MRI as a tool to identify inadequate treatment response in MS in clinical practice

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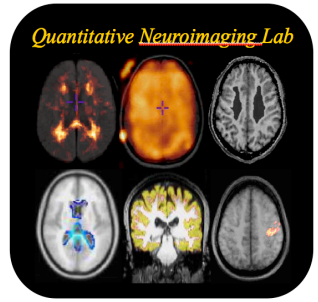
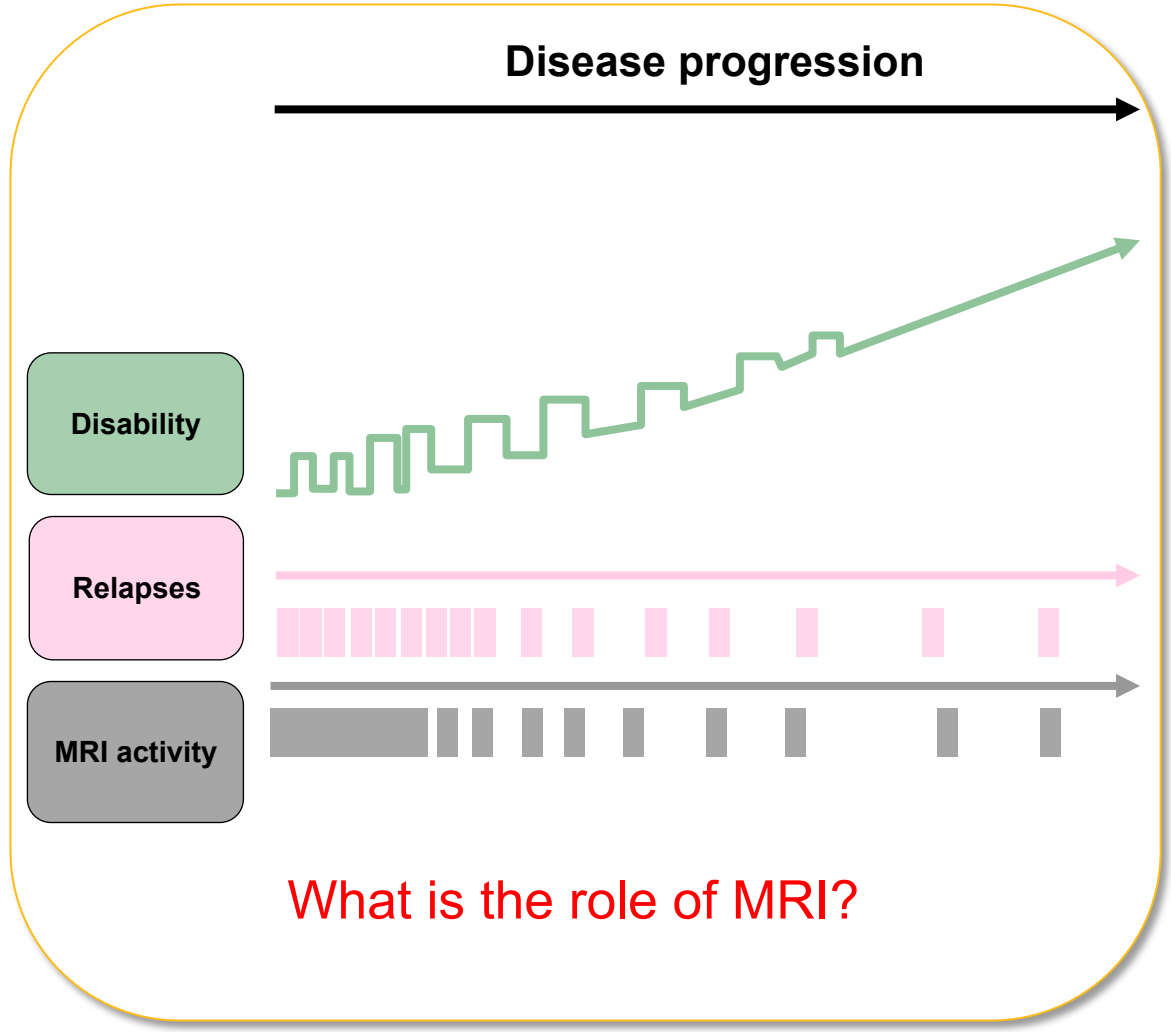


Assessment of treatment response

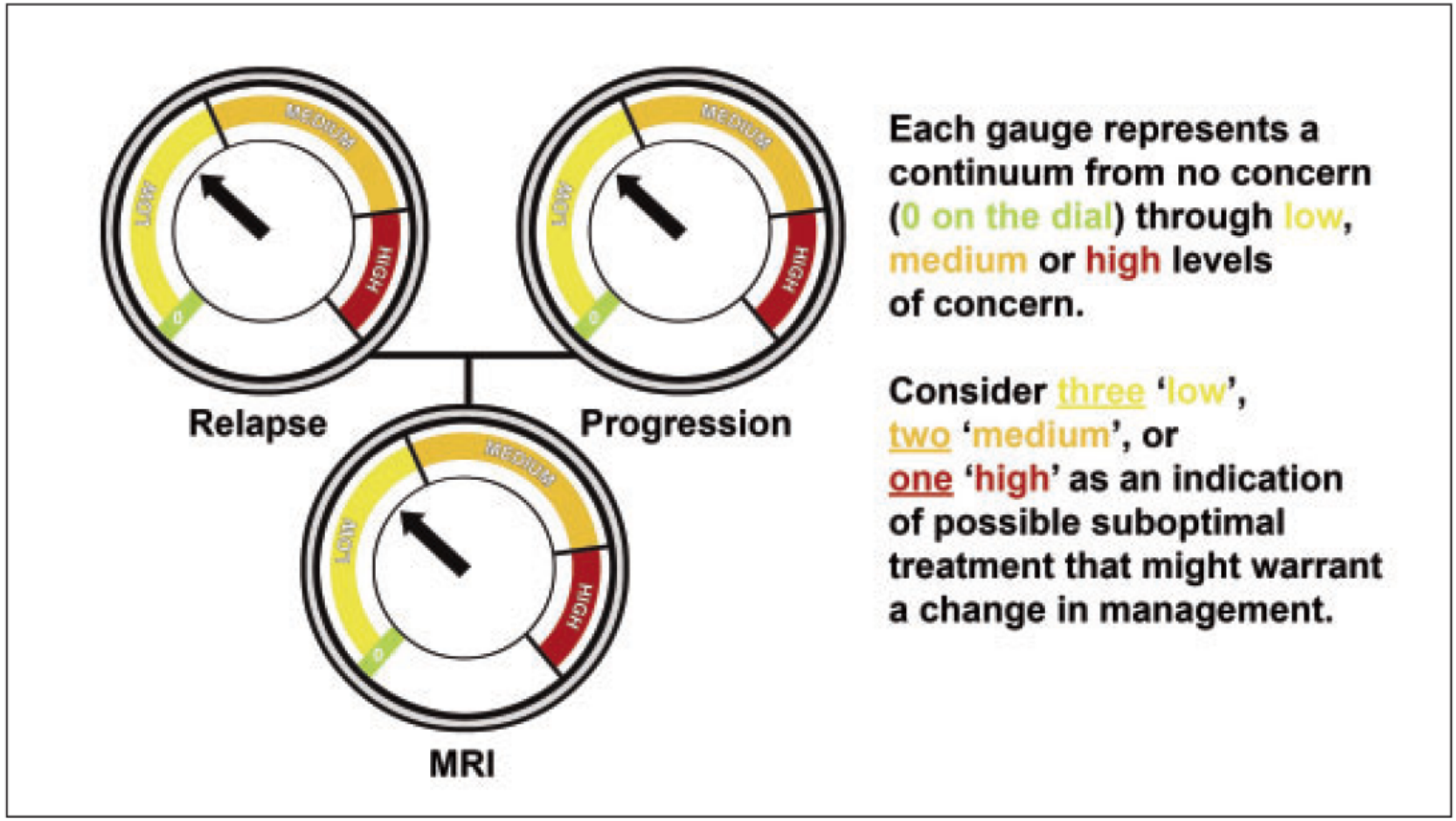


REVIEW ARTICLE

Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations

*Mark S. Freedman, Daniel Selchen, Douglas L. Arnold, Alexandre Prat, Brenda Banwell, Michael Yeung, David Morgenthau, Yves Lapierre, on behalf of the Canadian Multiple Sclerosis Working Group**

Can J Neurol Sci. 2013; 40: 307-323



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Can J Neurol Sci. 2013; 40: 307-323

Table 3: Recommendations for determining the level of concern when considering treatment modification based on annual MRI findings

	Level of concern		
Activity on MRI*	**Low**	**Medium**	**High**
New Gd-enhancing lesions OR Accumulation of new T2 lesions per year	1 lesion	2 lesions	≥3 lesions

Note: Routine follow-up MRI with gadolinium (Gd) is recommended 6-12 months after initiating therapy for RRMS (or in CIS if therapy is not initiated). Note: New T2 lesions that are also enhancing on the same scan are only counted once as unique active lesions. *The presence of Gd-enhancing lesions is more reliable than new T2 lesion counts. New T2 lesion counts require high-quality comparable MRI scans and interpretation by highly qualified individuals[77].

Assessing treatment response to interferon-β

Is there a role for MRI?

Ruth Dobson, PhD, MRCP
Richard A. Rudick, MD
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Klaus Schmierer, PhD, FRCP
Gavin Giovannoni, PhD, FRCP

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ABSTRACT

Objective: Interferon-β (IFN-β) has been shown to reduce relapse rates in multiple sclerosis; however, the clinical response appears to vary among individuals. Can early MRI be used to identify those patients who have a poor response to treatment?

Methods: A systematic review of studies examining differential treatment response and clinical endpoints in groups defined as responders or nonresponders to IFN-β was performed. Meta-analytic techniques were used to combine study results where appropriate.

Results: Patients with MRI evidence of poor response to IFN-β treatment as defined by either ≥2 new hyperintense T2 lesions or new gadolinium-enhancing lesions had significantly increased risk of both future relapses and progression as defined by the Expanded Disability Status Scale. There appeared to be an increased risk of poor outcomes 16 years after treatment initiation in those with an initial poor response to treatment. Previous evidence has shown this not to be the case in placebo arms of clinical trials.

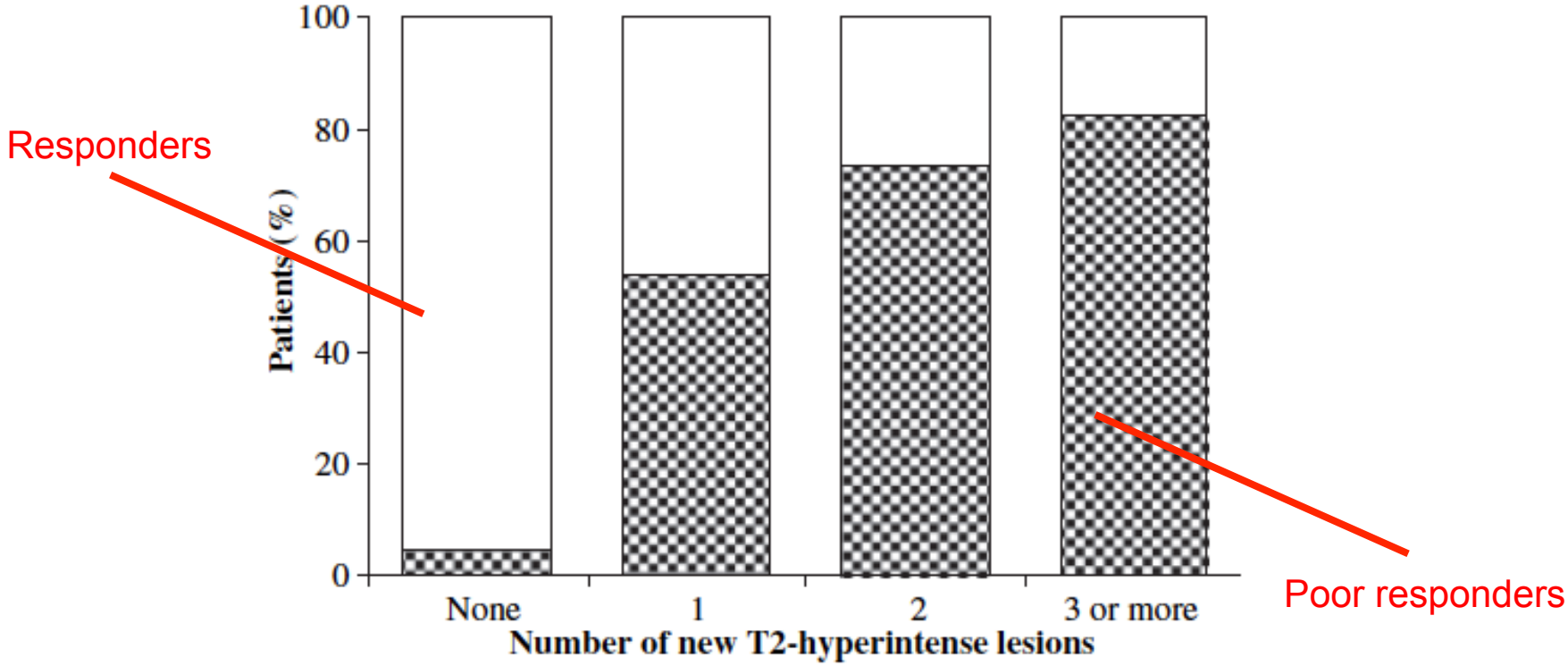
Conclusions: For those patients starting IFN-β, early MRI, within 6 to 24 months after starting treatment, has the potential to provide important information when counseling patients about the likelihood of future treatment failure. This can inform treatment decisions before clinical relapses or disease progression. *Neurology*® 2014;82:248–254

European Journal of Neurology 2009, **16:** 1202–1209 doi:10.1111/j.1468-1331.2009.02708.x

One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis

L. Prosperini[a], V. Gallo[a,b], N. Petsas[c], G. Borriello[a] and C. Pozzilli[a]

[a]*Multiple Sclerosis Centre, Department of Neurological Sciences, S. Andrea Hospital, "La Sapienza" University, Rome, Italy;* [b]*Division of Epidemiology, Public Health and Primary Care and Division of Neuroscience and Mental Health, Imperial College London, London, UK; and* [c]*Neurological Centre of Latium, Rome, Italy*



Poor Response defined as an increase of at least 1 point of EDD confirmed at 6 months

RESEARCH PAPER *Multiple Sclerosis* 2009; **15**: 848–853

Measures in the first year of therapy predict the response to interferon β in MS

J Río[1], J Castilló[1], A Rovira[2], M Tintoré[1], J Sastre-Garriga[1], A Horga[1], C Nos[1], M Comabella[1], X Aymerich[2] and X Montalbán[1]

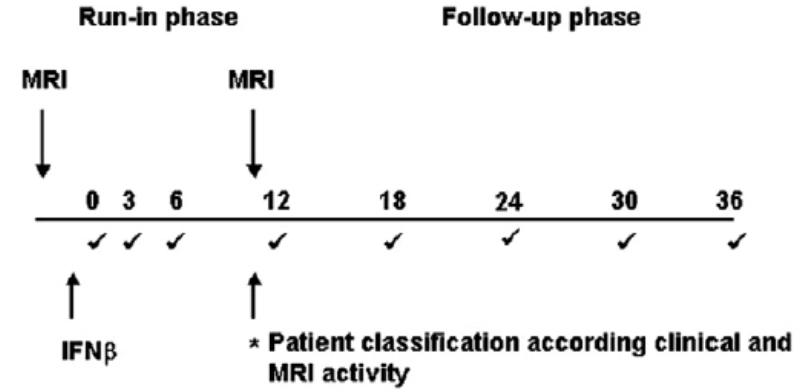


Figure 1 Study design.

Table 3 Risk of new relapses and increase of disability during the period of follow-up (months 12– 36) according the positivity for the different variables after 12 months of therapy

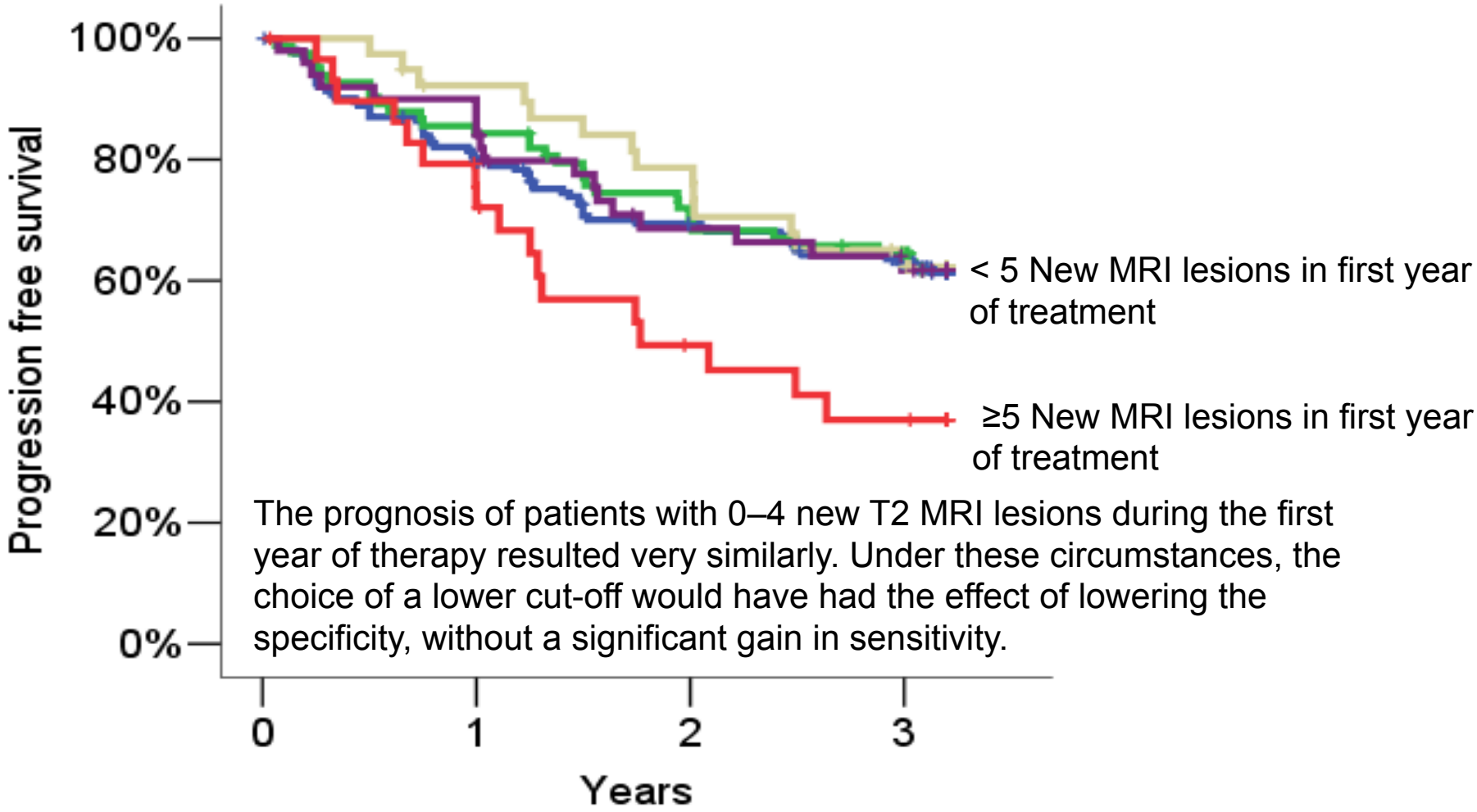
	N	Relapses		Progression	
		Odds ratio (CI)	Significance	Odds ratio (CI)	Significance
R+/P+/MRI+	11	9.8 (2.6–53.4)	0.0005	6.5 (1.9–23.4)	0.004
R+/P−/MRI+	18	8.3 (2.9–28.9)	<0.0001	4.4 (1.6–12.5)	0.004
R−/P+/MRI+	7	3.3 (0.8–15.6)	0.1	7.1 (1.6–33.9)	0.011
R+/P+/MRI−	5	1.8 (0.3–9.9)	0.5	3.9 (0.6–21.6)	0.1
R−/P+/MRI−	10	1.2 (0.3–4.3)	0.8	0.3 (0–2.1)	0.3
R+/P−/MRI−	17	1.1 (0.4–3.2)	0.8	0.5 (0.1–2.2)	0.4
R−/P−/MRI+	35	1.5 (0.7–3.4)	0.3	2.3 (0.9–4.4)	0.07
R−/P−/MRI−	119	1*		1*	

*Reference category

Scoring Treatment Response in RR MS

PRISMS Dataset

Relevance of new lesions in 1-year treatment on the risk of sustained disability



The prognosis of patients with 0–4 new T2 MRI lesions during the first year of therapy resulted very similarly. Under these circumstances, the choice of a lower cut-off would have had the effect of lowering the specificity, without a significant gain in sensitivity.

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–8

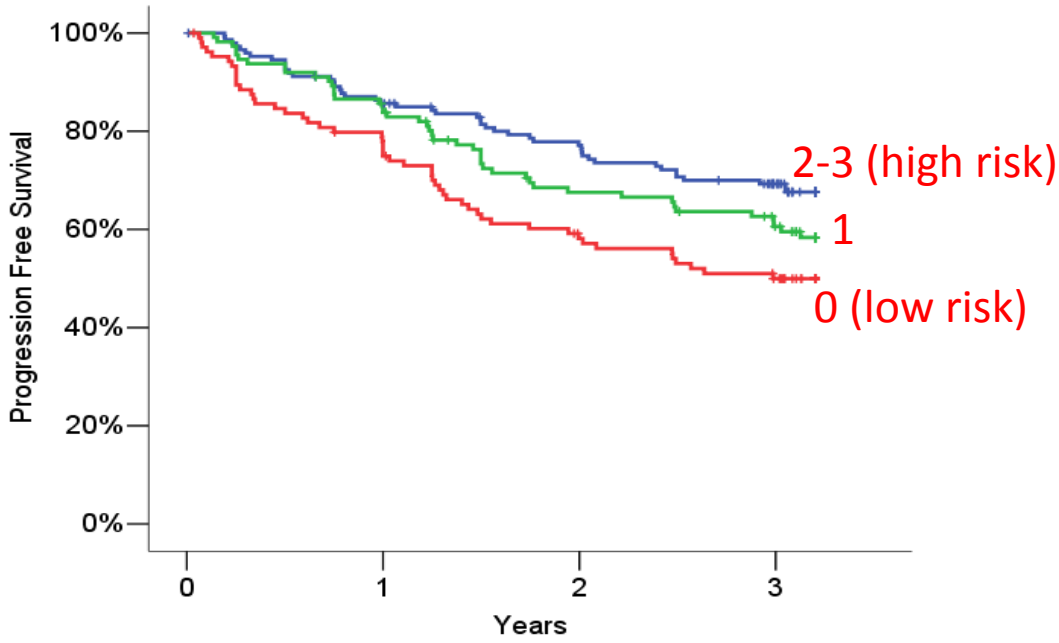
DOI: 10.1177/1352458512460605
msj.sagepub.com
SAGE

Scoring treatment response in patients with relapsing multiple sclerosis

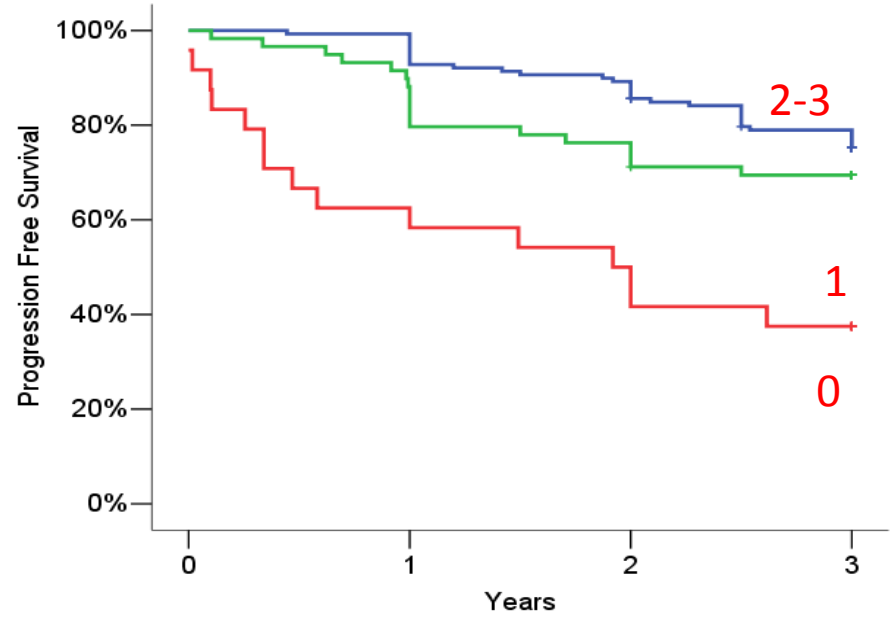
MP Sormani[1], J Rio[2], M Tintorè[2], A Signori[1], D Li[3], P Cornelisse[4], B Stubinski[4], ML Stromillo[5], X Montalban[2*] and N De Stefano[5*]

Score=0	new T2 lesions ≤ 5 & Relapses=0
Score=1	new T2 lesions ≤ 5 & Relapses=1 new T2 lesions > 5 & Relapses=0
Score=2	new T2 lesions ≤ 5 & Relapses=2 new T2 lesions > 5 & Relapses=1
Score=3	new T2 lesions > 5 & Relapses=2

Training set (PRISMS)



Validation set (Barcelona)

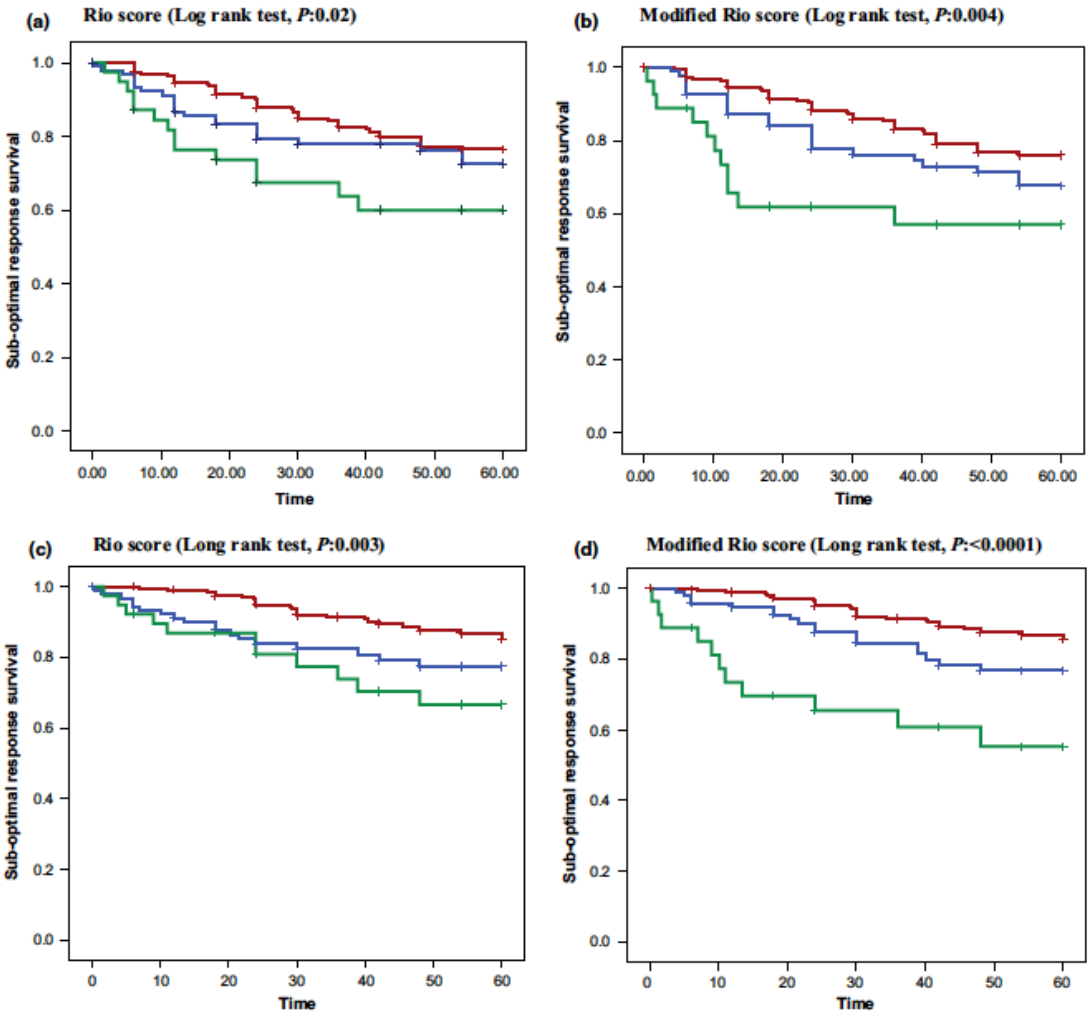


ORIGINAL ARTICLE

European Journal of Neurology 2015, **0**: 1–8

Validation of 1-year predictive score of long-term response to interferon-β in everyday clinical practice multiple sclerosis patients

M. Romeo[a], V. Martinelli[a], M. Rodegher[a], E. Perego[a], S. Maida[a], M. P. Sormani[b], G. Comi[a,c] and San Raffaele Multiple Sclerosis Clinical Group[1]



601 MS with 1y treatment and 5 y FU

1 Disability progression 1: EDSS progression ≥1.0 point sustained over at least 6 months and confirmed at the end of the follow-up.

2 Disability progression 2: EDSS progression ≥1.5 points for patients with baseline EDSS < 2.5 and 1 point for baseline EDSS of 2.5–5.5 sustained over at least 6 months and confirmed at the end of the follow-up.

	Sensitivity (%)	Specificity (%)	Accuracy (%)
Rio score			
Disability progression 1	45	67	62
Disability progression 2	54	68	65
Modified Rio score			
Disability progression 1	42	72	65
Disability progression 2	51	72	69

MAGNIMS Project - Participating Centers

MAGNIMS Project - Participating Centers

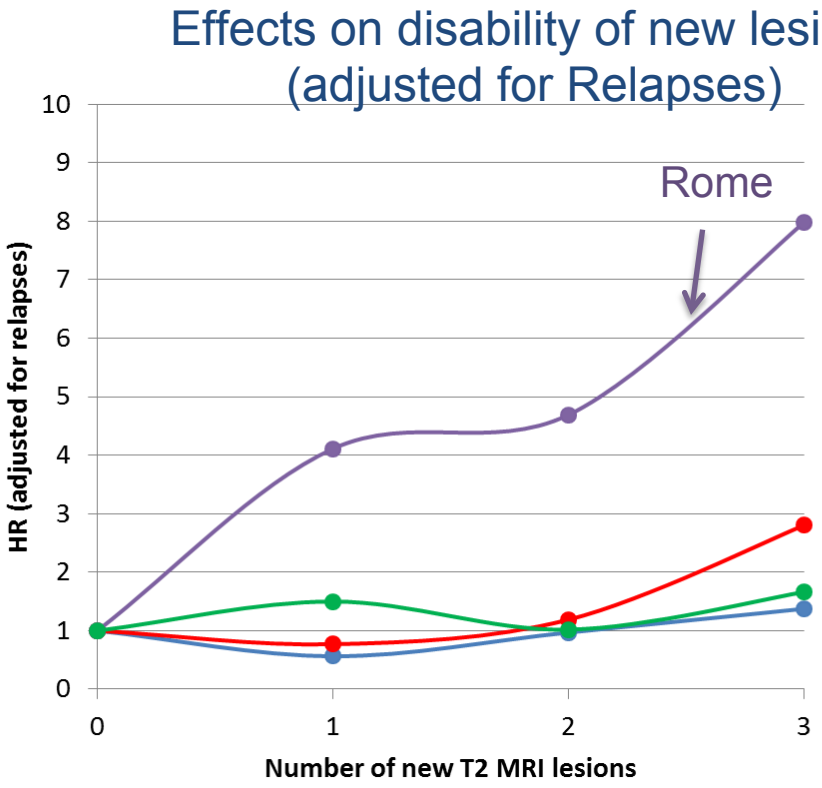
Center	Patient #	%
Rome	610	32.3
Milan	568	30.1
Barcelona	233	12.3
Bari	120	6.3
Cagliari	106	5.6
Siena	91	4.8
Verona	88	4.7
Graz	32	1.7
Napoli	27	1.4
Basel	14	.7
Total	1890	100

Center	Patient #	%
Rome	610	32.3
Milan	568	30.1
Barcelona	233	12.3
Other MAGNIMS	479	25.3
Total	1890	100

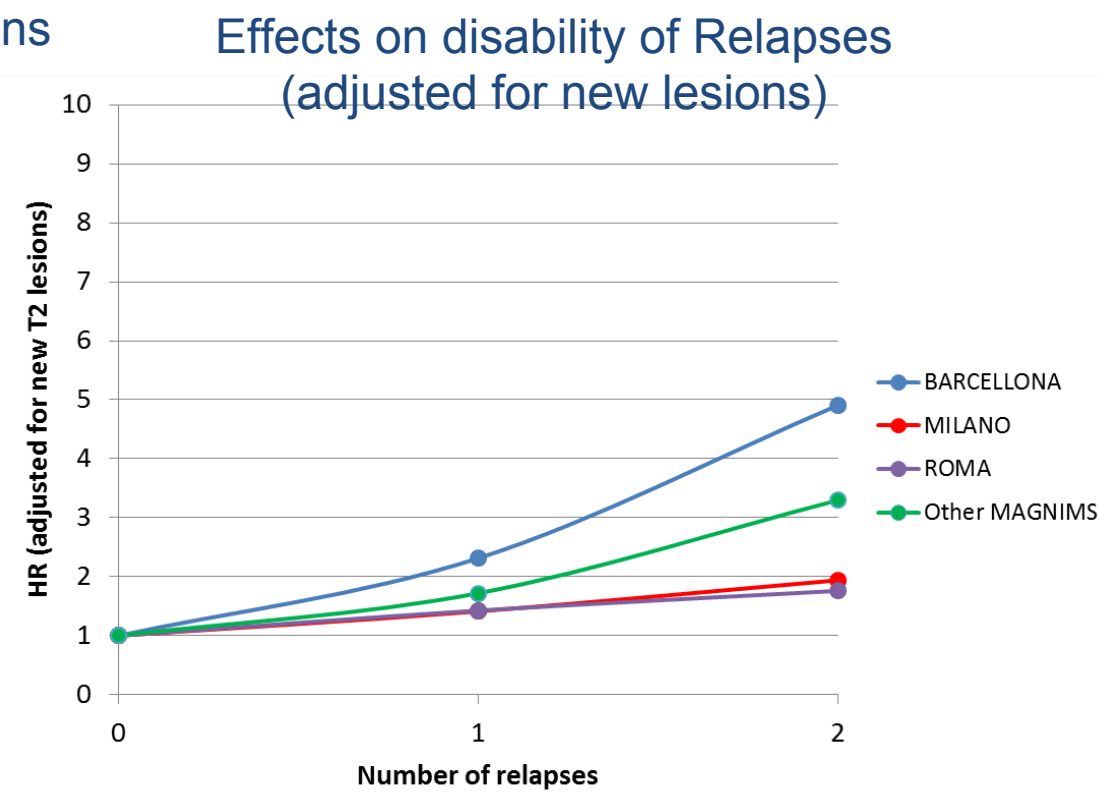
In the statistical analysis, centers with small sample size (<10% of the whole group) were grouped to allow heterogeneity tests among centers

MAGNIMS Dataset

Homogeneity of effects on disability of MRI lesions and relapses (multivariate analysis)



Test of heterogeneity of effects
p=0.003
Excluding Rome
P=0.44



Test of heterogeneity of effects
p=0.44

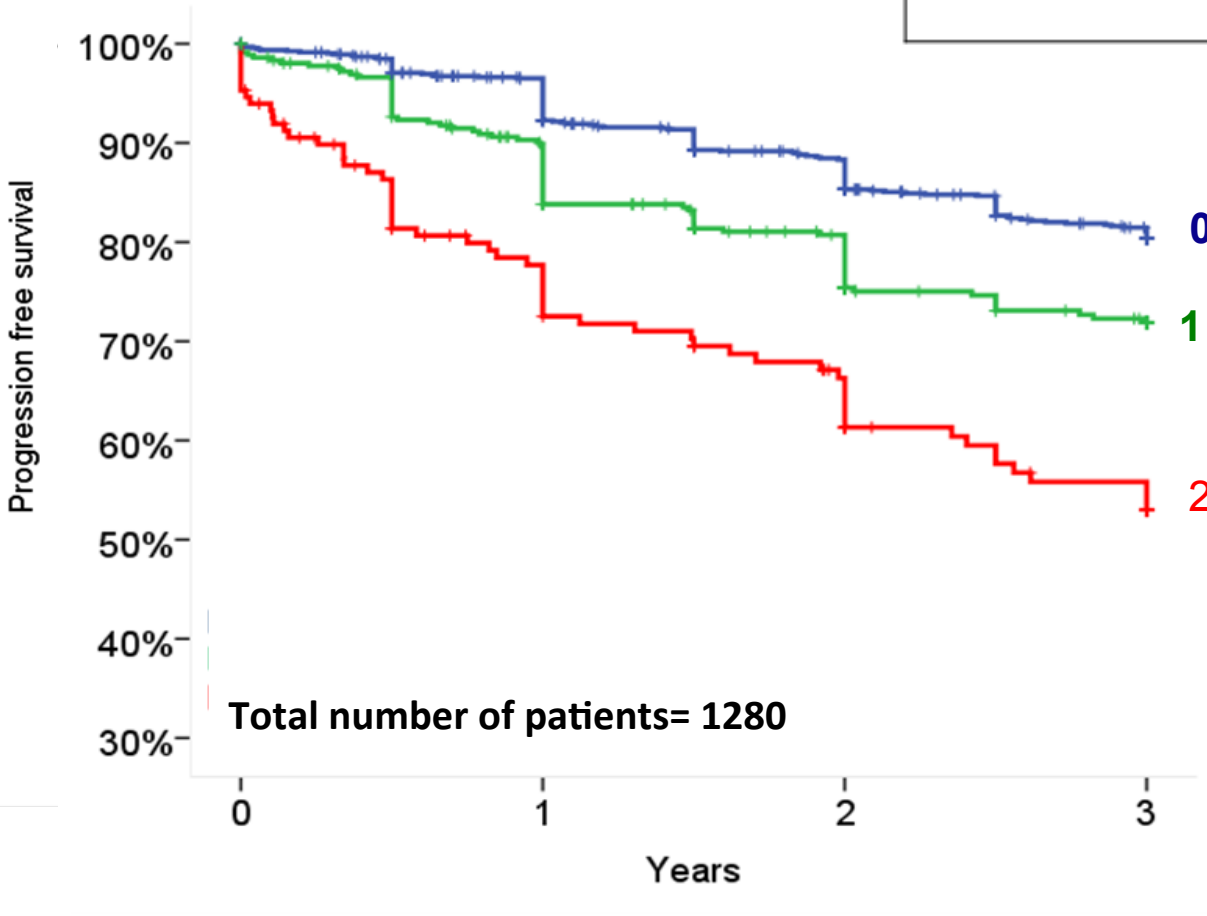
MAGNIMS Dataset

Multivariate analysis Cox Model (excluding ROME)

Variables	HR	95% CI		p
		Lower	Upper	
NewT2 lesions=0				0.005
NewT2 lesions=1	1.02	0.72	1.44	0.926
NewT2 lesions=2	0.99	0.66	1.49	0.978
NewT2 lesions=3	1.58	1.01	2.48	0.047
NewT2 lesions=4	2.25	1.33	3.78	0.002
NewT2 lesions=5	1.53	0.66	3.52	0.317
NewT2 lesions=6+	2.00	1.20	3.34	0.008
REL=0				0.000
REL=1	1.54	1.20	1.98	0.001
REL=2+	2.22	1.55	3.18	0.000

MAGNIMS Dataset

Score=0	new T2 lesions <3 & Relapses=0
Score=1	new T2 lesions <3 & Relapses=1 new T2 lesions ≥3 & Relapses=0
Score=2	new T2 lesions ≥3 & Relapses=1 Relapses≥2



0 Probability of progression = 19%

1 Probability of progression = 28%

2 Probability of progression = 48%

Score 0 vs scores 1 or 2:

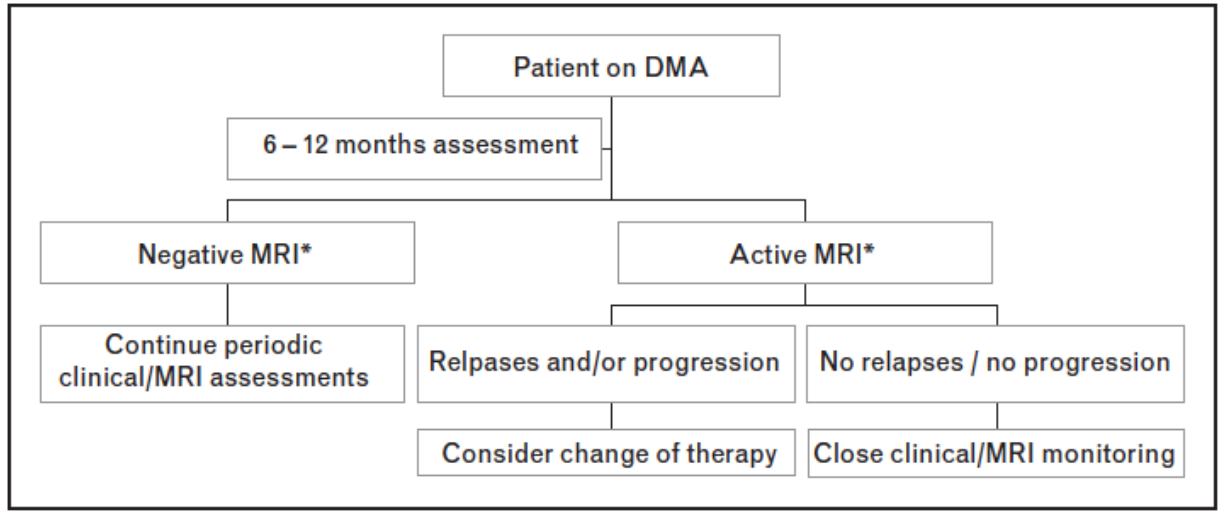
PPV= 34%,
NPV= 81%,
Sensitivity= 49%
Specificity= 73%,
Accuracy= 66%.

Multiple sclerosis: current treatment algorithms

Jordi Río, Manuel Comabella and Xavier Montalban

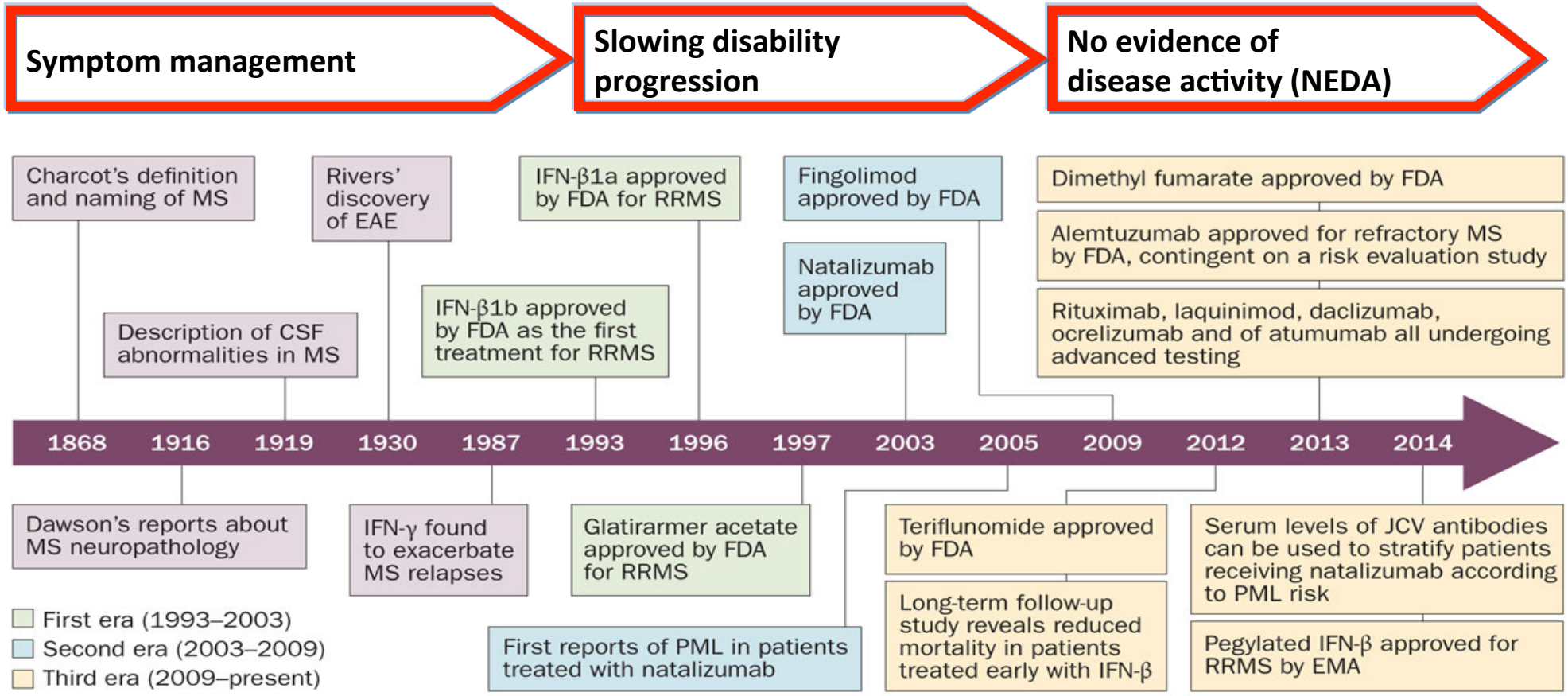
Current Opinion in Neurology 2011, 24:230–237

Figure 1 Proposed algorithm for the management of patients treated with disease-modifying agents



Reprinted with permission from [29]. *Consider active MRI when more than two active lesions appear. DMA, disease-modifying agent.

Treatment in MS: Paradigm shifts driven by emerging therapies

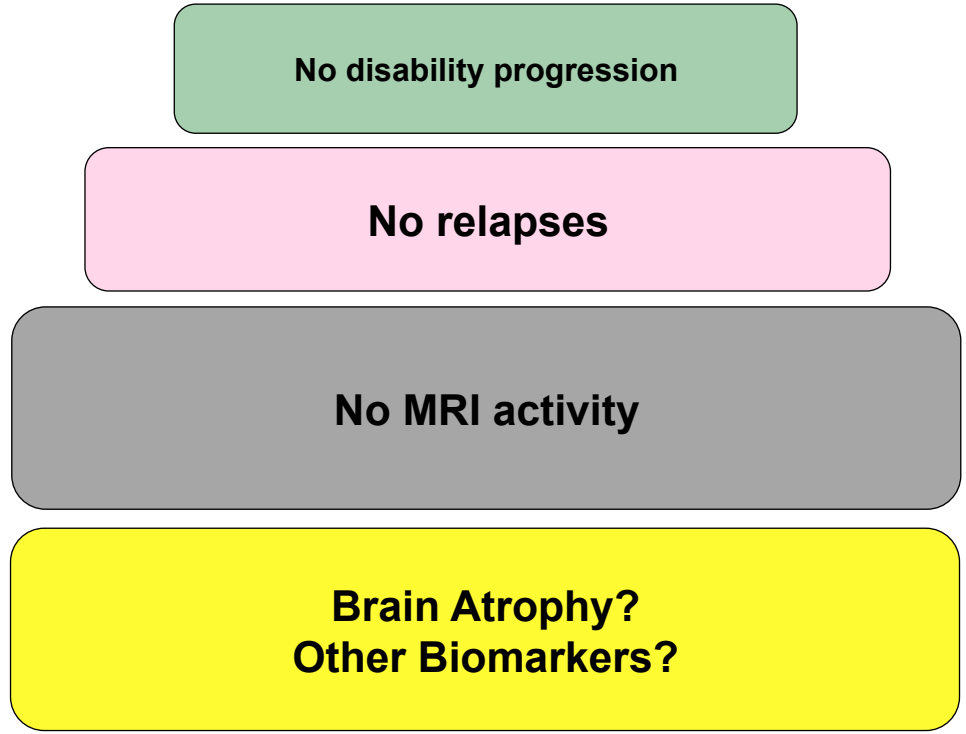


The growing availability of drugs active against MS over years leads to greater expectations

Ransohoff et al Nat Rev Neurol 2015

NEDA - Definition

- Lately, the term disease-free status has been replaced by NEDA (No Evident Disease Activity) because of the limits of our ability to evaluate the full extent of underlying disease activity



- NEDA has been evaluated in some MS clinical trials and few long-term studies of real-world MS cohorts

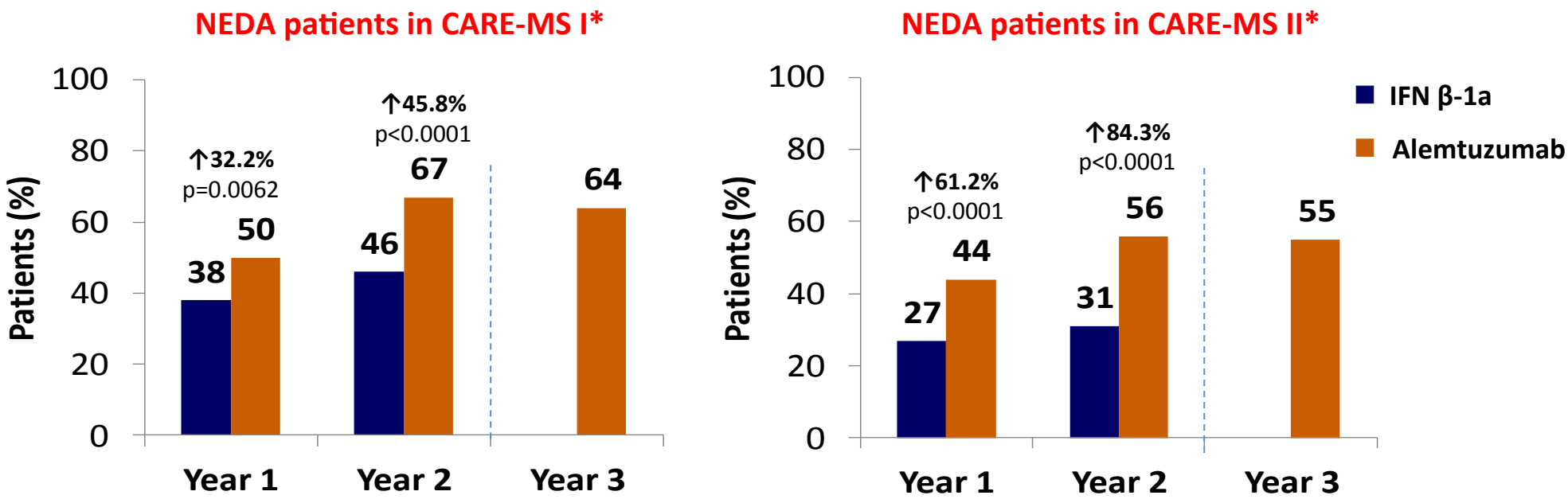
NEDA – Clinical trial data

- NEDA at 1 year
  - 34% for PegInterferon (ADVANCE)
  - 47% for Natalizumab (AFFIRM)
  - 39% for Daclizumab (SELECT)

- NEDA at 2 years
  - 37% for Natalizumab (AFFIRM)
  - 39% for Alemtuzumab (CARE-MS I)
  - 32% for Alemtuzumab (CARE-MS II)
  - 46% for Cladribine (CLARITY)
  - 28% for Dimethyl Fumarate (DEFINE)
  - 33% for Fingolimod (FREEDOMS)
  - 18% and 23% for Teriflunomide 7mg and 14mg (TEMSO)

- NEDA at 3 years
  - 19% for Glatiramer Acetate (CombiRx)
  - 21% for IFN-B 1a (CombiRx)
  - 33% for Glatiramer Acetate+IFNB1a (CombiRx)

Can NEDA be used to assess treatment response?



Post hoc analyses of trial data for patients with NEDA status
Data cannot be compared between trials because of different populations, lengths of treatment and definitions of NEDA

Havrdova E et al. Mult Scler J 2014;20(Suppl. 1):39 (FC1.4)

NEDA in Clinical Setting – Short Term (1y)

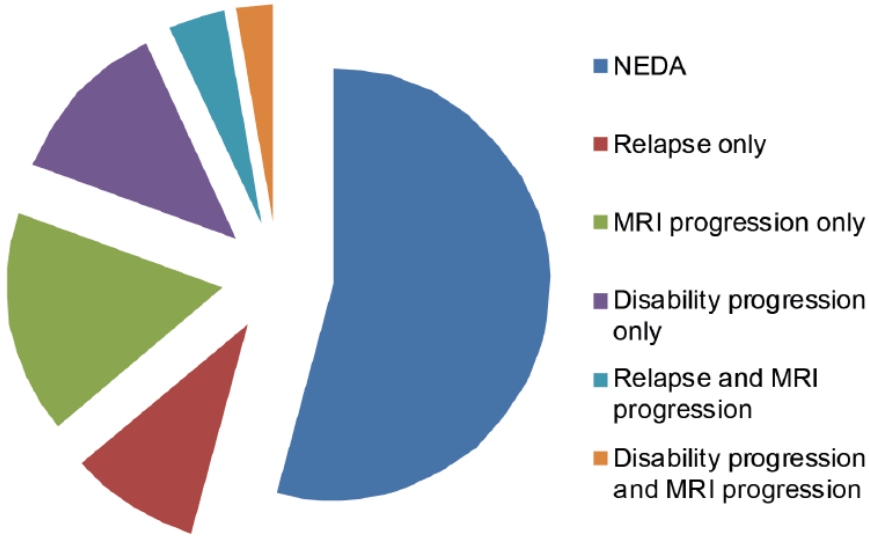


Fig 2. Evidence of disease activity at one-year follow-up. 54% of the patients were classified as NEDA after one year, while 46% of the patients showed either one or more evidences of disease activity.

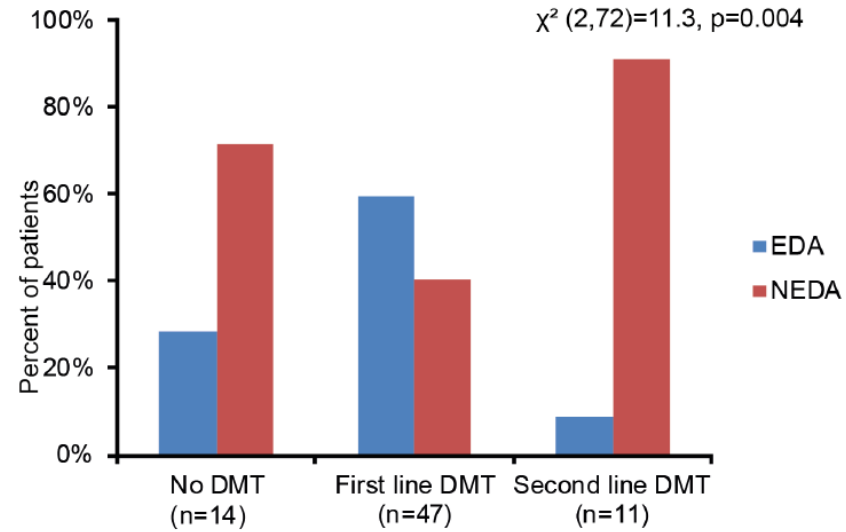
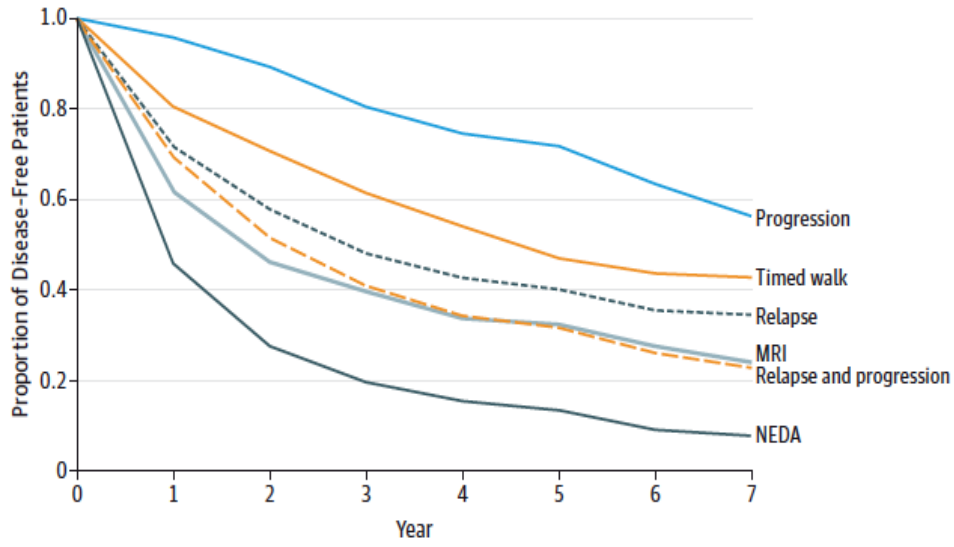


Fig 4. Disease activity in different treatment groups. Treatment groups as baseline of patients with EDA or NEDA one year later.

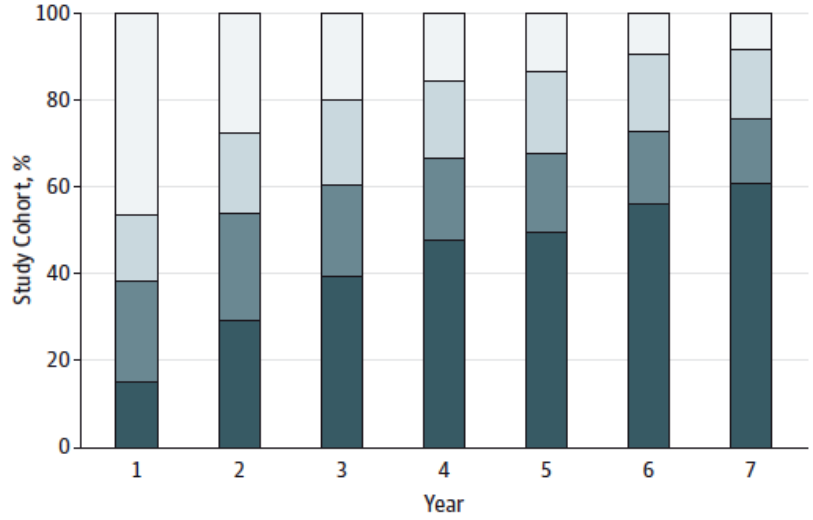
Nygaard et al PLOS ONE 2015

NEDA in Clinical Setting - Long-term FU (7y)

Figure 1. No Evidence of Disease Activity (NEDA) During 7 Years in the Overall Cohort



NEDA is difficult to sustain long-term even with treatment (only **17 of 216, ≈8%**) maintained NEDA status after 7 years.



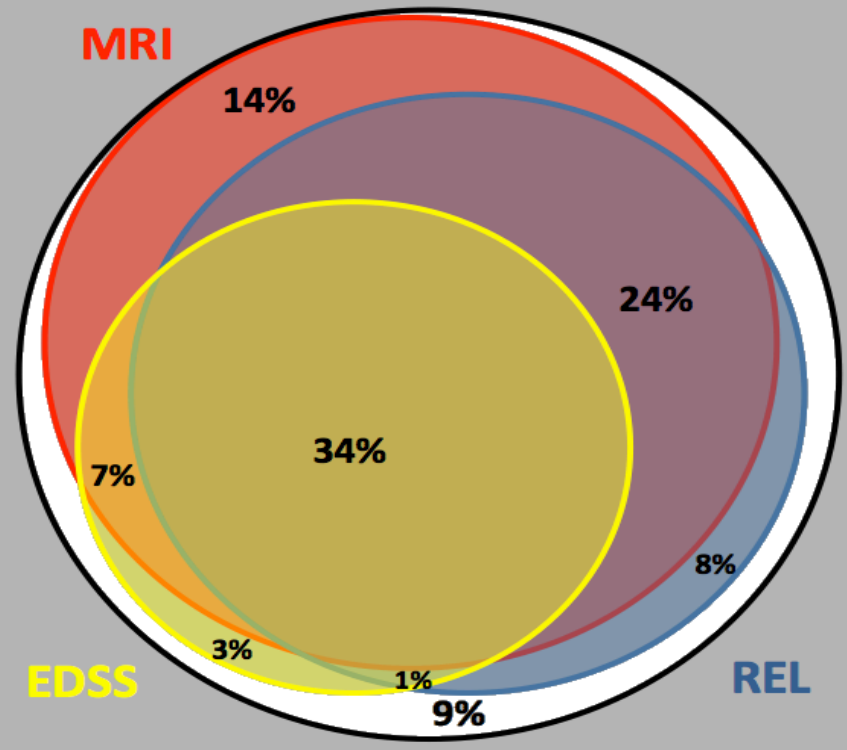
RESULTS A total of 99 of 215 patients (46.0%) had NEDA for clinical and MRI measures at 1 year, but only 17 of 216 (7.9%) maintained NEDA status after 7 years. No differences were found in NEDA status between patients with early vs established MS. A dissociation was found between clinical and MRI disease activity. Each year, 30.6% (64 of 209) to 42.9% (93 of 217) of the cohort had evidence of either clinical or MRI disease activity but not both. NEDA at 2 years had a positive predictive value of 78.3% for no progression (Expanded Disability Status Scale score change ≤0.5) at 7 years. Only minor improvement was found in the positive predictive values with additional follow-up of 1 to 3 years.

Rotstein et al JAMA Neurol 2015

NEDA in Clinical Setting - Long-term FU (10y)

MRI+ = 72/91 (79%)
REL+ = 61/91 (67%)
EDSS+ = 41/91 (45%)

8/91 (9%) = NEDA
31/91 (34%) = MRI+, REL+ and EDSS+
22/91 (24%) = MRI+ and REL+
6/91 (7%) = MRI+ and EDSS+
1/91 (1%) = REL+ and EDSS+
13/91 (14%) = MRI+ only
7/91 (8%) = REL+ only
3/91 (3%) = EDSS+ only



De Stefano et al Neurology in Press

Summary

- MRI helps in assessing treatment response.
- Combination of both clinical and MRI measures is the best way to assess treatment response
- Integrated scoring systems incorporating clinical and MRI measures of disease activity could be useful for a personalized approach to treatment
- NEDA is an important therapeutic goal in MS care. In clinical trials, this is a very interesting outcome measure. Clinical settings data have shown that this is difficult to sustain in the long term