Panel 2: McDonald 2010 diagnostic criteria for multiple sclerosis, with bullet points showing additional evidence required

At least two attacks with objective clinical evidence of at least two lesions

None

At least two attacks with objective clinical evidence of one lesion

Dissemination in space shown by:

- At least one T2 lesion in at least two of four areas of the CNS typically affected in demyelination: periventricular, juxtacortical, infratentorial, and spinal cord
- Further clinical attack at a different site

One attack with objective clinical evidence of at least two lesions

Dissemination in time shown by:

- Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions on a single scan or a new T2 and/or gadolinium-enhancing lesion on follow-up MRI
- Second clinical attack

One attack with objective clinical evidence of one lesion

Dissemination in space shown by:

- At least one T2 lesion in at least two of four areas of the CNS typically affected in demyelination: periventricular, juxtacortical, infratentorial, and spinal cord
- Second clinical attack at a different site

Dissemination in time shown by:

- Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions on a single scan or a new T2 and/or gadolinium-enhancing lesion on follow-up MRI
- Second clinical attack

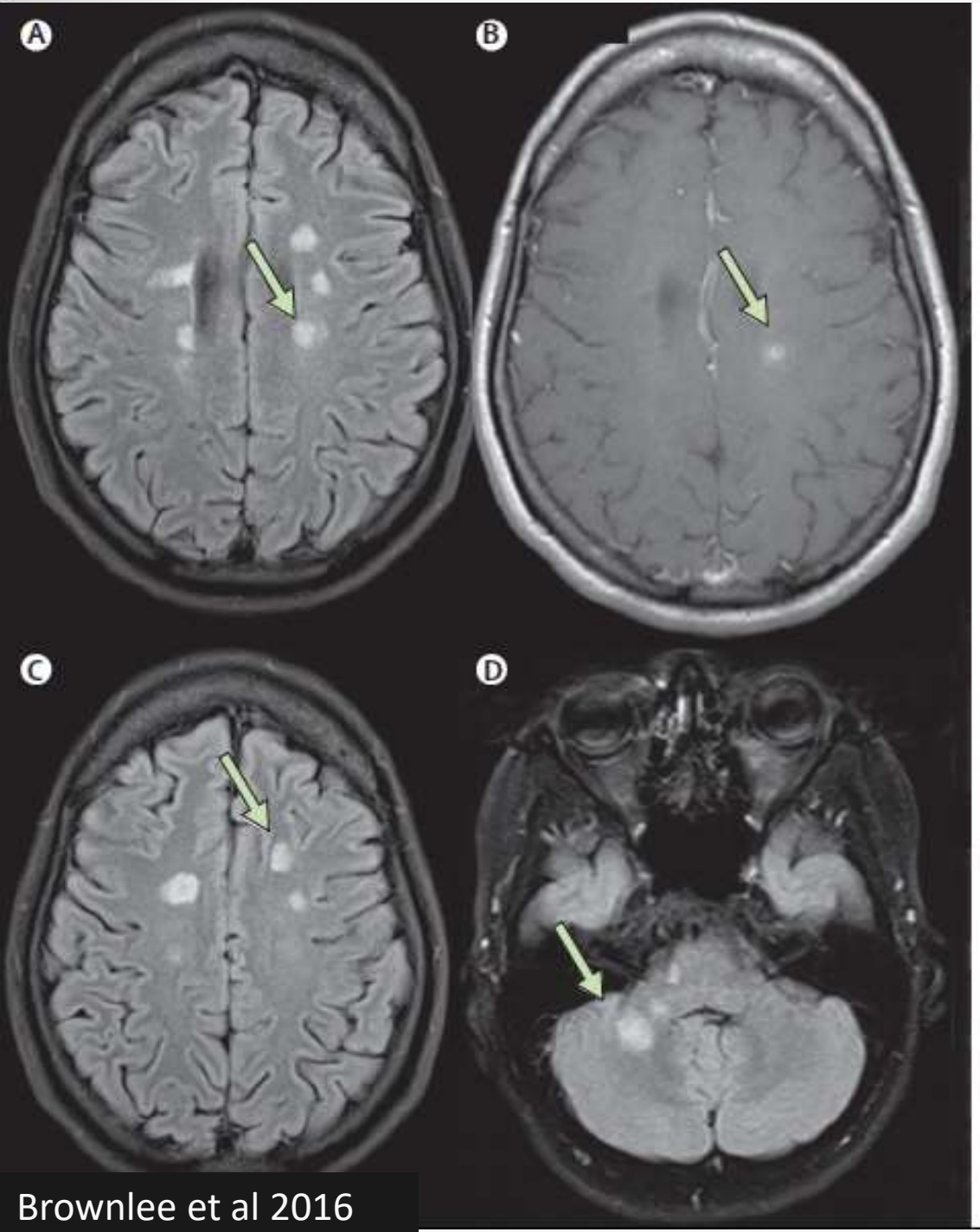
1 year of disease progression (retrospectively or prospectively determined)

Presence of two of:

- At least one T2 brain lesion in at least one multiple sclerosis-characteristic region: periventricular, juxtacortical, or infratentorial
- At least two T2 spinal cord lesions
- Positive CSF (at least two oligoclonal bands not present in serum, elevated IgG index, or both)

Modified from Polman and colleagues.[1]

Brownlee et al 2016



Brownlee et al 2016

EDSS

10 Morte per SM

9-9.5 Completamente dipendente

8 - 8.5 Costretto a letto o alla sedia; necessita di aiuto per la cura di sé

7- 7.5 Costretto alla sedia

6 - 6.5 Necessita di appoggio per deambulare

5 - 5.5 Aumento delle limitazioni nelle capacità deambulatorie

4-4.5 La disabilità è moderata

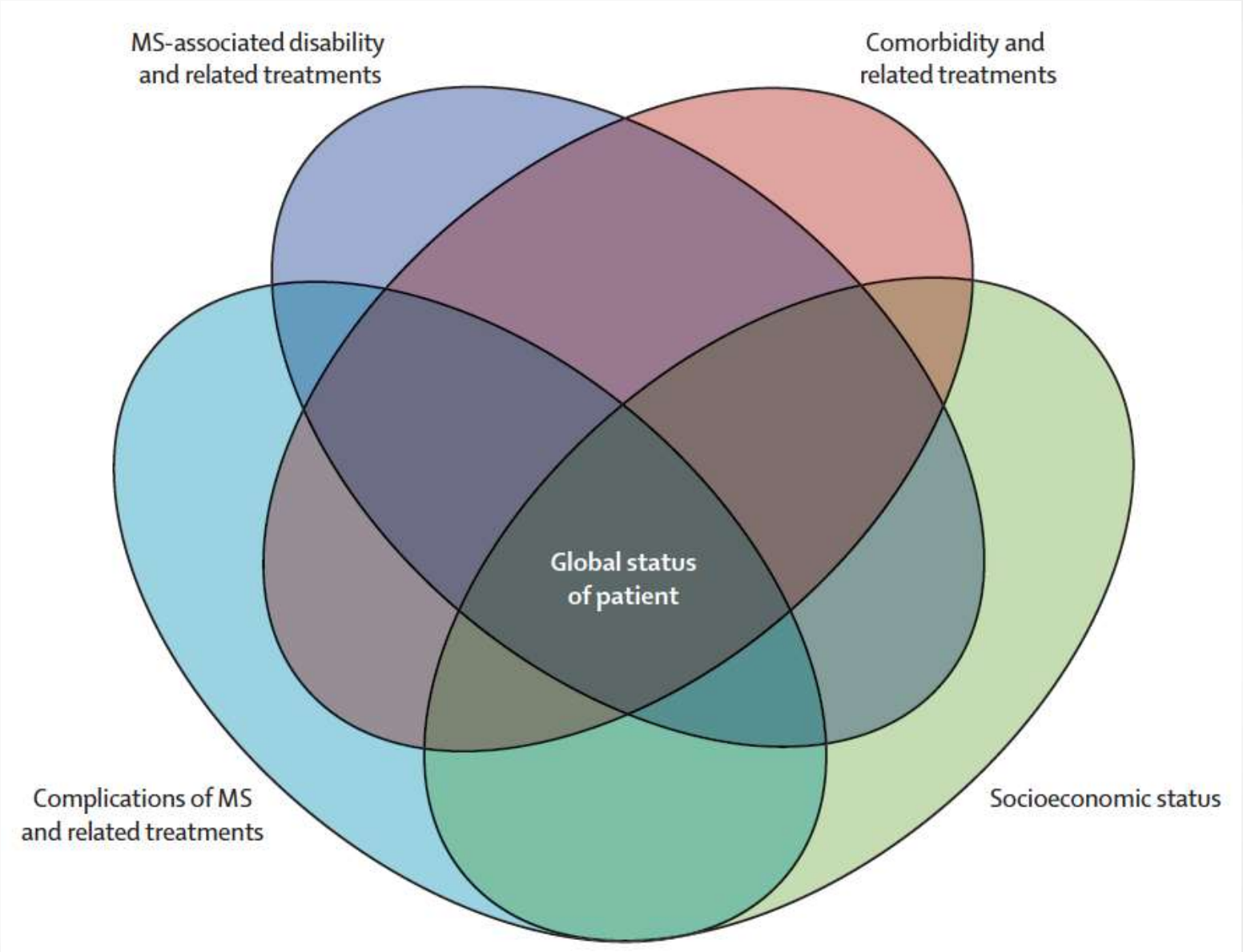
3-3.5 La disabilità è lieve o moderata

2-2.5 La disabilità è minima

1-1.5 Nessuna disabilità

0 Esame neurologico normale

Factors that affect the health status of patients with multiple sclerosis



Marrie RA et al 2010

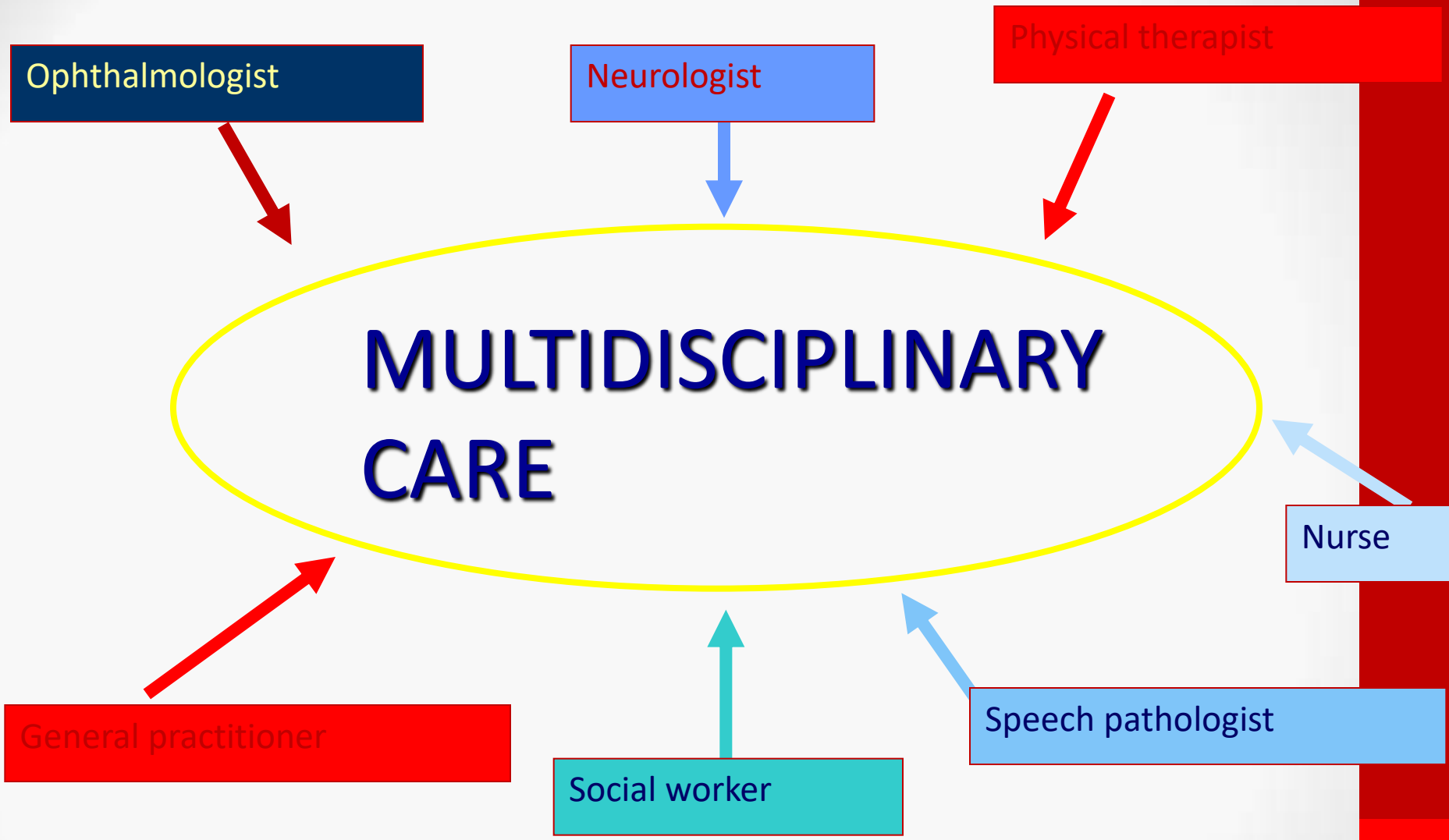
Table 2. The prevalence of comorbidity in multiple sclerosis in population-based studies.

Comorbidity	No. studies	I^2 statistic	Meta-analysis estimate (95% CI)
Alcohol abuse	1	-	14.8*
Anxiety	8	99.2	21.9 (8.76-35)
Asthma	3	93.1	7.46 (2.50-12.4)
Autoimmune			
Ankylosing spondylitis	1	-	1.78*
Diabetes type I	4	66.7	0.02 (0-0.58)
IBD	1	–	0.78*
Myasthenia gravis	1	–	0.20*
Psoriasis	1	–	7.74*
Rheumatoid arthritis	2	3.94	2.92 (1.8-4.0)
SLE	1	–	2.90*
Thyroid disease	3	95.4	6.44 (0.19-12.7)
Bipolar disorder	1	–	5.83*
Cancer			
All types	5	90.8	2.23 (1.18–3.29)
Breast	1	–	2.01[a]
Digestive system	1	–	–
Thyroid	1	–	0.48[a]
Vulvar	1	–	0.67[a]
Lung	1	–	
Skin cancer	1	–	0.48[a]
Multiple myeloma	0	–	0.97[a]
Cardiac arrhythmia	1	–	4.5[a]
Chronic lung disease	2	99.3	10.0 (0–20.9)
Congestive heart disease	1	–	1.8[a]
Depression	15	97.3	23.7 (17.4–30)
Diabetes	8	98.0	0.76 (0.67–0.84)
Diabetes type II	1	–	8.57
Drug abuse	1	–	2.5[a]
Epilepsy	11	93.9	3.09 (2.01–4.16)
Eye disease			
Cataracts	2	–	–
Glaucoma	2	–	–
Macular degeneration	-	–	–
Fibromyalgia	1	–	6.82[a]
Gastrointestinal			
IBS	1	–	12.2[a]
Viral hepatitis	1		3.45[a]
Hyperlipidemia	3	94.9	10.9 (5.6–16.1)
Hypertension	2	89.9	18.6 (13.9–23.2)
Ischemic heart disease	3	97.6	2.50 (0–5.77)
Peripheral vascular disease	2	88.2	2.40 (0–5.14)
Psychosis	2	97.8	4.3 (0–10.3)
Stroke (any)	2	97.4	3.28 (0–8.98)

A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview

Ruth Ann Marrie, Jeffrey Cohen, Olaf Stuve, Maria Trojano, Per Soelberg Sorensen, Stephen Reingold, Gary Cutter and Nadia Reider

Multiple Sclerosis Journal
2015, Vol. 21(3) 263–281
DOI: 10.1177/1352458514564491



Compston A. Treatment and management of multiple sclerosis in Mc Alpine's Multiple Sclerosis. 3rd ed. London: Churchill Livingstone 1998.

	Dose and route of administration	Efficacy			Safety and tolerability*	
		Relapse rate (% reduction)	Disease progression (% reduction)	MRI activity† (% reduction)	Common side-effects	Serious adverse effects
Interferon beta-1a; MSCRG[3] trial; n=301	30 µg, every week, intramuscularly	32% (18%‡)	37%	27%§ (NS)	Injection-site reactions, flu-like syndrome, increased liver enzymes, depression	Very rare liver toxicity
Interferon beta-1a; PRISMS[4] trial; n=560	44 µg, three times a week, subcutaneously	33%	31%	78%	Injection-site reactions, flu-like syndrome, increased liver enzymes, depression	Rare liver toxicity
Interferon beta-1b; MSSG[5] trial; n=372	250 µg, every other day, subcutaneously	34%	29% (NS)	83%	Injection site reactions, flu-like syndrome, increased liver enzymes, depression	Very rare liver toxicity
Glatiramer acetate; CMSSG[6] trial; n=251	20 mg, daily, subcutaneously	29%	12% (NS)	35%	Injection-site reactions, lipoatrophy, flu-like syndrome, systemic reaction	None
Natalizumab; AFFIRM[7] trial; n=942	300 mg, every 4 weeks, intravenously	68%	54%	83%	Infusion reactions and infections	Rare hypersensitivity reactions, progressive multifocal leukoencephalopathy¶
Fingolimod; FREEDOMS 1[8] trial, n=1272; and FREEDOMS 2[9] trial, n=1083	0·5 mg, every day, orally	54% and 50%	37% and 28% (NS)	75% and 74%	Bradycardia, heart block, macular oedema, infections	Generalised varicella-zoster infection¶, progressive multifocal leukoencephalopathy ¶, herpes encephalitis¶
Mitoxantrone; MIMS[10] trial; n=194	12 mg/m^2, every 3 months, intravenously	68%	64%	85%	Nausea, alopecia, leukopenia, menstrual irregularities	Cardiotoxicity¶, therapy-related acute leukaemia¶
Teriflunomide; TEMSO[11] trial, n=1086; and TOWER[12] trial, n=1165	14 mg, every day, orally	37% and 32%	30% and 33%	69%; not assessed	Diarrhoea, hair thinning, skin rashes	None
Dimethyl fumarate; DEFINE[13] trial, n=1237; and CONFIRM[14] trial, n=1430	240 mg, twice a day, orally	53% and 44%	38% and 21% (NS)	85% and 71%	Flushing, gastrointestinal symptoms	Progressive multifocal leukoencephalopathy¶
Alemtuzumab‖; CARE-MS I[15] trial, n=578; and CARE-MS II[16] trial, n=628	12 mg, once a day for 5 days and, after 12 months, once a day for 3 days; intravenously	55% and 48%	30% (NS) and 41%	(NS) and (NS)	Infusion reactions, cytokine-release syndrome, infections	Thyroid disorders, immune thrombocytopenia¶ Good-Pasture's syndrome

NS=not significant. *Clinical trials and post-marketing studies. †New or enlarged T2-lesions. ‡All patients. §Gadolinium-enhancing lesions. ¶Fatal cases. ‖Comparison with subcutaneous interferon beta-1a

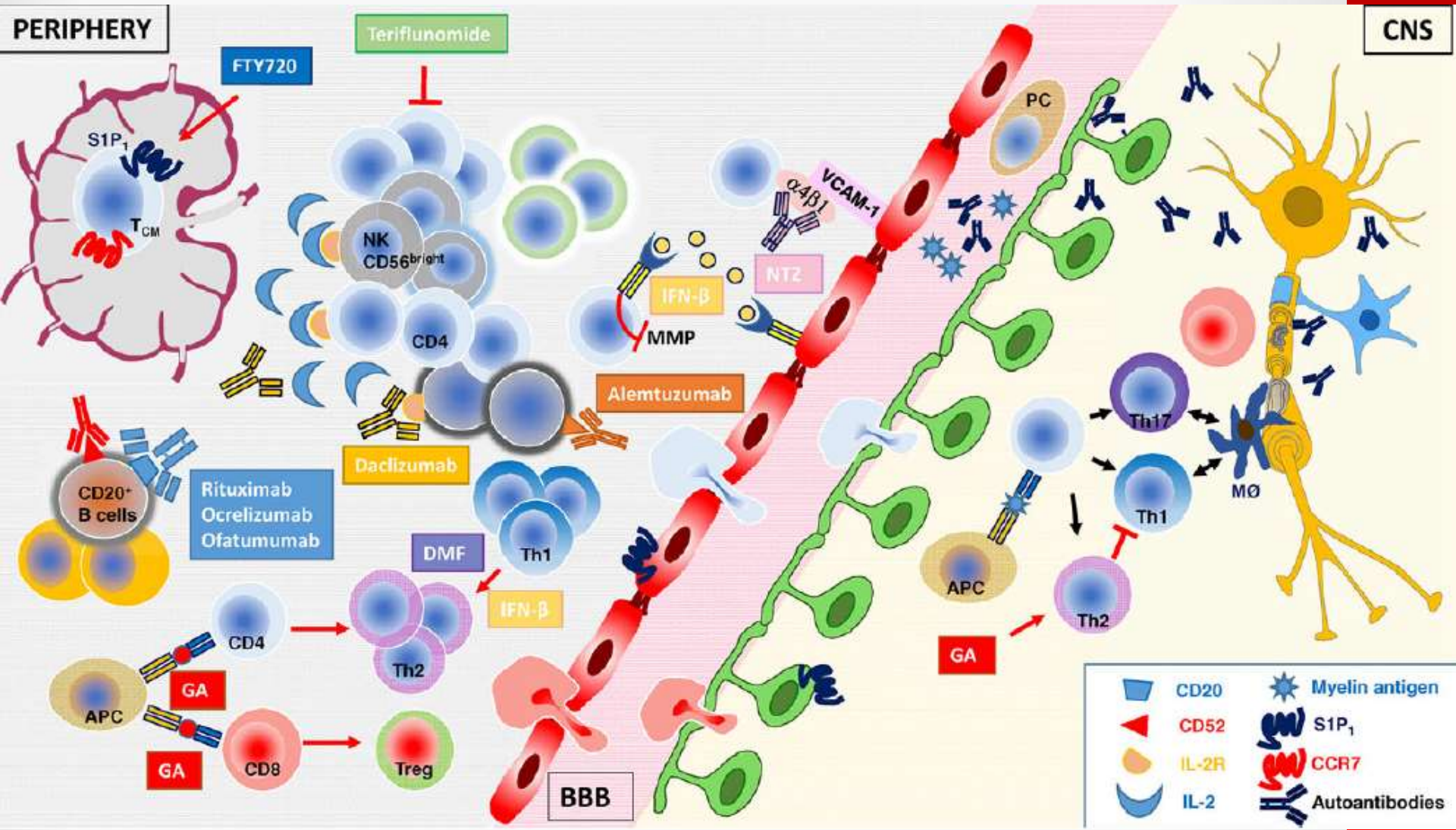
Table 1: **Results of placebo-controlled trials of drugs approved for treatment of relapsing-remitting multiple sclerosis**

Comi et al 2016

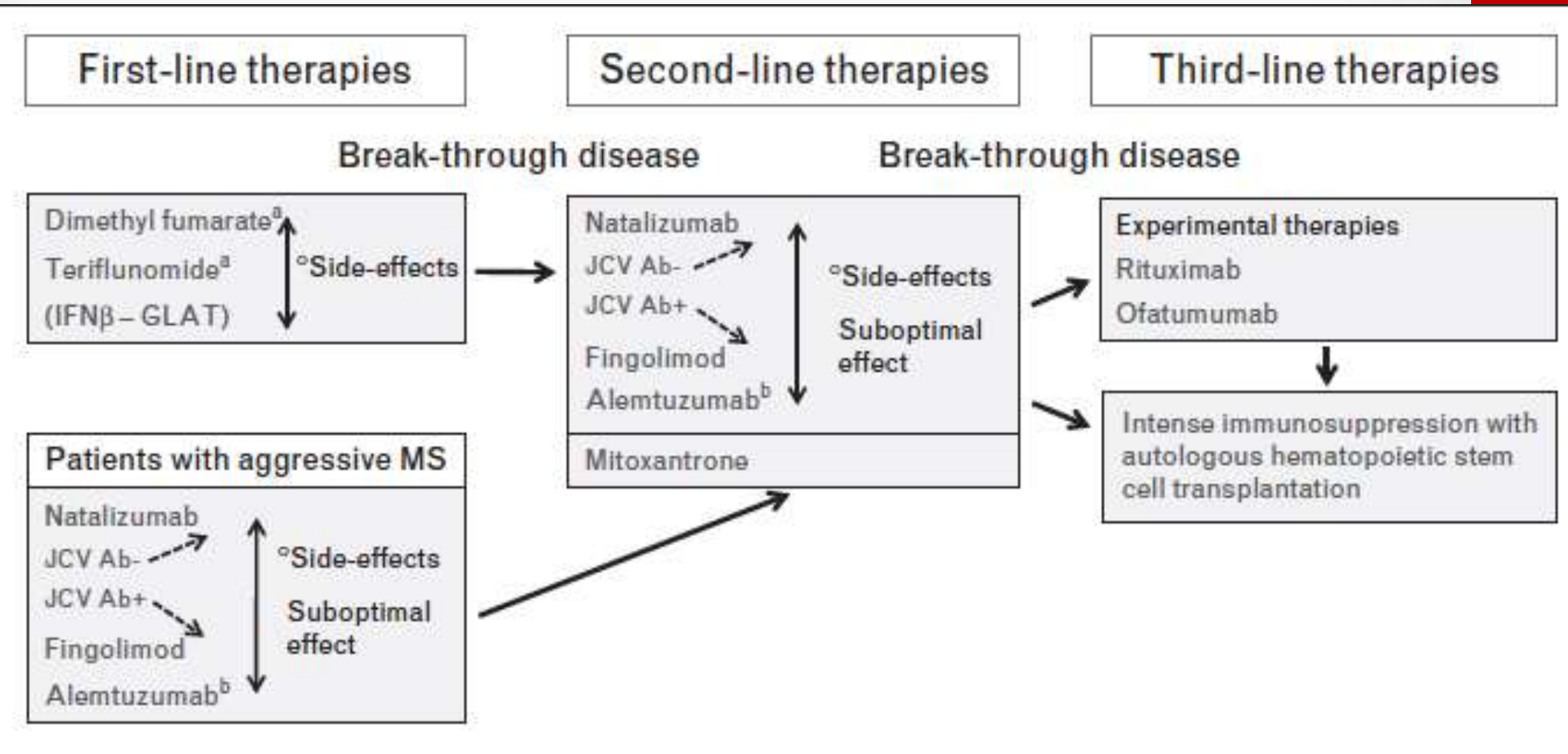
Medication	Route/ frequency	Efficacy vs. PBO	Impact on relapses vs. active Tx	Adverse events
Interferon β-1b	SC/QOD	34% reduction in ARR at ~2 years	Comparable with GA	Flu-like symptoms, transaminase elevation, skin site reactions and frequent NABs
Interferon β-1a	IM/QOW	18% reduction in ARR at ~2 years	Inferior to interferon β-1a SC TIW, GA, FNG and DAC-HYP in reducing relapses	Flu-like symptoms and transaminase elevation
Interferon β-1a	SC/TIW	30% reduction in ARR at ~2 years	Comparable with GA, superior to interferon β-1a IM	Flu-like symptoms, transaminase elevation, skin site reactions and frequent NABs
Pegylated interferon β-1a	SC/QOW	39% reduction in ARR at ~1 year		Flu-like symptoms, transaminase elevation and skin site reactions
Glatiramer acetate	SC/QD SC/TIW	29% reduction in ARR at ~2 years	Comparable with interferon β-1b and interferon β-1a TIW, superior to interferon β-1a IM in ARR reduction	Skin site reaction and postinjection systemic reaction
Dimethyl fumarate	PO/BID	34 and 53% reduction in ARR at ~ 2 years		Flushing, GI symptoms and PML
Fingolimod	PO/QD	55% reduction in ARR at 2 years	Superior to interferon β-1a QW in ARR reduction	Transaminase elevation, bradyarrythmia, macular edema, PRESS, PML, Cryptococccosis, Kaposi sarcoma and primary CNS lymphoma
Teriflunomide	PO/QD	31 and 36% reduction in ARR at ~2 years	Similar to interferon β-1a SC	Transaminase elevation, teratogenicity and TEN
Mitoxantrone	IV/Q 3 months	38% reduction in ARR at ~2 years		Cardiotoxicity, promyelocytic leukemia and transaminase elevation
Natalizumab	IV/Q 4 weeks	67% reduction in ARR at ~2 years		PML, HSV encephalitis and hepatotoxicity
Alemtuzumab	IV/annual		Superior to interferon β-1a	De-novo autoimmunity, herpes reactivation, Burkitt's lymphoma and Listeria
Daclizumab[a]	SC/month		Superior to interferon β-1a IM in reducing relapses	Transaminase elevation and cutaneous reactions
Ocrelizumab[a]	IV/6 months		Superior to interferon β-1a SC in reducing relapses	Herpes reactivation

[a]Approval expected based on positive outcome of pivotal trials. Adapted from [1,2].
ARR, annualized relapse ratio; BID, twice daily; CNS, central nervous system; DAC-HYP, daclizumab-high yield process; FNG, fingolimod; GA, glatiramer acetate; HSV, herpes simplex virus; IM, intramuscular; IV, intravenous; NAB, neutralizing antibody; PBO, placebo; PO, by mouth; PML, progressive multifocal leukoencephalopathy; PRESS, posterior reversible encephalopathy syndrome; QOD, every other day; QOW, every other week; S epidermal necrolysis; TIW, three times weekly.

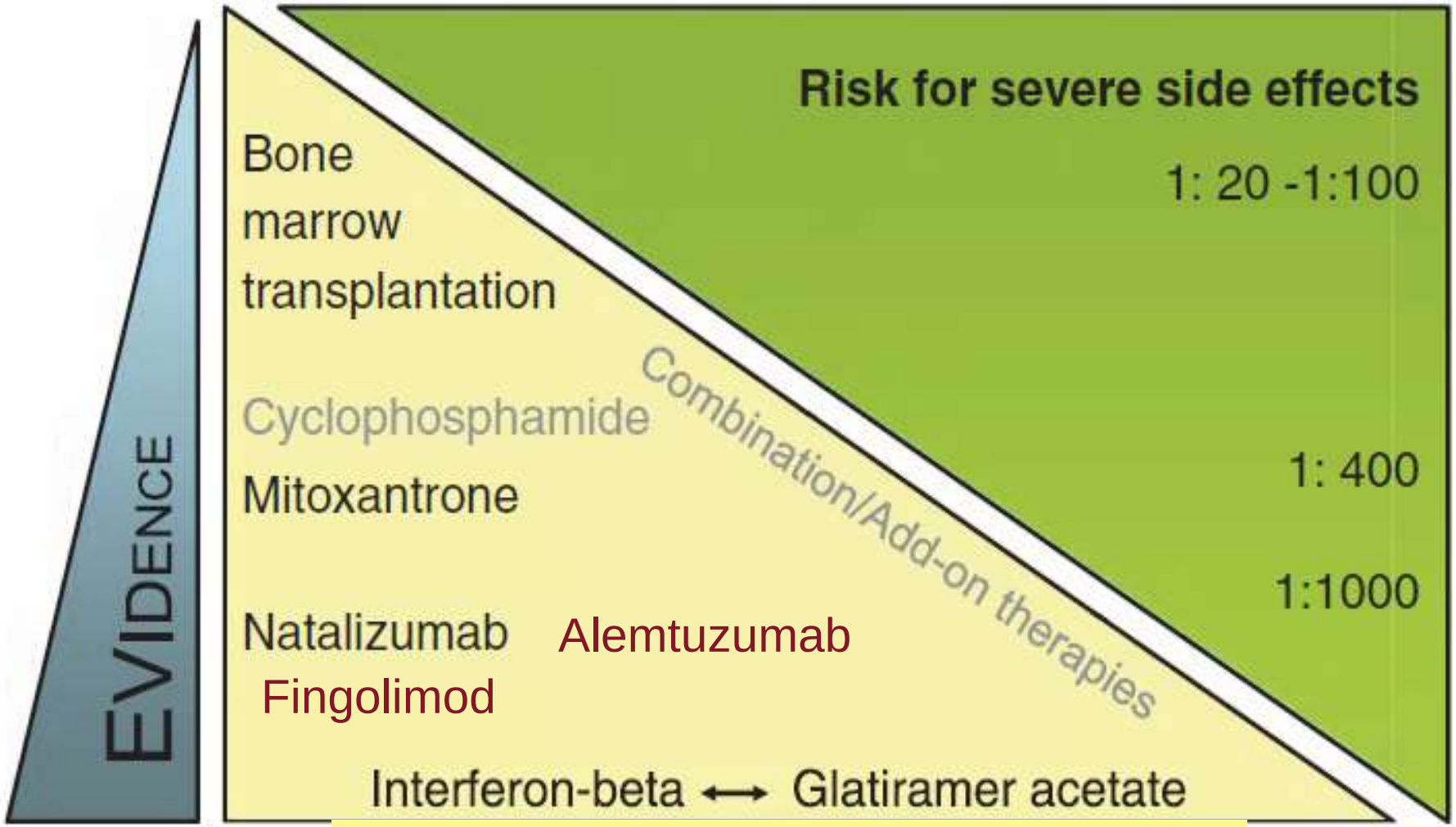
Curr Opin Neurol 2016, 29:263–271



Martin et al 2016



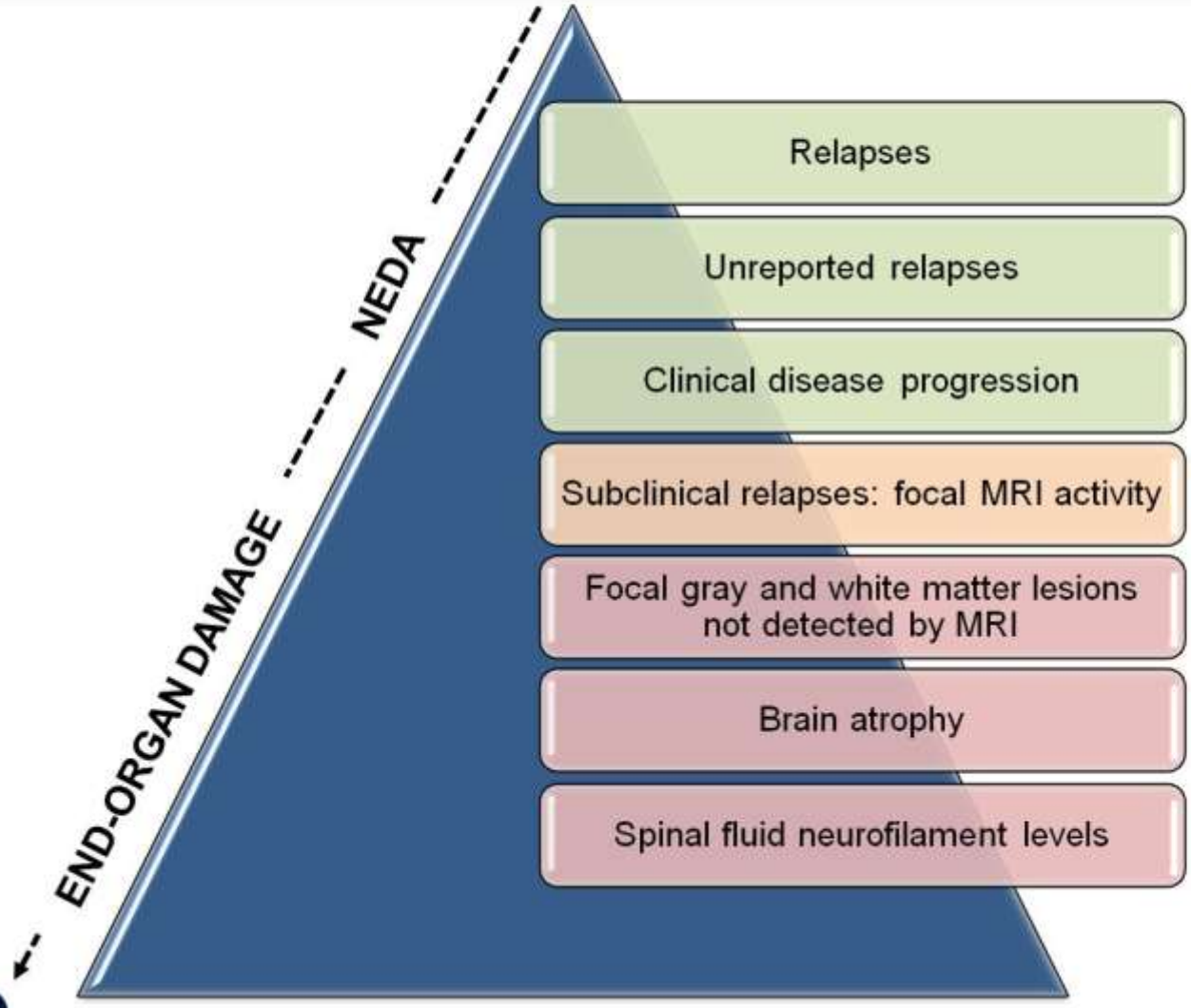
Sorensen 2014



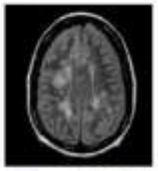
Peg-interferon----Teriflunomide---- Fumarato

Modificato: Rieckmann P et al 2008

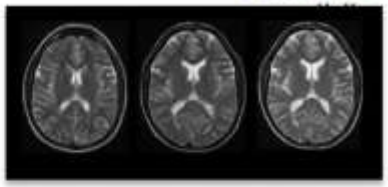
MS Iceberg



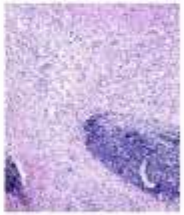
Clinical activity



Focal MRI

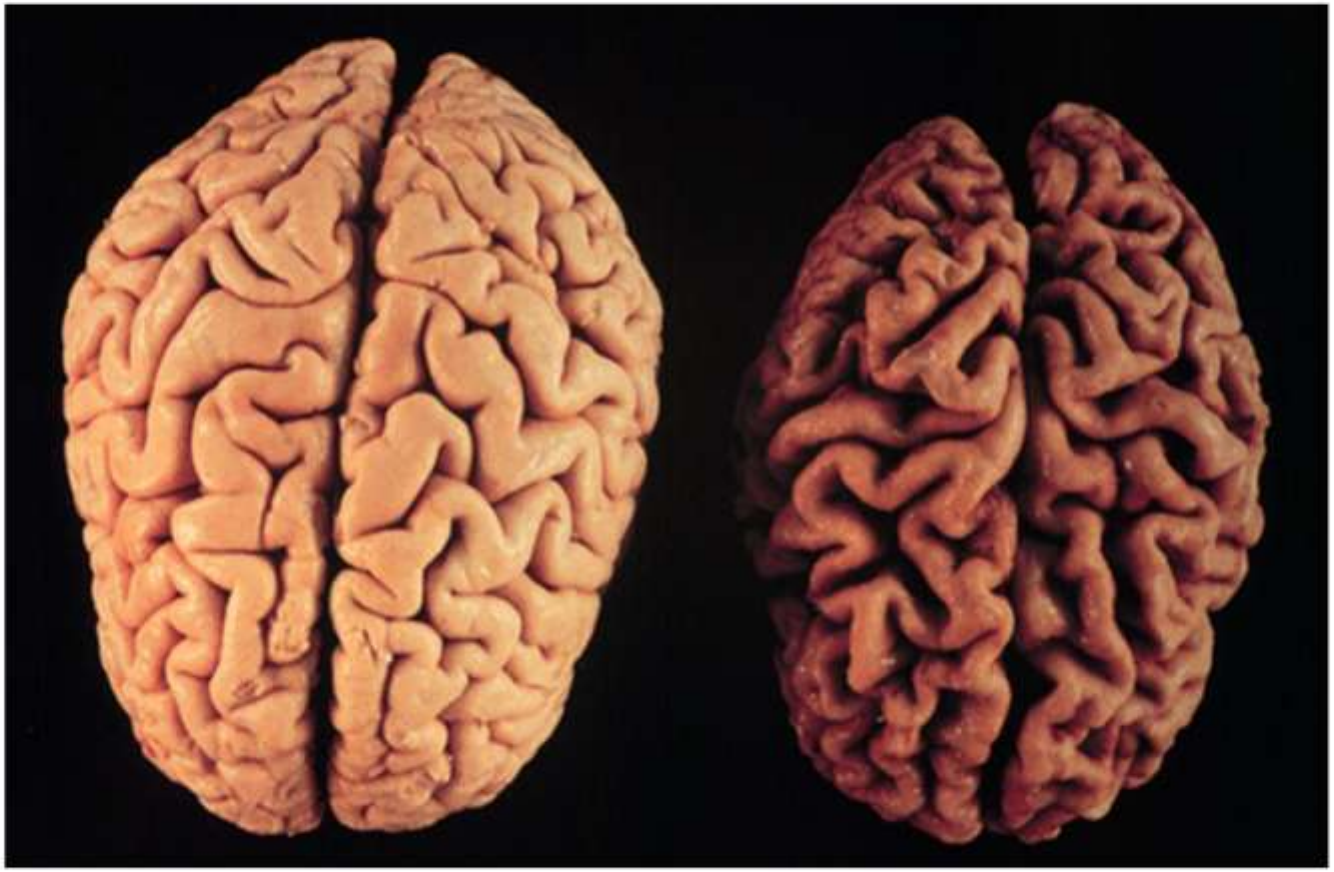


Hidden focal and diffuse MRI activity



Microscopic or biochemical pathology

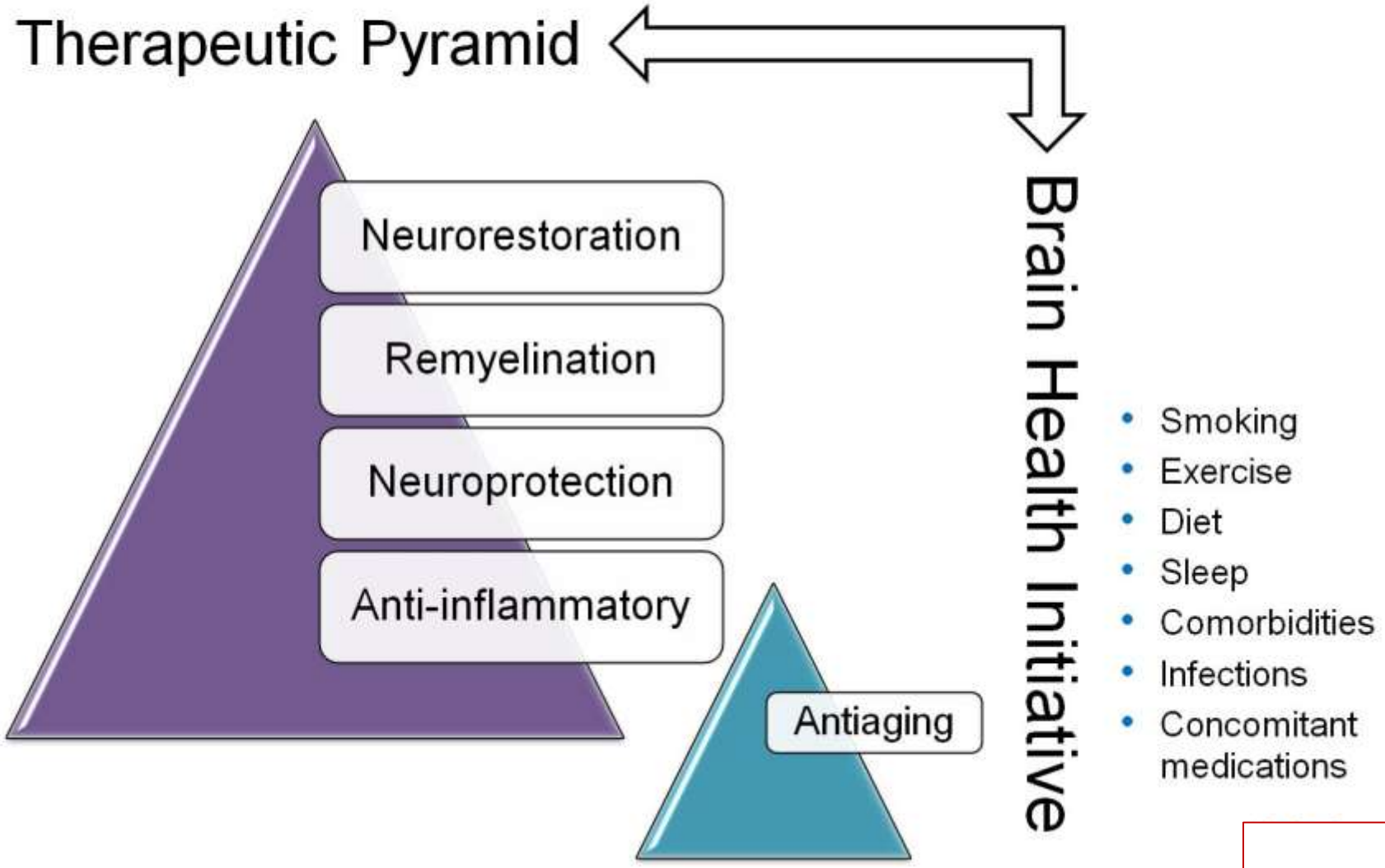
End-organ Damage

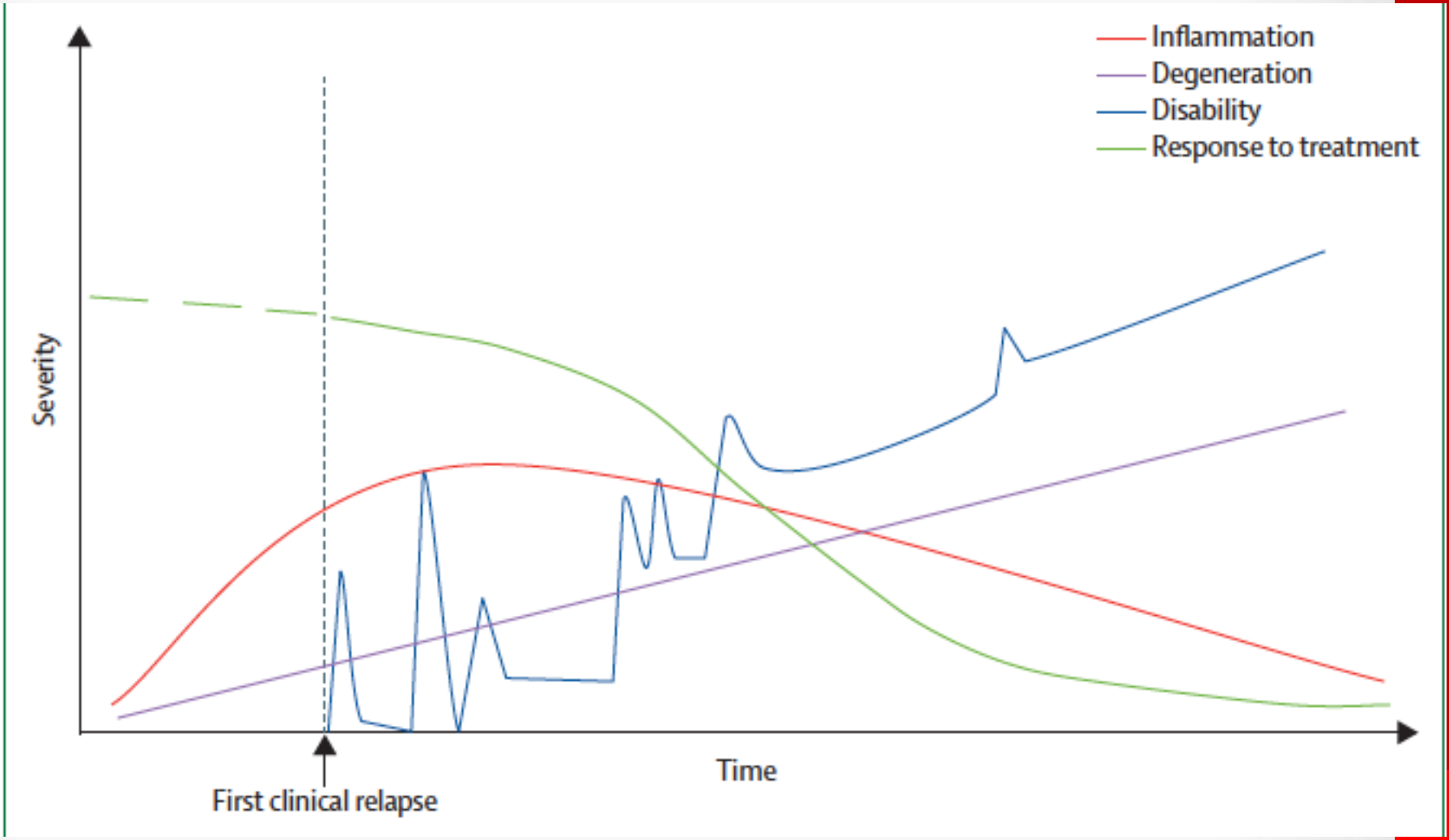


Control MS

 Image courtesy of Klaus Schmierer, MBBS, PhD, FRCP.

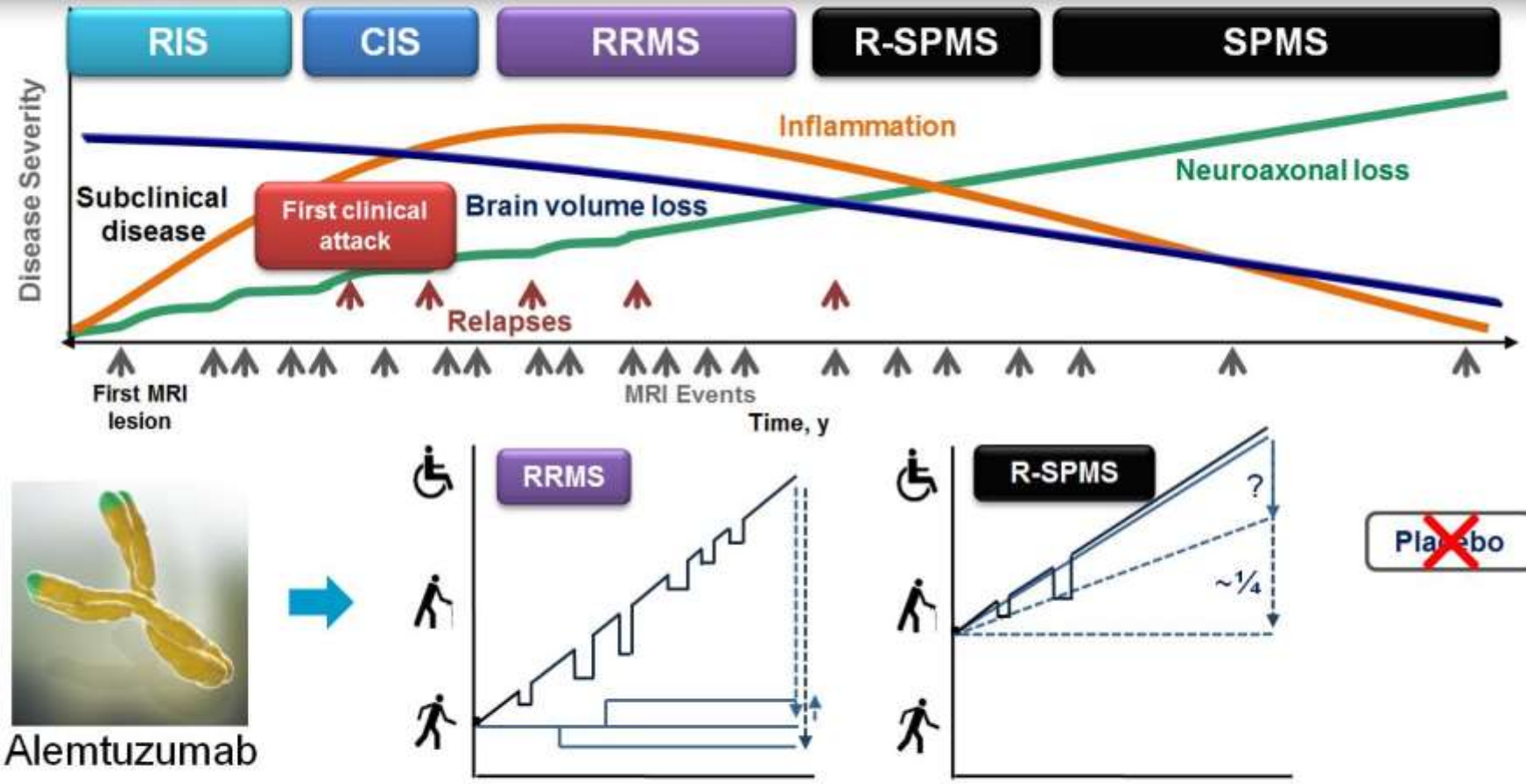
Therapeutic Hierarchy





Comi et al 2016

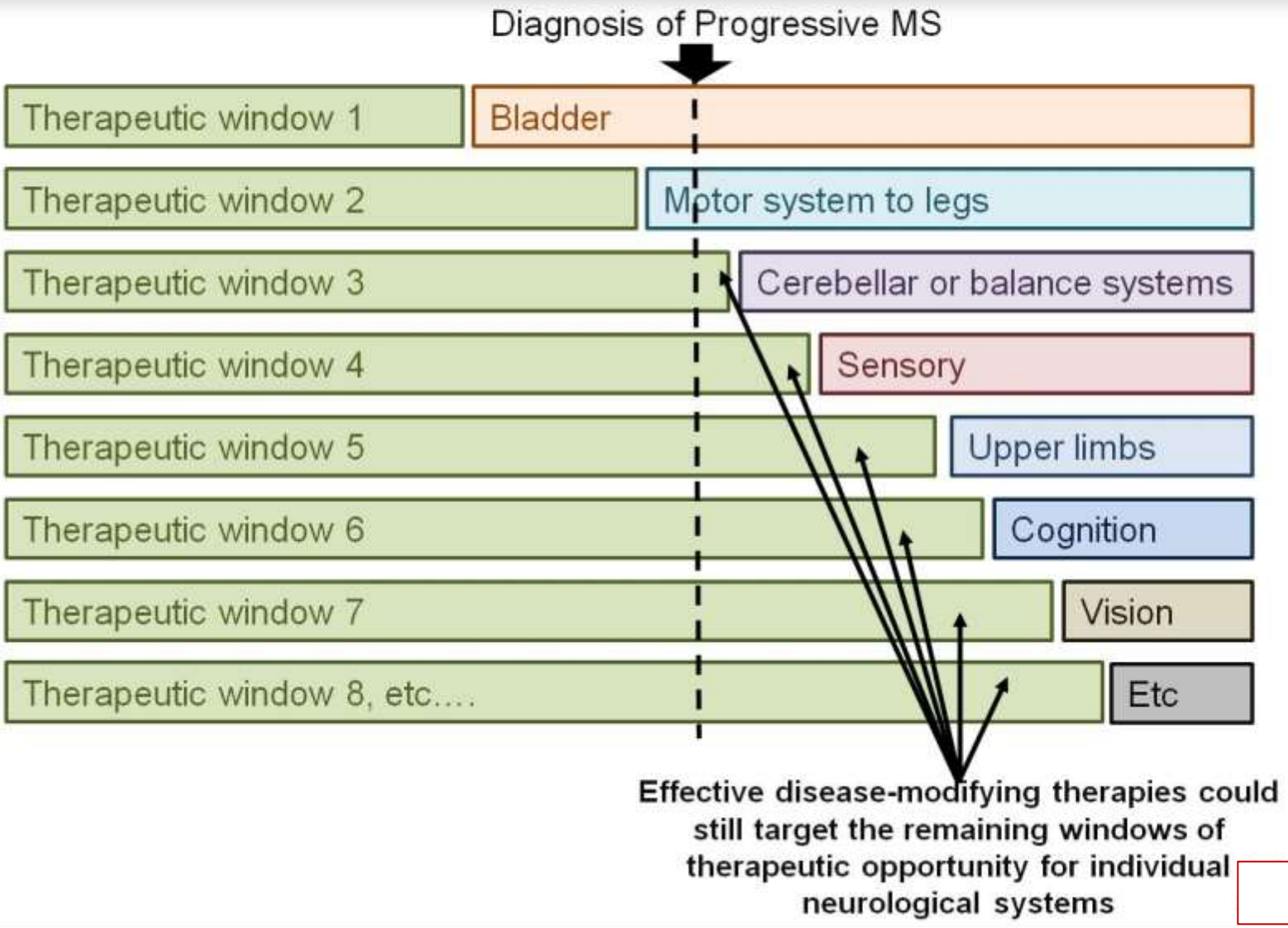
Window of Therapeutic Efficacy



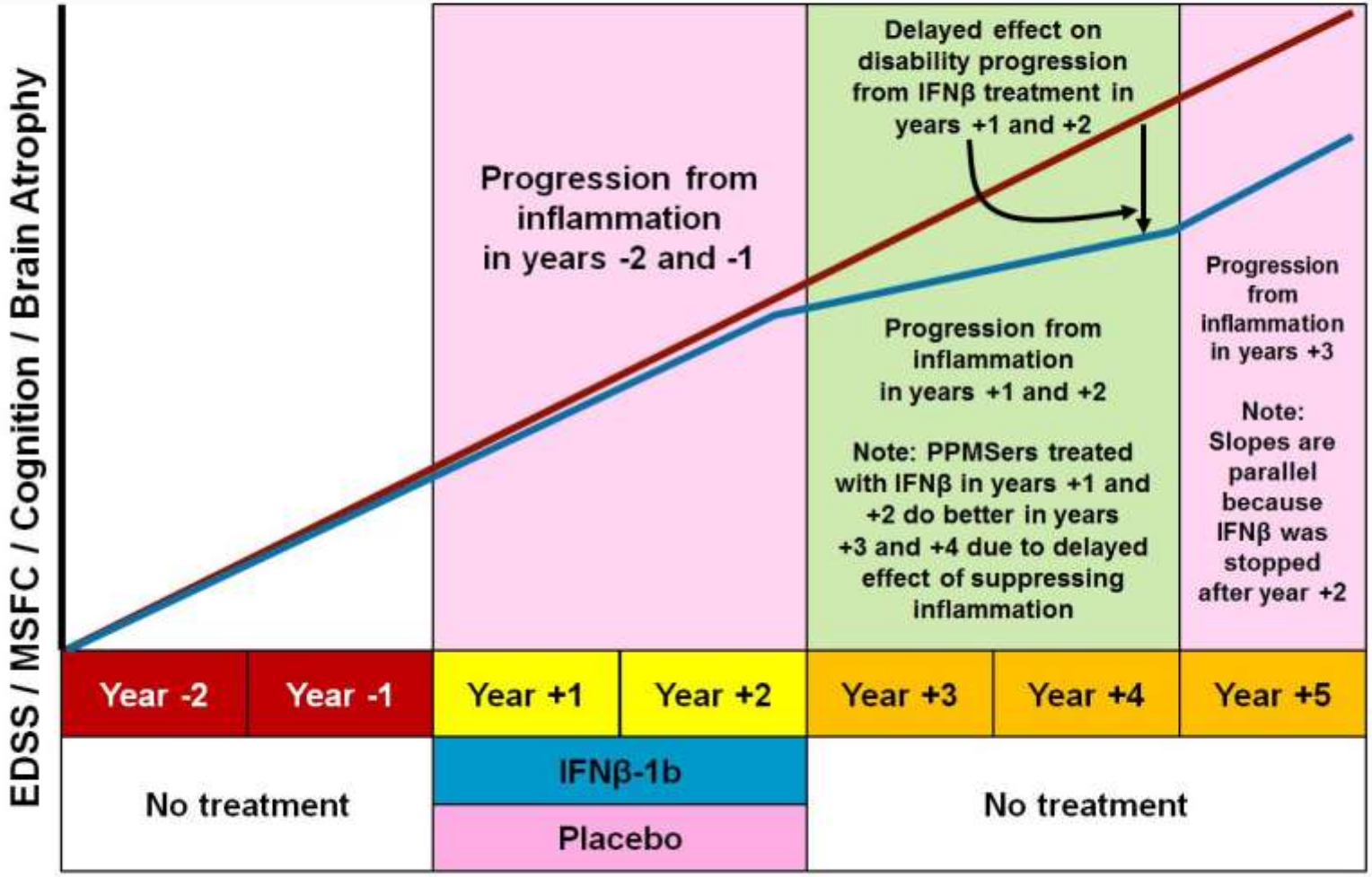
RIS = radiologically isolated syndrome; CIS = clinically isolated syndrome; RRMS = relapsing-remitting MS; R-SPMS = relapsing secondary progressive MS; SPMS = secondary progressive MS; PPMS = primary progressive MS.

Coles AJ, et al. *J Neurol.* 2006;253:98-108.[44]

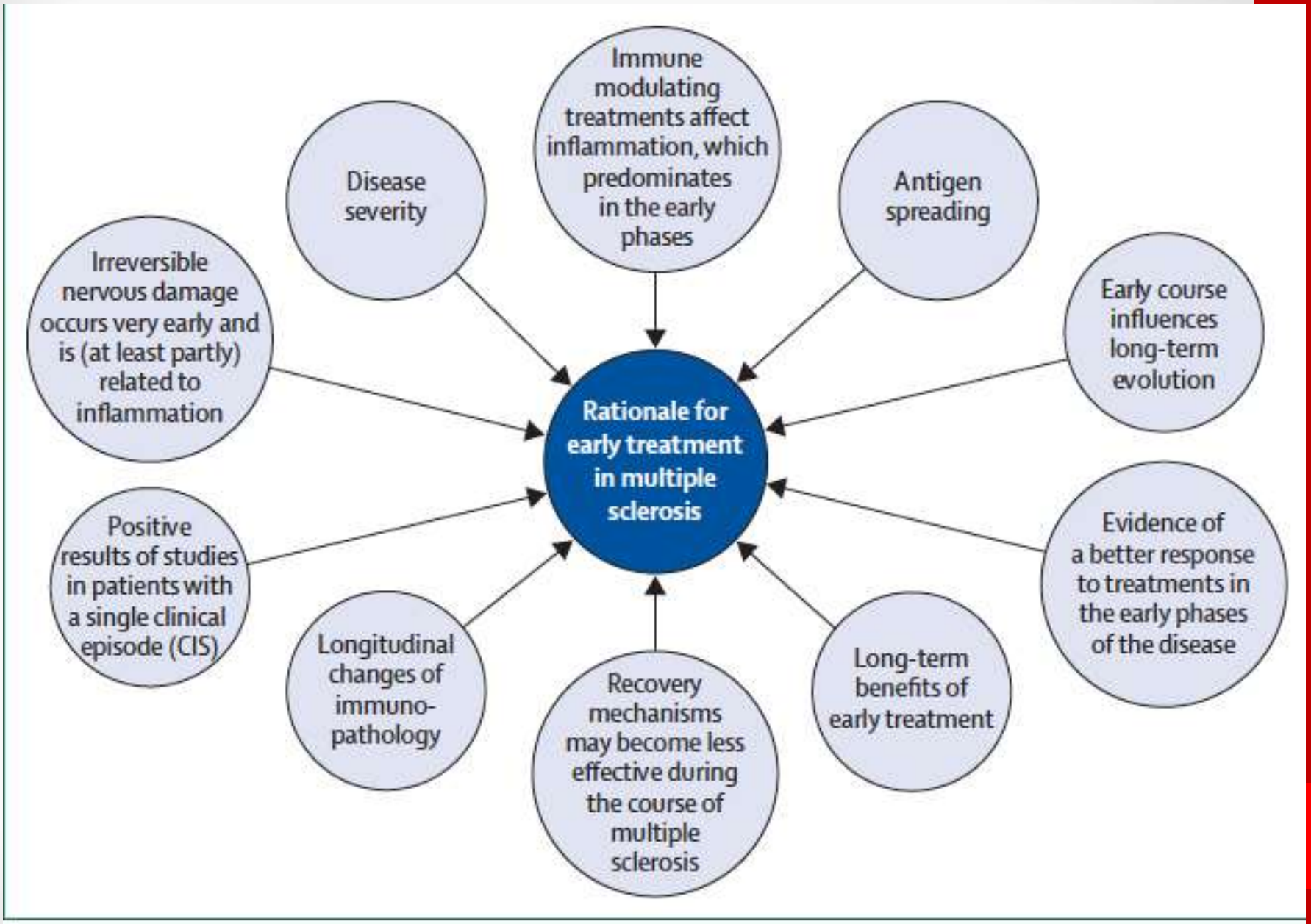
The Asynchronous Progressive MS Hypothesis



Therapeutic Lag



Tur C, et al. *Arch Neurol.* 2011;68:1421-1427.[45]



Comi et al 2016

Table Phase 3 Drug Pipeline for Multiple Sclerosis

Nonproprietary name	Manufacturer	Indication	Drug category	Estimated FDA submission date
Daclizumab high-yield process	Biogen Idec and AbbVie	RRMS	Interleukin-2 inhibitor	April 29, 2015
Masitinib	AB Science	PPMS, SPMS	Tyrosine kinase inhibitor	2017
Laquinimod	Teva and Active Biotech	RRMS	Immunomodulator[a]	2017 or beyond[b]
Ponesimod	Actelion	RRMS	Sphingosine-1-phosphate receptor 1 inhibitor	2018
Siponimod	Novartis	RRMS, PPMS, SPMS	Sphingosine-1-phosphate receptors 1 and 5 inhibitor	2017
Ozanimod	Celgene	RRMS, PPMS, SPMS	Sphingosine-1-phosphate receptors 1 and 5 inhibitor	2018
Ocrelizumab	Genentech	PPMS, SPMS	CD20-positive B-cell–targeting monoclonal antibody	2016

Radik et al 2015

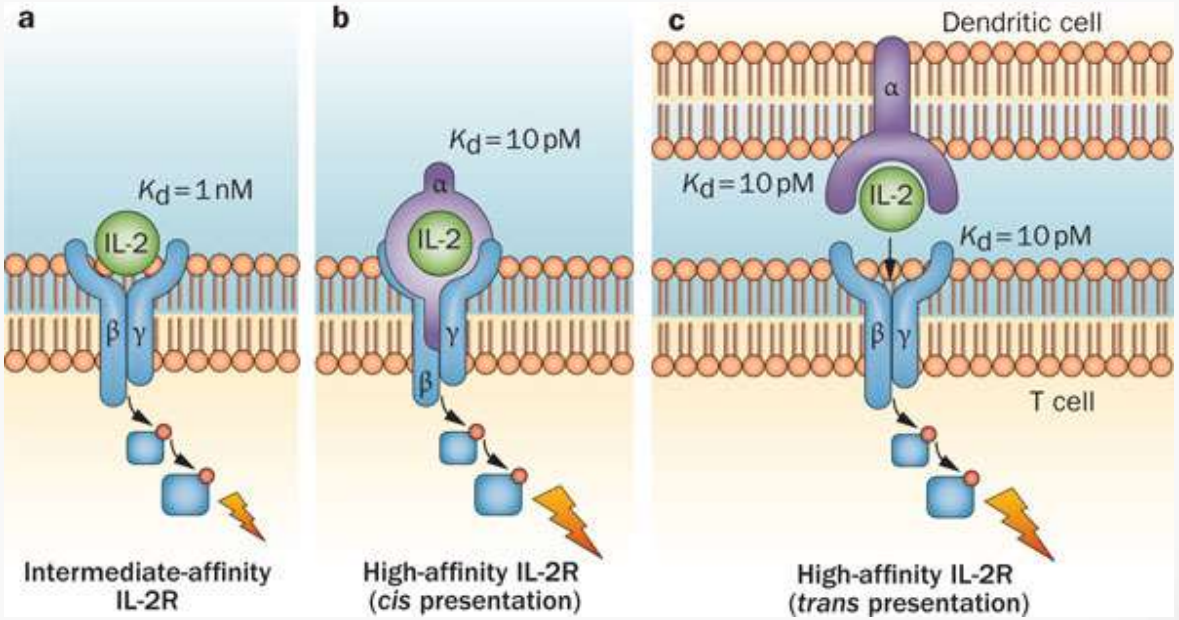
Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis

L. Kappos, H. Wiendl, K. Selmaj, D.L. Arnold, E. Havrdova, A. Boyko, M. Kaufman, J. Rose, S. Greenberg, M. Sweetser, K. Riester, G. O'Neill, and J. Elkins

N Engl J Med 2015;373:1418-28.

Anti-CD25 of the IgG1 class

- Stops generation of the high affinity IL2 receptor
- Blocks expansion and activation of T cells
- Increases regulatory natural killer cells (CD65^{bright})



The NEW ENGLAND JOURNAL of MEDICINE

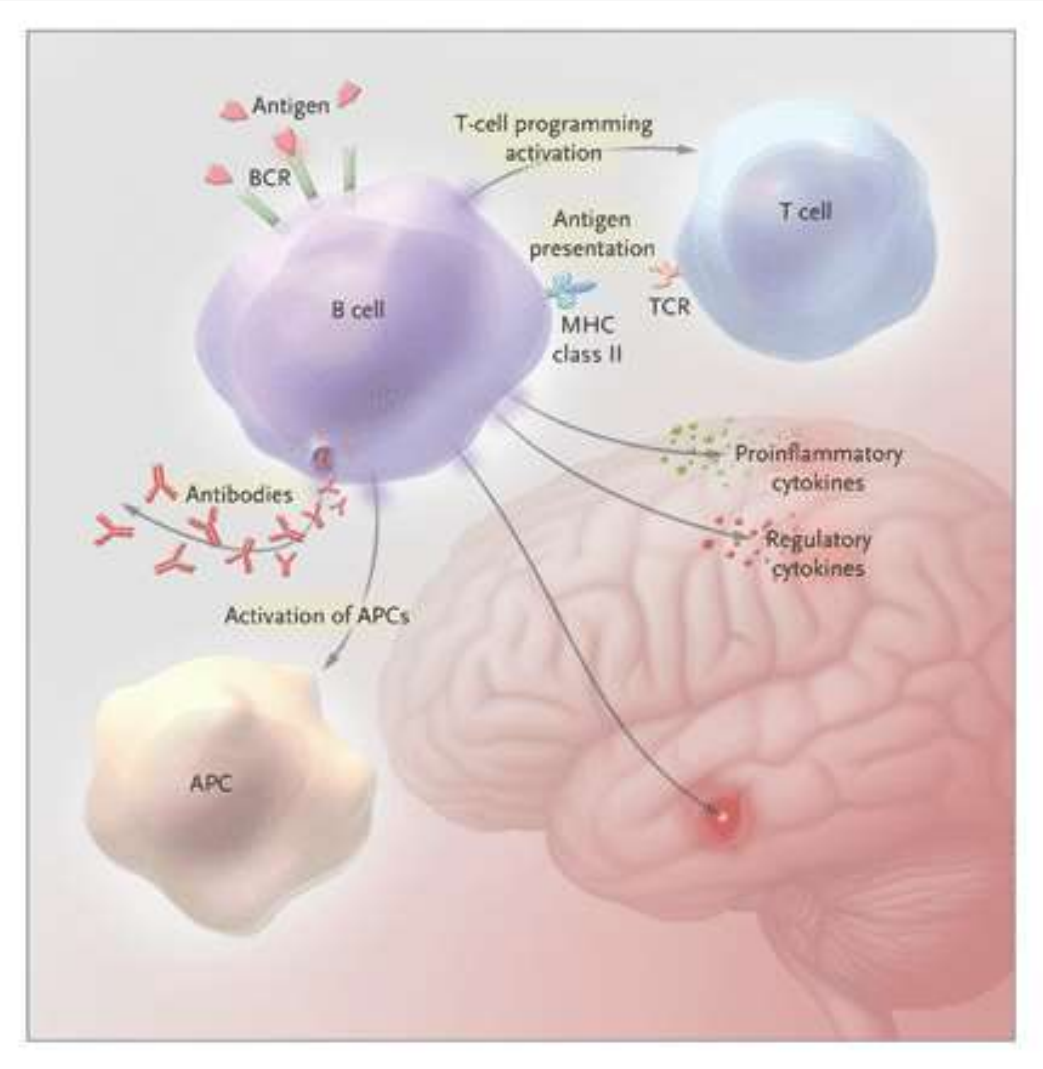
ORIGINAL ARTICLE

A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis

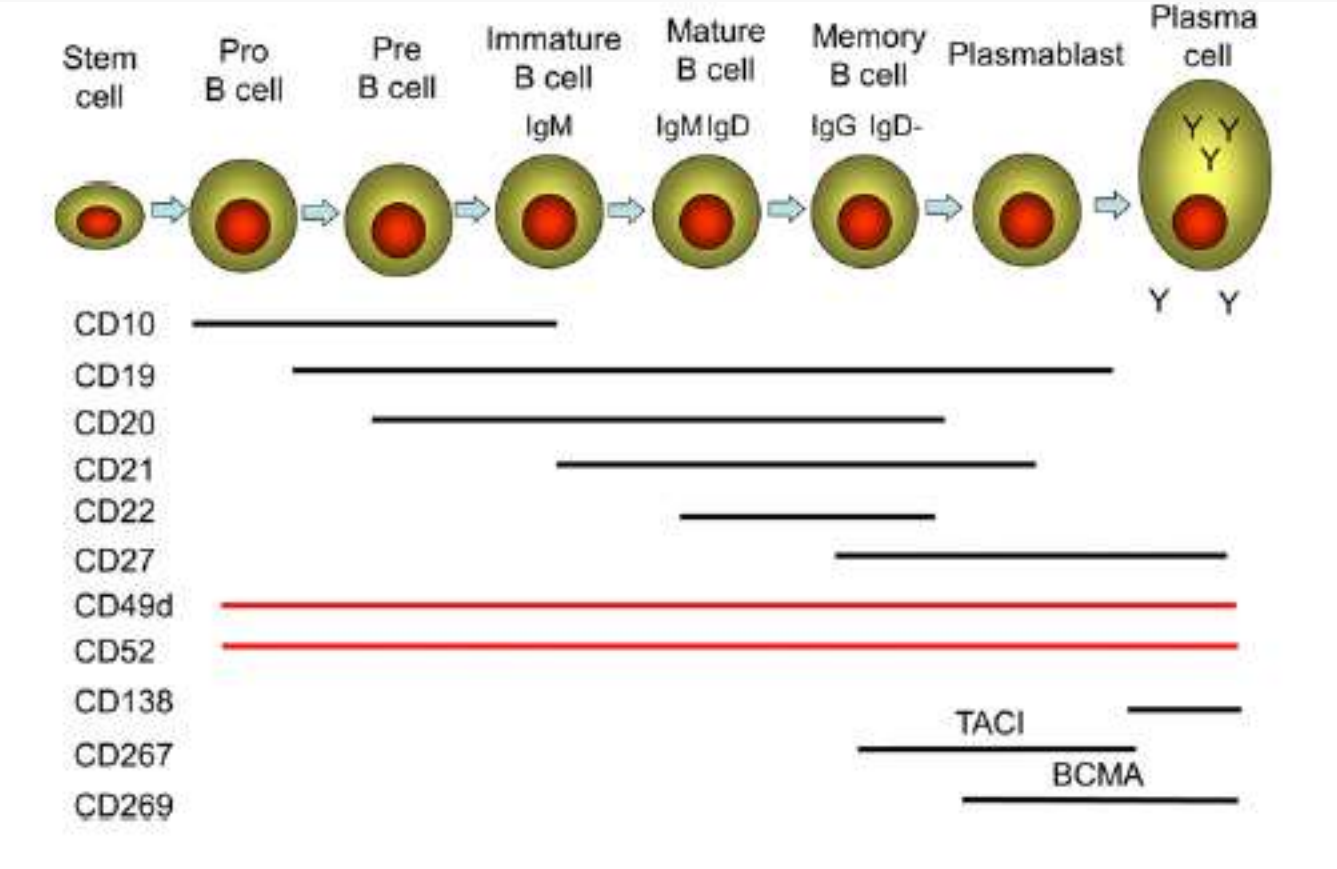
Gavin Giovannoni, M.B., B.Ch., Ph.D., Giancarlo Comi, M.D., Stuart Cook, M.D., Kottil Rammohan, M.D., Peter Rieckmann, M.D., Per Soelberg Sørensen, M.D., D.M.Sc., Patrick Vermersch, M.D., Ph.D., Peter Chang, Ph.D., Anthony Hamlett, Ph.D., Bruno Musch, M.D., Ph.D., and Steven J. Greenberg, M.D., for the CLARITY Study Group*

This article (10.1056/NEJMoa0902533) was published on January 20, 2010, at NEJM.org.

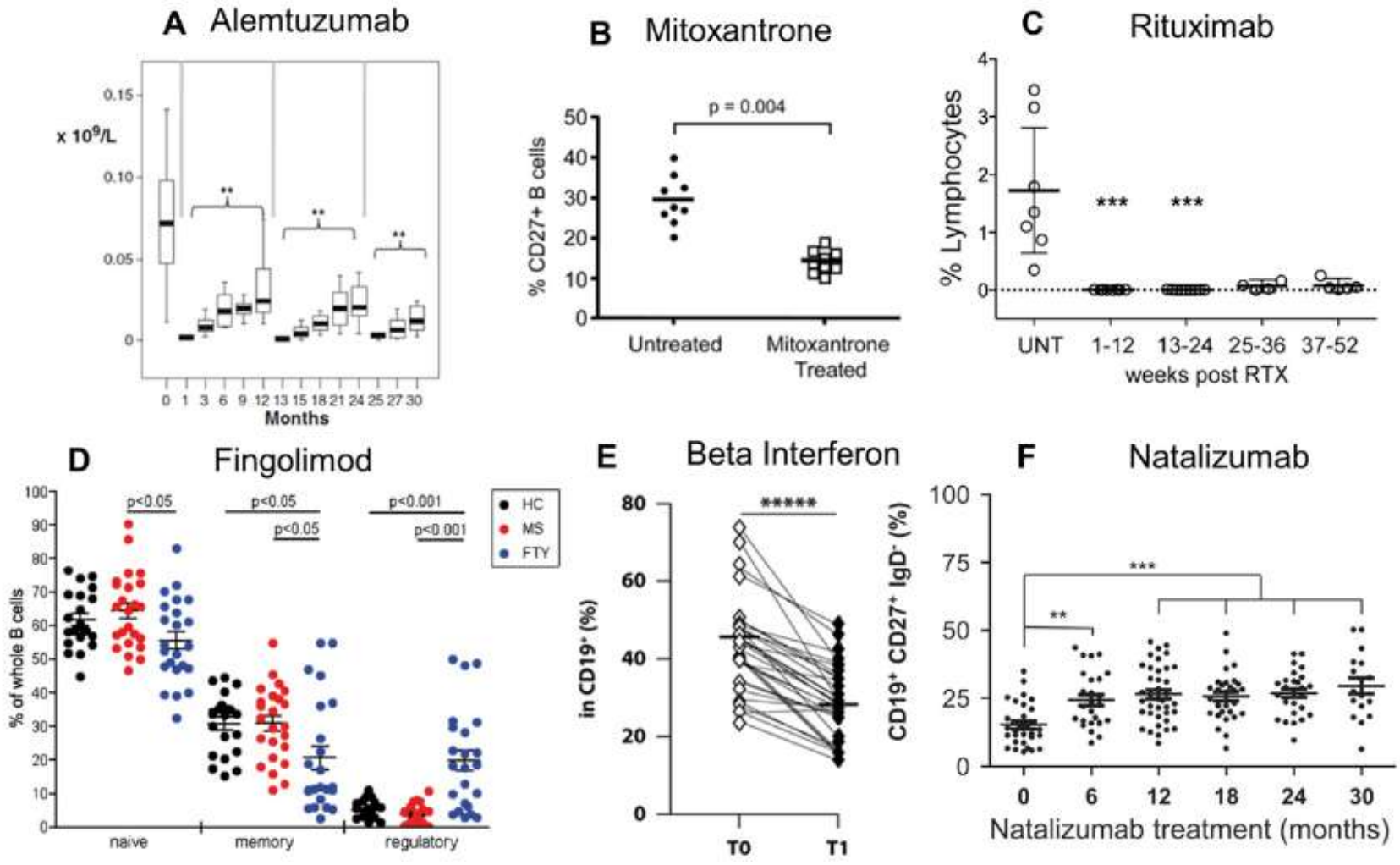
The B-Cell
Old Player, New Position on the Team



McFarland HF, et al. *N Engl J Med*. 2008;358:664-665.



D. Baker et al. / EBioMedicine 16 (2017) 41–50



D. Baker et al. / EBioMedicine 16 (2017) 41–50

B-Cell Therapies

- Depletion of B cells via B-cell-targeted therapies has been shown to ameliorate MS disease activity

Biologic	Molecular Characteristic	Mechanism of Action
Rituximab	Murine/human chimeric monoclonal IgG1	Targets humoral arm of immune system
Ocrelizumab	Humanized (90%) monoclonal IgG1	Targets only B lymphocytes for depletion
Ofatumumab*	Fully human monoclonal IgG1	Suppresses activation of B lymphocytes

*Binds to different CD20 region than rituximab or ocrelizumab.

Stevenson E, et al. *Novel Therapies in Multiple Sclerosis: A Mechanistic View.* 2015:13-22.

Trials in Primary progressive MS

Table 3. DMD trials in progressive multiple sclerosis (PROMISE, OLYMPUS, INFORMS and ORATORIO)

	PROMISE [41] (*N* = 943)	OLYMPUS [42] (*N* = 439)	INFORMS [43••] (*N* = 823)	ORATORIO [44••] (*N* = 943)	
				PBO (*n* = 244)	OCR (*n* = 488)
Demographics					
Male, *n* (%)	460 (48.8)	218 (49.7)	425 (51.6)	120 (49.1)	251 (51.4)
Age (years)	50.4 (8.3)	49.9 (8.9)	48,5 (8.4)	44.4 (8.3)	44.7 (7.9)
Caucasian, *n* (%)	747 (89.8)	402 (91.6)	791 (96.1)	–	–
Clinical Characteristics					
Time from symptom onset (years)	10.9 (7.5)	9.1 (6.6)	5.8 (2.4)	6.1 (3.6)	6.7 (4.0)
Time from diagnosis (years)	5.0 (5.1)	4.0 (4.2)	2.9	2.8 (3.3)	2.9 (3.2)
EDSS score	4.9 (1.2)	4.8 (1.4)	4.7 (1.0)	4.7 (1.2)	4.7 (1.2)
Prior use of DMT, *n* (%)	–	154 (35.1)	179 (22)	30 (12.2)	5.5 (11.3)
MRI characteristics					
% Patients with Gd + lesions	14.1	24.5	13.4	24.7	27.5
Number of Gd + lesions	0.45 (2.7)	–	0.3 (1.0)	0.6 (1.6)	0.2 (5.1)
Total volume of T2 lesions (cm^3)	–	9.2 (13.1)	9.8 (11.9)	10.9 (13.0)	12.7 (15.1)
Normalized brain volume (cm^3)	–	1205.75 (123.25)	1491.4 (85.5)	1469.9 (88.7)	1462.9 (83.9)

Baseline demographics and disease characteristics. All numbers mean (standard deviation) unless otherwise noted. DMT, disease modifying therapy; EDSS, expanded disability status scale; OCR, ocrelizumab; PBO, placebo.

PROMISE (GA);
OLYMPUS (RITUXIMAB);
INFORMS (FINGOLIMOD);
ORATORIO (OCRELIZUMAB)

Cree et al 2016

Biotin (Vitamin H)

Ongoing phase IIB/III randomized, double-blind, placebo-controlled trials of MD1003 (300 mg/day).

Study name	Primary objective	Primary efficacy endpoint	Study design/population	Anticipated completion date	EudraCT no.
MS-SPI	To demonstrate the superiority of MD1003 at 300 mg/day over placebo in clinical improvement of patients with spinal progressive MS	Proportion of patients with decreased EDSS[a] or ≥20% improvement in TW25 at month 9 (confirmed at month 12) compared with best baseline values	12 months' treatment followed by 12-month open-label extension phase (105 patients randomized 2:1)	Jan 2016	2013-002113-35
MS-ON	To demonstrate the superiority of MD1003 at 300 mg/day over placebo in the visual improvement of patients suffering from chronic visual loss after optic neuritis related to MS	Mean change in best corrected visual acuity (logMAR) at 100% contrast between baseline and month 6 of the diseased eye[b]	6 months' treatment followed by 12-month open-label extension phase (105 patients randomized 2:1)	Jan 2016	2013-002112-27
MD1003-AMN	To demonstrate the superiority of MD1003 at 300 mg/day over placebo in the clinical improvement of patients with AMN	Mean change of 2MWT time between month 12 and baseline	12 months' treatment followed by 12-month open-label extension phase (60 patients randomized 2:1)	2016	2014-000698-38

Sedel F et al 2015

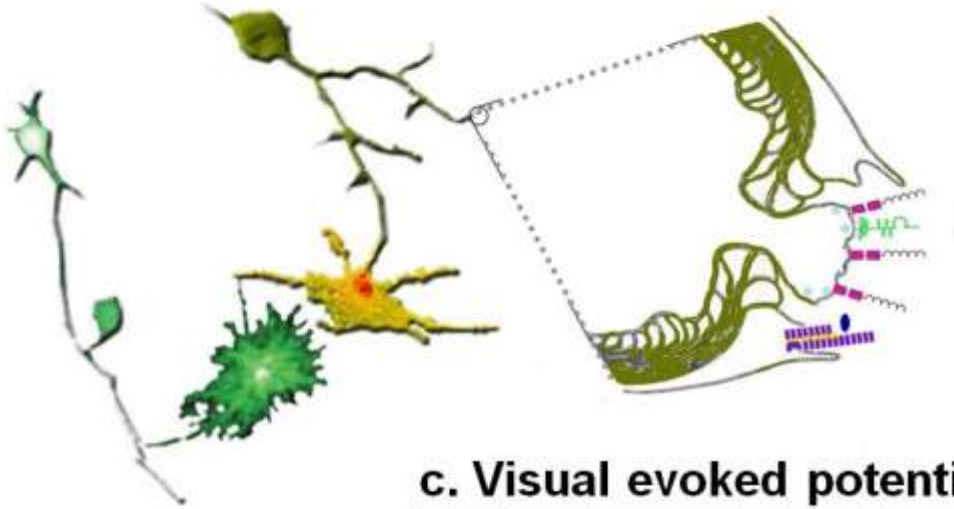
Le due facce della SM: necessità di un approccio combinato

infiammazione

Neuroprotezione

Remyelination

a.



Nogo, MAG, OMgP

Lingo-1-NgR-p75^{NTR}

GAP-43

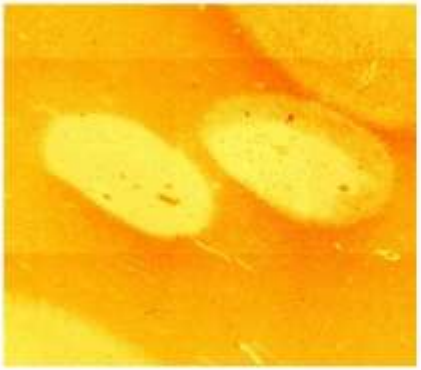
NCAM

Neuregulin

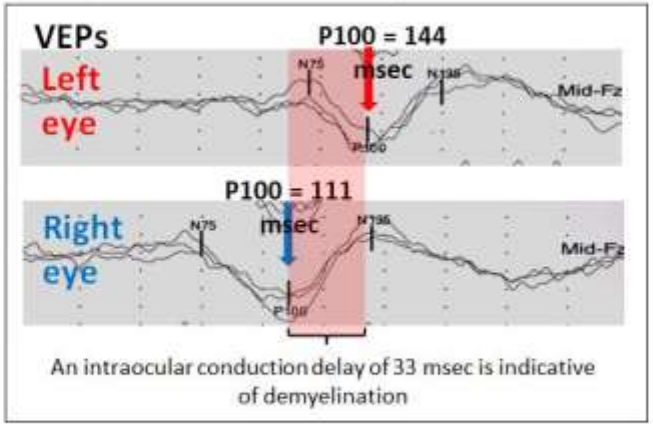
Agents in trial:

- Benztropine: anticholinergic
- BIIB033: anti-LINGO-1
- Clemastine: antihistamine
- GSK239512: histamine H(3) receptor antagonist
- IRX4204 and Bexarotene: RXR-agonist
- rHIgM22: oligodendrocyte target
- VX15: anti-SEMA4D

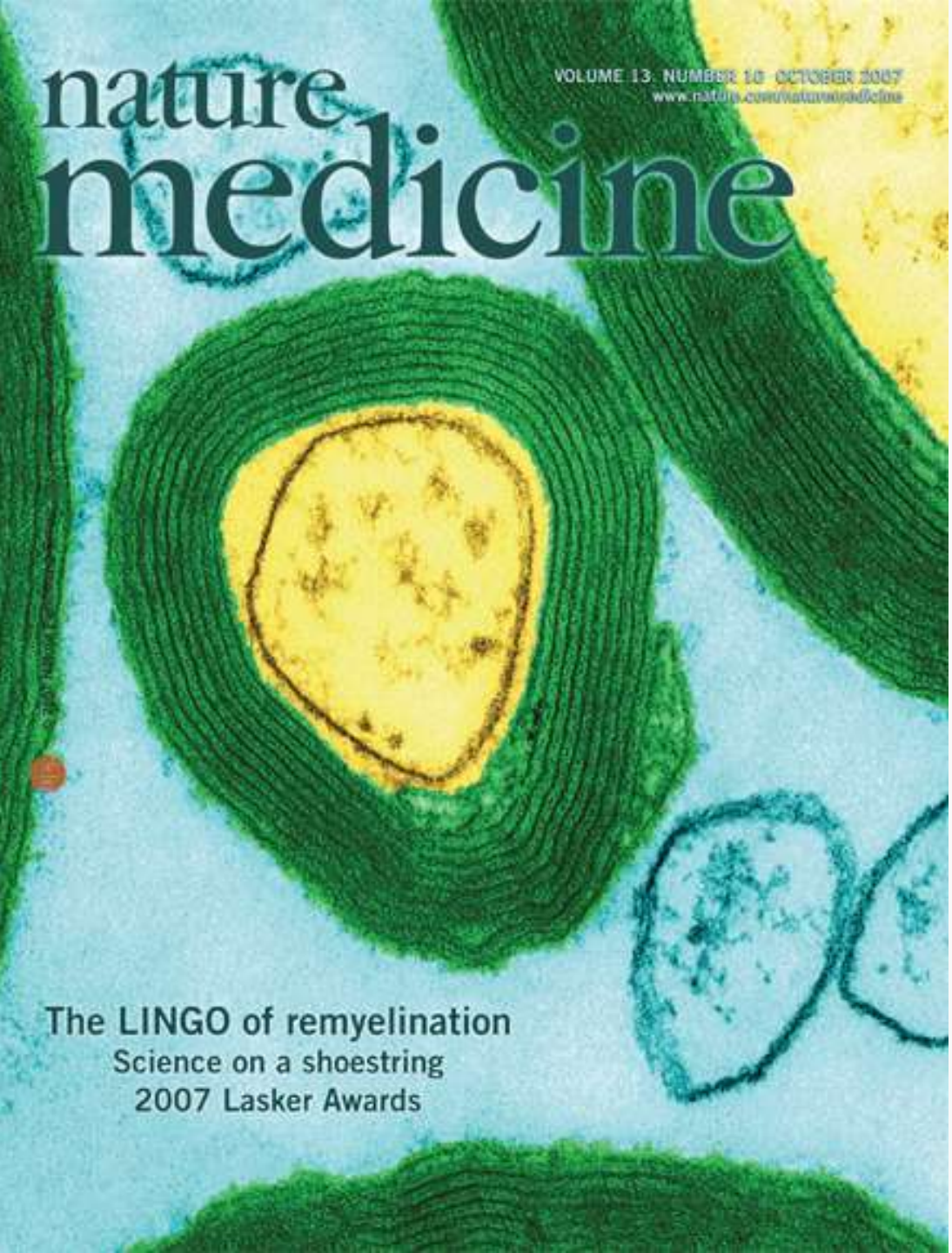
b.



c. Visual evoked potentials



a. Courtesy of Sharmilee Gnanapavan, MBBS, BmedSci, PhD. b. Courtesy of Klaus Schmierer, MBBS, PhD, FRCP. c. Courtesy of Gavin Giovannoni, MBBCh, PhD



Anti LINGO1

Human monoclonal antibody directed against LINGO-1

- ✓ LINGO-1 is a CNS-specific membrane glycoprotein that negatively regulates myelination/differentiation of oligodendrocytes
- ✓ It can affect axonal regeneration and retinal ganglion cell repair

Stevenson et al 2
Brugarolas et al 2

Randomized phase I trials of the safety/tolerability of anti-LINGO-1 monoclonal antibody BIIB033

OPEN

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Frederik Barkhof, MD
Isaac Melamed, MD
Hakop Gevorkyan, MD
Mike P. Wattjes, MD
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Edward Parr, PhD
Diego Cadavid, MD

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ABSTRACT

Objective: To evaluate the safety, tolerability, and pharmacokinetics (PK) of BIIB033 (anti-LINGO-1 monoclonal antibody) in healthy volunteers and participants with multiple sclerosis (MS).

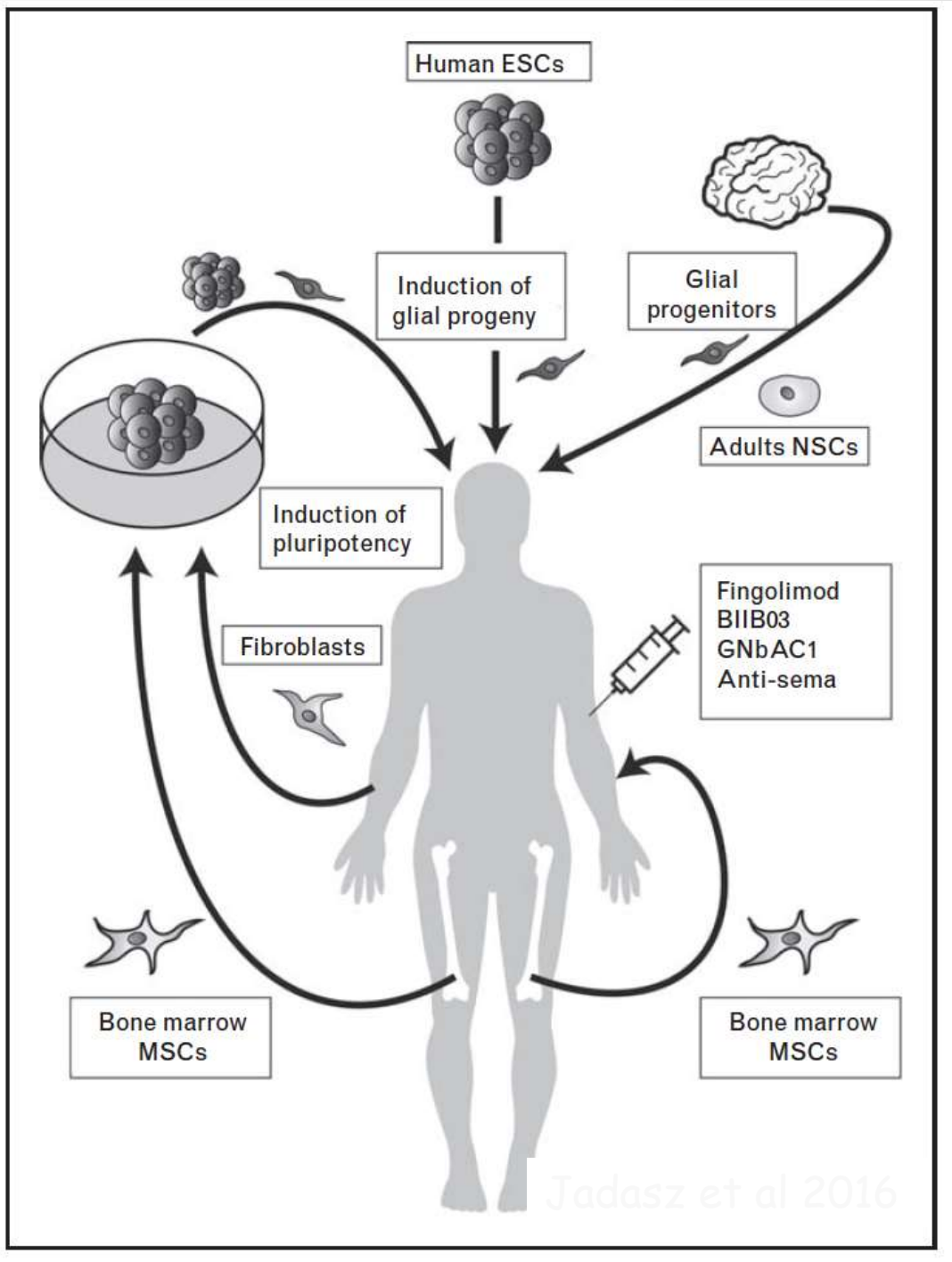
Methods: In 2 separate randomized, placebo-controlled studies, single ascending doses (SAD; 0.1–100 mg/kg) of BIIB033 or placebo were administered via IV infusion or subcutaneous injection to 72 healthy volunteers, and multiple ascending doses (MAD; 0.3–100 mg/kg; 2 doses separated by 14 days) of BIIB033 or placebo were administered via IV infusion to 47 participants with relapsing-remitting or secondary progressive MS. Safety assessments included adverse event (AE) monitoring, neurologic examinations, conventional and nonconventional MRI, EEG, optical coherence tomography, retinal examinations, and evoked potentials. Serum and CSF PK as well as the immunogenicity of BIIB033 were also evaluated.

Results: All 72 healthy volunteers and 47 participants with MS were included in the safety analyses. BIIB033 infusions were well tolerated. The frequency of AEs was similar between BIIB033 and placebo. There were no serious AEs or deaths. No clinically significant changes in any of the safety measures were observed. BIIB033 PK was similar between healthy volunteers and participants with MS. Doses of ≥10 mg/kg resulted in BIIB033 concentrations similar to or higher than the concentration associated with 90% of the maximum remyelination effect in rat remyelination studies. The incidence of anti-drug antibody production was low.

Conclusions: The emerging safety, tolerability, and PK of BIIB033 support advancing BIIB033 into phase II clinical development as a potential treatment for CNS demyelination disorders.

Classification of evidence: This study provides Class I evidence that BIIB033 is well tolerated and safe (serious adverse event rate 0%, 95% confidence interval 0–7.6%). ***Neurol Neuroimmunol Neuroinflammation* 2014;1:e18; doi: 10.1212/NXI.0000000000000018**

Sources, types and application/delivery routes of different progenitor and stem cell populations currently investigated for their potential to influence myelin repair



Autologous hematopoietic stem cell transplantation in multiple sclerosis

A phase II trial

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Francesca Gualandi, MD
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Eric Carreras, MD
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Luisa Vuolo, MD
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Massimo Filippi, MD
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Pasquale Iacopino, MD
Dominique Farge, MD
Riccardo Saccardi, MD
For the ASTIMS

ABSTRACT

Objective: To assess in multiple sclerosis (MS) the effect of intense immunosuppression followed by autologous hematopoietic stem cells transplantation (AHSCT) vs mitoxantrone (MTX) on disease activity measured by MRI.

Methods: We conducted a multicenter, phase II, randomized trial including patients with secondary progressive or relapsing-remitting MS, with a documented increase in the last year on the Expanded Disability Status Scale, in spite of conventional therapy, and presence of one or more gadolinium-enhancing (Gd+) areas. Patients were randomized to receive intense immunosuppression (mobilization with cyclophosphamide and filgrastim, conditioning with carmustine, cytosine-arabinoside, etoposide, melphalan, and anti-thymocyte globulin) followed by AHSCT or MTX 20 mg every month for 6 months. The primary endpoint was the cumulative number of new T2 lesions in the 4 years following randomization. Secondary endpoints were the cumulative number of Gd+ lesions, relapse rate, and disability progression. Safety and tolerability were also assessed. Twenty-one patients were randomized and 17 had postbaseline evaluable MRI scans.

Results: AHSCT reduced by 79% the number of new T2 lesions as compared to MTX (rate ratio 0.21, $p = 0.00016$). It also reduced Gd+ lesions as well as the annualized relapse rate. No difference was found in the progression of disability.

Conclusion: Intense immunosuppression followed by AHSCT is significantly superior to MTX in reducing MRI activity in severe cases of MS. These results strongly support further phase III studies with primary clinical endpoints. The study was registered as EUDRACT No. 2007-000064-24.

Neurology® 2015;84:981–988

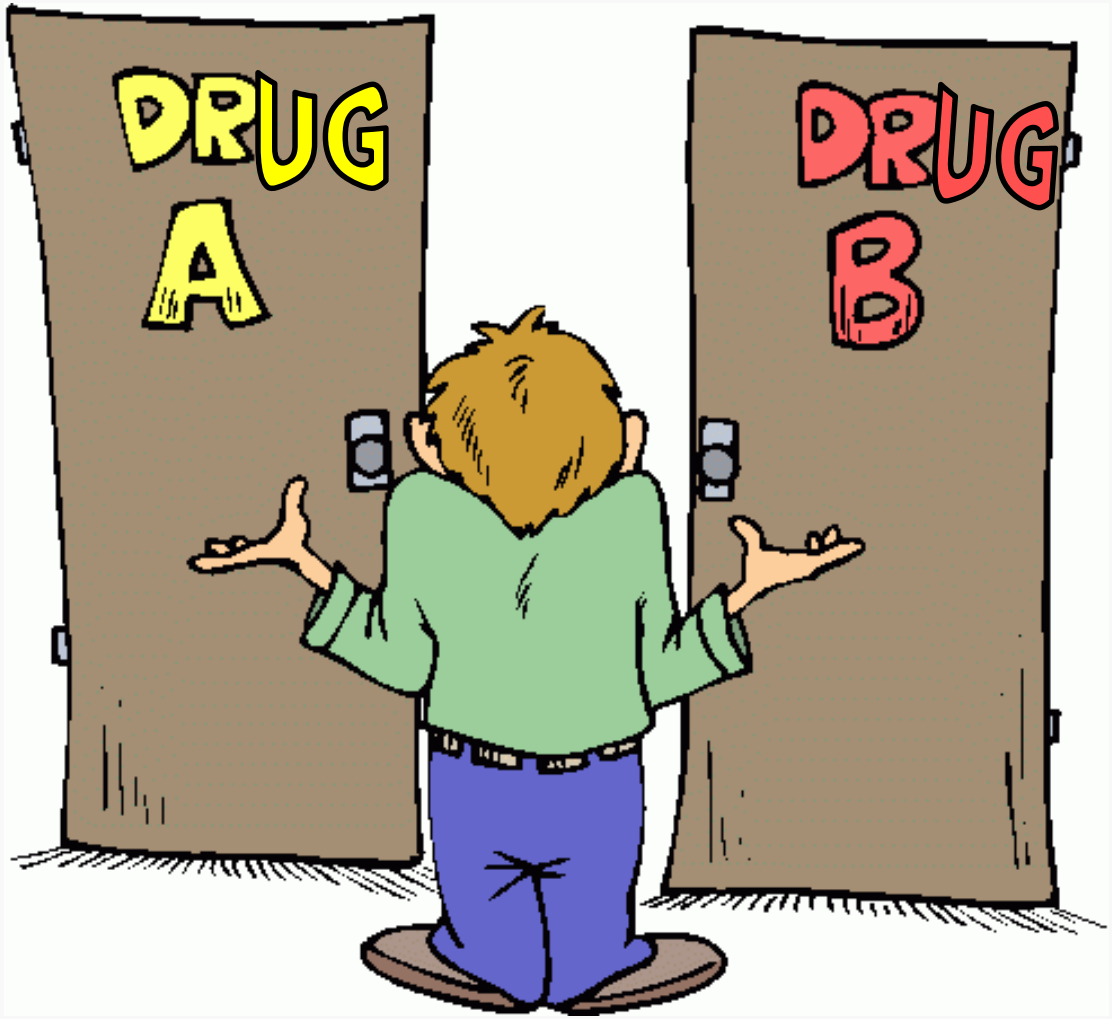
Table 1. Multiple sclerosis-related clinical trials with mesenchymal stem cells

MSC source	Administration	Indications	Patients (*n*)	Reference
Autologous freshly cultured bone marrow MSCs	IV	RRMS	9	[81]
Autologous culture-expanded bone marrow MSCs	IV and IT	SPMS	10	[82]
Autologous culture-expanded bone marrow MSCs	IV and IT	RRMS, SPMS and PPMS	15	[83]
Allogeneic umbilical cord MSCs	IV and IT (following preconditioning with CTX)	PPMS	1	[84]
Autologous culture-expanded bone marrow MSCs	IT	Treatment-refractory MS	10	[85]
Fresh bone marrow cells enriched for MSCs	IV	Chronic MS	6	[86]
Autologous nonexpanded adipose MSCs	IV	Treatment-refractory MS	3	[87]
Autologous culture-expanded bone marrow MSCs	IT	SPMS	10	[88]

CTX, cyclophosphamide; IT, intrathecally administered; IV, intravenously administered; MSCs, mesenchymal stem cells; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

Jadasz et al 2016

Choosing a Treatment?



Courtesy of Mark S. Freedman, M

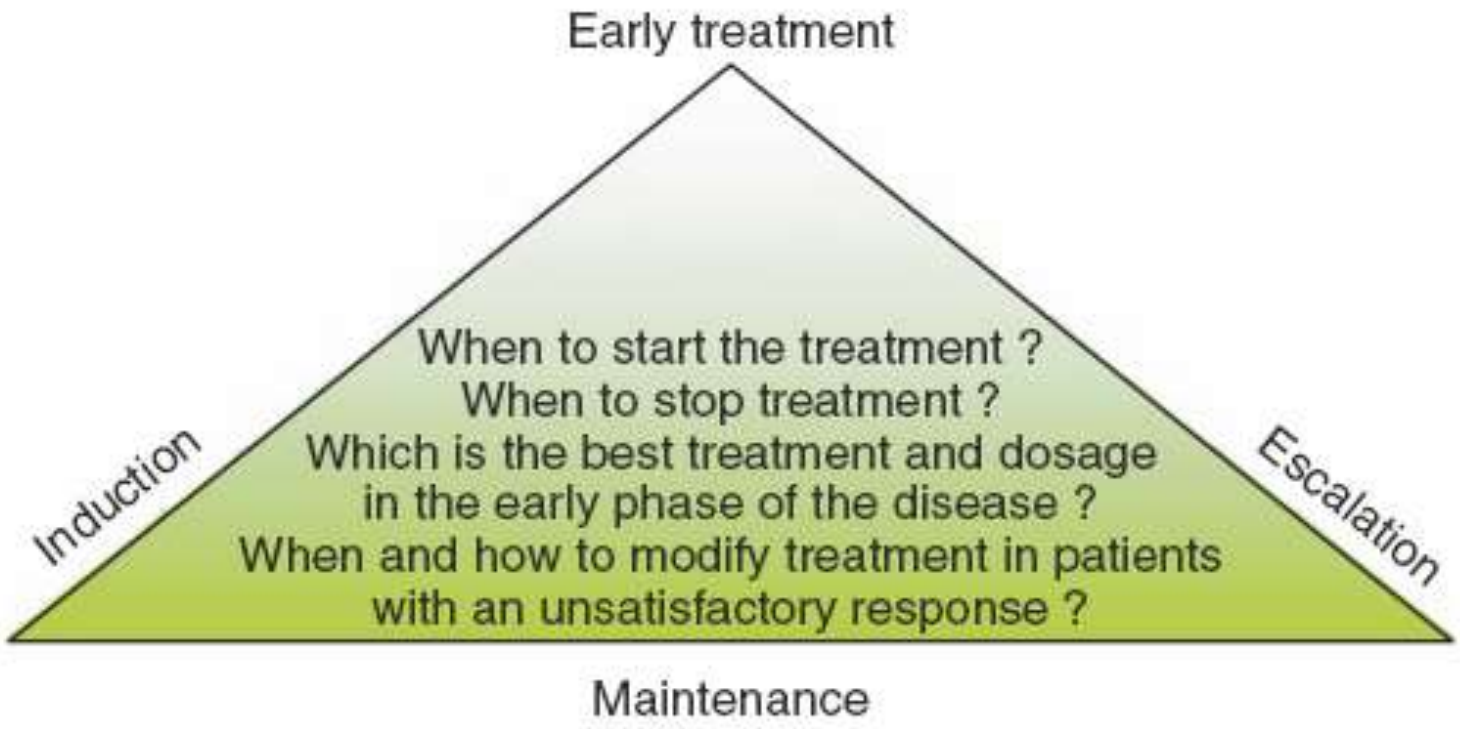


Figure 1. The challenge of immunomodulatory treatment. Finding the most effective treatment for an individual patient.

Rieckmann P et al 2008

ORIGINAL ARTICLES

New Natural History of Interferon-β–Treated Relapsing Multiple Sclerosis

Maria Trojano, MD,[1] Fabio Pellegrini, MscStat,[2] Aurora Fuiani, MD,[1] Damiano Paolicelli, MD,[1] Valentina Zipoli, MD,[3] Giovanni B. Zimatore, MD,[1] Elisabetta Di Monte, MD,[1] Emilio Portaccio, MD,[3] Vito Lepore, MD,[1] Paolo Livrea, MD,[1] and Maria Pia Amato, MD[3]

Ann Neurol 2007;61:300–306

Real-Life Impact of Early Interferonβ Therapy in Relapsing Multiple Sclerosis

M. Trojano, MD,[1] F. Pellegrini, MDeStat,[2] D. Paolicelli, MD,[1] A. Fuiani, MD,[1] G.B. Zimatore, MD,[1] C. Tortorella, MD,[1] I.L. Simone, MD,[1] F. Patti, MD,[3] A. Ghezzi, MD,[4] V. Zipoli, MD,[5] P. Rossi, MD,[6] C. Pozzilli, MD,[7] G. Salemi, MD,[8] A. Lugaresi, MD,[9] R. Bergamaschi, MD,[10] E. Millefiorini, MD,[11] M. Clerico, MD,[12] G. Lus, MD,[13] M. Vianello, MD,[14] C. Avolio, MD,[15] P. Cavalla, MD,[16] V. Lepore, MD,[2] P. Livrea, MD,[1] G. Comi, MD,[6] and M.P. Amato, MD[3]; for the Italian Multiple Sclerosis Database Network (MSDN) Group

Ann Neurol 2009;66:513–520

MULTIPLE SCLEROSIS JOURNAL | MSJ

Research Paper

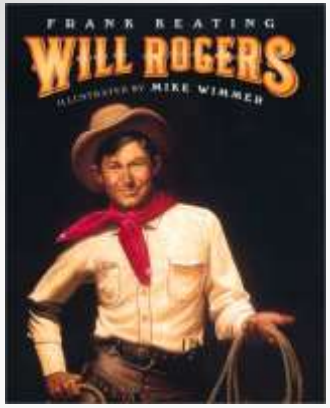
Influence of treatments in multiple sclerosis disability: A cohort study

Eleonora Cocco, Claudia Sardu, Gabriella Spinicci, Luigina Musu, Rita Massa, Jessica Frau, Lorena Lorefice, Giuseppe Fenu, Giancarlo Coghe, Serenella Massole, Maria Antonietta Maioli, Rachele Piras, Marta Melis, Gianluca Porcu, Elena Mamusa, Nicola Carboni, Paolo Contu and Maria Giovanna Marrosu

Multiple Sclerosis Journal

1–9

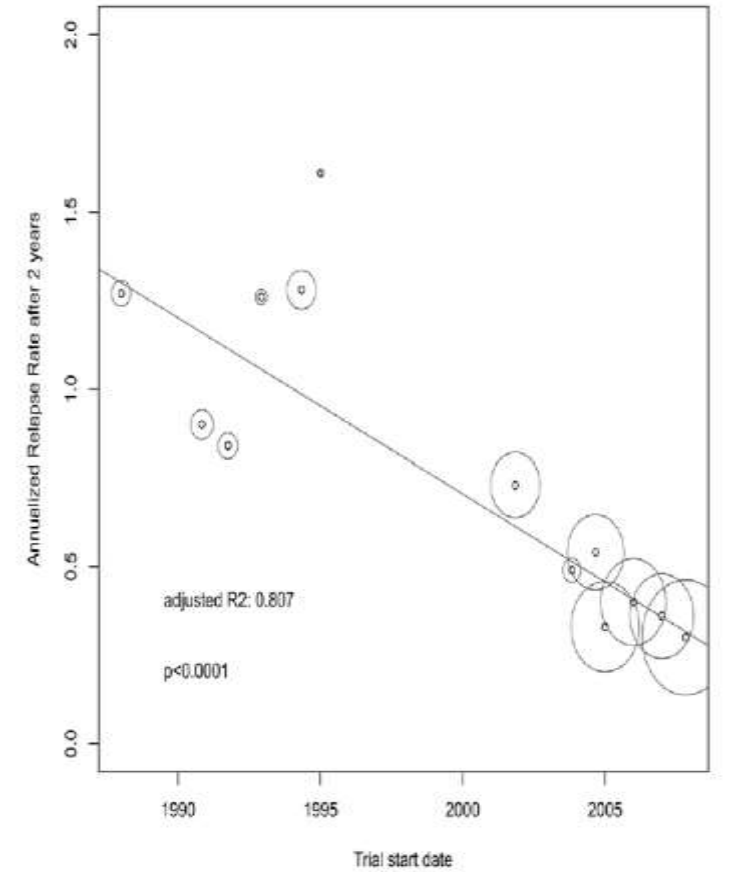
DOI: 10.1177/1352458514546708

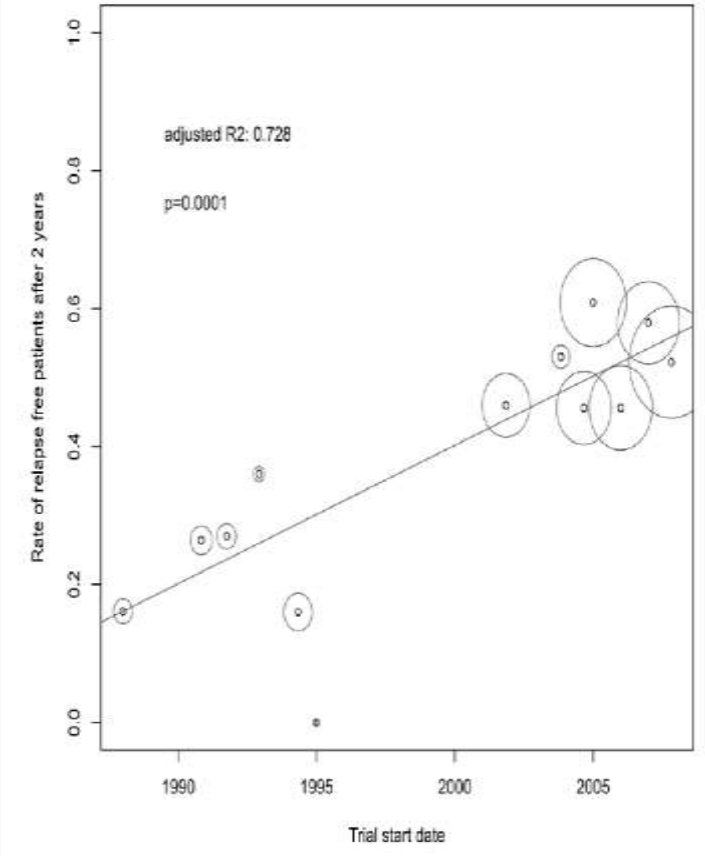


Placebo Cohorts in Phase-3 MS Treatment Trials – Predictors for On-Trial Disease Activity 1990-2010 Based on a Meta-Analysis and Individual Case Data

Jan-Patrick Stellmann[1]*, Anneke Neuhaus[2], Lena Herich[3], Sven Schippling[5], Matthias Roeckel[4], Martin Daumer[2], Roland Martin[5], Christoph Heesen[1]

PLOS ONE | November 2012 | Volume 7 | Issue 11 | e50347





EVIDENCE-BASED DERMATOLOGY: RESEARCH COMMENTARY

The Misperception That Clinical Trial Data Reflect Long-term Drug Safety

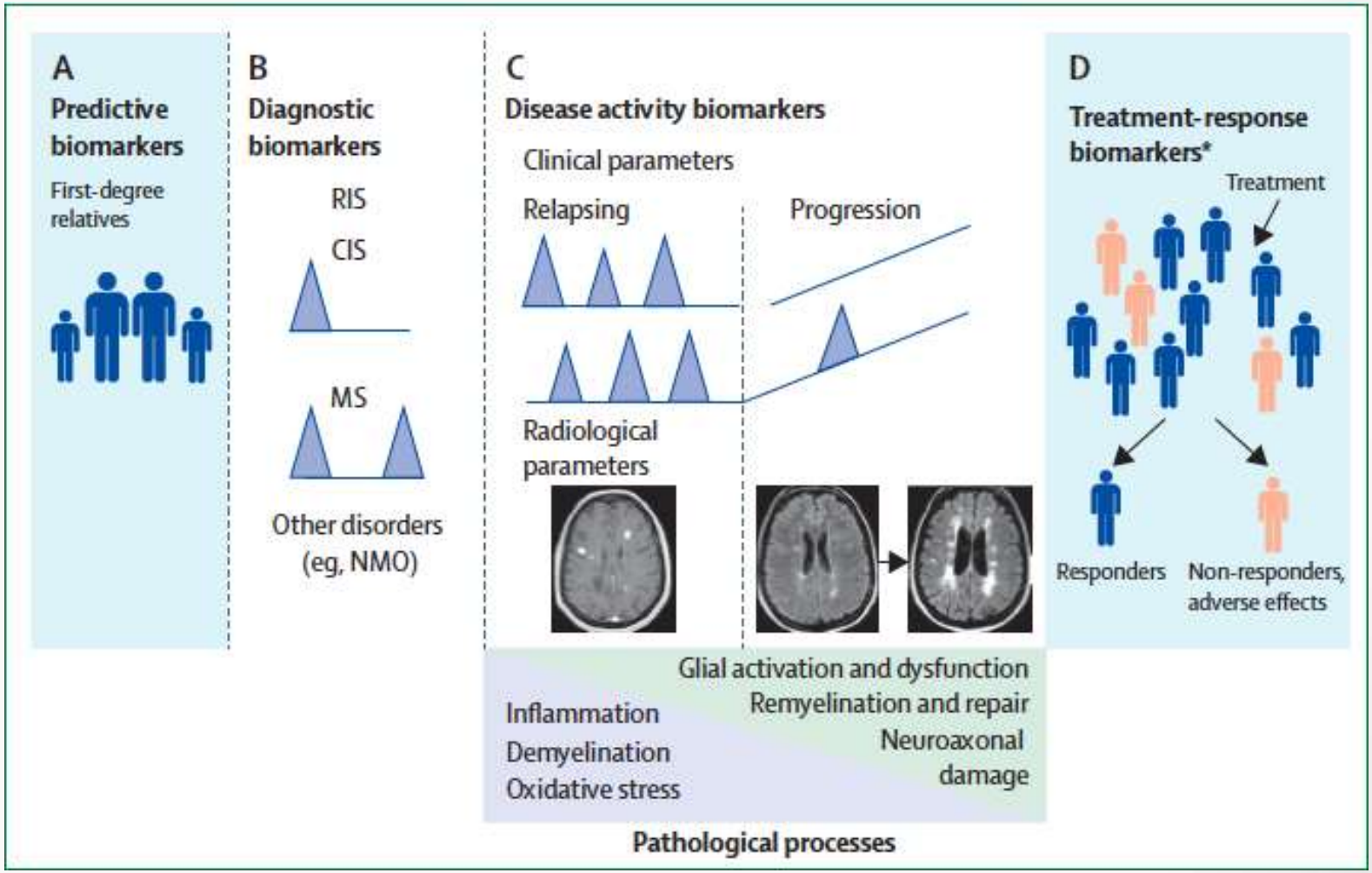
Lessons Learned From Efalizumab's Withdrawal

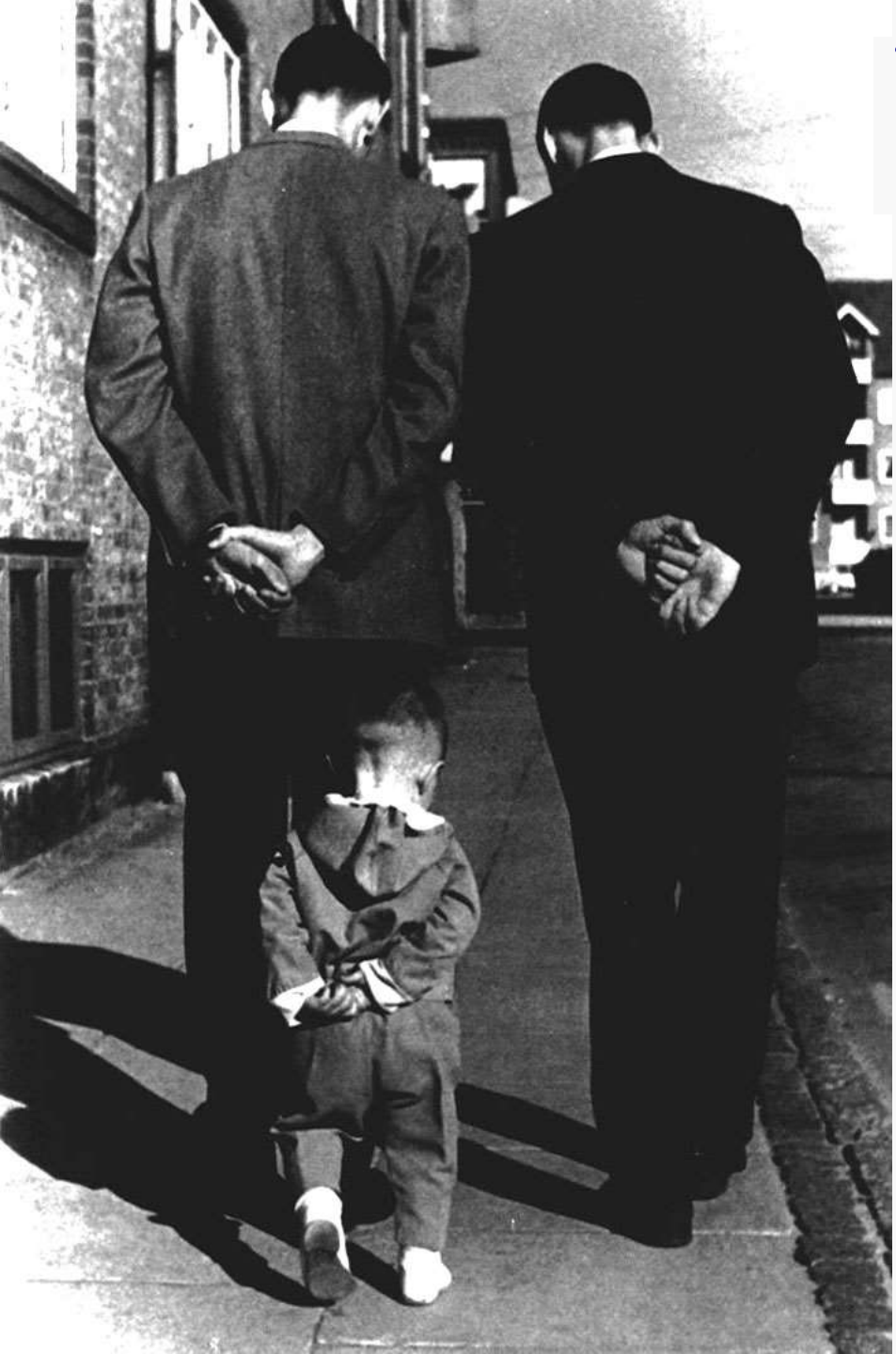
Nijsten T, et al. Arch Dermatol 2009;145:1037-39.

Body fluid biomarkers in multiple sclerosis

Manuel Comabella, Xavier Montalban

Lancet Neurol 2014; 13: 113–26





Il futuro della terapia della SM

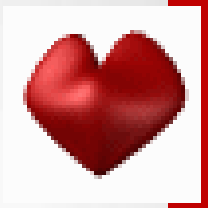
- Disponibilità di terapie con meccanismi d'azione diversi
- Approcci cellulari efficaci
- Combinzione di terapie immunomodulanti e neuroprotettive (e riparative)
- Migliore comprensione della eterogeneità della malattia
- Disponibilità di biomarkers
- Personalizzazione dei trattamenti
- Empowerment and engagement delle persone con MS

Centro Regionale per la diagnosi e la cura della SM

ASL 8/Università di Cagliari

Prof. Maria Giovanna Marrosu

TUTTI I PAZIENTI E I LORO FAMILIARI



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Grazie!!!