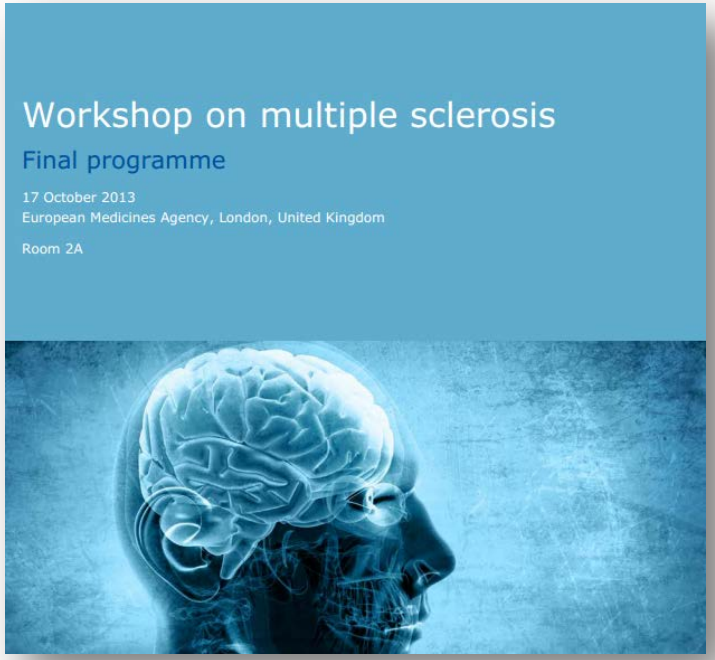
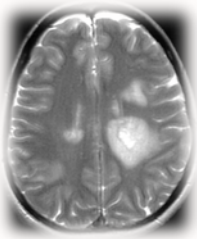
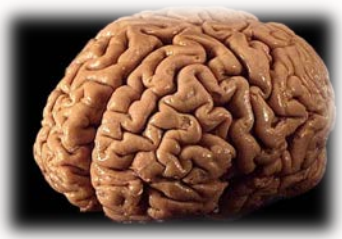


The staggered 2-step approach for treatments with profound effect on immunity

Gavin Giovannoni
Barts and The London





Disclosures

I 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, Almirall, 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.

emsp
european multiple sclerosis platform aisbl

A strong voice for persons with multiple sclerosis

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  - EMSP Member News
  - News from Europe
  - Next on EMSP Agenda?
  - Web Alert
- **EMSP Members**
- **Multiple Sclerosis**
- **Events**
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News

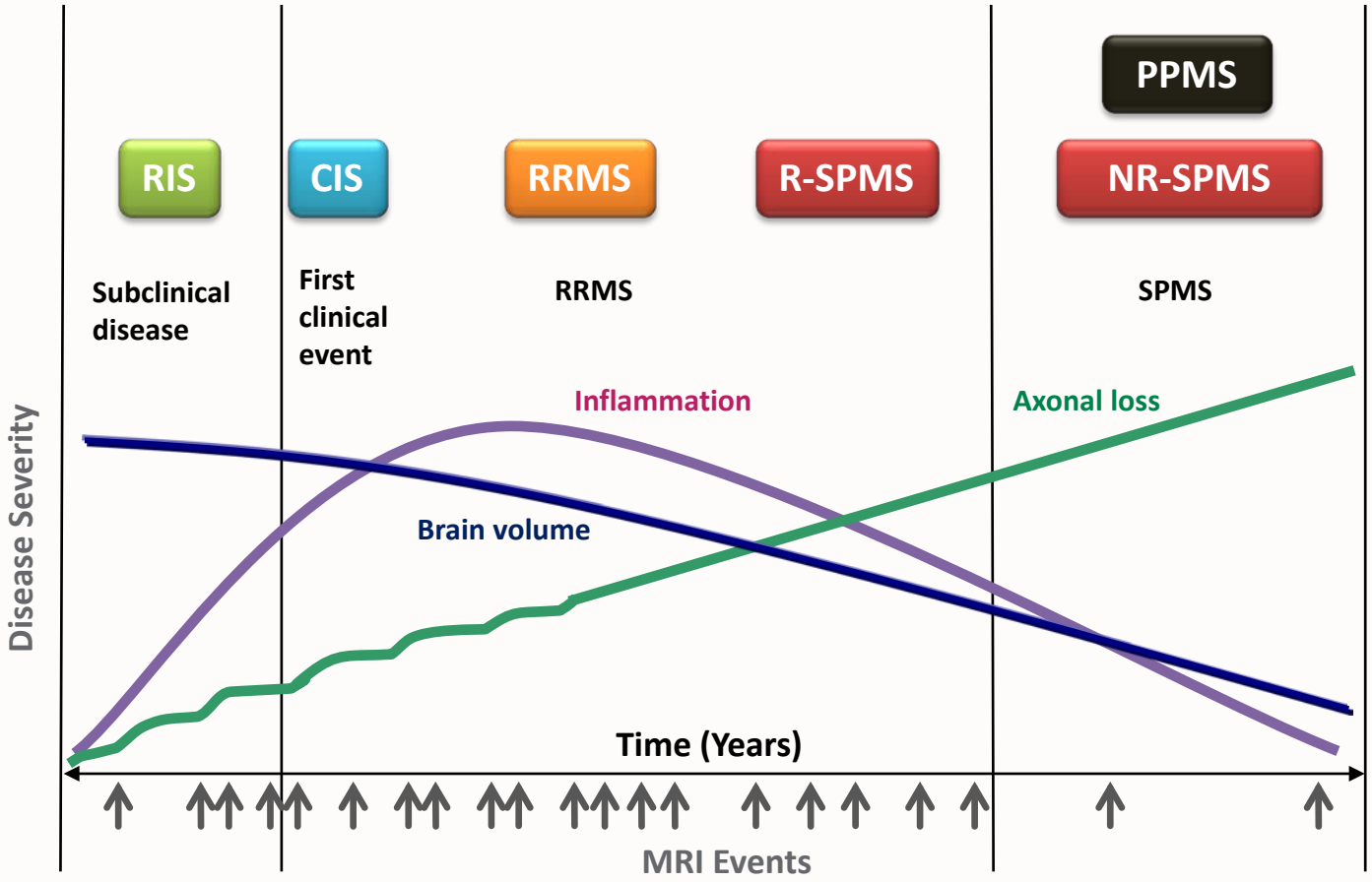
Select a news topic from the list below, then select a news article to read.

EMSP launched the Under Pressure project website

The European Multiple Sclerosis Platform (EMSP) together with its member societies launched, on May 29 - World MS Day 2013, www.underpressureproject.eu, a multimedia website revealing sharp discrepancies in the treatment, employment and empowerment of people with multiple sclerosis (MS) across Europe.

Welcome from Maggie Alexander

The Multiple Sclerosis Spectrum



Subclinical inflammation, demyelination, and neurodegeneration may be present for months, or even years, before a patient experiences clinical symptoms[1]

MRI=magnetic resonance imaging; RIS =radiologicallty-isolated syndrome; CIS=clinically-isolated syndrome; RRMS=relapsing-remitting MS; SPMS=secondary progressive MS
R-SPMS=relapsing SPMS; NR-SPMS=non-relapsing SPMS; PPMS=primary progressive MS

1. Stüve O et al. *Drugs* 2008;68:73-83; Image adapted from Compston A, Coles AJ. *Lancet* 2008;372:1502-17.

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

Pérez Akly, M.[1]; Zanga, G.[1]; Ciardi, 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 Favaloro Foundation

This study was supported by an IVAX Argentina research grant

TABLE 1. DEMOGRAPHIC DATA			
Variable	*Case*	*Control*	*p*
Sample	75	75	-
Sex (% women)	73,8	65,2	0,32
Age (mean, SD)	40,1 (11,1)	33,5 (10,1)	0,2
School drop (%)	3,3	2	0,467
Repetition rate (%)	8	6	0,48
Fatigue scale	**37,9**	**22,4**	**0,000**
Beck scale	31,3	30,1	0,325

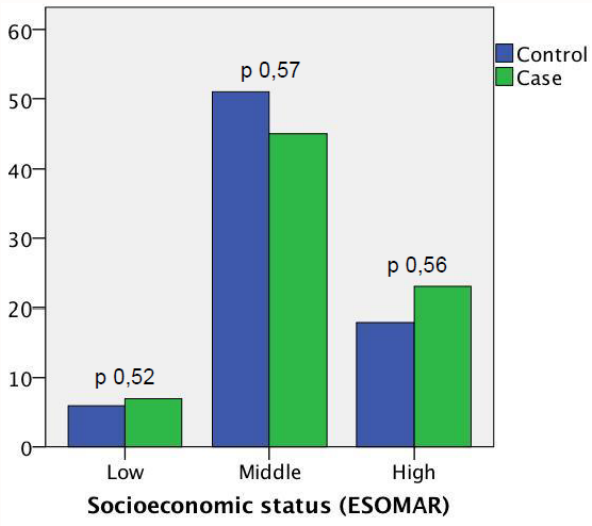


TABLA 2. SCHOOL PERFORMANCE			
Variable	*Case*	*Control*	*p*
Average 5° year	**6,7**	**7,8**	**0,004**
Average 4° year	**6,6**	**7,6**	**0,037**
Average 3° year	7,3	7,8	0,059
Mathematics 5° year	**6,7**	**7,6**	**0,02**
Mathematics 4° year	**6,4**	**7,3**	**0,04**
Mathematics 3° year	6,9	7,3	0,356
Literature 5° year	**6,8**	**7,8**	**0,003**
Literature 4° year	**6,6**	**7,5**	**0,046**
Literature 3° year	**6,8**	**7,3**	**0,027**

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

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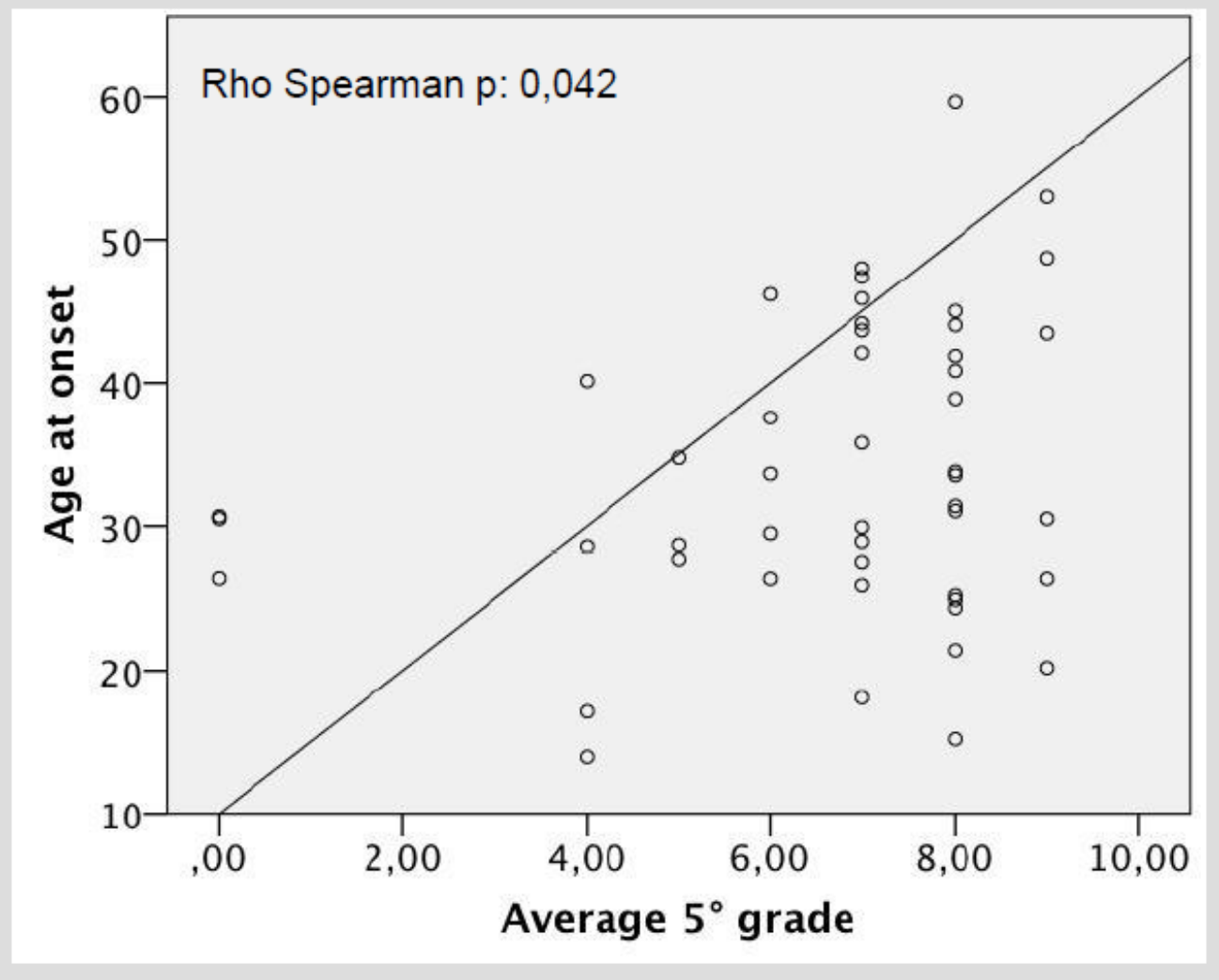
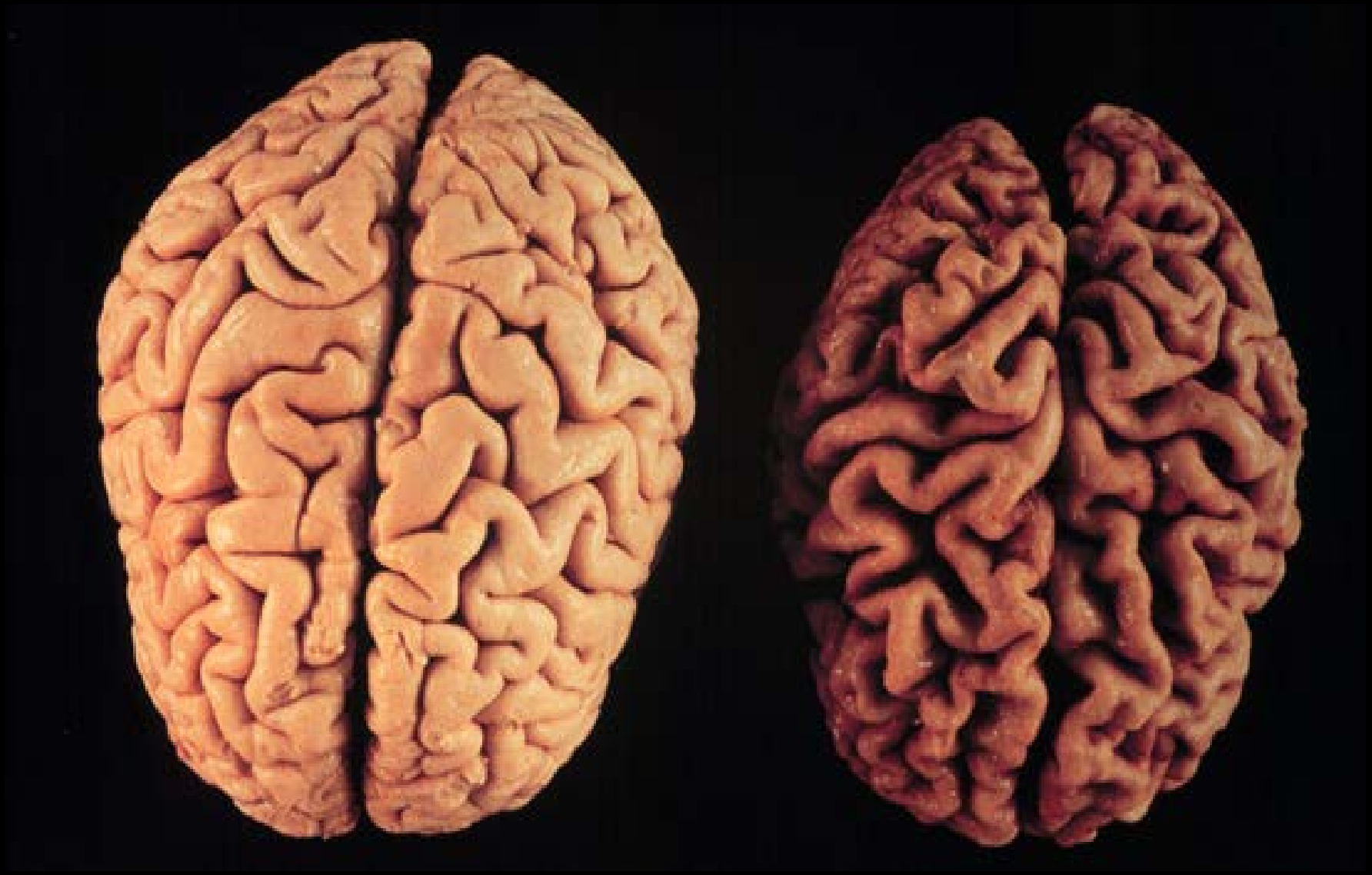
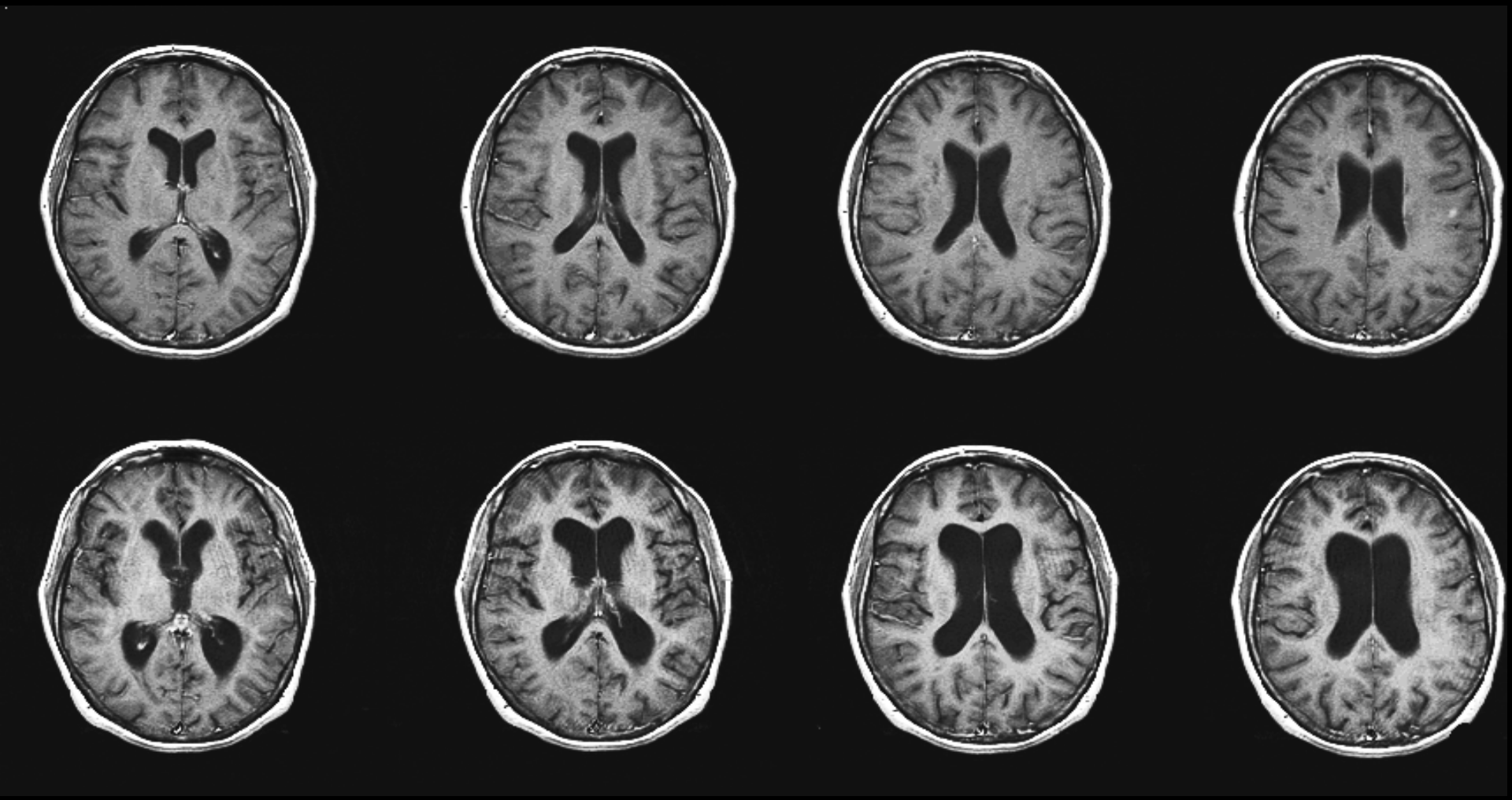




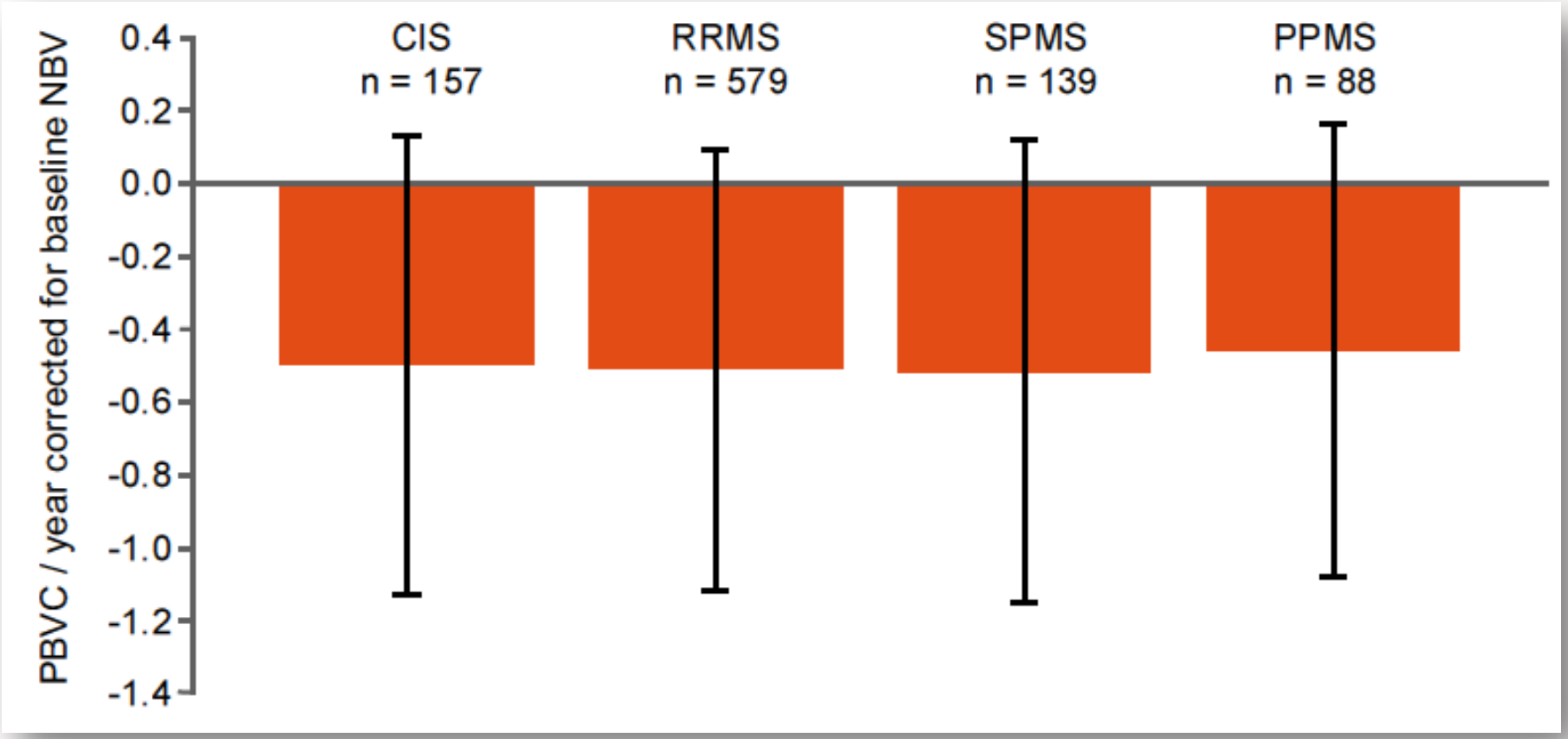
Control

Multiple sclerosis



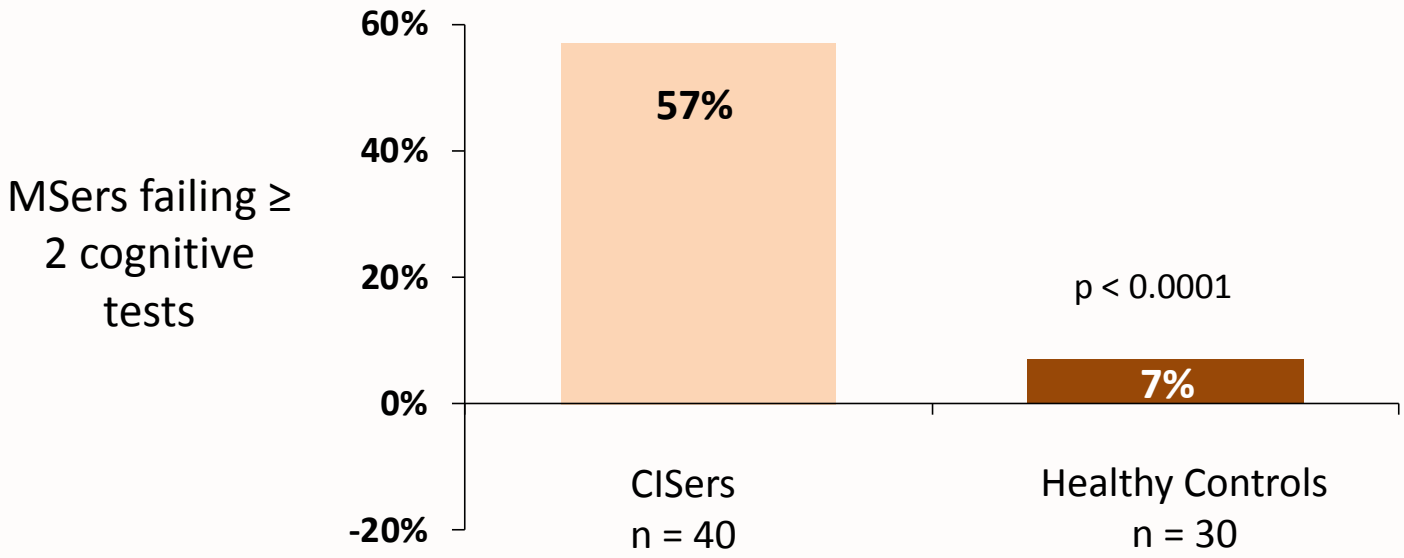
Brain atrophy occurs across all stages of the disease

n= 963 MSers



De Stefano, et al. Neurology 2010

Cognition in early multiple sclerosis



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

Feuillet et al. Mult Scler. 2007.

Post-inflammatory neurodegeneration

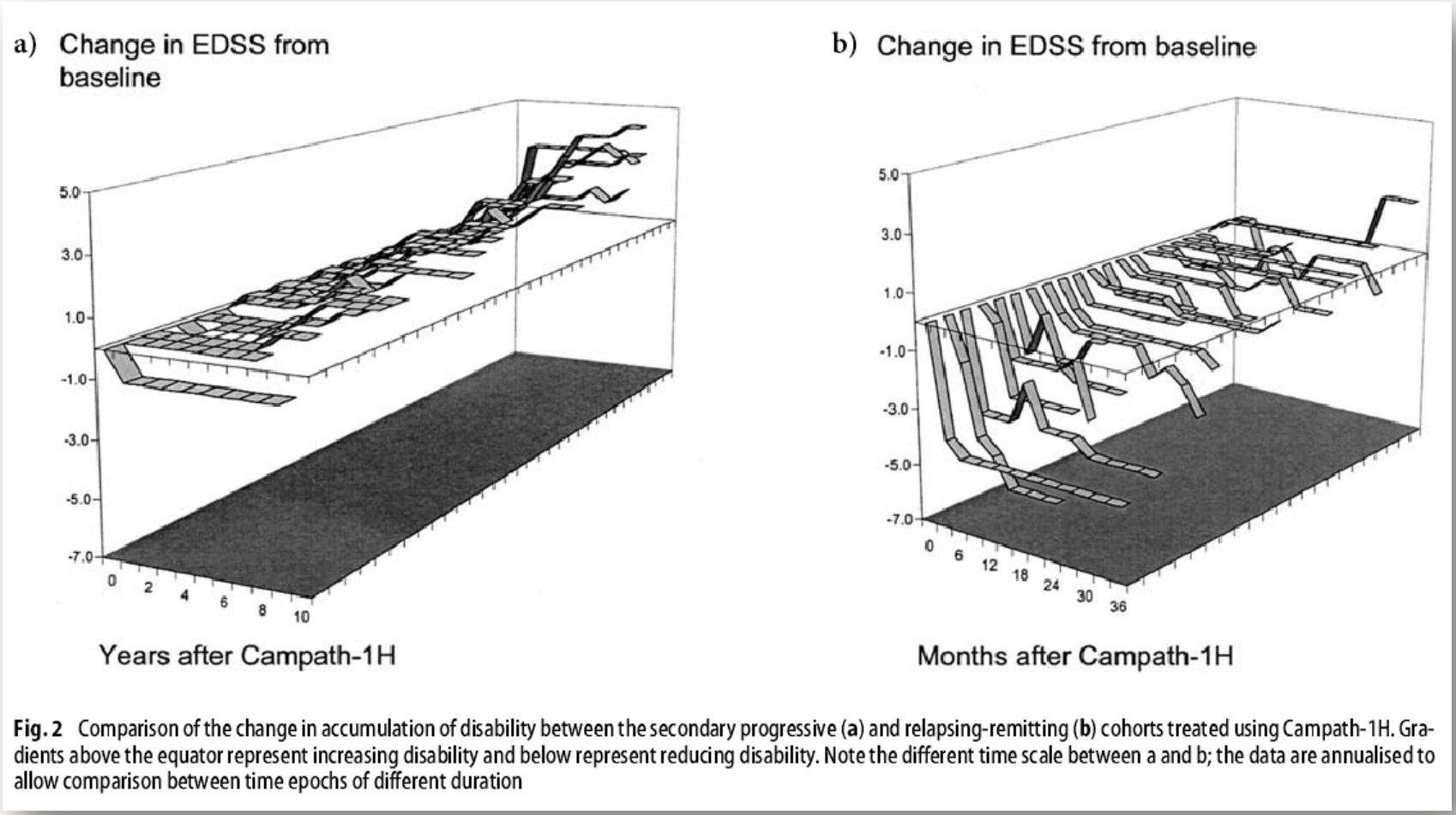


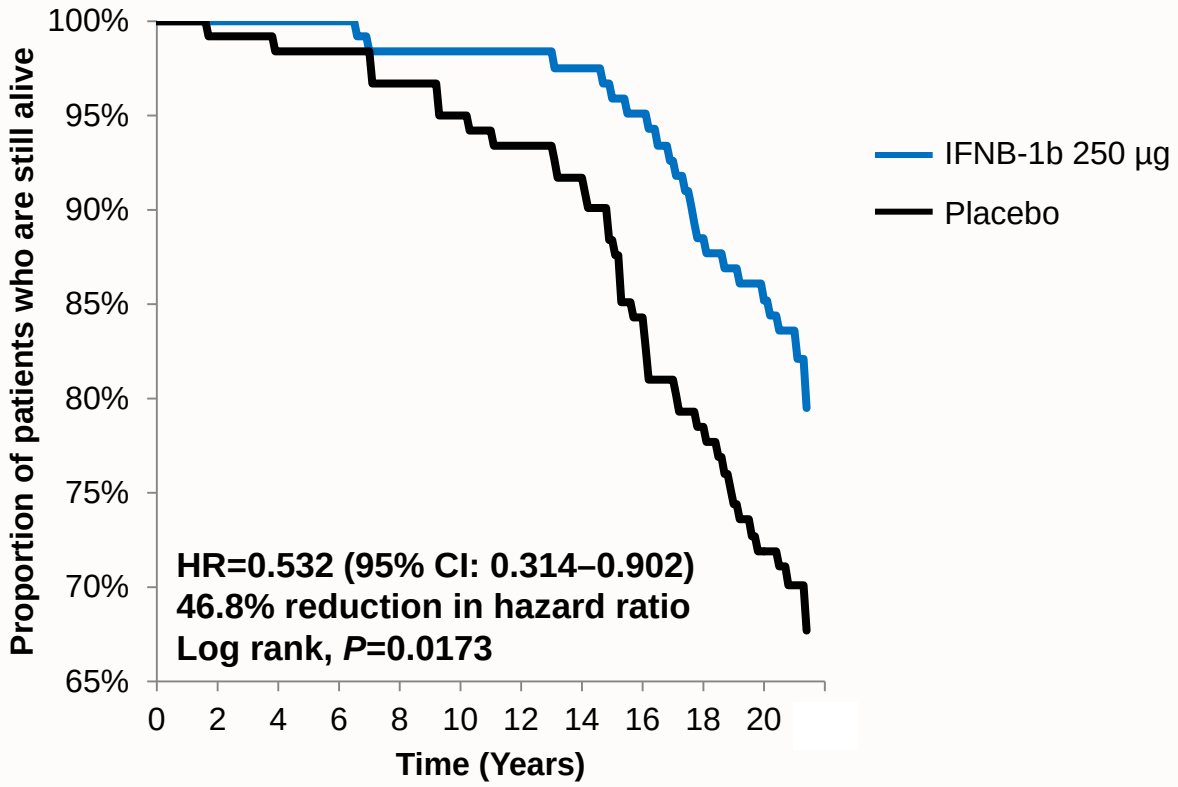
Fig. 2 Comparison of the change in accumulation of disability between the secondary progressive (**a**) and relapsing-remitting (**b**) cohorts treated using Campath-1H. Gradients above the equator represent increasing disability and below represent reducing disability. Note the different time scale between a and b; the data are annualised to allow comparison between time epochs of different duration

Coles et al. J Neurol. 2006 Jan;253(1):98-108.

21-year long-term follow-up of IFNb-1b study

time from study randomization to death

Early treatment (3 years) with IFNb-1b was associated with a 47% reduction in the risk of dying over 21 years compared with initial placebo treatment



At risk:					
IFNB-1b 250 µg	124	124	121	118	104
Placebo	123	120	117	109	88

Goodin et al Neurology. 2012 Apr 24;78(17):1315-22.

Occupational functioning

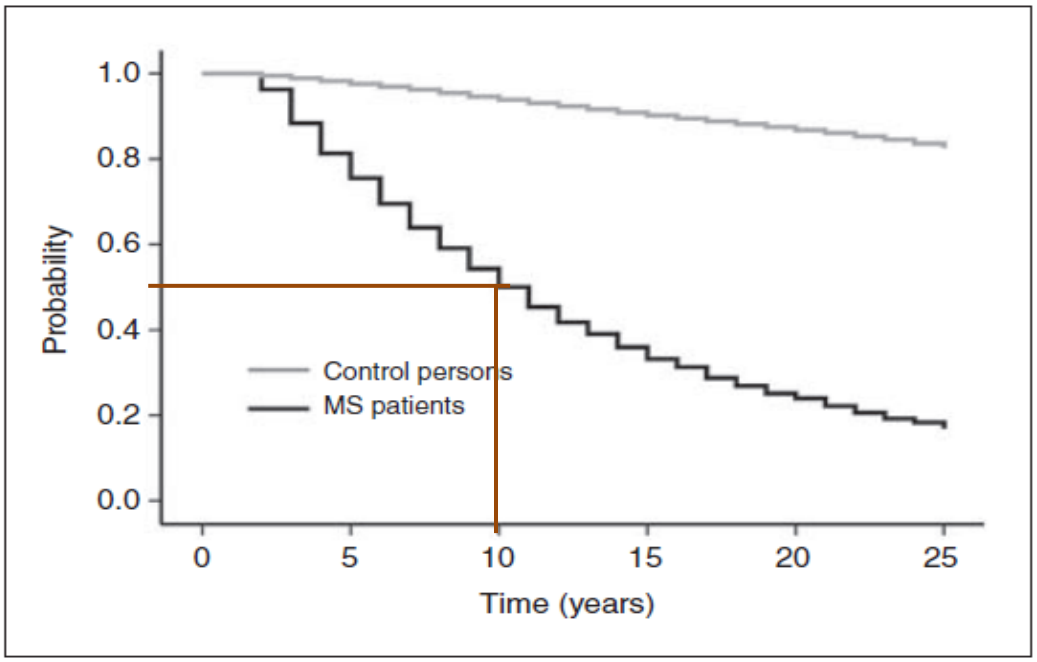
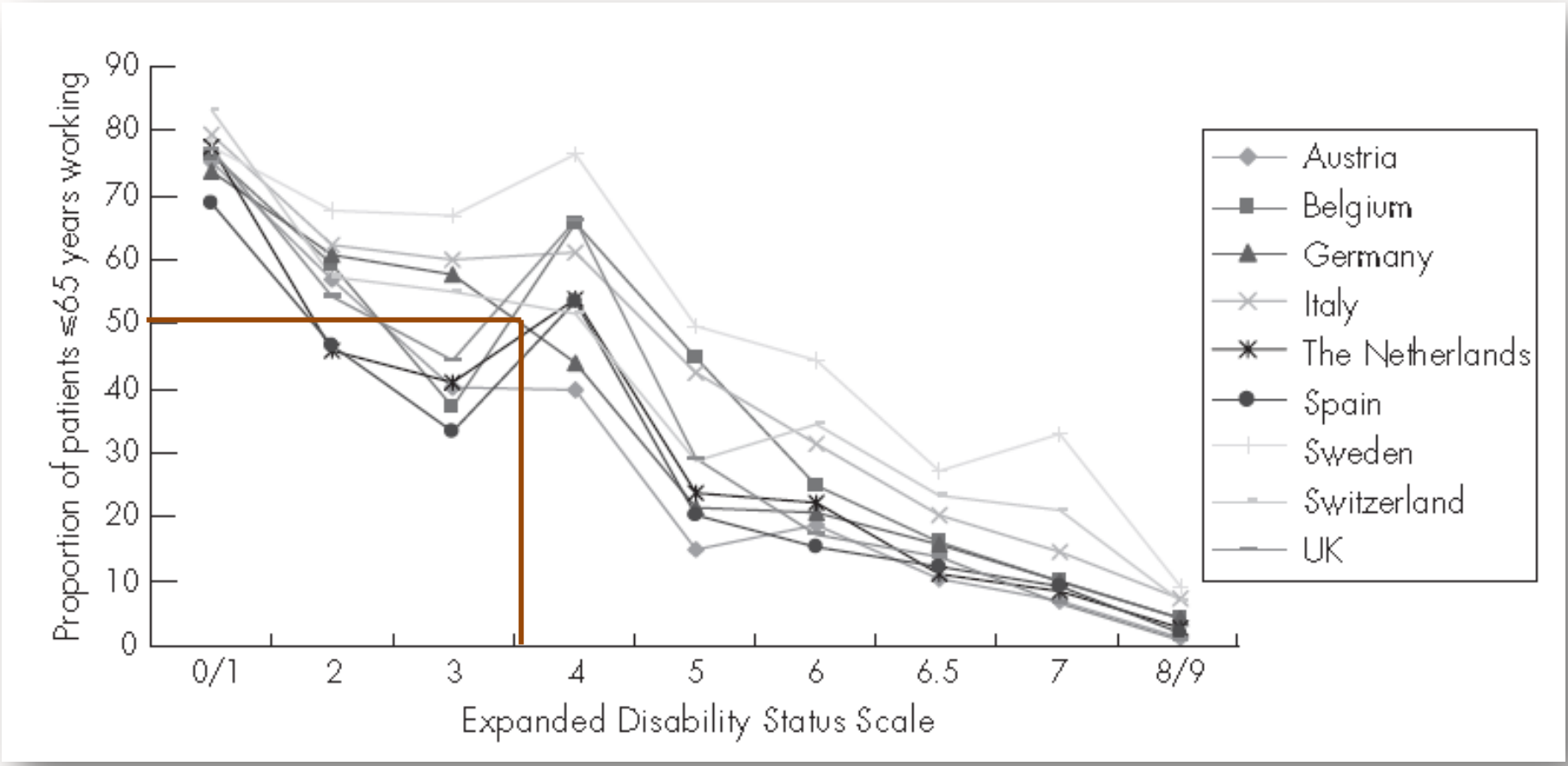


Figure 1. Probability of remaining in active employment after onset of multiple sclerosis. Key: grey, controls; black, patients.

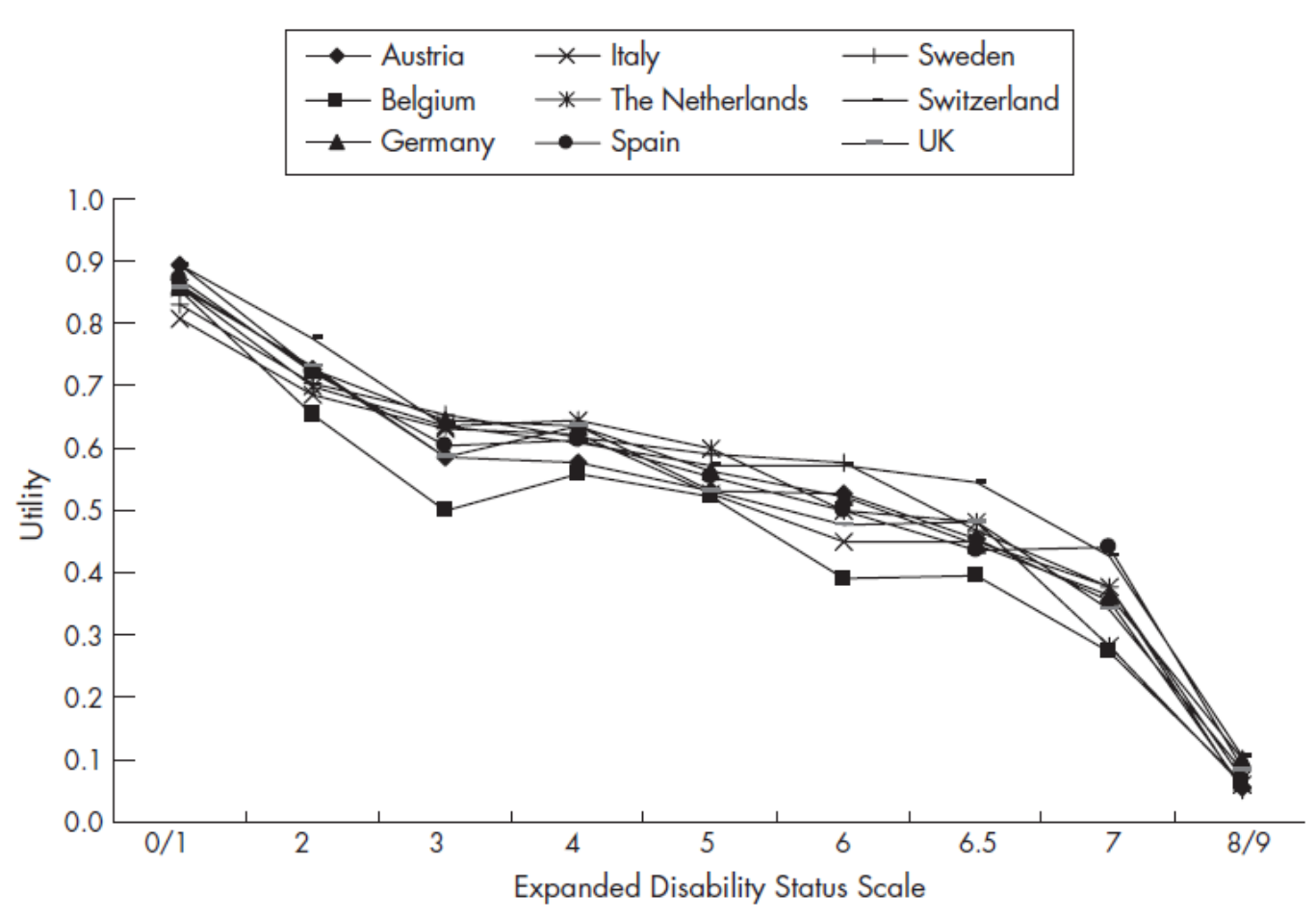
Pfleger et al. Multiple Sclerosis 2010; 16(1) 121–126.

At what level of physical disability does unemployment occur?



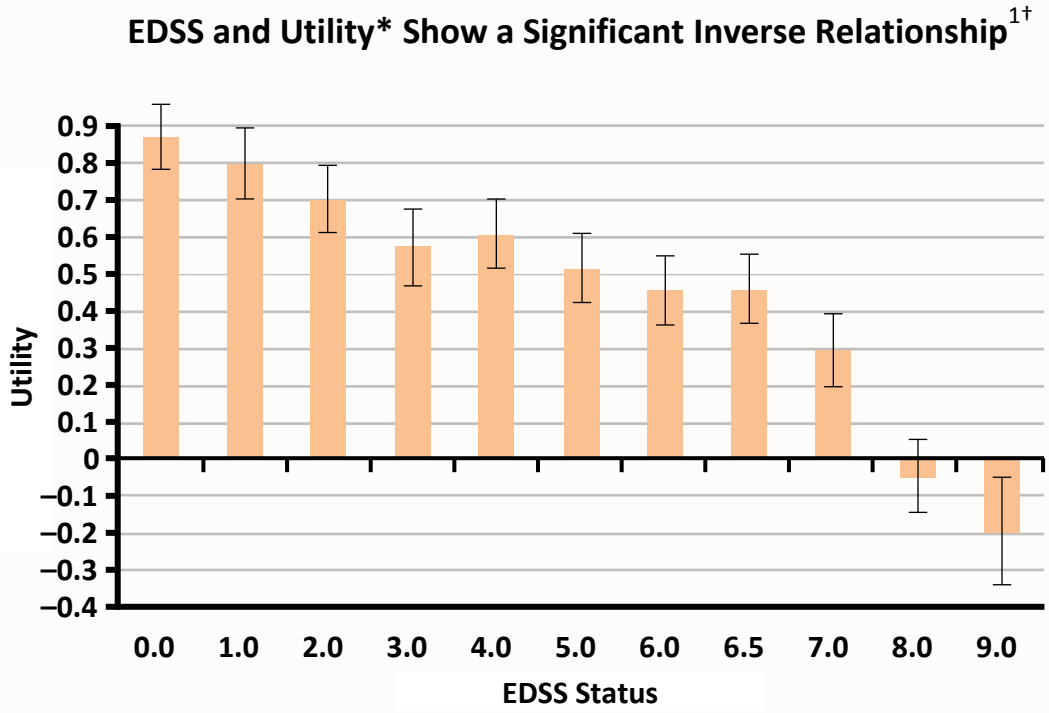
Kobelt et al. Neurol Neurosurg Psychiatry 2006;77:918–926.

Quality of life of patients with MS in Europe



Kobelt et al. J Neurol Neurosurg Psychiatry 2006;77:918–926.

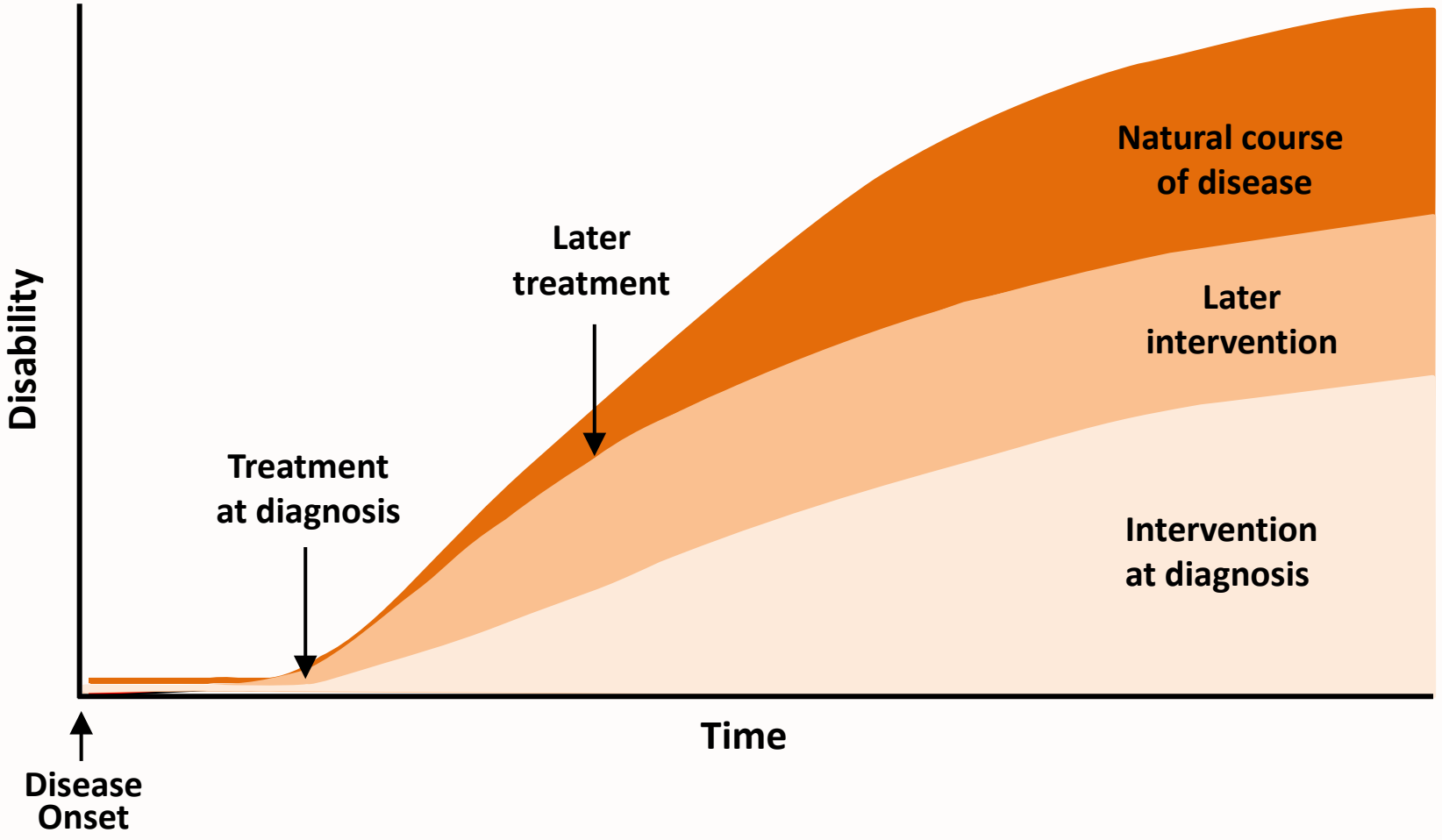
The Effect of MS on Quality of Life



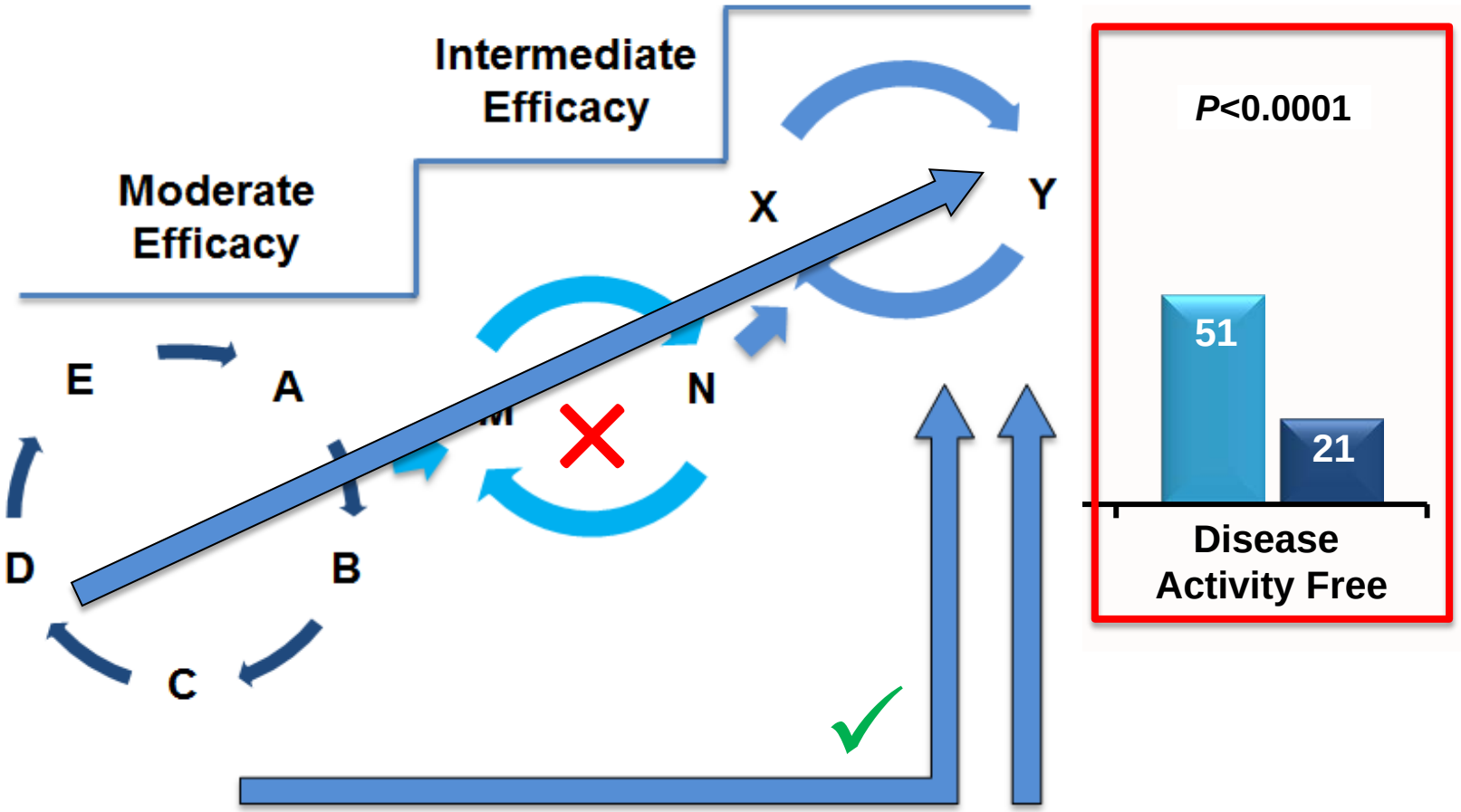
- MS is one of the most common causes of neurological disability in young adults[2]
- Natural history studies indicate that it takes a median time of 8, 20, and 30 years to reach the irreversible disability levels of EDSS scores 4.0, 6.0, and 7.0, respectively[3]

*Utility measures are derived from EQ-5D using the EuroQoL instrument; †error bars depict 95% CIs. Half points on EDSS are not shown on graph axis, except at EDSS score 6.5.
EDSS=Expanded Disability Status Scale; EQ-5D=European Quality of Life-5 Dimensions; QoL=quality of life.
1. Adapted from Orme M et al. *Value In Health.* 2007;10:54-60; 2. WHO and MS International Foundation (MSIF). http://apps.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1 &codcol=15&codcch=747. Accessed March 6, 2012; 3. Confavreaux C et al. *Brain* 2003; 176:770-782. 4. Compston A, Coles A. *Lancet.* 2008;372:1502-1517.

Theoretical model: treat early and effectively



Escalation to Natalizumab Is More Effective Than Switching Between IFN/GA



Should multiple sclerosis be redefined as a dementia?

Definition of dementia

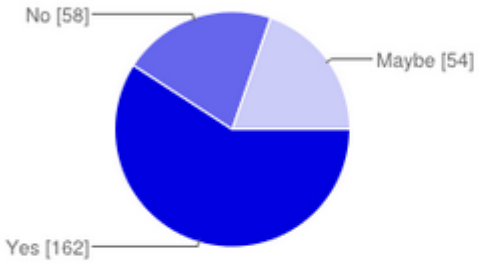
Dementia is a loss of mental ability severe enough to interfere with normal activities of daily living, lasting more than six months, not present since birth, and not associated with a loss or alteration of consciousness.

- Normal activities of daily living
  - Physical ✓
  - Mental ✓
  - Social ✓
  - Occupational ✓
- Lasting more than six months ✓
- Not present since birth ✓
- Not associated with a loss or alteration of consciousness ✓

281 responses

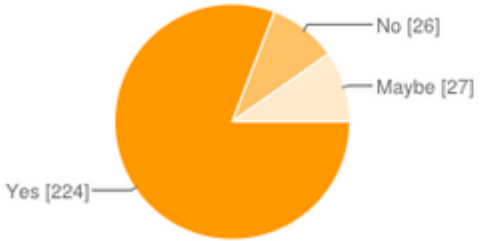
Summary See complete responses

Do you agree that MS is a dementing illness?



Yes	**162**	58%
No	**58**	21%
Maybe	**54**	19%

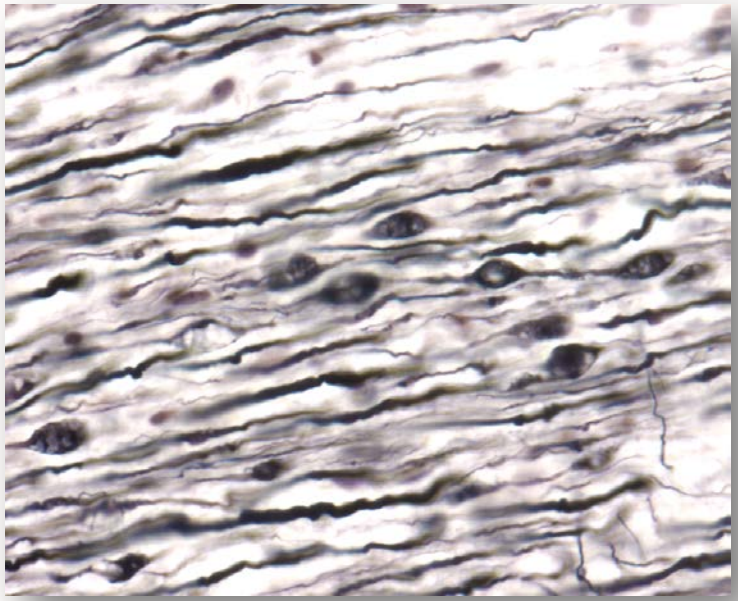
Do you think MSers should be allowed early effective treatment to prevent cognitive impairment or dementia?



Yes	**224**	80%
No	**26**	9%
Maybe	**27**	10%

What is the pathological substrate of MS dementia?

11,000 to 1



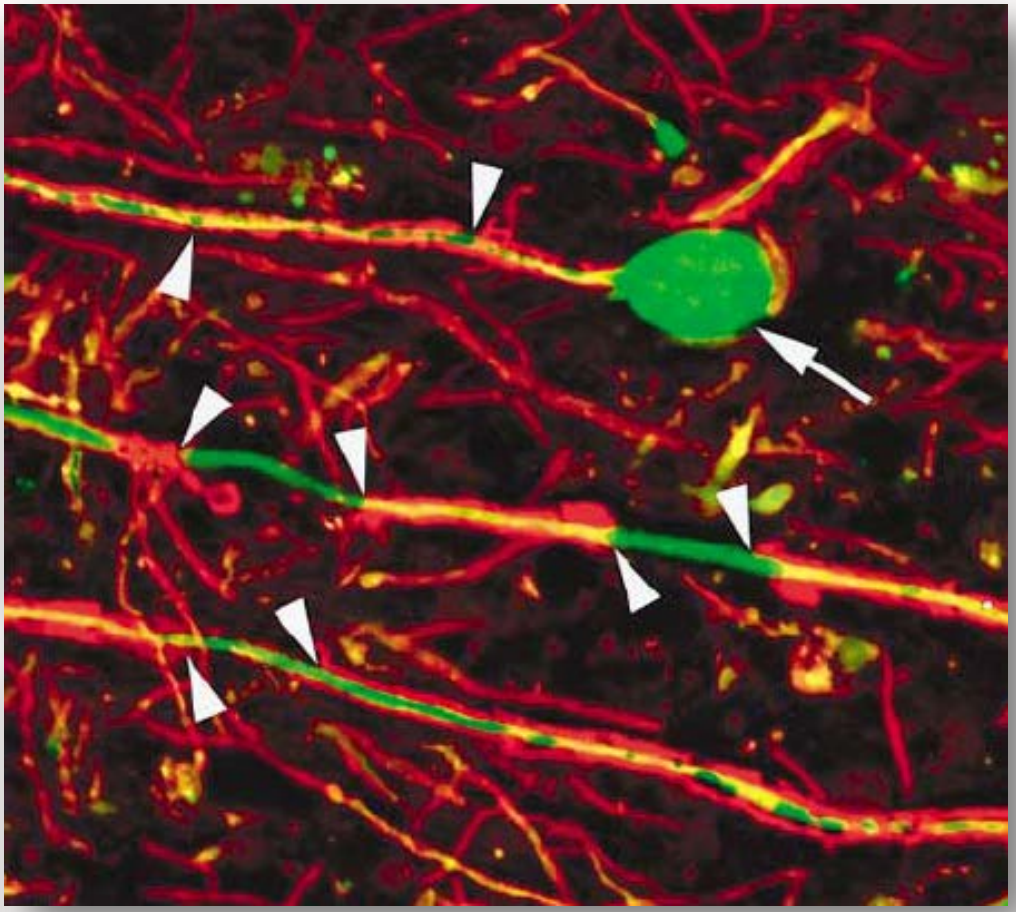


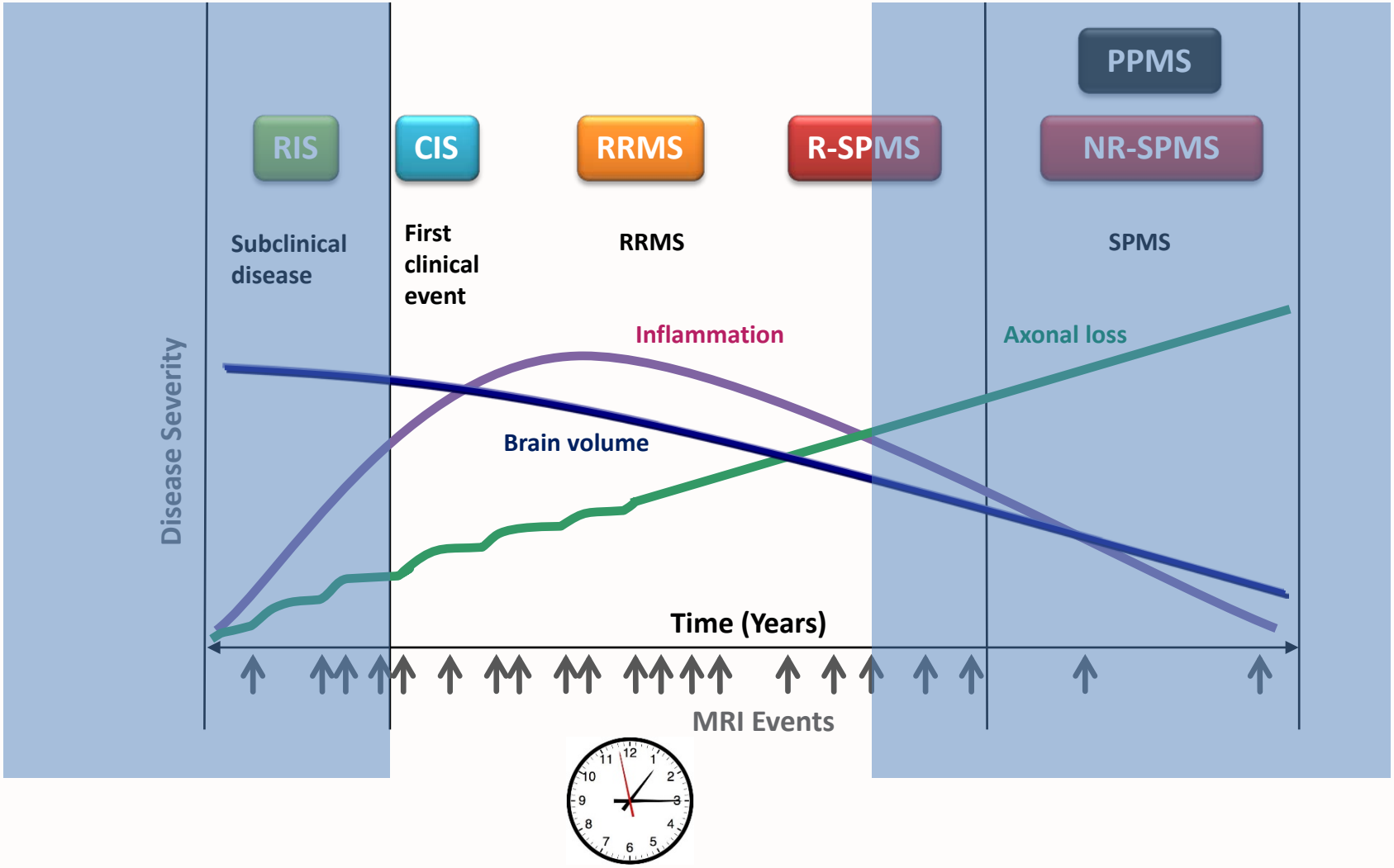
TABLE 2. DISTRIBUTION AND NUMBER OF TRANSECTED AXONS IN MULTIPLE-SCLEROSIS LESIONS.

TISSUE (NO. OF PATIENTS)	NO. OF LESIONS ANALYZED	NO. OF TRANSECTED AXONS/mm³*
Active lesions (3)	5	11,236±2775
Chronic active lesions (4)	13	
Edge		3138±688
Core		875±246
Nonlesion white matter (5)	11	17±2.8
Control white matter (4)	5	0.7±0.7

Trapp, et al. NEJM 1998;338:278-85

Defining the window of opportunity to treat MS?

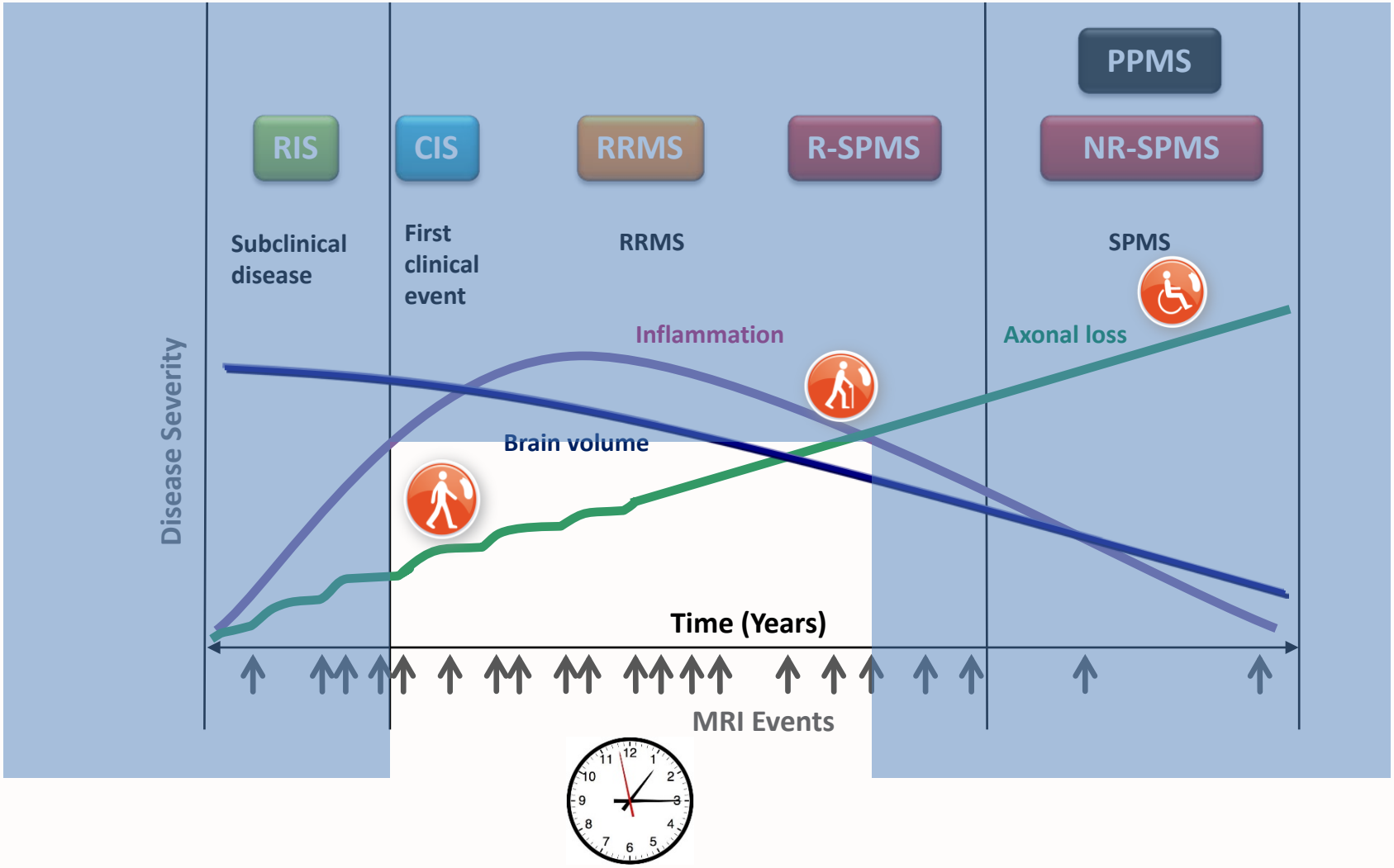
“The window of opportunity”



MRI=magnetic resonance imaging; RIS =radiologicallty-isolated syndrome; CIS=clinically-isolated syndrome; RRMS=relapsing-remitting MS; SPMS=secondary progressive MS
R-SPMS=relapsing SPMS; NR-SPMS=non-relapsing SPMS; PPMS=primary progressive MS

1. Stüve O et al. *Drugs* 2008;68:73-83; Image adapted from Compston A, Coles AJ. *Lancet* 2008;372:1502-17.

“The window of opportunity”



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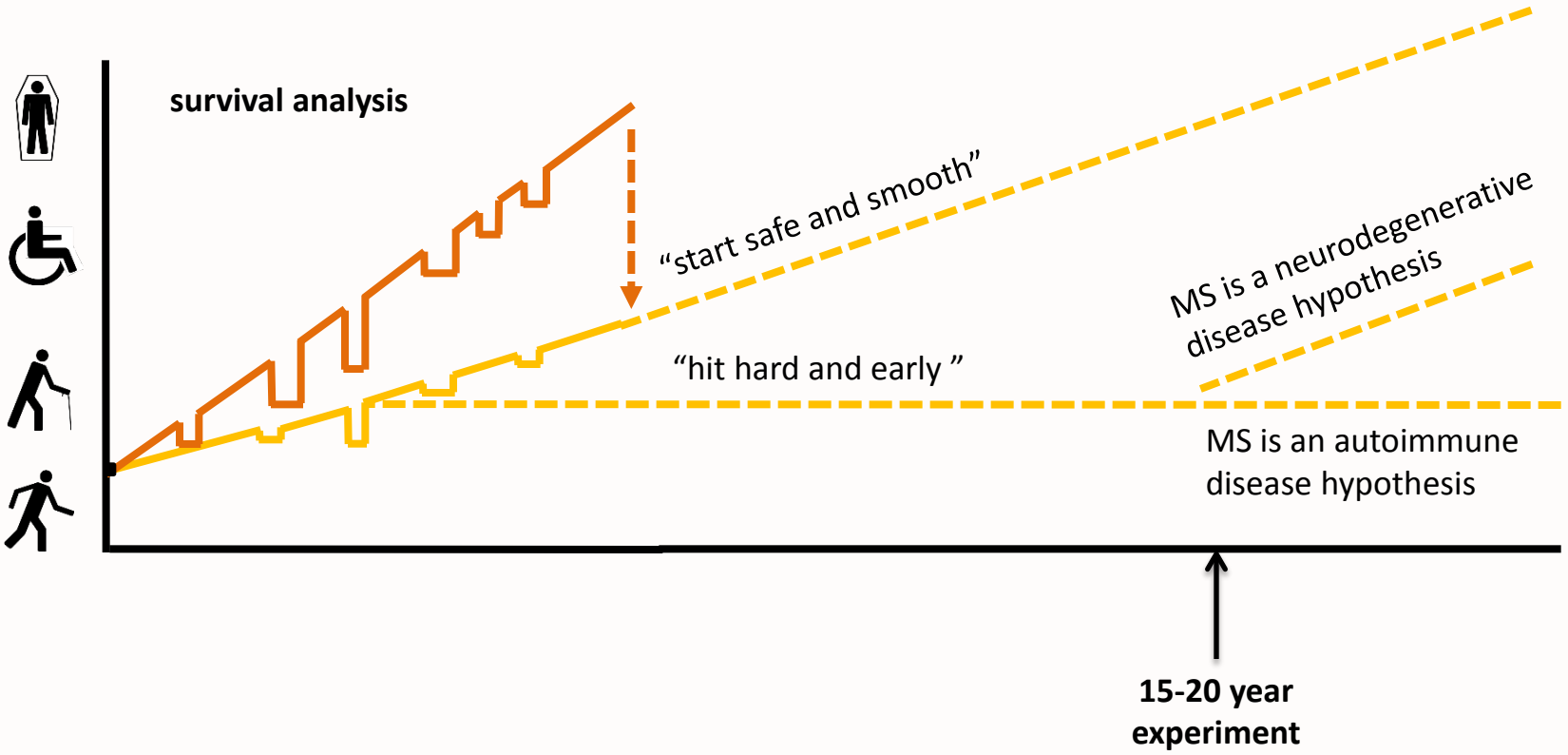
1. Stüve O et al. *Drugs* 2008;68:73-83; Image adapted from Compston A, Coles AJ. *Lancet* 2008;372:1502-17.

Choosing a treatment strategy?

What is your treatment philosophy?

maintenance-escalation vs. induction



Adjusting to a Diagnosis of Multiple Sclerosis

Diagnosis

If I was to offer one piece of advice for those newly diagnosed with multiple sclerosis (MS) it would be avoid the internet. 'Knowledge is Power' as one national MS Society website proclaims. However, for someone with 24/7 access to the internet, and a research-based job, researching the disease had become somewhat of an obsession since my diagnosis.

I was diagnosed with MS in May 2004 age 39. Unlike many who are diagnosed there were no earlier signs of anything wrong. Indeed, in 2001 following my office medical, the doctor congratulated me for being a "model patient". However, in March 2004, I noticed that I wasn't shaving properly with my right hand and that I had become 'de-sensitised' from the waist down. I went to my GP practice three or four times in the following weeks and was eventually referred to a neurologist. Having medical insurance proved a mixed blessing: I saw a neurologist privately within a week; had an MRI the next week; and was told that I had MS the next week. Too much to take in too quickly!

What's MS really about?

Following my diagnosis, I wanted to find out more about the disease and to find an answer to the "why me?" question. I started searching the internet for answers, starting first with the national MS Society websites. Initially, I was quite upbeat as many of the national MS society websites appeared very positive about the future. Most reported that, for relapsing remitting MS, there were now treatments that could reduce relapses and the number of lesions with better ones in the pipeline. The aims of the various national MS societies also appeared impressive – "a world without MS"; "to end the devastating effects of MS"; "to find a cure" etc.

But my searching of the national MS society websites also uncovered a much more serious side to this disease. I knew that MS could involve pins and needles, and loss of feeling, but the list of symptoms on these websites were something I had not been prepared for: visual impairment / blindness; paralysis; mobility problems; bladder and bowel problems; speech problems; sexual problems; depression; and something called cognitive problems (including memory problems). Also, for the first time, I came across the term 'near normal lifespan'. I also encountered terms such as respite care, and reference to your partner becoming your 'carer'.

As my research increased, the disease seemed to get worse and worse. Many of the websites were visited by patients with more 'advanced' MS, or carers of such patients. Adverts for mobility aids, hoists, adapted cars began to play on my mind as I started to think of a future I never believed could be mine. How long could I work for? Why am I saving for a retirement? Would I see my young children grow up? The prospect of mobility problems were a particular concern – not only because I loved playing sport, but because mobility problems would end my career (my commute involves: walking to the station; overground trains; underground trains; lots of steps etc).

I was also reminded constantly about the disease through: (i) family members / friends posting me articles about miracle treatments such as Goat's serum, and a stem cell cure available in Holland; (ii) news reports of someone being prosecuted for growing cannabis for MS pain / spasticity; (iii) news reports of the 'loving husband' who helped his wife with MS commit suicide to end her suffering. Everywhere I looked there seemed to be an article about MS, or a celebrity with or affected by MS: Alan Osmond; Richard Pryor; Jacqueline du Pre; JK Rowling.

In the three years since my diagnosis the way the disease is viewed appears (to me) to have changed - MS is now often described as a neuro-degenerative disease in addition to being an inflammatory disease (the chicken and egg issue of what comes first has still to be pinned down). Many research articles have highlighted the involvement of grey matter damage in addition to white matter (myelin).

While the internet can provide hope...it can also expose a patient to the realities of a disease

Rather than being a focal disease based on lesions, MS is now considered to be a global disease of the CNS. A recent piece of research using a very powerful scanner (8 Tesla) showed that there were lots more lesions which could not be seen by normal scanners. Urgh! My research also introduced me to the world of axonal degeneration. Gone are the days when MS was just a disease where myelin was damaged. Loss of neurons and axons are now seen as the cause of irreversible disability.

Treatments

My research on treatments also left me confused. The national MS websites refer to 100+ MS drugs in trial. These include those targeting T-cells, B-cells and drugs used for other diseases such as cancer. Minocycline seems to have been examined as a possible MS treatment for some time. Then there are a host of other agents: statins; Low Dose Naltrexone (LDN); Vitamin D supplements; heavy duty antibiotics (on the basis that MS is caused by chlamydia pneumoniae); and anti-virals. Neuro-protective agents are also being examined.

Stem cells are considered by many as a possible future "cure"/ repair strategy for degenerative disease such as MS. While I'm glad to see that the UK's leading lights in Cambridge and Bristol are pushing forward in this area, there would appear to be many more years' research before such a treatment makes it to market. Of course, unproven and potentially unsafe stem cell treatments have been offered in countries where appropriate testing does not appear to be an issue. My father offered me the £15,000 to go to Holland. Thankfully, I didn't accept this!

In terms of my own treatment, I was given steroids at the time of my diagnosis and for subsequent relapses. I started my disease-modifying drug in February 2006. Unfortunately, I had further relapses in June 2006 and a very bad one at the start of October 2006. An aim of the current disease-modifying drugs is to 'slow down' the disease. But my research could not identify what bit of the disease the treatment was 'modifying' and whether it was working for me. In October I came off my disease-modifying drug as, in late November 2006, I was given the chance to be given a more powerful treatment currently being trialed – which I had come across through my internet searching! So far I am doing very well following this treatment. Mentally I feel better as I consider that I have given the disease as big a 'whack' as I could.

So in my experience, it has taken almost three years to adjust to the diagnosis. I am still working full time and am now beginning to cut down on the time I spend looking at MS websites. I'm not sure how 'normal' my response has been. But, at the end of the day, an MS patient is being asked to take on board a huge range of major changes to their lives: having a disease for the rest of one's life; possibly watching yourself deteriorate (quickly or slowly); possibly having a shorter life than the 'norm'; dealing with potentially major changes to your employment, family life, and interests (be they diving, running, hill-walking etc).

Like many with MS, I keep my fingers crossed that the big breakthroughs in understanding the disease are not too far away and that the drugs companies can develop treatments that can shut the disease down (and perhaps promote some repair!). I will, no doubt, check the web to see what comes out of this year's ECTRIMS and ACTRIMS meetings. Clinicians may wish to suggest to those newly diagnosed with MS that they do not spend too long undertaking 'research' on the internet. While the internet can provide hope, in terms of highlighting future treatments in the pipeline, it can also expose a patient to the realities of a disease (a hard one for me has been the issue of 'brain atrophy') which can be very difficult to adjust to.

Mr Ian Rogers

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not be seen by normal scanners. Urgh! My research also introduced me to the world of axonal degeneration. Gone are the days when MS was just a disease where myelin was damaged. Loss of neurons and axons are now seen as the cause of irreversible disability.

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Ian Rogers. ACNR 2007: 7(3);14.

Crippled by MS, golfer Tony was told he'd never play again. But an astonishing new drug has proved all the doctors wrong

By JILL PARSONS
UPDATED: 00:44, 11 November 2008

When professional golfer Tony Johnstone woke one Sunday morning with a numb left hand, he assumed he'd slept awkwardly. But as the day wore on, the numbness travelled throughout his left side, freezing his face and affecting his balance.

Panicking, he became convinced he was having a stroke.

In fact, it was the start of a journey that saw him eventually diagnosed with the disease multiple sclerosis and told that his successful career was at an end.

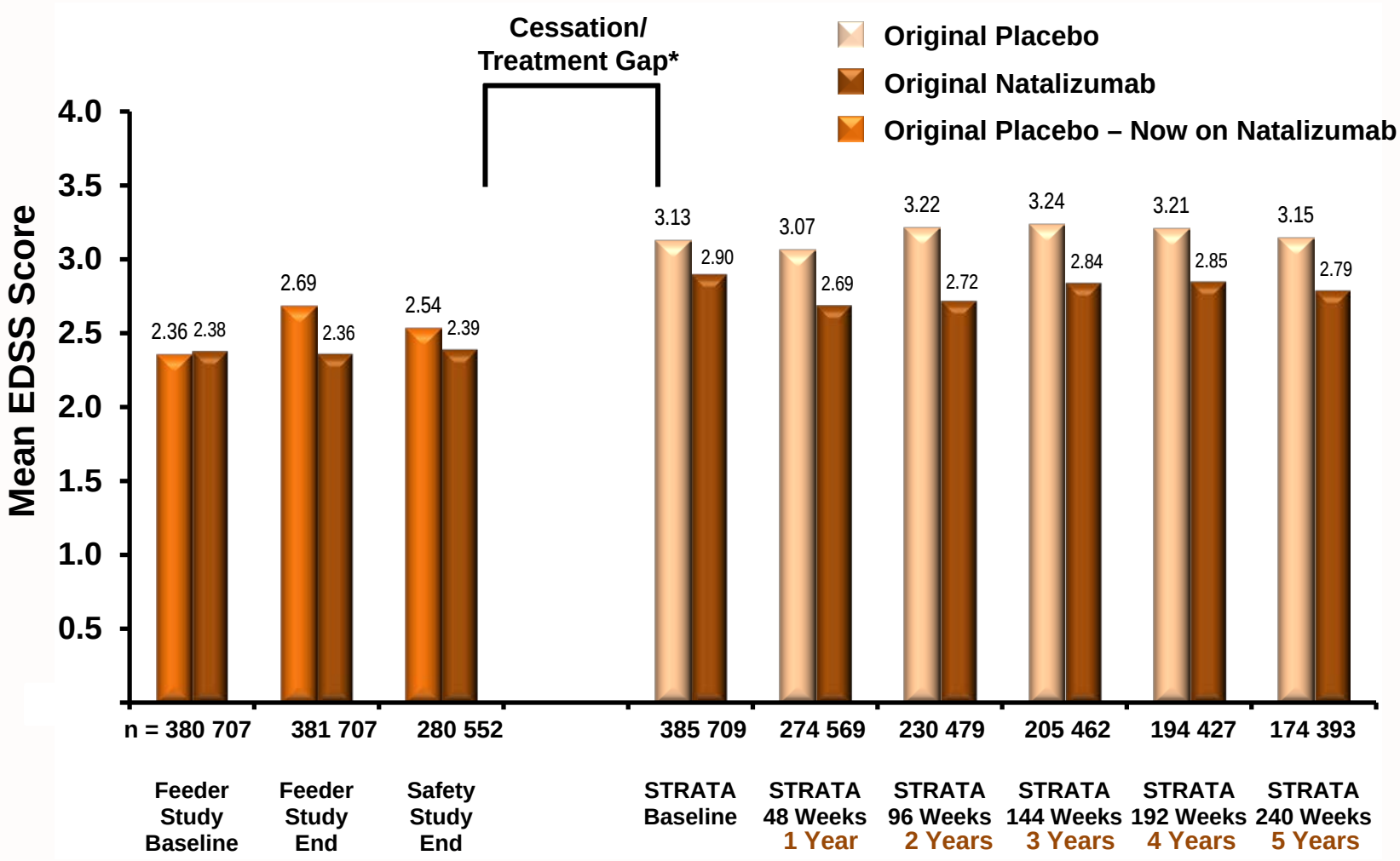
By that time, Tony was struggling to open a door, had difficulty remembering his own children's names and, as poor balance and fatigue took hold, he could barely walk, let alone play golf.

Yet five years after receiving this news, Tony has made a 'miraculous' recovery; he can now run 5km, is in excellent health and his memory is, he says, as good as anyone else his age.

And in June this year came his sweetest victory, winning the Jersey

Back on course: Five years after golfer Tony Johnstone was diagnosed with multiple sclerosis he is making a great recovery thanks to a new drug

STRATA: Patients Had Stable EDSS Scores for Up to 5 Years



**P*<0.0001

Kappos L et al. Presented at ECTRIMS; October 10–13, 2012; Lyon, France P520.

Multiple Sclerosis Research

Barts and The London
School of Medicine and Dentistry

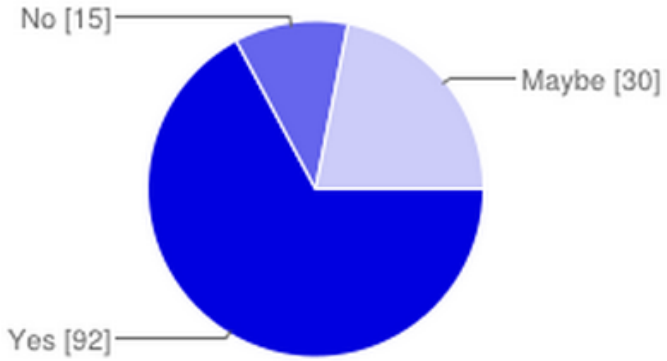
A BLOG FOR PEOPLE WITH MS AND THEIR FAMILIES

"INTERPRETING GOOD, BAD AND OTHER RESEARCH NEWS"

138 responses

Summary See complete responses

If you had the option for early aggressive treatment, would you choose it over safer first-line treatments?



Yes	**92**	67%
No	**15**	11%
Maybe	**30**	22%

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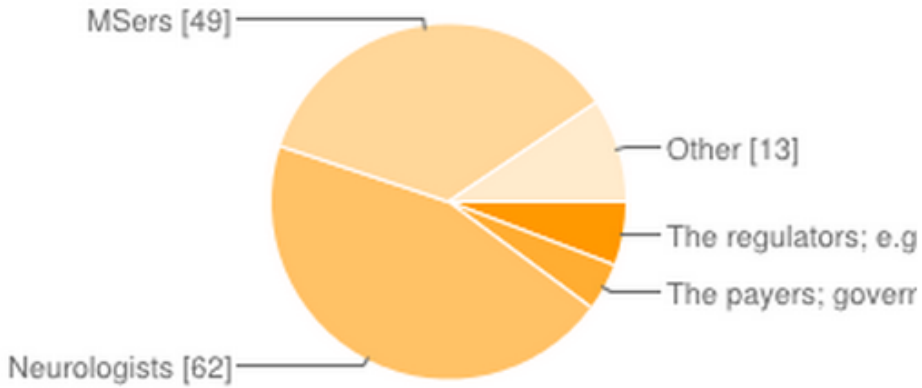
Who should make the decision regarding which MS treatments are accessible to MSers with early disease?



The regulators; e.g. EMA or FDA

The payers; governments or insurance companies

Neurologists

MSers

Other

European Commission Approves Genzyme's Multiple Sclerosis Treatment Lemtrada™ (alemtuzumab)

- Follows Recent European Commission Approval of Multiple Sclerosis Treatment Aubagio® (teriflunomide)

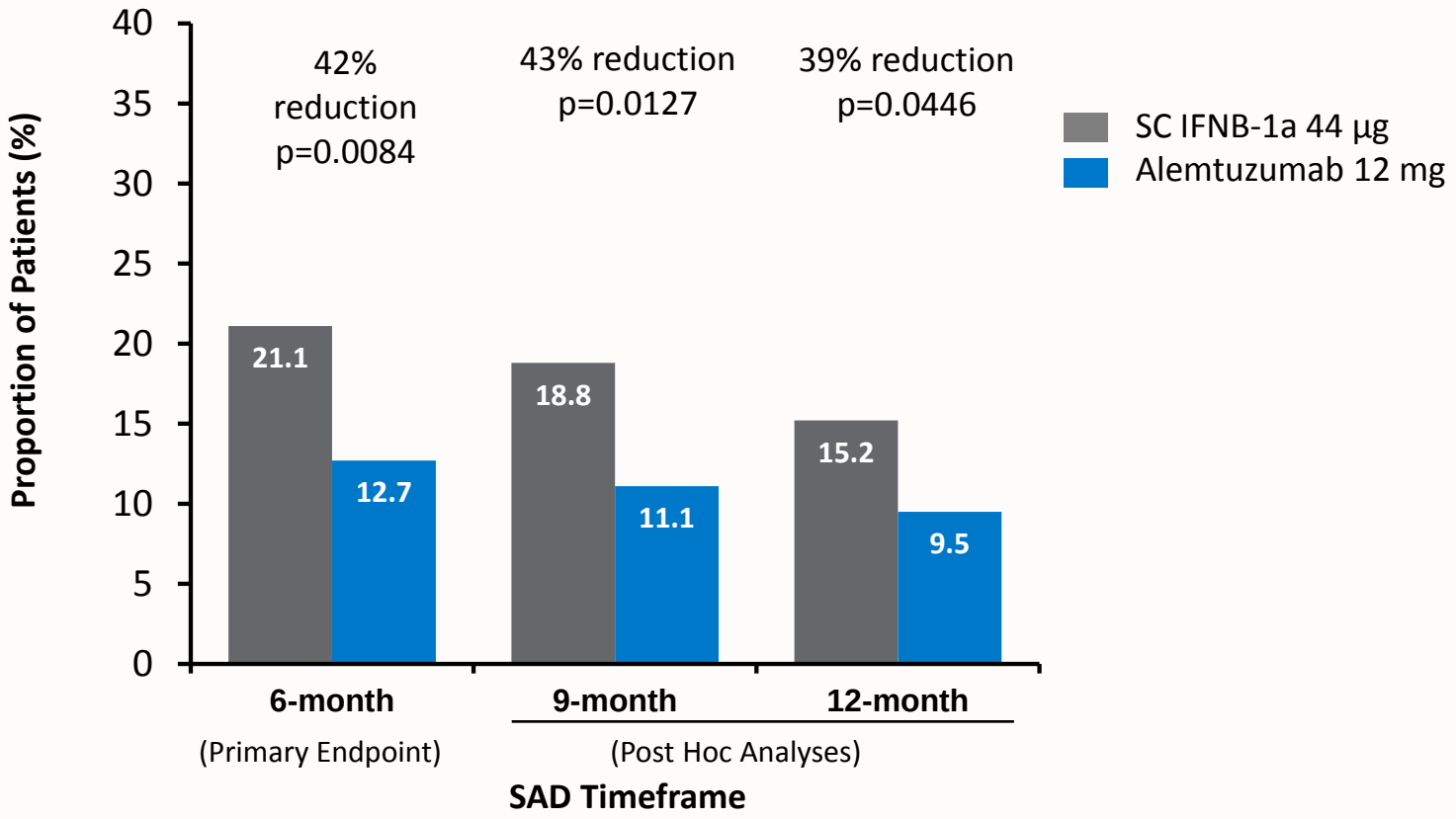
- Approvals Set the Stage for Launches Throughout EU and Strongly Position Genzyme as a Committed Partner to the MS Community

Paris, France – September 17, 2013

EU Indication and Usage

Lemtrada is indicated in the European Union for the treatment of adult patients with relapsing remitting multiple sclerosis with active disease defined by clinical or imaging features.

CARE-MS II: Risk of Sustained Disability over Intervals of up to 1 Year



Alemtuzumab reduced the risk of disability accumulation sustained for intervals of up to 1 year vs. SC IFNB-1a

Includes events with onset during 2-year core study, and confirmation in the extension.
Data on file, Genzyme Corporation.

Definition of dementia

Dementia is a loss of mental ability severe enough to interfere with normal activities of daily living, lasting more than six months, not present since birth, and not associated with a loss or alteration of consciousness.

- Normal activities of daily living
  - Physical ✓
  - Mental ✓
  - Social ✓
  - Occupational ✓
- Lasting more than six months ✓
- Not present since birth ✓
- Not associated with a loss or alteration of consciousness ✓

*"Multiple sclerosis is possibly a **preventable** dementia."*