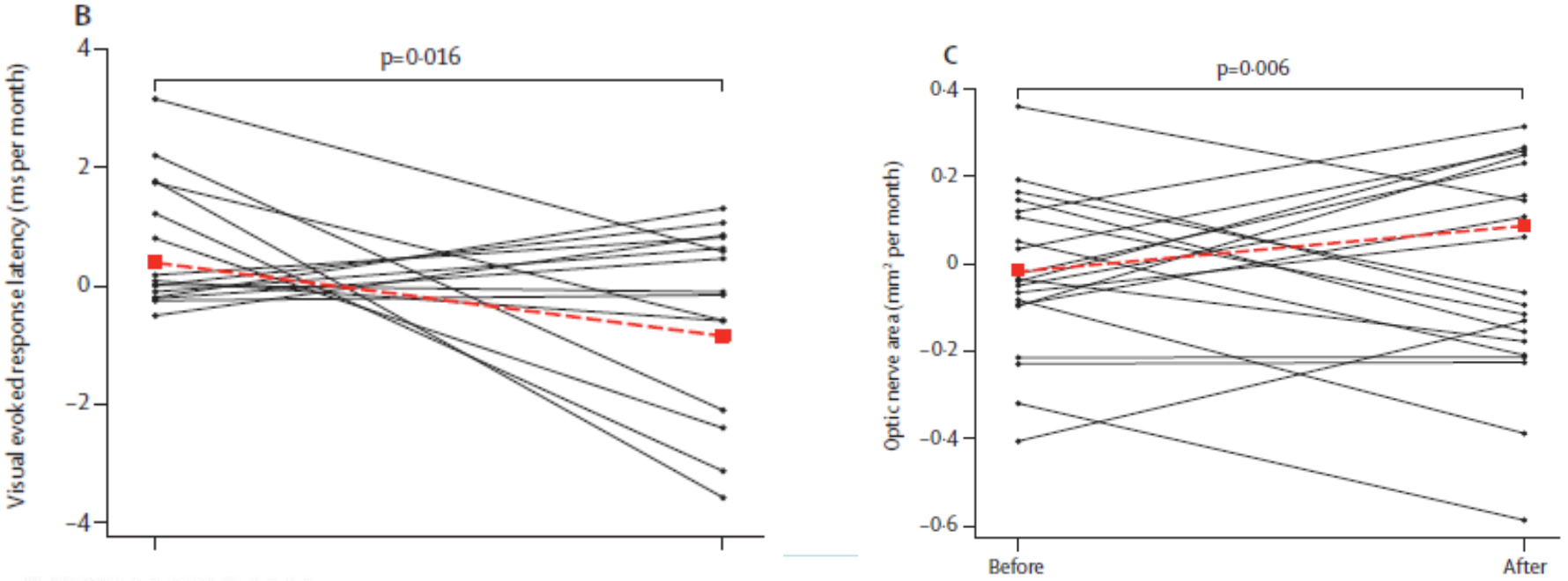
Lancet Neurology Feb 2012

10 patients with secondary progressive MS
Studied visual system

INTERNATIONAL
PROGRESSIVE MS ALLIANCE

Autologous mesenchymal stem cells in secondary progressive MS

- 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)**



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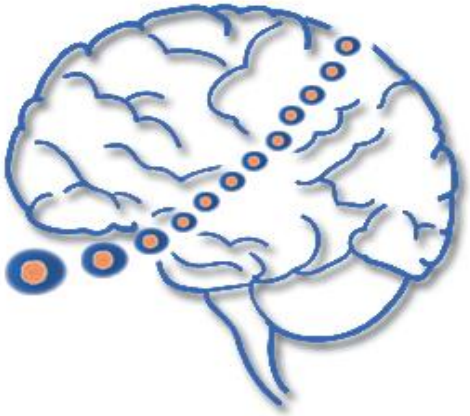
Connick et al Lancet Neurology 2012



IMSCTSG

International Mesenchymal Stem Cell Transplantation Study Group

- 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

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arsep fondation

MS National Multiple Sclerosis Society

CMSC THE CONSORTIUM OF MULTIPLE SCLEROSIS CENTERS

MS Multiple Sclerosis Society of Canada

SCLEROSI MULTIPLA ONLUS fondazione italiana un mondo libero dalla SM

MESEMS Trial

- 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

Mission

To expedite the development of effective disease modifying and symptom management therapies for progressive forms of multiple sclerosis

ms international federation

National Multiple Sclerosis Society

Fondazione Italiana Sclerosi Multipla — un mondo libero dalla SM

Multiple Sclerosis Society

MS Australia

MS Multiple Sclerosis Society of Canada

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Sclerose foreningen

New Perspectives

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–7

DOI: 10.1177/1352458512458169
msj.sagepub.com
SAGE

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

Robert J. Fox[1], Alan Thompson[2], David Baker[3], Peer Baneke[4], Doug Brown[5], Paul Browne[4], Dhia Chandraratna[4], Olga Ciccarelli[2], Timothy Coetzee[6], Giancarlo Comi[7], Anthony Feinstein[8], Raj Kapoor[9], Karen Lee[10], Marco Salvetti[11], Kersten Sharrock[12], Ahmed Toosy[2], Paola Zaratin[13] and Kim Zuidwijk[14]

Multiple Sclerosis Society of Canada

MS RESEARCH

Multiple Sclerosis Society

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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

Scientific Steering Committee

* Alan Thompson, UK, Chair
* Timothy Coetzee, USA
* Kathy Smith, USA
* Paola Zaratin, Italy
* Dhia Chandraratna, MSIF
* Ceri Angood, MSIF
* Susan Kolhaas, UK
Kim Zuitwijk, Netherlands
* Karen Lee, Canada

Giancarlo Comi, Italy , co-Chair
* Bruce Bebo, USA
Robert Fox, USA
Marco Salvetti, Italy

Nick de Rijke, UK
Raj Kapoor, UK
Per Soelberg Sorensen Denmark
Anthony Feinstein, Canada

Countries actively involved in the Alliance

Long term commitment towards PMSA goal

2013 – 2021 PLAN

2013 – 2017 HORIZON 1

- CHALLANGES AWARDS 2013 - 2016
- COLLABORATIVE TEAM AWARDS 2014 - 2017

2017 – 2021 HORIZON 2/3

- INNOVATIVE OPERATIVE FUNDING MODELS TO ACELERATE RESEARCH

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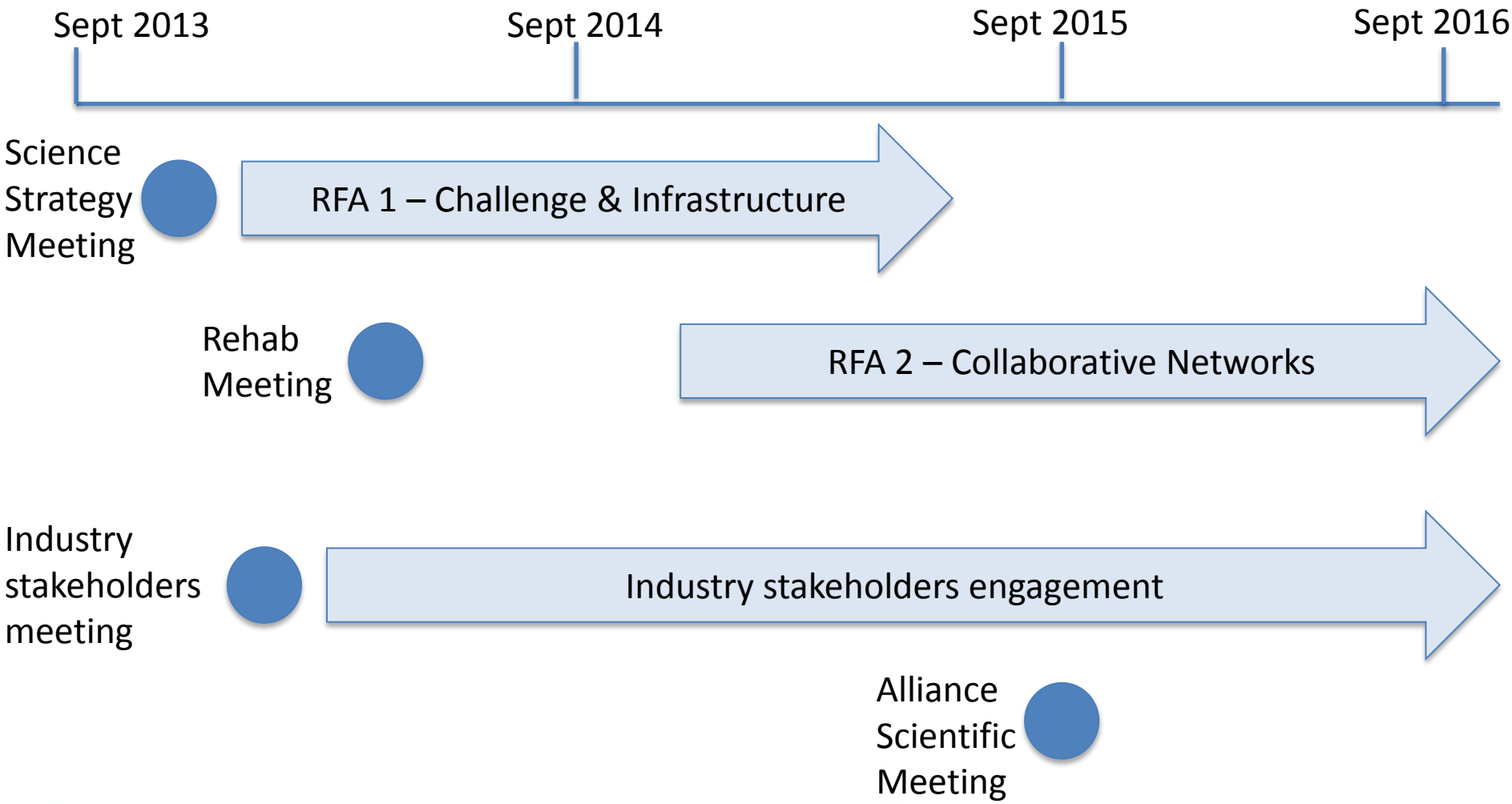
Scientific Strategy Timeline



RFA-1 Progress

- 195 applications received from researchers in 22 countries
- Convened two scientific peer review committees (Basic and Clinical Committees)
  - Comprised of 41 research scientists and clinicians from Australia, Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK and US
- 22 projects, from 11 countries, approved for funding

RFA 1 Summary

- **Clinical trials and outcome measures/biomarkers:** About a third of the awards (32%) are focused on the design of clinical trials and development of outcomes measure or biomarkers that are desperately needed to accelerate the development of treatments for progressive MS.
- **Underlying pathology of progression:** Another third of the awards are focused on understanding the underlying cause or pathophysiology that drives progressive disease.
- **Gene studies:** The Alliance portfolio includes three studies examining the genetics of progressive MS. One of these studies, from the International MS Genetics Consortium will bring together researchers form 15 different countries to search for genetic variants influencing the risk for progressive MS.
- **Developing new disease models:** The Alliance portfolio includes two studies focused on the development of new progressive MS models.
- **Rehabilitation trials:** The remainder of the portfolio is focused on clinical trials of new rehabilitation strategies to improve the lives of people living with progressive MS.

Fishburn, C.S. *SciBX* 7(38); doi:10.1038/scibx.2014.1114
Published online Oct. 2, 2014

SciBX
Science-Business eXchange

TRANSLATIONAL NOTES

Progressive thinking in MS

By C. Simone Fishburn, Executive Editor

NATURE NEWS

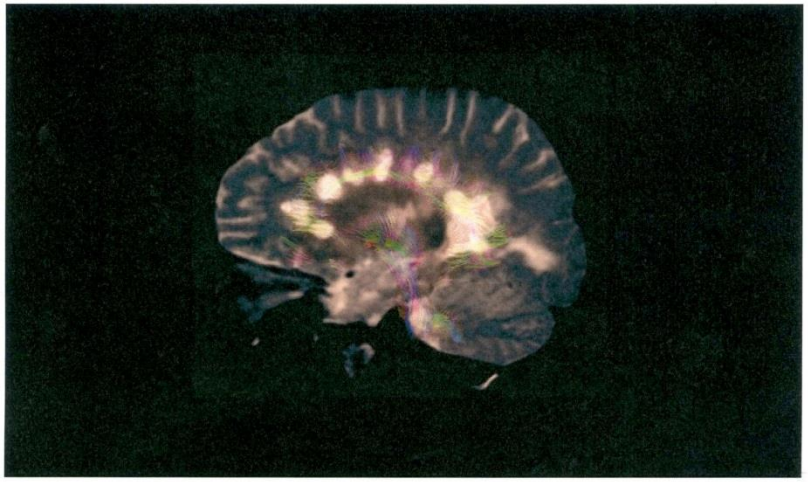
Global initiative targets progressive multiple sclerosis

Goal to develop treatments for a refractory form of the disease.

Elie Dolgin

17 September 2014

BOSTON, MASSACHUSETTS



Zephyr/SPL

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Collaborative Network Awards

Designed to support pre-clinical and/or clinical translational research that address major obstacles and focus on these key research areas:

- Drug discovery programs that identify and validate molecular and cellular targets and screen and characterize drug candidates, which may be either repurposed or first-in-human drugs
  - **Expected Impact - Development of one or more pre-clinical drug candidates within the 4 year funding period**

- Discovery, advancement and validation of new or existing, biological or imaging biomarkers
  - **Expected Impact - Development of meaningful outcome measures that could be integrated into early clinical development within 4 year funding period**

- Proof-of-concept trials and trial designs, including, trials in remyelination, neuroprotection, enhanced plasticity, other first-in-human, exploratory clinical trials for progressive MS, including both pharmacological and rehabilitative strategies/interventions
  - **Expected Impact – Initiation of clinical trials of new interventions for progressive MS within the 4 year funding period**

Two-Stage RFA 2 Structure and Process

- First-stage: Collaborative Network Planning Award
  - Duration: 12 months
  - Amount: up to €50,000
  - Quantity: up to 10 awards

- Second-stage: Collaborative Network Award
  - Duration: 4 years
  - Amount: up to €1 million/year/award
  - Quantity: 2-3 awards

This week….

- The Alliance has just released a new Request for Applications for **Collaborative Network Awards**. The purpose of the new grant round is to enable and leverage global collaborative networks of excellence engaged in transformative research. Networks must consist of at least three organizations and a minimum of three countries must be represented in the network.

- **Phase I Collaborative Network Planning Awards - 12 months**

- Applications accepted from 15th December 2014 through 31st January 2015

Added Value of the Alliance

- Providing multiple avenues for experts and scientists from around the world to meet and discuss the most urgent issues in Progressive MS research

- Growing global commitment to Progressive MS research to €22 million over the next 5 years

- For the first time ever, MS Societies are funding research together without considering geography – simply funding the best science anywhere in the world

Challenges ahead

- Understand relevant aspects of human MS pathology
  - Validate a pre-clinical model that emulates human pathology
  - Develop high through-put screening tools
- Validate a Phase II outcome biomarker
  - Use trials to advance methodology
- Develop accepted clinical outcome measures
- Drive symptomatic treatments and rehabilitation

www.endprogressivems.org

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