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The role of MRI in modern management of and treatment decisions in MS

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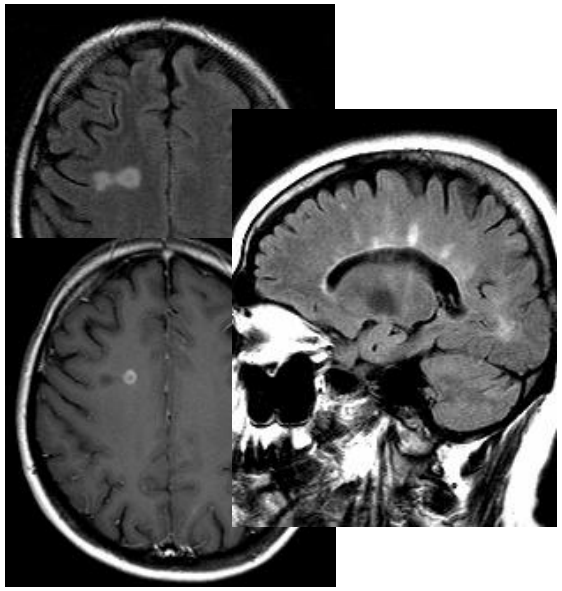
Vienna, September 25, 2013



Disclosures

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- I serve on scientific advisory boards for Bayer-Schering, Biogen Idec, Genzyme, Merck Serono, Pfizer, Novartis, Perceptive Informatics and Teva Pharmaceutical Industries Ltd.

- I serve on the editorial boards of Cerebrovascular Diseases, Multiple Sclerosis Journal, the Polish Journal of Neurology and Neurosurgery, Stroke, and the Swiss Archives of Neurology and Psychiatry

- I have received speaker honoraria and support from Biogen Idec, Bayer Schering, Merck Serono, Novartis, Sanofi-Aventis and Teva Pharmaceutical Industries Ltd.

Objectives

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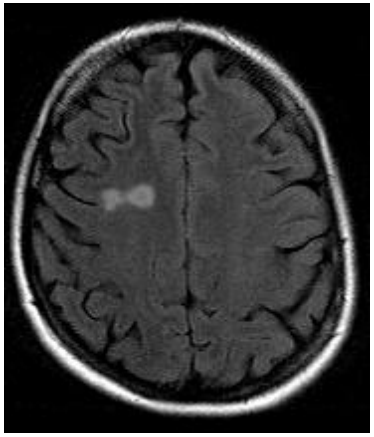
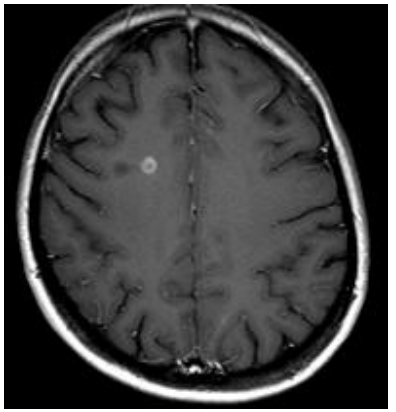
- What MRI metrics are available to evaluate disease activity / disease progression
  - Focal changes
  - Global changes
- What was and is their utility in treatment trials
- How can this experience be used in individual patient management / for treatment decisions



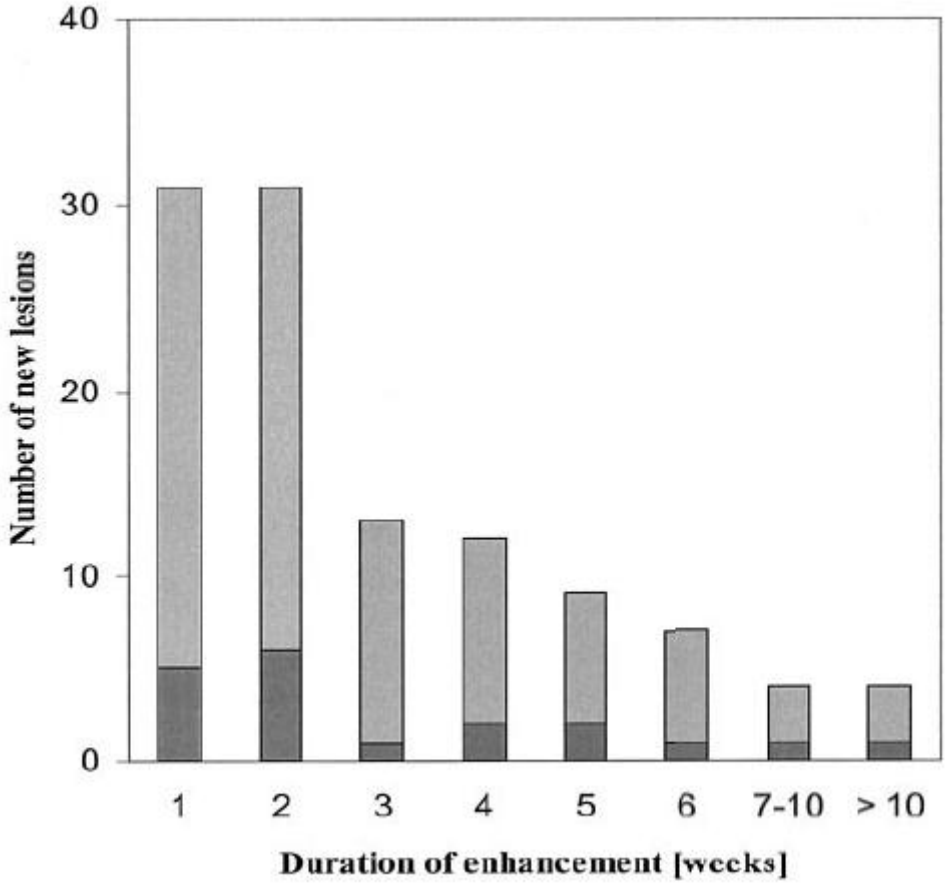
Inflammation / Active lesion



- Gadolinium enhancement indicates break down of blood brain barrier
- Active lesions enhance for 2 – 6 weeks
- Modification of enhancement by
  - Dosage of and delay after contrast material application
  - Imaging parameters
  - Steroid treatment
- Outcome variables
  - Active scan
  - Number of contrast-enhancing lesions / scan or cumulative lesion number

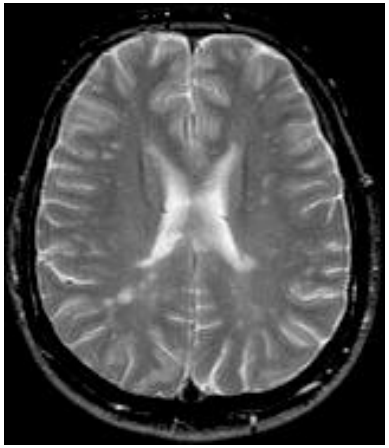
Duration of contrast enhancement in 26 RRMS patients on weekly MRI

Cotton F et al., Neurology 2003; 60:640-646

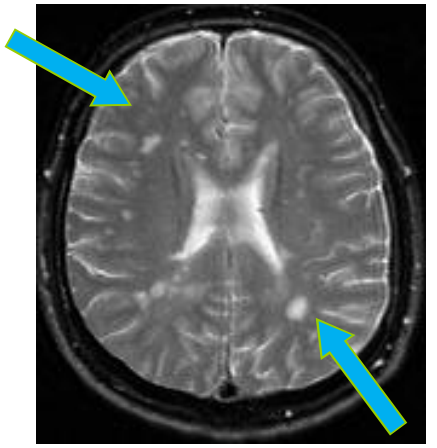


Dark grey : subgroup of lesions potentially affected by corticotherapy (n= 21); „natural history lesions n= 92

- 28.3 % of CE lesions seen on one MR exam only
- Average duration of enhancement. 3.1 weeks (median 2 weeks)



New T2 lesions (enlarging lesions)



- Occurrence of new (focal) T2 lesions is consistent with new areas of MS related tissue damage
- Usually associated with contrast enhancement in acute stage but persistent
- Modifications by
  - Imaging parameters (sequence, slice thickness, etc.)
- Outcome variables
  - Number of new T2 lesions
  - Number of enlarging T2 lesions

Number of newly active lesions
(new and enlarging T2 and new contrast enhancing lesions)

Critique

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- Limited predictive value of contrast enhancing lesions for further relapses (Kappos L. et al., 1999)

- Limited correlation of new lesions and / or of T2 lesion load with disability

Correlation of MRI measures and disability

T2 lesion volume – EDSS (cross-sectional correlations)				
Morrissey and colleagues[15]	1993	89	CIS	0.55[b]
Paty and colleagues[16]	1993	372	RR	0.23[c]
Gass and colleagues[17]	1994	43	RR/SP	0.33[d]
van Walderveen and colleagues[20]	1995	48	RR/SP	0.30[d]
Truyen and colleagues[22]	1996	46	RR/SP	0.46[b]
Gawne-Cain and colleagues[23]	1998	56	RR/SP	0.49[c]
Lycklama à Nijeholt and colleagues[24]	1998	60	RR/SP	0.33[c]
Molyneux and colleagues[25]	1998	73	RR/SP	0.31[c]
Riahi and colleagues[26]	1998	39	RR	0.60[b]
van Waesberghe and colleagues[27]	1998	41	RR/SP	0.17
Molyneux and colleagues[28] (baseline)	2001	718	SP	0.09[c]
Molyneux and colleagues[28] (year 3)	2001	718	SP	0.15[c]
Schreibner and colleagues[29]	2001	86	RR/SP	0.48[b]
Ciccarelli and colleagues[30]	2002	41	RR/SP	0.53[c]
New T2 lesions – ΔEDSS (longitudinal correlations)				
Khoury and colleagues[18]	1994	18	RR/SP	0.14[d]
Filippi and colleagues[19]	1995	213	RR/SP	0.13[d]
Molyneux and colleagues[28]	2001	718	SP	0.18[c]
ΔT2 lesion load – ΔEDSS (longitudinal correlations)				
van Walderveen and colleagues[20]	1995	48	RR/SP	0.19
Truyen and colleagues[22]	1996	46	RR/SP	0.11
Molyneux and colleagues[25]	1998	73	RR/SP	0.09
Molyneux and colleagues[28]	2001	718	SP	0.17[c]

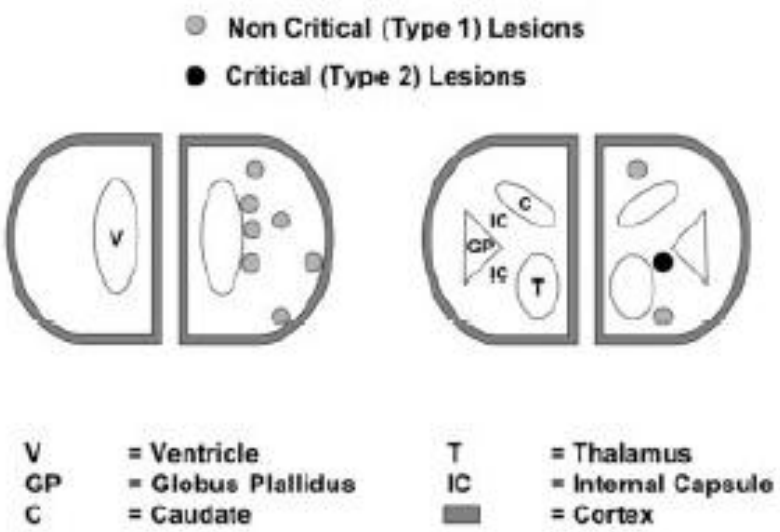
[a]Spearman's rank correlations (except in Molyneux and colleagues,[28] which used another rank correlation method).

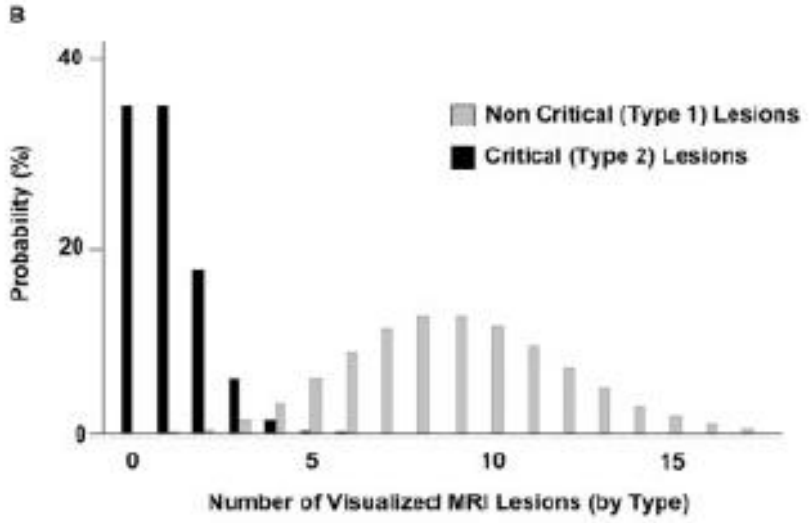
[b]$p < 0.001$; [c]$p < 0.0001$; [d]$p < 0.05$; [e]$p < 0.01$.

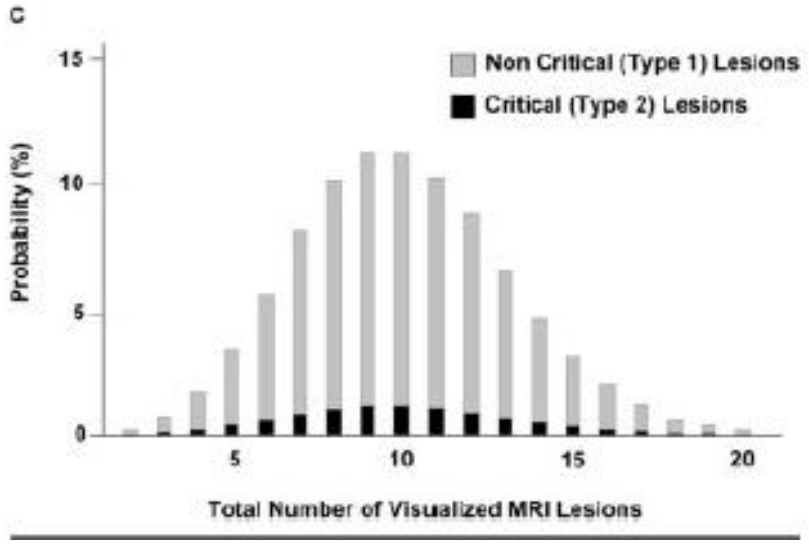
ρ = correlation coefficient; EDSS = extended disability status scale; CIS = clinically isolated syndrome; RR = relapsing-remitting; SP = secondary progressive.

Goodin SD, Ann Neurol 2006;59:597-605

MRI lesions contribute to disability but with different weights depending on lesion type, location, etc.

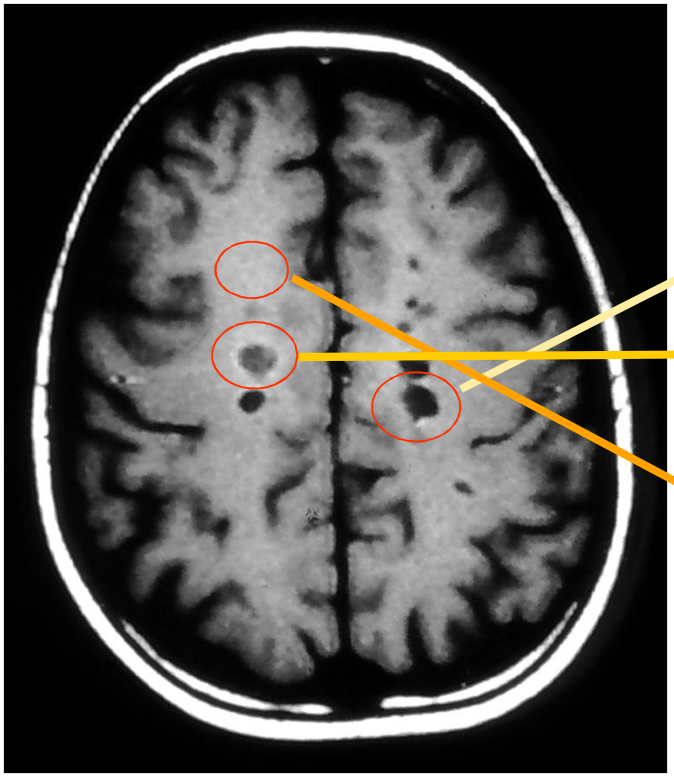






Goodin SD, Ann Neurol 2006;59:597-605

“Black holes“ – MR marker of different severity of tissue destruction

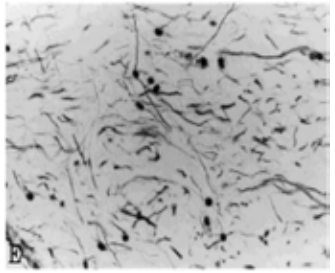


Bodian axonal density

Marked hypo-intensity

Discrete hypo-intensity

NAWM



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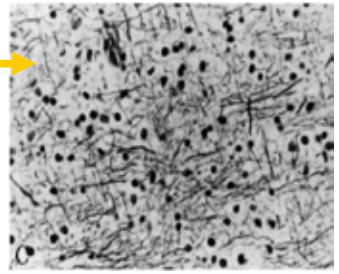

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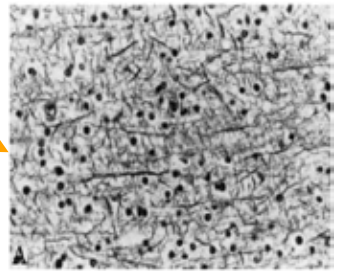
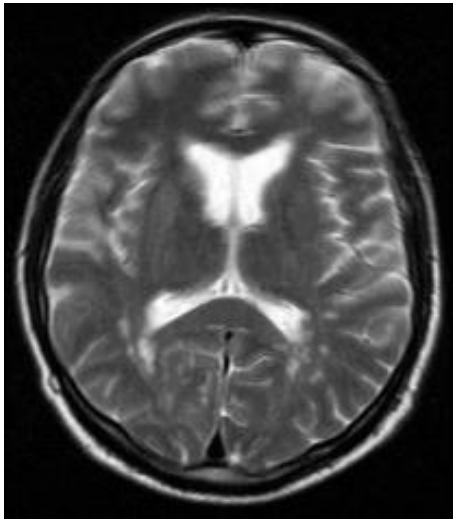
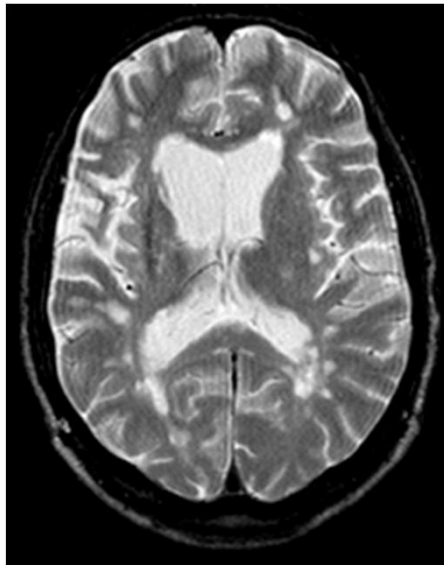


100%

van Waesberghe JH et al. *Ann Neurol*. 1999



Brain volume changes



- Indicative of alterations in tissue integrity (including cell loss) and composition (including water)
- Frequently associated with „neurodegeneration“
- Modifications by
  - Imaging parameters (sequence, slice thickness, etc.)
  - Analysis tools
- Various measurement techniques and outcome variables
  - Linear and regional measures
  - Segmentation based methods
  - Registration based methods

Brain volume changes in MS

Table 1 Mechanisms that may decrease brain volume in multiple sclerosis

	Beneficial	Non-tissue-related (fluid shifts)	Fluctuating	Irreversible
Natural history			Demyelination (reduced via remyelination); loss of glial cells (reduced via recruitment and differentiation)	Axonal loss; Wallerian degeneration
DMA-related			Inhibition of "good" inflammation	Chemotoxicity; protein catabolism
DMA-induced pseudoatrophy	Resolution of inflammation and edema	Change in electrolyte balance and vascular permeability; dehydration		

DMA = disease-modifying agent.

Zivadinov R. et al., Neurology 2008;71:136-144

Inverse dynamics of same mechanism(s) may increase brain volume !

AJNR
American Journal of Neuroradiology

Published July 12, 2012 as 10.3174/ajnr.A3107

ORIGINAL RESEARCH

Reliability of Longitudinal Brain Volume Loss Measurements between 2 Sites in Patients with Multiple Sclerosis: Comparison of 7 Quantification Techniques

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C. Confavreux
F. Cotton

BACKGROUND AND PURPOSE: Brain volume loss is currently a MR imaging marker of neurodegeneration in MS. Available quantification algorithms perform either direct (segmentation-based techniques) or indirect (registration-based techniques) measurements. Because there is no reference standard technique, the assessment of their accuracy and reliability remains a difficult goal. Therefore, the purpose of this work was to assess the robustness of 7 different postprocessing algorithms applied to images acquired from different MR imaging systems.

MATERIALS AND METHODS: Nine patients with MS were followed longitudinally over 1 year (3 time points) on two 1.5T MR imaging systems. Brain volume change measures were assessed using 7 segmentation algorithms: a segmentation-classification algorithm, FreeSurfer, BBSI, KN-BSI, SIENA, SIENAX, and JI algorithm.

RESULTS: Intersite variability showed that segmentation-based techniques and SIENAX provided large and heterogeneous values of brain volume changes. A Bland-Altman analysis showed a mean difference of 1.8%, 0.07%, and 0.79% between the 2 sites, and a wide length agreement interval of 11.66%, 7.92%, and 11.94% for the segmentation-classification algorithm, FreeSurfer, and SIENAX, respectively. In contrast, registration-based algorithms showed better reproducibility, with a low mean difference of 0.45% for BBSI, KN-BSI and JI, and a mean length agreement interval of 1.55%. If SIENA obtained a lower mean difference of 0.12%, its agreement interval of 3.29% was wider.

CONCLUSIONS: If brain atrophy estimation remains an open issue, future investigations of the accuracy and reliability of the brain volume quantification algorithms are needed to measure the slow and small brain volume changes occurring in MS.

Table 1: Description of the mean, standard deviation, and median percentages of atrophy between the 7 techniques at 6 and 12 months on MRI1

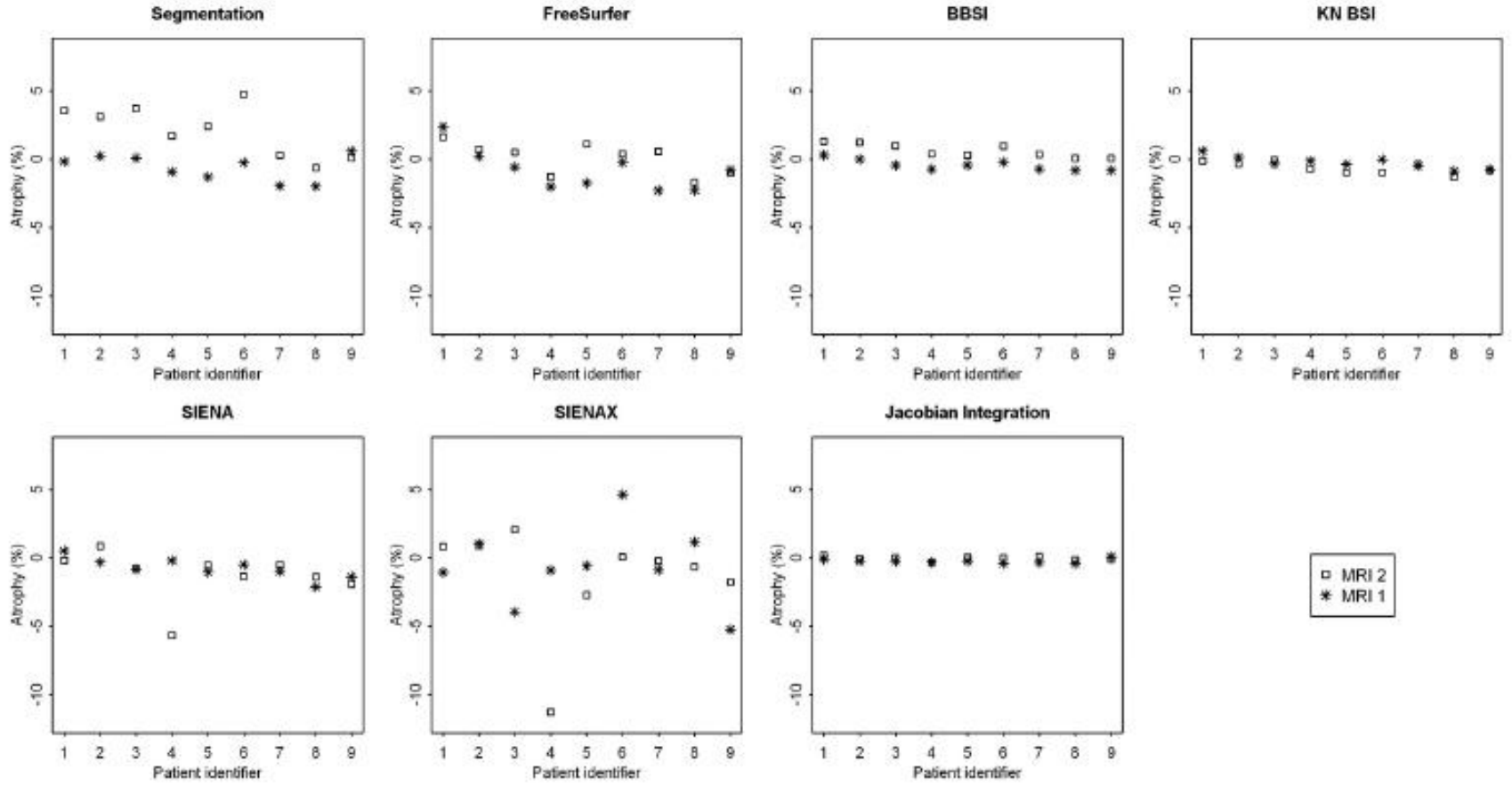
	6 months			12 months		
Technique	Mean	SD	Median	Mean	SD	Median
Segmentation-classification	−0.03	2.87	−0.73	−0.64	0.95	−0.26
FreeSurfer	−0.53	0.74	−0.61	−0.83	1.51	−0.81
BBSI	−0.32	0.29	−0.33	−0.45	0.39	−0.46
KN-BSI	−0.29	0.37	−0.38	−0.26	0.45	−0.34
SIENA	−0.30	0.51	−0.34	−0.78	0.76	−0.85
SIENAX	−0.94	2.26	−0.80	−0.66	2.88	−0.88
JI	−0.26	0.12	−0.24	−0.26	0.16	−0.27

Table 2: Description of the mean, standard deviation and median percentages of atrophy between the 7 techniques at 6 and 12 months on MRI2

	6 months			12 months		
Technique	Mean	SD	Median	Mean	SD	Median
Segmentation-classification	1.78	1.13	1.76	2.08	1.86	2.39
FreeSurfer	−0.60	1.37	−0.74	0.08	1.15	0.50
BBSI	0.53	0.20	0.55	0.61	0.49	0.35
KN-BSI	−0.62	0.33	−0.68	−0.65	0.43	−0.75
SIENA	−0.19	0.69	−0.13	−1.29	1.83	−0.76
SIENAX	−0.14	1.42	0.22	−1.44	3.96	−0.23
JI	−0.07	0.24	−0.06	−0.06	0.15	−0.03

Durand-Dubief F. et al., AJNR Am J Neuroradiol. 2012 Nov;33(10):1918-24

Percentages of brain volume change at 12 months obtained between sites MRI1 (*) and MRI2 (o) by 7 different techniques



Durand-Dubief F. et al., AJNR Am J Neuroradiol. 2012 Nov;33(10):1918-24

Measures of disease activity and tissue damage

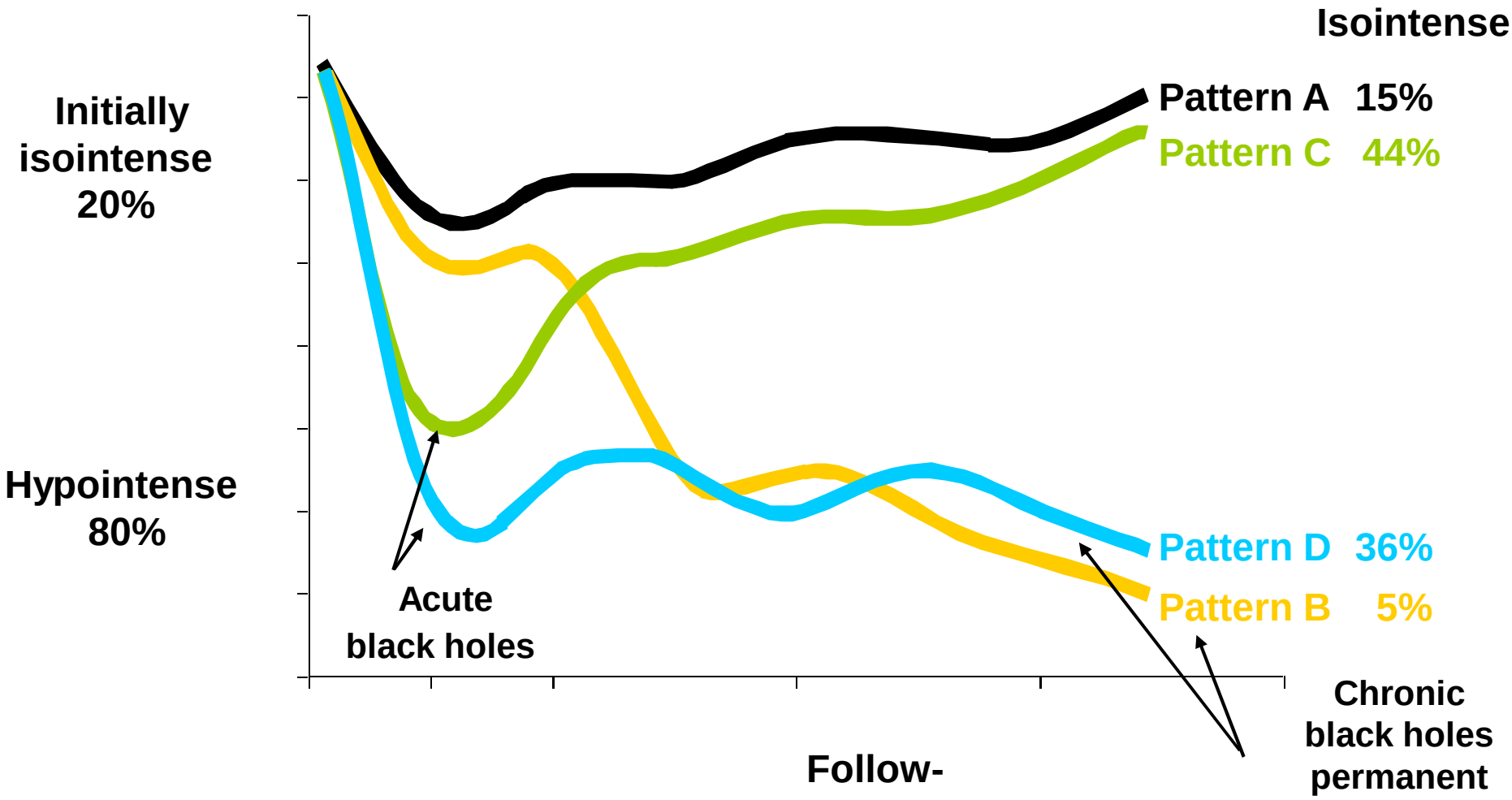
Table 2. MRI Techniques that might Prove to be Useful for Monitoring MS Treatment Trials

MRI Techniques	Pathophysiologic Information Expected
Diffusion-weighted MRI/diffusion tensor MRI metrics	Tissue/fibre tract integrity
Magnetization transfer MRI	Tissue composition, eg, remyelination
Proton magnetic resonance spectroscopy	Metabolic information, eg, axonal integrity, extent of gliosis
Volume changes of tissue compartments (segmentation)	Specific effects on gray and white matter compartments
Spinal cord MRI (atrophy, tissue composition, etc.)	Evaluation of prominent location of damage such as in progressive MS
Functional MRI	Brain plasticity, eg, adaptation, remodeling

Fazekas F. et al., J Neuroimag 2007;17:50S -55S

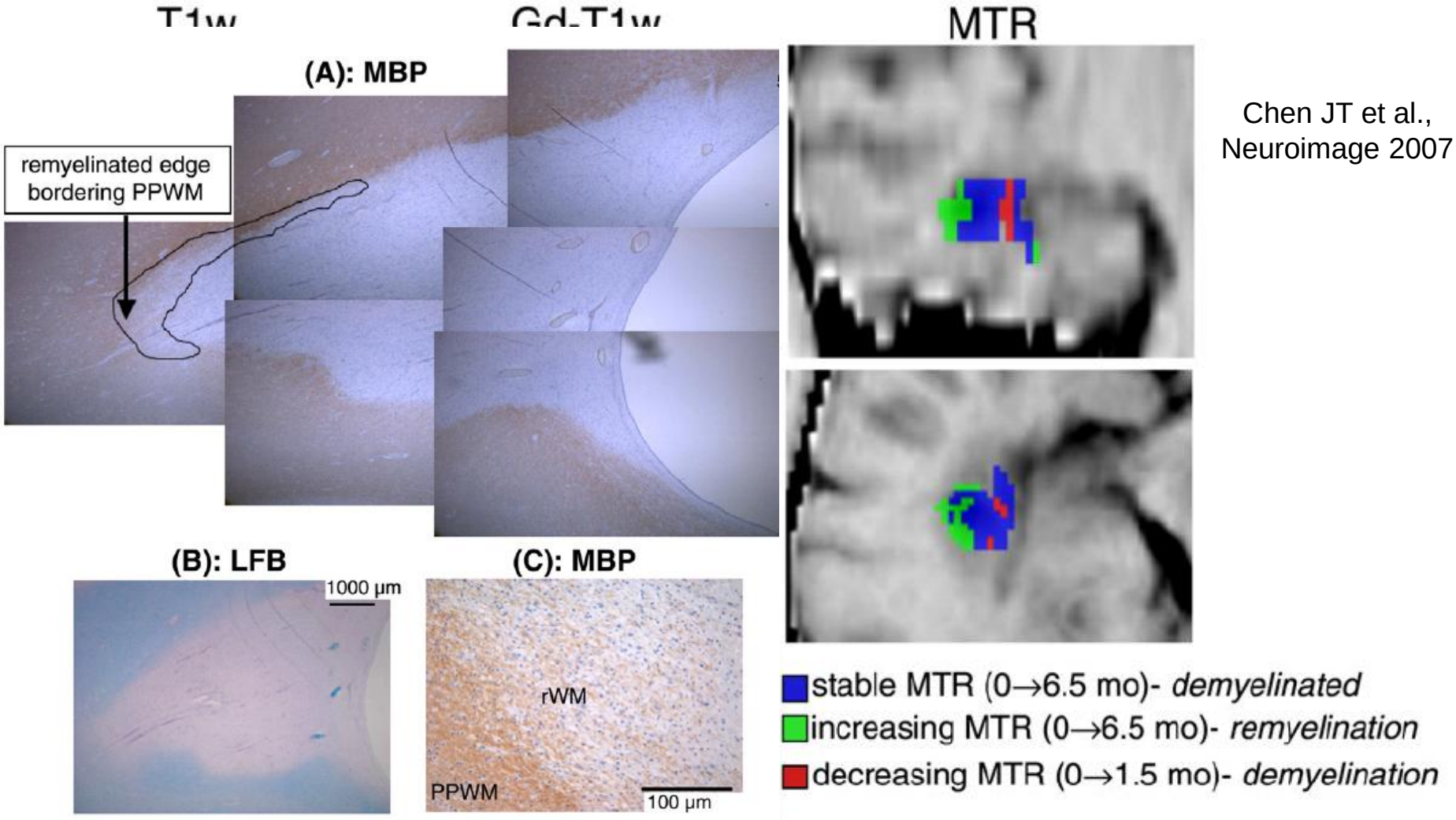
Magnetic Transfer Ratio (MTR)

Higher Pathological Specificity Than Conventional MRI



van Waesberghe JH *et al.,* AJNR Am J Neuroradiol. 1998;19:675-683

Histopathologic validation of MTR changes in a single lesion



Chen JT et al., Neuroimage 2007

Original Research

Quantitation of Brain Tissue Changes Associated With White Matter Hyperintensities by Diffusion-Weighted and Magnetization Transfer Imaging: The LADIS (Leukoaraiosis and Disability in the Elderly) Study

Stefan Ropele, PhD,[1*] Alexandra Seewann, MD,[2,3] Alida A. Gouw, MD,[2,3] Wiesje M. van der Flier, MD,[2,3] Reinhold Schmidt, MD,[1,4] Leonardo Pantoni, MD, PhD,[5] Domenico Inzitari, MD,[5] Timo Erkinjuntti, MD, PhD,[6] Philip Scheltens, MD, PhD,[2] Lars O. Wahlund, MD, PhD,[7] Gunhild Waldemar, MD, DMSc,[8] Hugues Chabriat, MD, PhD,[9] José Ferro, MD, PhD,[10] Michael Hennerici, MD,[11] John O'Brien, MD,[12] Anders Wallin, MD, PhD,[13] Peter Langhorne, MD, PhD,[14] Marieke C. Visser, MD, PhD,[2] Frederik Barkhof, MD, PhD,[2,3] and Franz Fazekas, MD[1] on behalf of the LADIS study group

Purpose: To explore the value of diffusion-weighted imaging (DWI) and magnetization transfer imaging (MTI) for the improved detection and quantification of cerebral tissue changes associated with ageing and white matter hyperintensities (WMH).

Materials and Methods: DWI (n = 340) and MTI (n = 177) were performed in nine centers of the multinational Leukoaraiosis And DISability (LADIS) study investigating the impact of WMH on 65- to 85-year-old individuals without prior disability. We assessed the apparent diffusion coefficient (ADC) and magnetization transfer ratio (MTR) of normal appearing brain tissue (NABT) and within WMH and related them to subjects' age and WHM severity according to the Fazekas score.

Results: ADC and MTR values showed a significant intersite variation, which was stronger for the MTR. After z-transformation multiple regression analysis revealed WMH severity and age as significant predictors of global ADC and MTR changes. Only lesional ADC, but not MTR was related to WMH severity.

Conclusion: ADC and MTR are both sensitive for age and WMH related changes in NABT. The ADC is more sensitive for tissue changes within WMH and appears to be more robust for multicenter settings.

Key Words: brain; ageing; white matter hyperintensities; magnetization transfer; diffusion
J. Magn. Reson. Imaging 2009;29:268–274.

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THE IMPACT OF INCIDENTAL white matter hyperintensities (WMH) on cerebral functioning is supported by an increasing number of investigations. These studies encompass observations from healthy elderly popula-

Table 1
Total LADIS Cohort and Subjects That Took Part in the ADC and MTR Substudy*

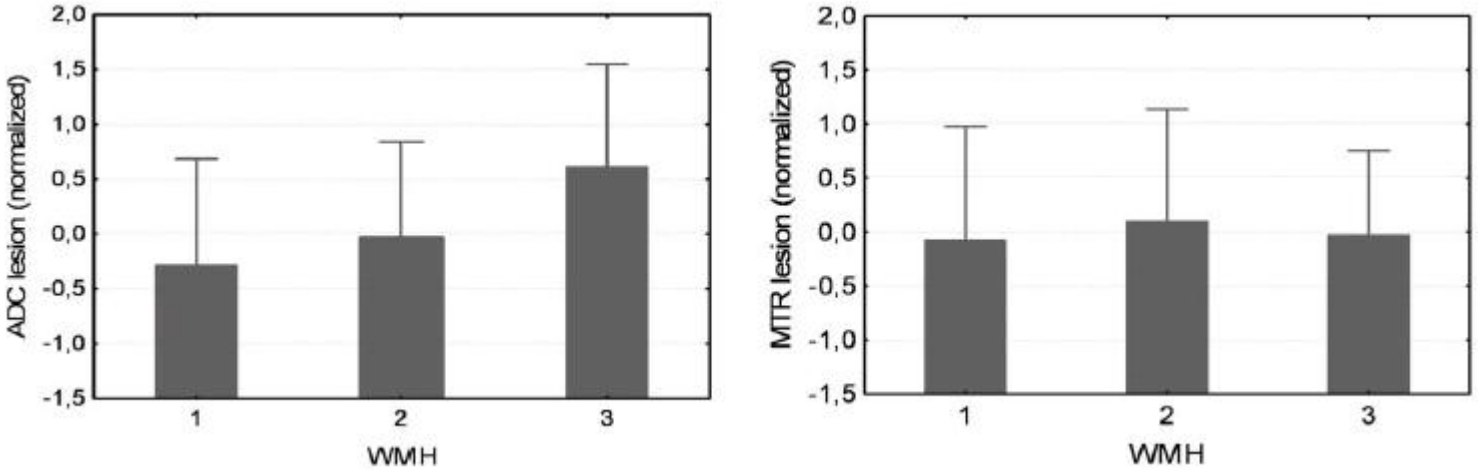
	Total LADIS cohort	ADC subgroup	MT subgroup
n	639	340	177
Mean age (SD)	74.1 (5.0)	73.9 (5.0)	74.5 (5.0)
Gender			
Female	351 (54.9%)	184 (54.1%)	91 (51.4%)
Male	288 (45.1%)	156 (45.9%)	86 (48.6%)
WMH score			
1	284 (44.5%)	155 (45.6%)	71 (40.1%)
2	197 (30.8%)	108 (31.8%)	68 (38.4%)
3	158 (24.7%)	77 (22.6%)	38 (21.5%)

*The subgroups did not differ from the total LADIS cohort with respect to age, sex, and WMH severity.

Table 2
Results of the Univariate Regression Analysis Showing the Effect of Age and WMH Severity on Lesional and Global ADC and MTR Values as Expressed by the Correlation Factor

	Age		WMH score	
	MTR (n = 177)	ADC (n = 340)	MTR (n = 0.03	ADC 0.34*
Lesion	0.09	−0.04	0.34*	0.03
NABT mean	−0.33*	0.35*	−0.29*	0.25*
NABT peak height	−0.39*	−0.34*	−0.30*	−0.31*
NABT peak position	−0.15*	0.19*	−0.27*	−0.15*

*The asterisks indicate a *P* value less than 0.05.



Mean ADC Values of Lesions and NABT Histograms Obtained at Individual Centers*

Center	Scanner	Global mean	Peak position	Lesion
1	Gyroscan NT Intera (Philips)	1055.3 (222.9)	729,7 (140.9)	982,0 (103.0)
2	Magnetom Sonata (Siemens)	1272,3 (94.7)	820,6 (41.2)	1224,3 (127.9)
3	Magnetom Vision (Siemens)	1155.5 (102.8)	712,8 (63.5)	968,0 (115.3)
4	Genesis Signa (GE)	1079.6 (117.6)	743.6 (98.8)	1174.3 (169.8)
5	Genesis Signa (GE)	1095.5 (113.6)	776.2 (70.86)	1228.46 (170.0)
6	Gyroscan Intera (Philips)	1175.9 (812.2)	812.2 (29.0)	1161.4 (120.8)
7	Magnetom Vision plus (Siemens)	1332.7 (114.0)	938.9 (106.9)	1294.0 (113.9)
8	Magnetom Vision (Siemens)	1396.7 (141.0)	1026.2 (112.1)	1414.8 (128.8)

*The standard deviation is given in parentheses. All diffusion coefficients are given in 10^{-6} mm^2/s.

Correlation Factors From an Univariate Correlation Analysis of Age on Global and Lesional ADC per Center

Center	n	Global mean	Peak height	Peak position	Lesion
1	34	0.58*	−0.54*	0.19	0.02
2	48	0.23	−0.45*	0.13	0.00
3	27	0.59*	−0.60*	0.41*	0.34
4	61	0.33*	−0.38*	0.15	0.14
5	20	0.68*	−0.67*	0.57*	0.47
6	45	0.19	−0.32*	0.12	−0.04
7	59	0.42*	−0.21	0.32*	0.20
8	46	0.10	−0.14	−0.08	−0.18

*The asterisk indicates a *P* value less than 0.05.

Learning objectives

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- What MRI metrics are available to evaluate disease activity / disease progression
  - Focal changes
  - Global changes
- What was / is their utility in treatment trials
- How can this experience be used in individual patient management / for treatment decisions

Magnetic Resonance Imaging as a Potential Surrogate for Relapses in Multiple Sclerosis: A Meta-analytic Approach

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Objective: The aim of this work was to evaluate whether the treatment effects on magnetic resonance imaging (MRI) markers at the trial level were able to predict the treatment effects on relapse rate in relapsing-remitting multiple sclerosis.

Methods: We used a pooled analysis of all the published randomized, placebo-controlled clinical trials in relapsing-remitting multiple sclerosis reporting data both on MRI variables and relapses. We extracted data on relapses and on MRI "active" lesions. A regression analysis weighted on trial size and duration was performed to study the relation between the treatment effect on relapses and the treatment effect on MRI lesions. We validated the estimated relation on an independent set of clinical trials satisfying the same inclusion criteria but with a control arm other than placebo.

Results: A set of 23 randomized, double-blind, placebo-controlled trials in relapsing-remitting multiple sclerosis was identified, for a total of 63 arms, 40 contrasts, and 6,591 patients. A strong correlation was found between the effect on the relapses and the effect on MRI activity. The adjusted R^2 value of the weighted regression line was 0.81. The regression equation estimated using the placebo-controlled trials gave a satisfactory prediction of the treatment effect on relapses when applied to the validation set.

Interpretation: More than 80% of the variance in the effect on relapses between trials is explained by the variance in MRI effects. Smaller and shorter phase II studies based on MRI lesion end points may give indications also on the effect of the treatment on relapse end points.

Ann Neurol 2009;65:268–275

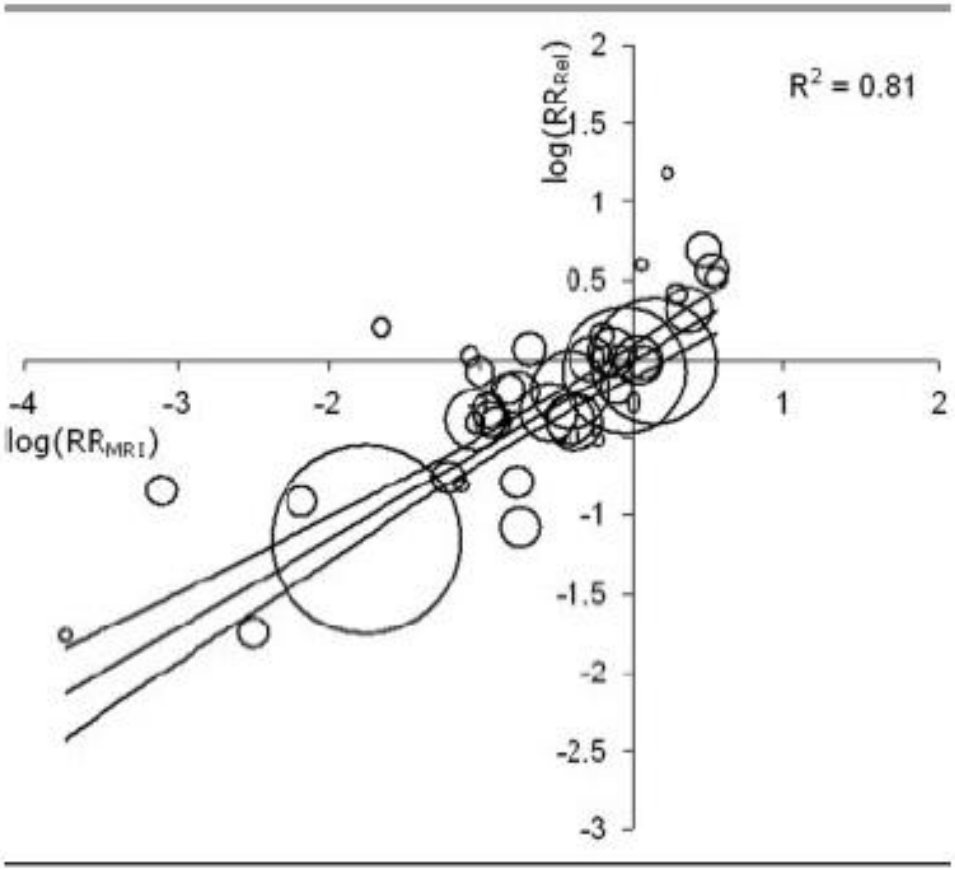

Fig 1. Treatment effect on magnetic resonance imaging lesions (x-axis) versus treatment effect on clinical relapses (y-axis). Both treatment effects are expressed as rate ratios (RRs) on a log scale. Each circle *represents a contrast versus placebo and its dimension the weight of the contrast, proportional to trial size and duration.* Solid line *represents the weighted regression line with the 95% confidence band. log(RR_{Rel}) = logarithm of the relapse rate ratio; log(RR_{MRI}) = logarithm of the magnetic resonance imaging lesions rate ratio.*

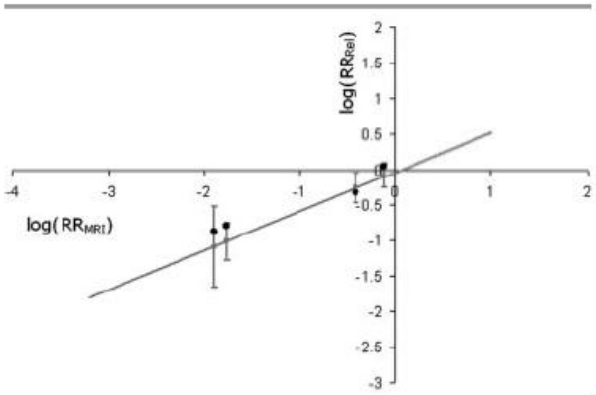

Fig 3. Validation of the regression line: the treatment effect on relapses as estimated by the regression line is compared with that really observed in four randomized, controlled trials not used to estimate the regression equation. Solid line *represents the estimated regression line;* bars *are the 95% prediction intervals of the estimated treatment effects on relapse rates estimated by the observed treatment effect on magnetic resonance imaging (MRI) lesions;* black dots *are the observed treatment effects on relapse rates. RR = rate ratio; log(RR_{Rel}) = logarithm of the relapse rate ratio; log(RR_{MRI}) = logarithm of the MRI lesion rate ratio.*

Sormani MP et al, Ann Neurol 2009;65:268-275

Combined MRI lesions and relapses as a surrogate for disability in multiple sclerosis

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ABSTRACT

Objective: In multiple sclerosis (MS), the aim of therapies is to prevent the accumulation of irreversible disability. This is difficult to assess given the short time course of clinical trials. MRI markers and relapses are often used as surrogate of disability in MS studies, but their validity remains controversial. We sought to validate, at the individual patient level, MRI lesions and relapses as surrogates for disability progression over the course of MS trials.

Methods: Individual patient data from a large, placebo-controlled trial of interferon β-1a in relapsing-remitting MS (RRMS) were analyzed. The Prentice criteria were applied to evaluate surrogacy of 1-year MRI active lesions and relapses for disability worsening (Expanded Disability Status Scale [EDSS]) over the 2-year follow-up.

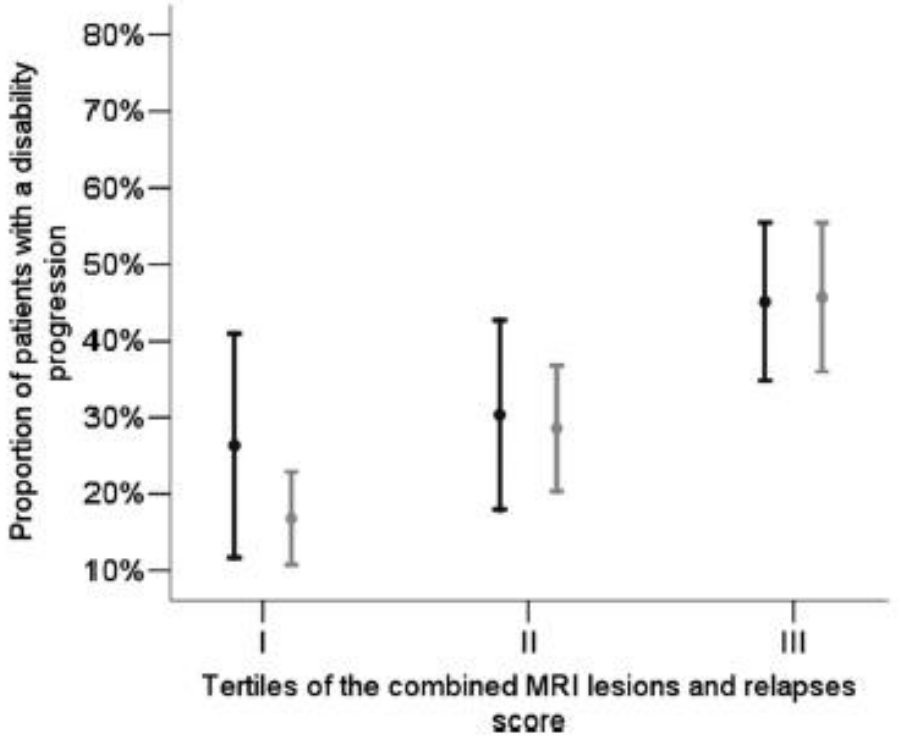
Results: All Prentice criteria were satisfied. Treatment reduced by 31% the odds of having EDSS worsening over 2 years, reducing the mean number of MRI lesions by 61% and the mean number of relapses by 36% over 1 year. Both 1-year MRI lesion activity and relapses, when considered independently, accounted for more than 60% of the treatment effect on 2-year EDSS worsening. A combination of 1-year MRI lesion activity and relapses explained 100% of the treatment effect on EDSS worsening over 2 years.

Conclusions: A combined measure of 1-year changes in MRI lesions and relapses after interferon therapy fully estimated the corresponding effect on 2-year EDSS worsening. This short-term combined measure appears to be a surrogate for disability progression over a longer term when evaluating the effect of interferon in RRMS. *Neurology*® 2011;77:1684–1690

Table 1 MRI and clinical outcomes for the patients included in the surrogacy analysis

	Placebo (n = 187)	Interferon β-1a (n = 373)
MRI T2 active lesions, mean (range)		
1 year	7.6 (0–69)	2.9 (0–49)
2 years	12.8 (0–89)	5.5 (0–73)
Relapses, mean (range)		
1 year	1.5 (0–5)	0.96 (0–5)
2 years	2.6 (0–10)	1.8 (0–10)
Proportion of patients with disability progression (SE), %		
1 year	29 (3)	18 (2)
2 years	37 (4)	29 (2)

Figure Treatment effect on disability is fully explained by a combination of MRI activity and relapses



Proportion of patients with a disability progression over 2 years according to risk groups defined as the tertiles of the distribution of the combined score of MRI active lesions and relapses during the first year of the study (I tertile: 0–0.25, II tertile: 0.26–0.80, III tertile: 0–81+; see the text and appendix e-1 for details). Progression was defined as an increase of at least 1 Expanded Disability Status Scale point confirmed after 3 months. Black points represent placebo patients and gray points represent interferon-treated patients. The bars represent 95% confidence intervals.

MRI monitoring of immunomodulation in relapse-onset multiple sclerosis trials

Frederik Barkhof, Jack H. Simon, Franz Fazekas, Marco Rovaris, Ludwig Kappos, Nicola de Stefano, Chris H. Polman, John Petkau, Ernst W. Radue, Maria P. Sormani, David K. Li, Paul O'Connor, Xavier Montalban, David H. Miller and Massimo Filippi

Abstract | Over the past 15 years, MRI lesion activity has become the accepted surrogate primary outcome measure in proof-of-concept placebo-controlled clinical trials of new immunomodulating therapies in relapse-onset multiple sclerosis (MS). In parallel, the number of patients that are available for the placebo arm of trials has declined, and more-aggressive drugs are being developed. A critical review is warranted to ensure efficient MRI—and patient—resource utilization. Recently, an international panel reviewed the methodology for efficient use of MRI-monitored trials in relapse-onset MS. In this article, we provide up-to-date recommendations for scan acquisition, image analysis, outcome-measure definition and standards of reporting. Factors to consider for optimizing trial design, such as outcome measure selection and the unique requirements of phase II and phase III trials, including active-comparator studies, are outlined. Finally, we address safety considerations in the use of MRI in MS trials, and the safety-related responsibilities of the various parties involved in conducting such trials.

Barkhof, F. *et al. Nat. Rev. Neurol.* advance online publication 6 December 2011; doi:10.1013/nrneurol.2011.190

Table 2 | Study design for randomized clinical trials in relapse-onset multiple sclerosis

Trial type	Duration	MRI parameter	Sampling	Surrogacy for:	Estimated sample size per arm*	
					Placebo-controlled	Interferon-controlled
Phase II	6–12 months	Primary:				
		Active lesions (CUA)	Every 4–6 weeks	Disease activity	70–90	120–200
		Secondary or exploratory:				
		Brain volume (global or regional)	Every 3 months	Disease progression	NA	NA
		Evolution of active lesions into 'black holes'	Every 4–6 weeks	Neurodegeneration	NA	NA
Phase III	24 months or longer	Primary:				
		Active lesions (CUA)	Every 6–12 months	Disease activity	80–120	150–180
		T2-lesion volume	Every 6–12 months	Disease activity or progression	120–160	160–200
		T1-lesion volume	Every 6–12 months	Disease progression	220–280	280–340
		Brain volume (global or regional)	Every 6–12 months	Neurodegeneration	40–70	40–70
		Secondary or exploratory:				
		Global or regional MTR or DTI	Every 6–12 months	Disease progression	NA	NA
Phase III for clinically isolated syndrome	24 months or longer	Primary:				
		Active lesions (CUA)	Every 3 months	Disease activity	80–120	150–180
		T2-lesion volume	Every 6–12 months	Disease activity or progression	160–200	200–240
		T1-lesion volume	Every 6–12 months	Neurodegeneration	240–300	300–360
		Brain volume (global or regional)	Two time points	Disease progression	70–170	70–170
		Secondary or exploratory:				
		Global/regional MTR or DTI	Every 6–12 months	Disease progression	NA	NA

*Estimates based on showing 50% treatment effect with 90% power, using primary MRI descriptors from published trials in relapsing–remitting multiple sclerosis[5,65,69] and clinically isolated syndrome.[72] Abbreviations: CUA, combined unique activity; DTI, diffusion tensor imaging; MTR, magnetization transfer ratio; NA, not applicable.

Barkhof F et al., Nat Rev Neurol 2011;8:13-21

Table 1 | Recommended MRI scan protocol

Parameter	Two-dimensional (axial)	Three-dimensional (sagittal)
Resolution	3 mm slices ($n \geq 46$); contiguous or interleaved; 1 mm in-plane resolution	1 mm partitions ($n \geq 160$); long echo trains; 1 mm in-plane resolution
Planning	Internal landmarks (for example, subcallosal line)	Automated (for example, AC–PC line)
Procedure time	~30 min	~35 min
Order of sequences		
Pre-contrast	Insert long IV line; perform 'scout' images; T1 SE	Insert long IV line; perform 'scout' images; T1 GE
Inject gadolinium	0.1 mmol/kg	0.1 mmol/kg
Post-contrast	T2 and PD or FLAIR; T1 SE	T2 and FLAIR; T1 GE

Abbreviations: AC, anterior commissure; FLAIR, fluid-attenuated inversion recovery; GE, gradient-echo; IV, intravenous; PC, posterior commissure; PD, proton density; SE, spin-echo.

Barkhof F et al., Nat Rev Neurol 2011;8:13-21

Table 3 | Shared responsibility of safety monitoring

Safety aspect	Local investigators	Steering committee and sponsor	MRI analysis center	DSMB
Primary safety	Exclude patients with contraindications Minimize risk of nephrogenic systemic fibrosis	Stipulate contraindications in protocol	Instruction at investigator meeting	Ensure only eligible patients are enrolled Examine opportunistic disease events
Opportunistic disease	Screening by local radiologist for unexpected findings	Institute and review regulations	Provide training and/or formal analysis	Review procedures and adverse events
Disease acceleration	None (avoid unblinding)	Define criteria for reconsent	Group level: timely data transfers for DSMB review Individual level: provide DSMB alerts	Group level: identify trends that may lead to early termination Individual level: flag cases for reconsent

Abbreviation: DSMB, data safety monitoring board.

Barkhof F et al., Nat Rev Neurol 2011;8:13-21

J Neurol
DOI 10.1007/s00415-012-6762-5

REVIEW

Recommendations to improve imaging and analysis of brain lesion load and atrophy in longitudinal studies of multiple sclerosis

H. Vrenken · M. Jenkinson · M. A. Horsfield · M. Battaglini · R. A. van Schijndel · E. Rostrup · J. J. G. Geurts · E. Fisher · A. Zijdenbos · J. Ashburner · D. H. Miller · M. Filippi · F. Fazekas · M. Rovaris · A. Rovira · F. Barkhof · N. de Stefano · MAGNIMS Study Group

Received: 10 November 2012 / Accepted: 12 November 2012

Abstract Focal lesions and brain atrophy are the most extensively studied aspects of multiple sclerosis (MS), but the image acquisition and analysis techniques used can be further improved, especially those for studying within-patient changes of lesion load and atrophy longitudinally. Improved accuracy and sensitivity will reduce the numbers of patients required to detect a given treatment effect in a trial, and ultimately, will allow reliable characterization of individual patients for personalized treatment. Based on open issues in the field of MS research, and the current state of the art in magnetic resonance image analysis methods for assessing brain lesion load and atrophy, this paper makes recommendations to improve these measures for longitudinal studies of MS. Briefly, they are (1) images should be acquired using 3D pulse sequences, with near-isotropic spatial resolution and multiple image contrasts to allow more comprehensive analyses of lesion load and atrophy, across timepoints. Image artifacts need special attention given their effects on image analysis results. (2) Automated image segmentation methods integrating the assessment of lesion load and atrophy are desirable. (3) A standard dataset with benchmark results should be set up to facilitate development, calibration, and objective evaluation of image analysis methods for MS.

The members of MAGNIMS Study Group Steering Committee are A. Rovira, N. de Stefano, X. Montalban, F. Barkhof, C. Enzinger, M. Filippi, J. Frederiksen, L. Kappos, O. Ciccarelli, J. Palace, H. Vrenken, M.A. Rocca, T. Yousry.

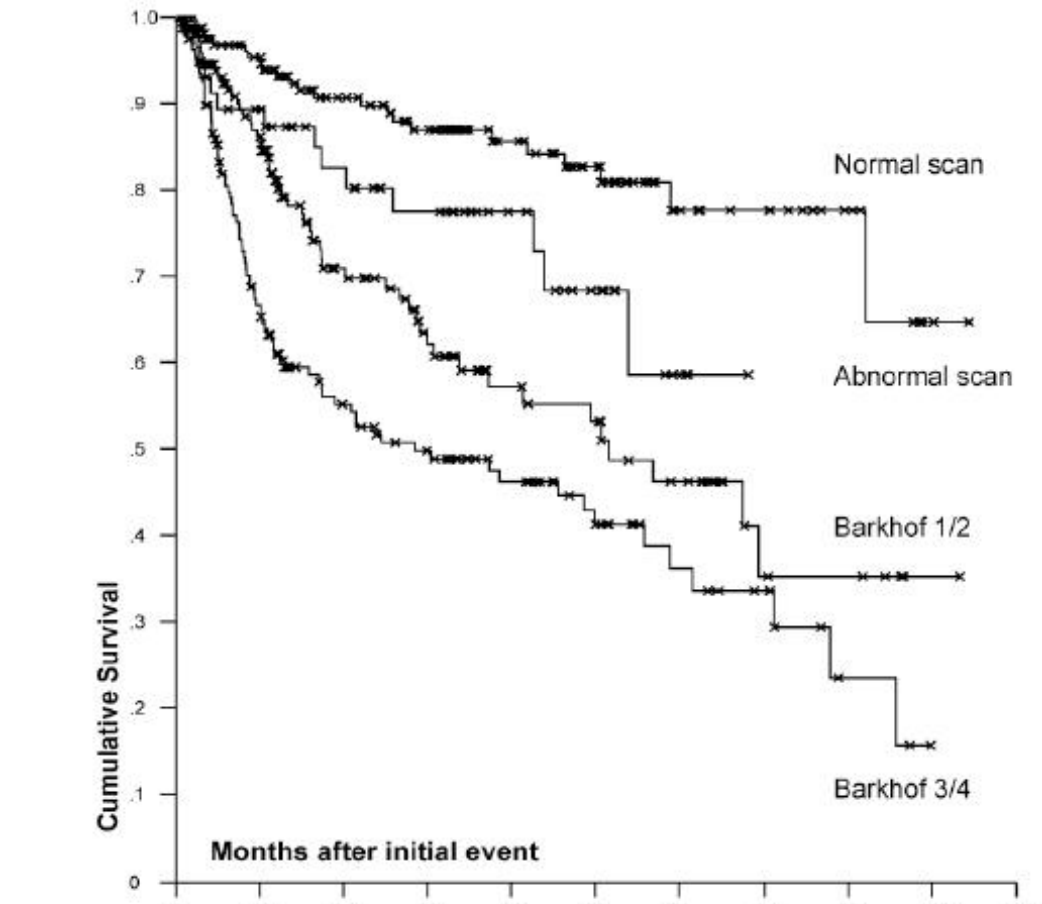
Clinical practice

Medical University of Graz

- MRI measures of disease activity need to be
  - simple / easy accessible
  - sensitive to change
  - need to provide clinically relevant information
- Lesion measures
  - active (Gd enhancing) lesions
  - new (T2) lesions

- Can these measures help to predict the course of MS ?

MAGNIMS – CIS cohort: remaining free of second attack, i.e. from conversion to CDMS



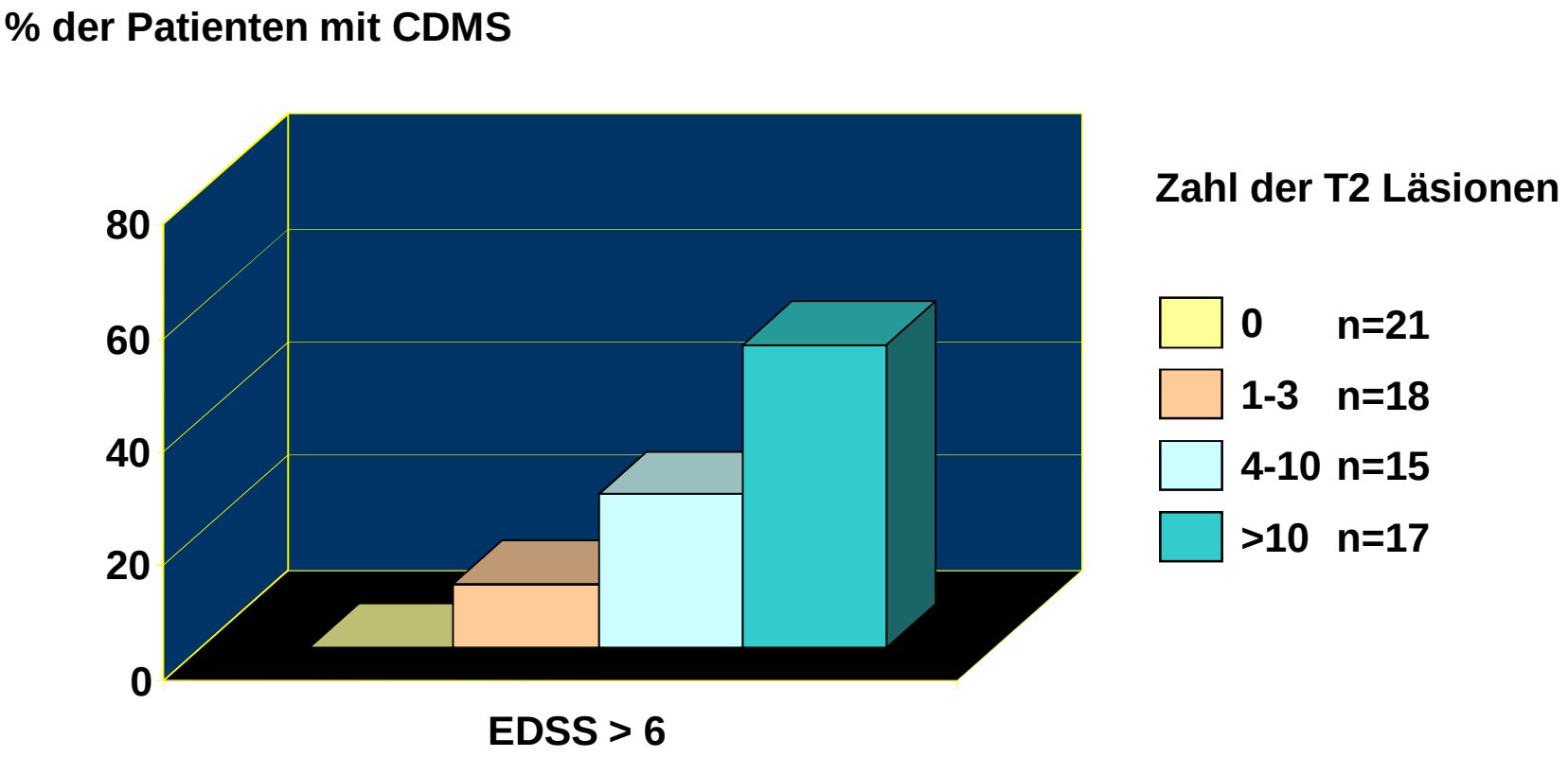
Korteweg T et al., Lancet Neurol 2006

Clinically isolated syndrome and MRI: 10 year follow-up

	Asymptomatic MR lesions				
	0	1	2-3	4-10	>10
Patients (n)	27	3	16	15	20
Development of CDMS	3(11%)	1(33%)	14(87%)	13(87%)	17(85%)
EDSS >3	0	0	5(31%)	4(27%)	14(75%)

O‘ Riordan et al, 1998;121:495-503

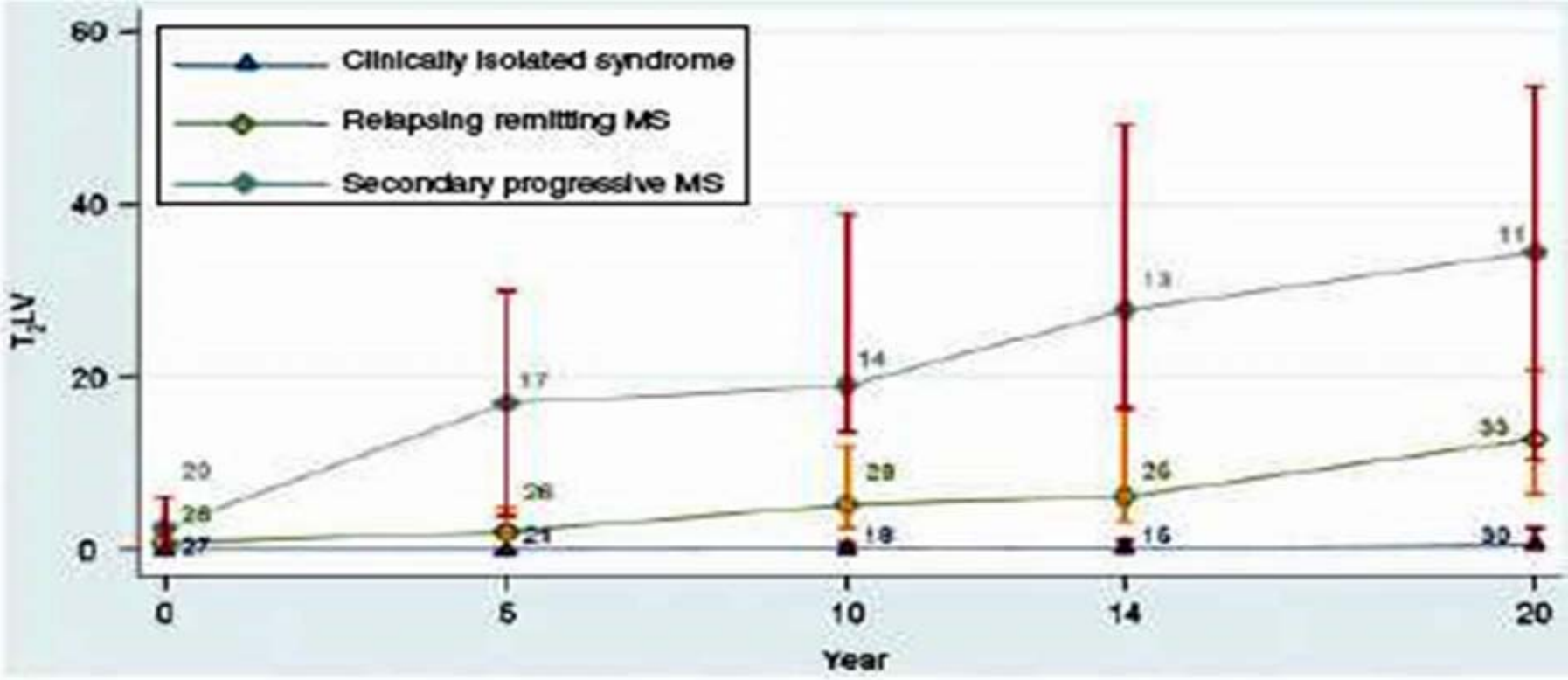
MRT Ausgangsbefund und Behinderung nach 14 Jahren



Brex et al. NEJM 2002

Disability and T_2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis

Fisniku et al., Brain, 2008



Further attacks following a clinically isolated syndrome

Tintoré M et al., Neurology 2006:67:986-972

Table 1 *Patients converting to CDMS or MS according to number of Barkhof criteria or number of lesions in baseline MRI*

	CDMS					MS (McDonald)	
	N1/N2	%	HR	95% CI	Mean survival time (SE)	N1/N2	%
No. Barkhof criteria							
0	5/59	9	1*		103.3 (3.5)	6/59	10.2
1–2	16/34	44	6.1	2.2–16.6	77.7 (6.9)	20/36	55.6
3–4	45/61	61	17.0	6.7–43.5	46.8 (5.3)	53/61	86.9
No. lesions							
0	4/52	7.7	1*		104.8 (3.2)	5/52	9.6
1–3	7/23	30.4	4.3	1.3–14.8	83.6 (9.1)	8/23	34.8
4–9	9/18	50	7.4	2.3–24.5	71.3 (9.6)	14/18	77.8
10 or more	46/63	73	19.3	6.8–54.6	47.7 (5.3)	52/63	82.5

* 1: Reference category.

CDMS = clinically definite multiple sclerosis; N1/N2 = ratio between patients fulfilling CDMS or MS and total number of patients fulfilling the baseline MRI criteria; HR = hazard ratio (adjusted by age, sex, and topography of first attack); 95% CI = confidence interval. Mean survival time to CDMS is expressed in months.

Development of EDSS ?$3 five years after a clinically isolated syndrome

Tintoré M et al., Neurology 2006:67:986-972

Table 2 *Patients reaching EDSS 3.0 according to baseline MRI or clinical status*

	EDSS ≥ 3.0				
	N1/N2	%	HR	95% CI	Mean survival time (SE)
No. Barkhof criteria					
0	3/59	5.1	1*		114.2 (3.0)
1–2	5/36	13.4	1.9	0.4–8.1	100.5 (3.5)
3–4	15/61	24.6	3.9	1.1–13.6	98.2 (3.9)
No. lesions					
0	3/52	5.8	1*		105.9 (3.1)
1–3	2/23	8.7	1.3	0.2–8.0	113.8 (3.9)
4–9	2/18	11.1	1.4	0.2–8.7	98.6 (4.3)
10 or more	16/63	25.4	3.6	1.0–12.7	97.8 (3.9)
Clinical status					
CIS	5/90	5.6	1*		106.7 (2.1)
CDMS	18/66	27.3	4.3	1.6–11.7	100.1 (3.9)

* 1: Reference category.

EDSS = Expanded Disability Status Scale; N1/N2 = ratio between patients reaching an EDSS of 3.0 and total number of patients in each category according to baseline MRI or clinical status; HR = hazard ratio (adjusted by age, sex, topography of first attack, and disease-modifying drugs); 95% CI = confidence interval. Mean survival time to CDMS is expressed in months; CIS = clinically isolated syndromes;
CDMS = clinically definite multiple sclerosis.

Identification of patients at high risk to convert to clinically definite MS

Risk of CDMS	Barkhof[1] Median follow up: 39 months		Brex[2] risk at 1 year		CHAMPS[3] risk at 2 years	
All Patients	0.45	n = 74	0.26	n = 68	0.39	n = 190
≥ 9 T2 hyperintense lesions	0.80	n = 30	0.44	n = 25	0.56[4]	n = 40
≥ 1 Gd-enhancing lesions	0.71	n = 28	0.52	n = 21		

1 Barkhof et al., Brain 1997; 120:2059-2069. 2 Brex et al., J Neurol Neurosurg Psychiatry 2001; 70:390-393. 3 Jacobs et al., N Engl J Med 2000; 343:898-904. 4 Data on file – Subgroup of patients with at least on Gd+ lesion AND 9 T2 lesions.

Predicting the severity of relapsing-remitting MS: The contribution of cross-sectional and short-term follow-up MRI data

Multiple Sclerosis Journal
17(6) 695–701

DOI: 10.1177/1352458510394454
msj.sagepub.com
SAGE

C Enzinger[1,2], S Fuchs[1], A Pichler[1], M Wallner-Blazek[1], M Khalil[1], C Langkammer[1], S Ropele[1] and F Fazekas[1]

- 84 patients with comprehensive clinical and MRI data from cross-sectional and 2 year follow-up examinations were reassessed after a mean of 10.8 +/-2.7 years to investigate prediction of the MSSS or conversion to SPMS.
- In univariate analysis the „black hole ratio“ at baseline (p=0.017, beta=0.148) and at first follow-up (p=0.007, beta=0.154) was the only MRI parameter showing a significant correlation with the MSSS.
- In a multiple regression model, the independent predictive value of imaging variables became statistically non-significant. The latest MSSS was predicted primarily by the baseline EDSS (r2=0.28; p<0.001).
- The „black hole ratio“ at baseline explained 9.5 % of variance of conversion to SPMS (P=0.033)

Predicting short-term disease activity in MS

Multivariates Modell zur Vorhersage weiterer Schübe
Arbeitsdaten: n = 539 Patientinnen
Validierungsdaten: n = 117 PatientInnen

Table 2 Predictive value of clinical and MRI variables for the occurrence of multiple sclerosis relapses in the working sample of patients

Variables	Unit	HR	95% CI	p
Age at onset*	1 y	0.98	0.97-1.002	0.075
Disease duration	1 y	0.99	0.97-1.01	0.29
Prior 2-year relapses*	1	1.22	1.11-1.33	<0.001
EDSS*	1 point	1.13	1.02-1.26	0.024
Gd-enhancing lesions*	1	1.03	1.02-1.05	<0.001
Gd-enhancing lesion volume*	1 mL	1.20	1.09-1.31	<0.001
T2-hyperintense lesion volume*	1 mL	1.009	1.001-1.018	0.03
T1-hypointense lesion volume	1 mL	1.013	0.98-1.05	0.48

/ariables entering the multivariable analysis.
IR = hazard ratio; EDSS = Expanded Disability Status Scale; Gd = gadolinium.

Sormani MP et al., Neurology 2007;69:1230-1235

Predicting short-term disease activity in MS

Multivariates Modell zur Vorhersage weiterer Schübe
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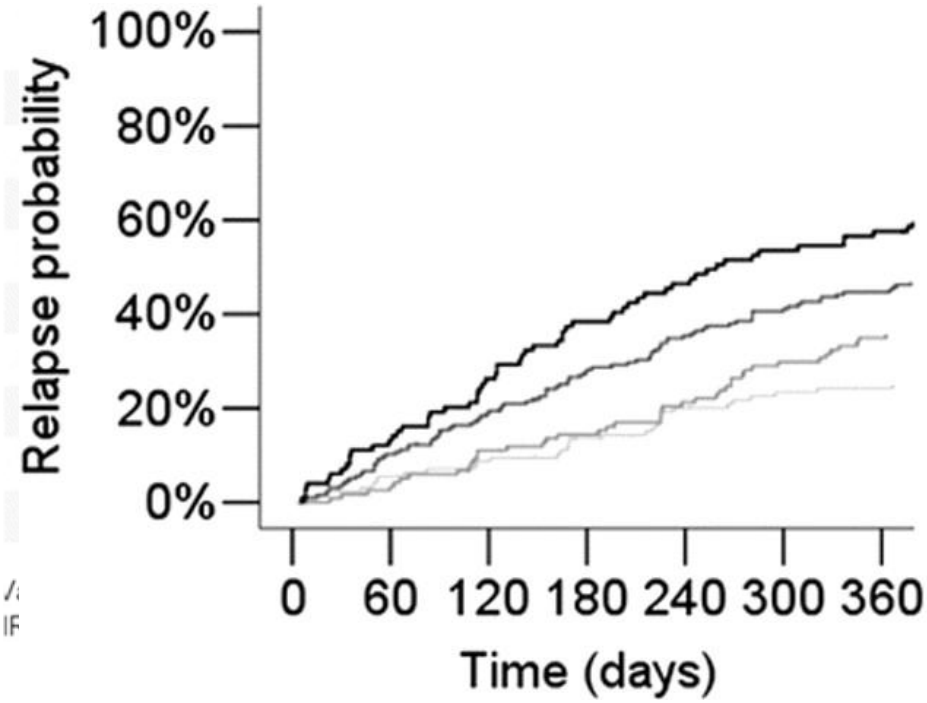
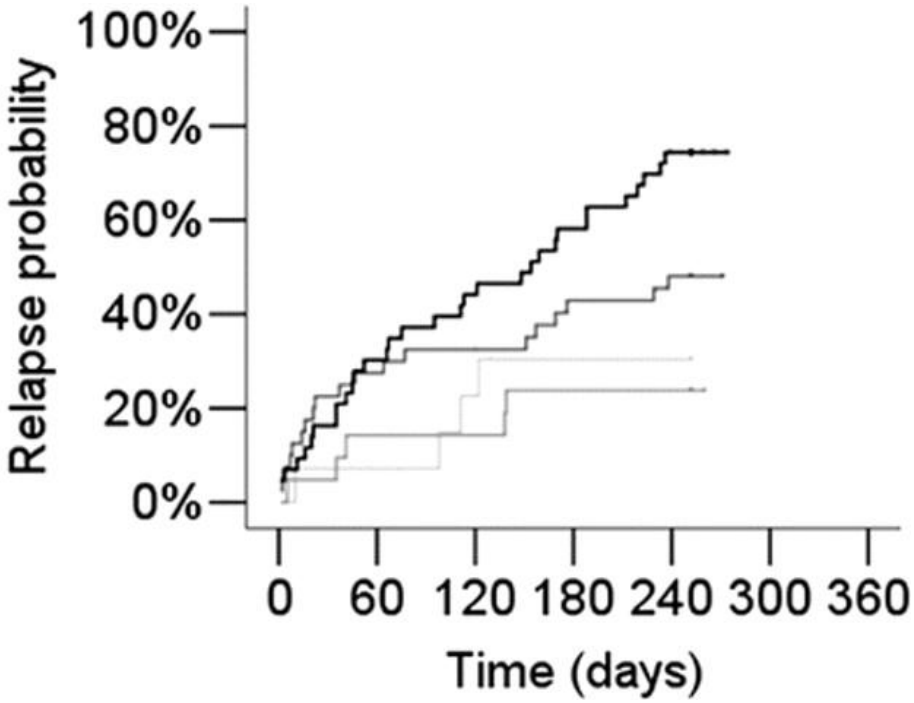




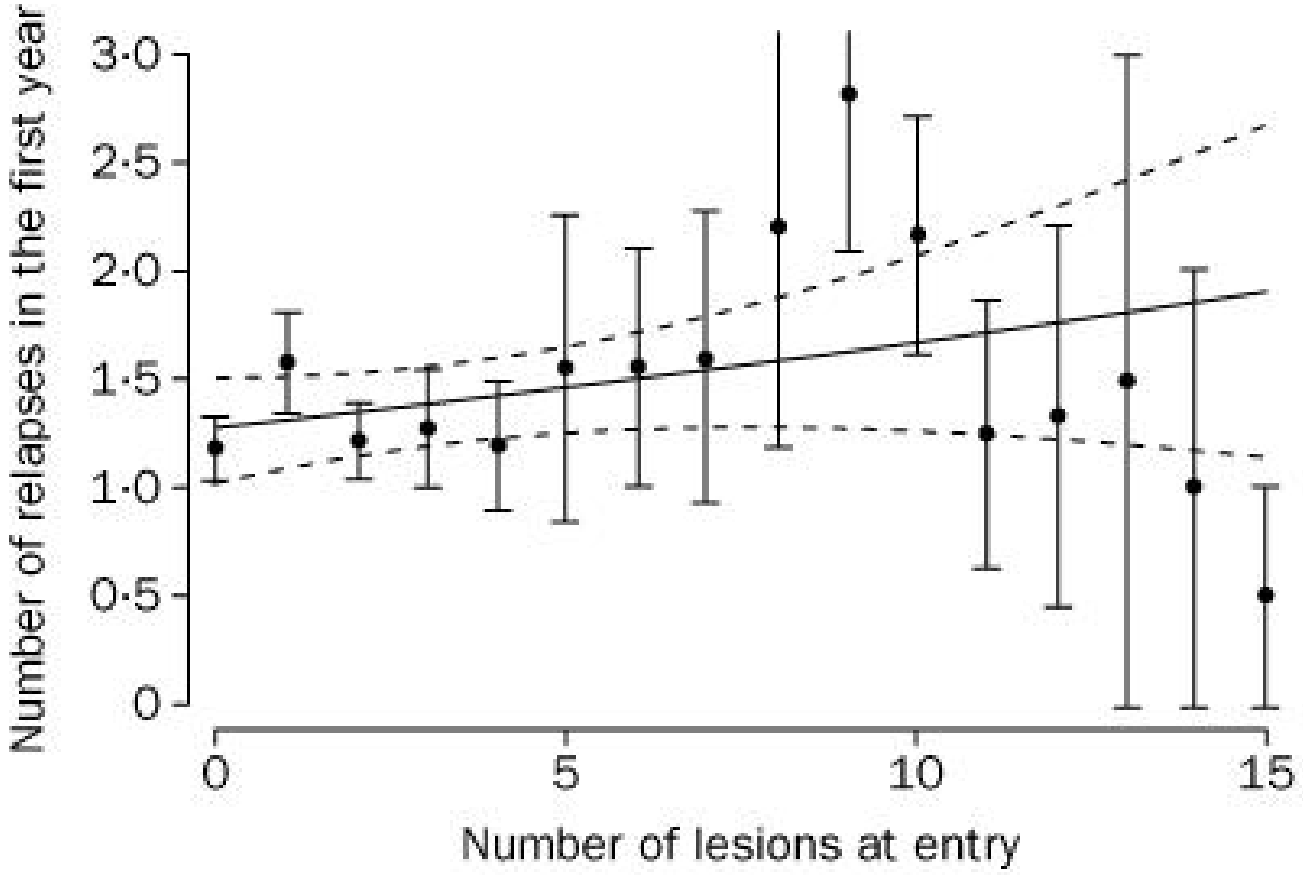
Sormani MP et al., Neurology 2007;69:1230-1235

Gd- Aufnahme als Prädiktor eines nächsten Schubes

Gadolinium-enhancing-lesion count	n	RR per 5 lesions	p
First year			
At entry	215	1.09	0.100
Mean of entry at 6 months	215	1.06	0.257
Mean of all monthly scans months 0-6	170	1.13	0.023
SD of all monthly scans months 0-6	170	1.27	0.020
Second year			
At entry	137	1.00	0.980
Mean of entry at 6 months	137	1.08	0.301
Mean of all monthly scans months 0-6	91	1.15	0.128
SD of all monthly scans months 0-6	91	1.59	0.010

Kappos L. et al., Lancet 1999;353:964-969

Vorhersagewert kumulativer KM-Läsionen



Kappos L. et al., Lancet 1999;353:964-969

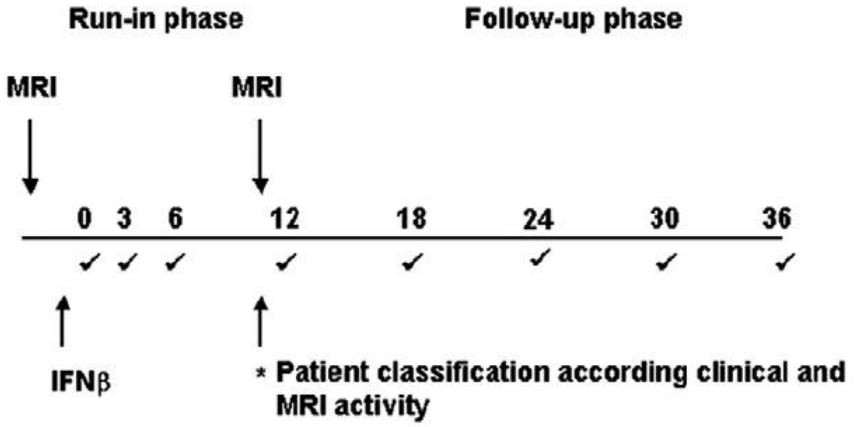
- Can MRI measures serve to define treatment failure ?

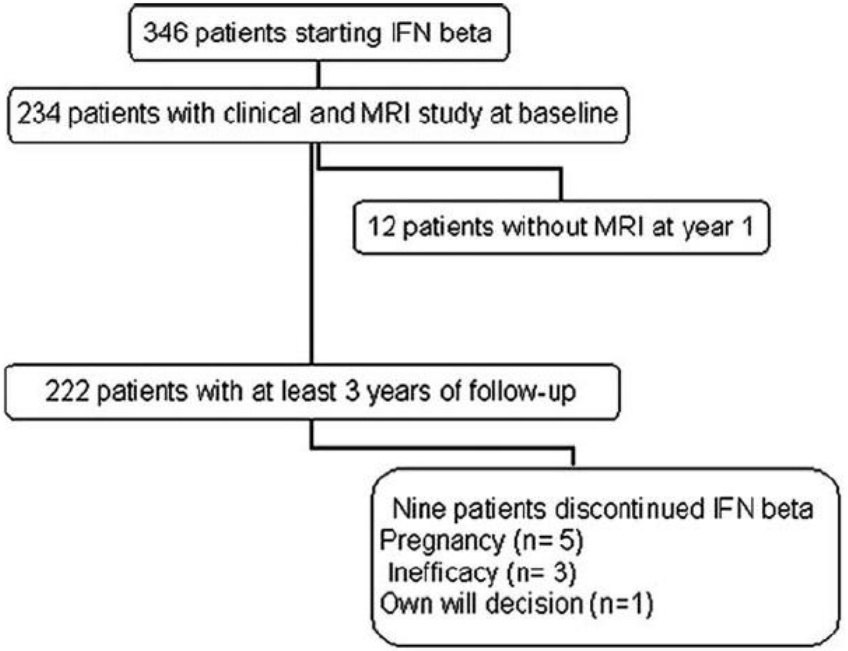
RESEARCH PAPER

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]





Outcome variables

Definition of inadequate treatment response during 24 months of follow-up

- Presence of relapses
- Disease progression ; increase in EDSS ?Q 1 point sustained for ?Ž6 months

Predictor variables

R+ = ? 1 relapse within first year

P+ = increase of ?ë1 EDSS point within first year

MRI+ = > 2 active lesions (new or enlarging T2 or Gd+ lesions)

Table 2 Risk of activity during the period of follow-up (months 12–36) according the positivity for the different variables after 12 months of therapy

	Odds ratio (CI)	Significance
One positive variable	1.4 (0.7–2.6)	0.3
Two positive variables	5.9 (2.5–15.6)	<0.0001
Three positive variables	13.2 (2.9–125.7)	0.0003

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

MULTIPLE SCLEROSIS JOURNAL | MSJ

Scoring treatment response in patients with relapsing multiple sclerosis

Multiple Sclerosis Journal
19(5) 605–612

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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*]

Abstract

Background: We employed clinical and magnetic resonance imaging (MRI) measures in combination, to assess patient responses to interferon in multiple sclerosis.

Objective: To optimize and validate a scoring system able to discriminate responses to interferon treatment in patients with relapsing–remitting multiple sclerosis (RRMS).

Methods: Our analysis included two large, independent datasets of RRMS patients who were treated with interferons that included 4-year follow-up data. The first dataset ("training set") comprised of 373 RRMS patients from a randomized clinical trial of subcutaneous interferon beta-1a. The second ("validation set") included an observational cohort of 222 RRMS patients treated with different interferons. The new scoring system, a modified version of that previously proposed by Rio et al., was first tested on the training set, then validated using the validation set. The association between disability progression and risk group, as defined by the score, was evaluated by Kaplan Meier survival curves and Cox regression, and quantified by hazard ratios (HRs).

Results: The score (0–3) was based on the number of new T2 lesions (>5) and clinical relapses (0,1 or 2) during the first year of therapy. The risk of disability progression increased with higher scores. In the validation set, patients with score of 0 showed a 3-year progression probability of 24%, while those with a score of 1 increased to 33% (HR = 1.56; $p = 0.13$), and those with score greater than or equal to 2 increased to 65% (HR = 4.60; $p < 0.001$).

Conclusions: We report development of a simple, quantitative and complementary tool for predicting responses in interferon-treated patients that could help clinicians make treatment decisions.

Table 2. Distribution of patients according the modified Rio score criteria.

Modified Rio score on the training set (PRISMS database)		Modified Rio score on the validation set (Barcelona database)	
Score components	*n* (%)	Score components	*n* (%)
MRI criterion		MRI criterion	
≤ 5 new T2 lesions	335 (91.8)	≤ 4 new T2 lesions	183 (82.4)
> 5 new T2 lesions	30 (8.2)	> 4 new T2 lesions	39 (17.6)
Relapse criterion		Relapse criterion	
= 0 relapses	152 (41.6)	= 0 relapses	179 (76.8)
= 1 relapse	115 (31.5)	= 1 relapse	42 (18.0)
≥ 2 relapses	98 (26.8)	≥ 2 relapses	12 (5.1)
Modified Rio score		**Modified Rio score**	
0	148 (40.5)	0	147 (66.2)
1	112 (30.7)	1	52 (23.4)
2	86 (23.6)	2	19 (8.6)
3	19 (5.1)	3	4 (1.8)

MRI: magnetic resonance imaging.

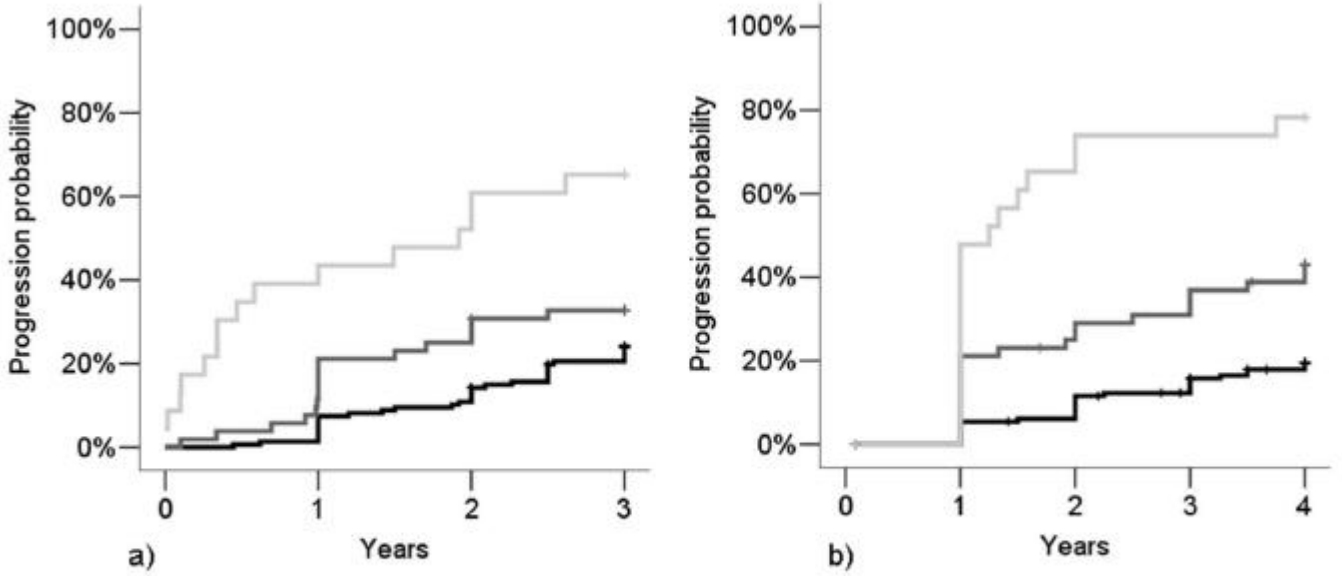


Figure 3. Probability of disability progression from the first year since interferon treatment started (3 years, (a)) and over the follow-up period (4 years, (b)), according to application of the modified Rio score on the "validation set" (Barcelona study data).

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**

ABSTRACT: The Canadian Multiple Sclerosis Working Group (CMSWG) developed practical recommendations in 2004 to assist clinicians in optimizing the use of disease-modifying therapies (DMT) in patients with relapsing multiple sclerosis. The CMSWG convened to review how disease activity is assessed, propose a more current approach for assessing suboptimal response, and to suggest a scheme for switching or escalating treatment. Practical criteria for relapses, Expanded Disability Status Scale (EDSS) progression and MRI were developed to classify the clinical level of concern as Low, Medium and High. The group concluded that a change in treatment may be considered in any RRMS patient if there is a high level of concern in any one domain (relapses, progression or MRI), a medium level of concern in any two domains, or a low level of concern in all three domains. These recommendations for assessing treatment response should assist clinicians in making more rational choices in their management of relapsing MS patients.

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].

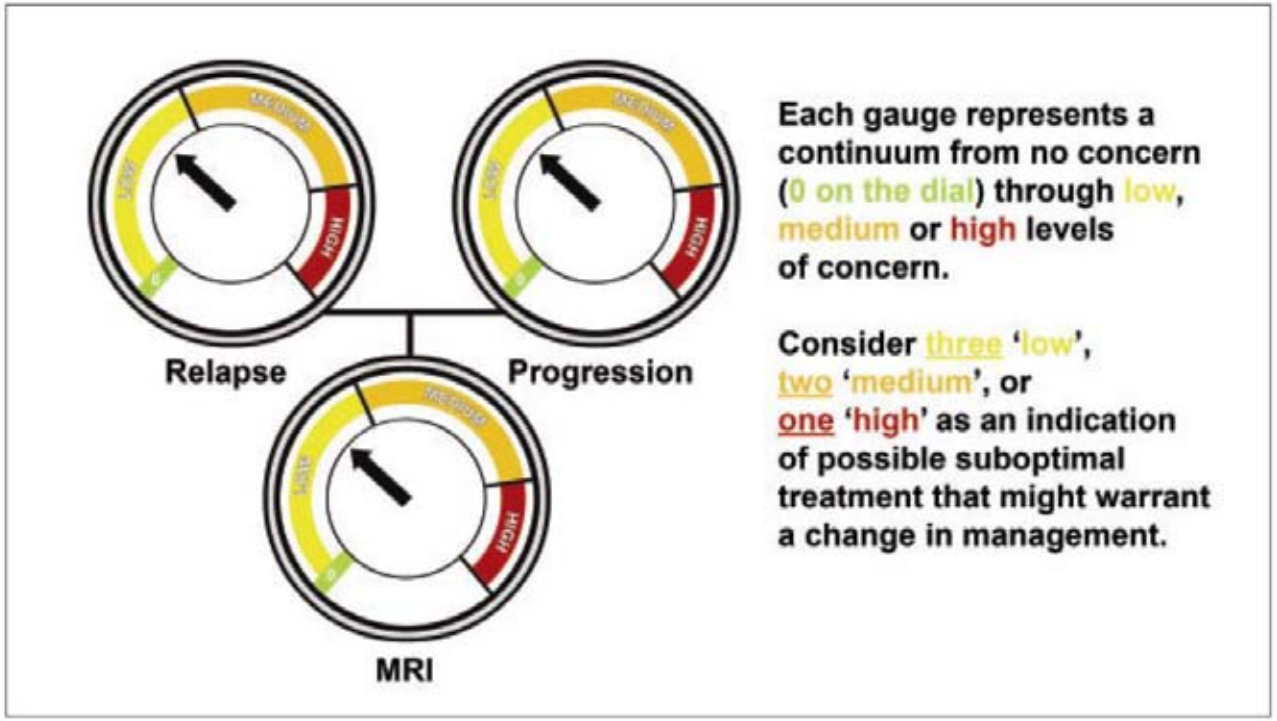
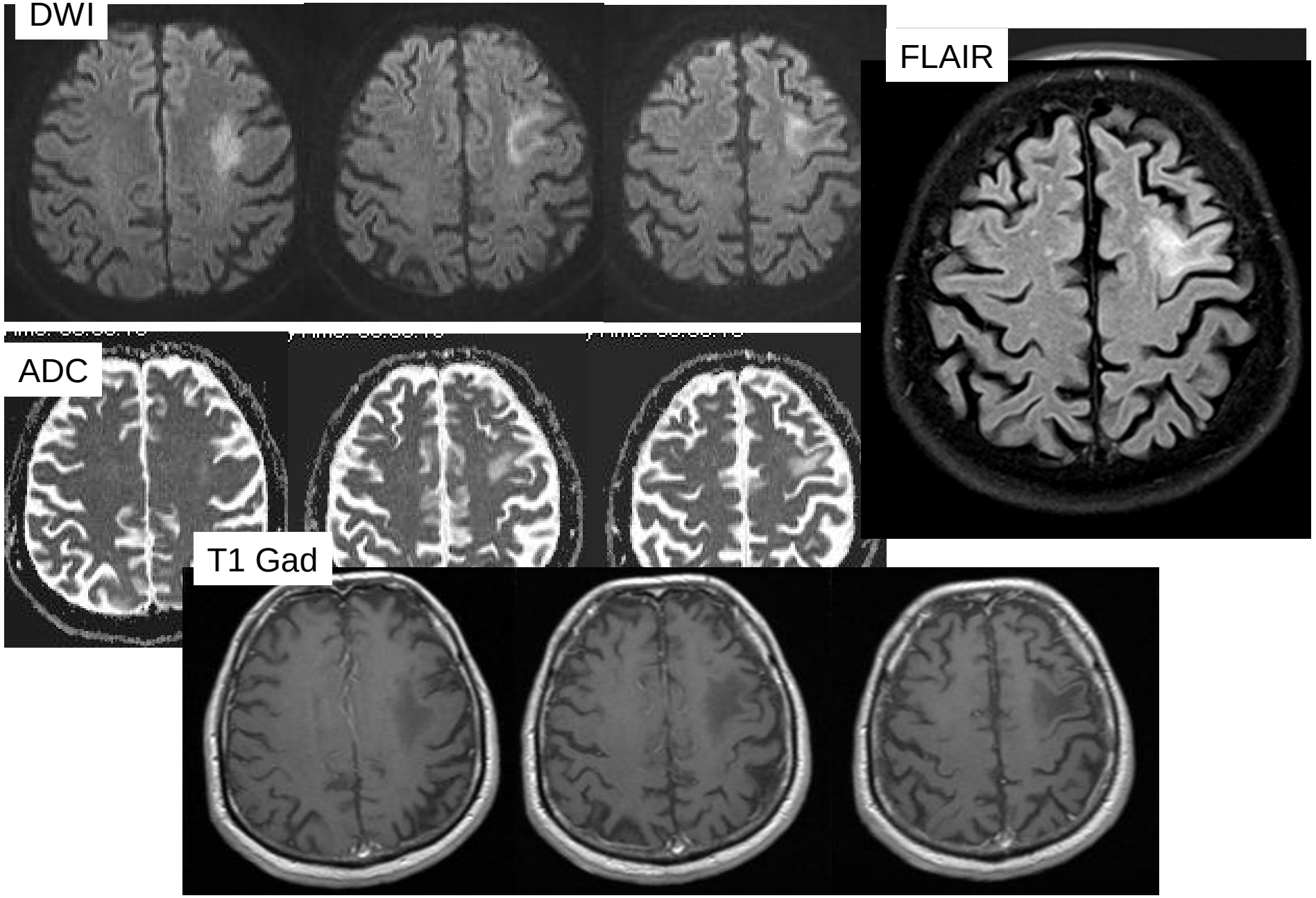


Figure 1: The Canadian treatment optimization model: assessing concern whether to modify a treatment regimen.

MRI to detect unwanted side effects of treatment



Conclusions

Medical University of Graz

- MRI has become an indespensible tool for the assessment of MS disease activity.
- In clinical trials changes in various morphologic markers have proven indicative of treatment effects and able to predict clinical response – at least on a group level.
- In clinical practice the number of reliable markers for disaease acitivity and their significance is more limited.
- Predictive information on the subsequent course of MS is conveyed early on but not at later stages of the disease.
- Decisions on treatment efficacy / for change of treatment need to rest strongly also on the clinical evaluation (e.g. further relapses, progression of disability) – but continuation of MRI activity can be a valuable supportive aspect.

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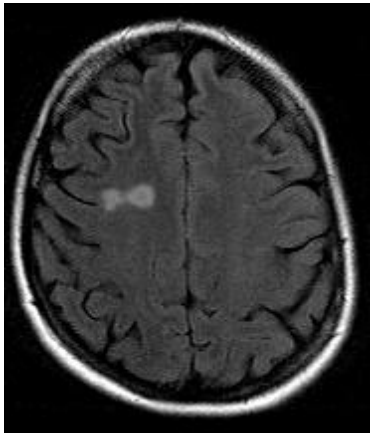
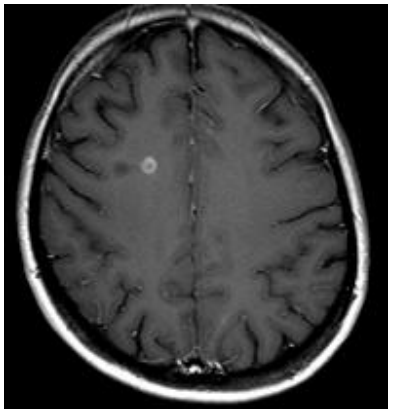


Inflammation / Active lesion



- Gadolinium enhancement indicates break down of blood brain barrier
- Active lesions enhance for 2 – 6 weeks
- Modification of enhancement by
  - dosage of and delay after contrast material application
  - Imaging parameters
  - Steroid treatment
- Outcome variables
  - Active scan
  - Number of contrast-enhancing lesions / scan or cumulative lesion number

Measures of disease activity and tissue damage

Table 1. MRI Variables with Proven Utility for Monitoring Treatment Effects in MS

MRI Variable	Pathophysiologic Information Provided
Gadolinium-enhancing lesions	Acute area of focal inflammation
New T2 lesions	New area of tissue damage
Enlarging T2 lesions	Enlarging area of tissue damage
T1 lesions (*black holes*)	Lesion with marked tissue damage
T2 lesion load	Total area of clearly abnormal brain tissue
T1 lesion load	Total area of marked tissue destruction
Brain atrophy/volume measures	Changes in brain volume due to several factors

Fazekas F. et al., J Neuroimag 2007;17:50S -55S

Brain volume changes in MS

Table 1 Mechanisms that may decrease brain volume in multiple sclerosis

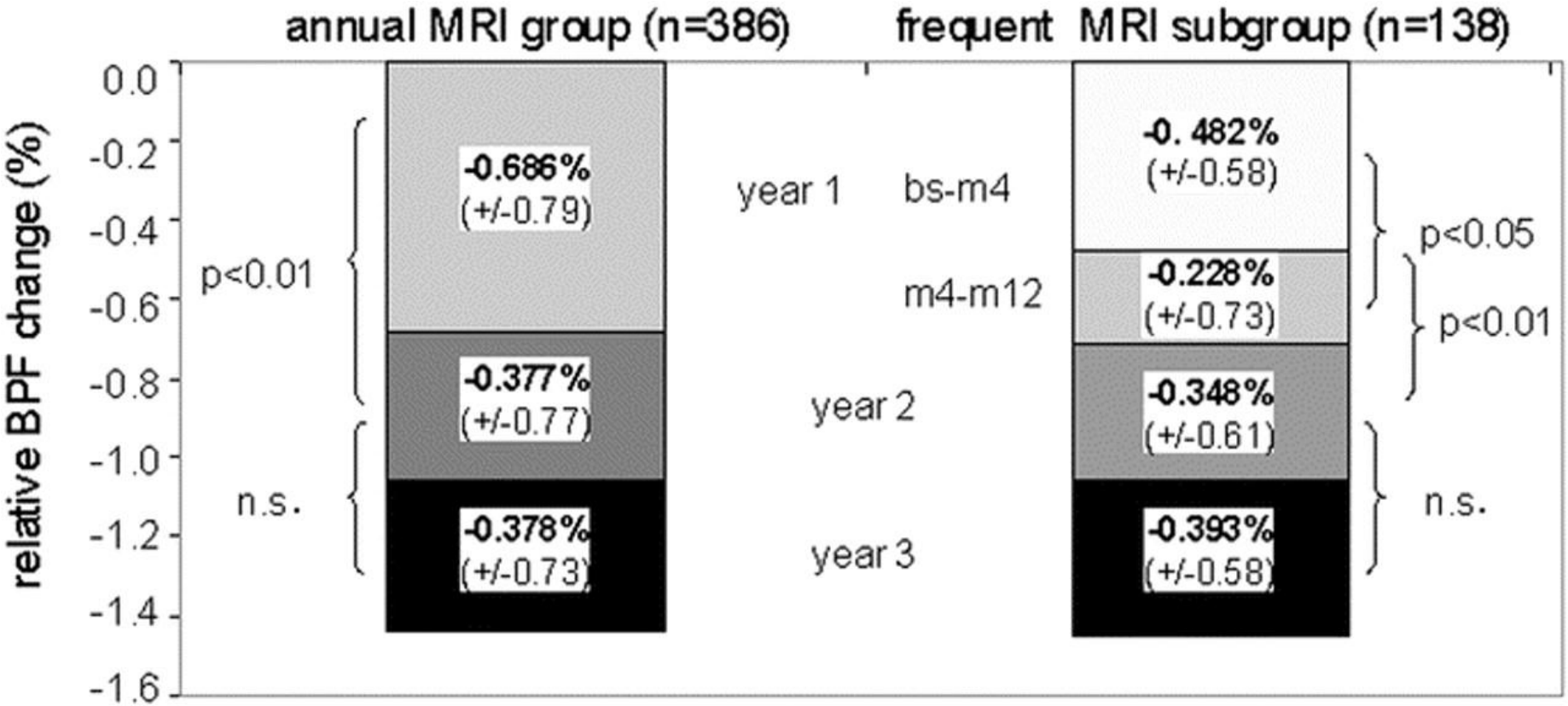
	Beneficial	Non-tissue-related (fluid shifts)	Fluctuating	Irreversible
Natural history			Demyelination (reduced via remyelination); loss of glial cells (reduced via recruitment and differentiation)	Axonal loss; Wallerian degeneration
DMA-related			Inhibition of "good" inflammation	Chemotoxicity; protein catabolism
DMA-induced pseudoatrophy	Resolution of inflammation and edema	Change in electrolyte balance and vascular permeability; dehydration		

DMA = disease-modifying agent.

Zivadinov R. et al., Neurology 2008;71:136-144

Inverse dynamics of same mechanism(s) may increase brain volume !

Rate of brain atrophy during treatment with INFß-1a



Hardmeier M. et al., Neurology 2005;64:236-240

Table 2 Effect of disease-modifying agents on brain volume (BV) changes in multiple sclerosis (MS) in placebo-controlled and open-label controlled studies

Treatment	Trial design	Duration, mo (no. of patients)	Disease type	Treatment effect on BV
IM IFN-β-1a (30 μg weekly)[14]	PLC	24 (140)	RRMS	S (12-24 mo)
IM IFN-β-1a (30 μg vs 60 μg weekly)[20]	DB, PG	36 (386)	RRMS	S (12-24 mo), S (24-36 mo)
IM IFN-β-1a (30 μg weekly vs no treatment)[25]	OLC	36 (54)	RRMS	S (0-36 mo)
SC IFN-β-1a (66 μg or 132 μg weekly)[18]	PLC	24 (519)	RRMS	NS
SC IFN-β-1a (66 μg or 132 μg weekly)[24]	PLC, OLC (baseline vs FU)	84-96 (382)	RRMS	NS
GA (20 mg daily)[31]	PLC in the 0-9 mo; OLC in the 9-18 mo	18 (239)	RRMS	NS
GA (20 mg daily)[13]	PLC in the 0-9 mo; OLC in the 9-18 mo	18 (194)	RRMS	S (9-18 mo), S (0-18 mo)
GA (20 mg daily)[33]	PLC	24 (27)	RRMS	S (0-24 mo)
GA (20 mg daily)[33]	OLC (baseline vs FU)	80.4 (135)	RRMS	S (0-80.4 mo)
IVMP (1 g daily for 5 d)[17]	OLC	60 (81)	RRMS	S (0-60 mo)
Natalizumab[15]	PLC	24 (942)	RRMS	S (12-24 mo)
IVIg[40]	PLC	12 (127)	RRMS	S (0-12 mo)
SC IFN-β-1a (22 μg weekly)[26]	PLC	24 (163)	CIS	S (0-24 mo)
IVIg[41]	PLC	24 (318)	SPMS	S (0-24 mo)
SC IFN-β-1b (875 μg weekly)[19]	PLC	36 (95)	SPMS	NS
Cladribine (0.7 or 2.1 mg/kg)[42]	PLC	12 (159)	SPMS, PPMS	NS
IM IFN-β-1a (60 μg weekly)[27]	PLC	24 (50)	PPMS	NS

Changes in BV are not comparable across trials due to differences in MRI analysis techniques, disease type, trial designs, and patient populations. Open-label, uncontrolled studies, using brain volume measures to determine efficacy of disease-modifying agents, were not included in this table. Current evidence suggests that mobilization with high doses of cyclophosphamide during autologous hematopoietic stem cell transplantation increases the rate of BV loss compared with the rate prior to treatment.[35-37] Alemtuzumab did not show a significant effect on brain volume decline in patients with secondary progressive MS over 18 months.[43]

IM = intramuscular; IFN-β = interferon beta; PLC = placebo-controlled; RR = relapsing remitting; S = significant; DB = double-blind; PG = parallel group; OLC = open label controlled; NS = not significant; GA = glatiramer acetate; IVMP = IV methylprednisolone; IVIg = intravenous immunoglobulin; CIS = clinically isolated syndrome; SP = secondary progressive; PP = primary progressive; SC = subcutaneous.

Zivadinov R. et al., Neurology 2008;71:136-144

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

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See Reflection and Reaction page 647

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Course of brain volume change following treatment with lamotrigine

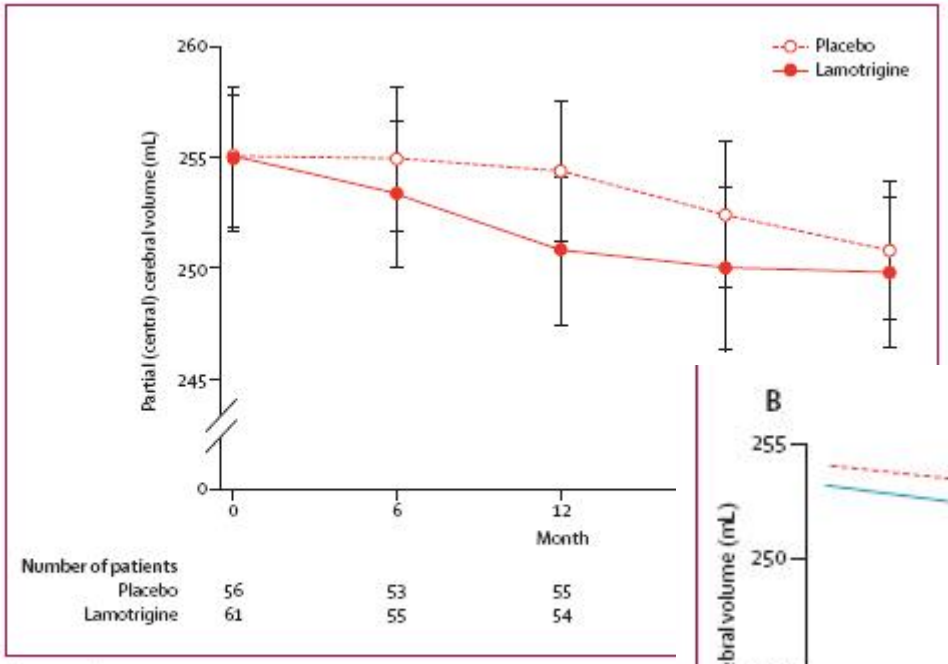

Figure 2: Primary outcome
Mean partial (central) cerebral volume by intention-to-treat comparison, including observations. Bars=SE.

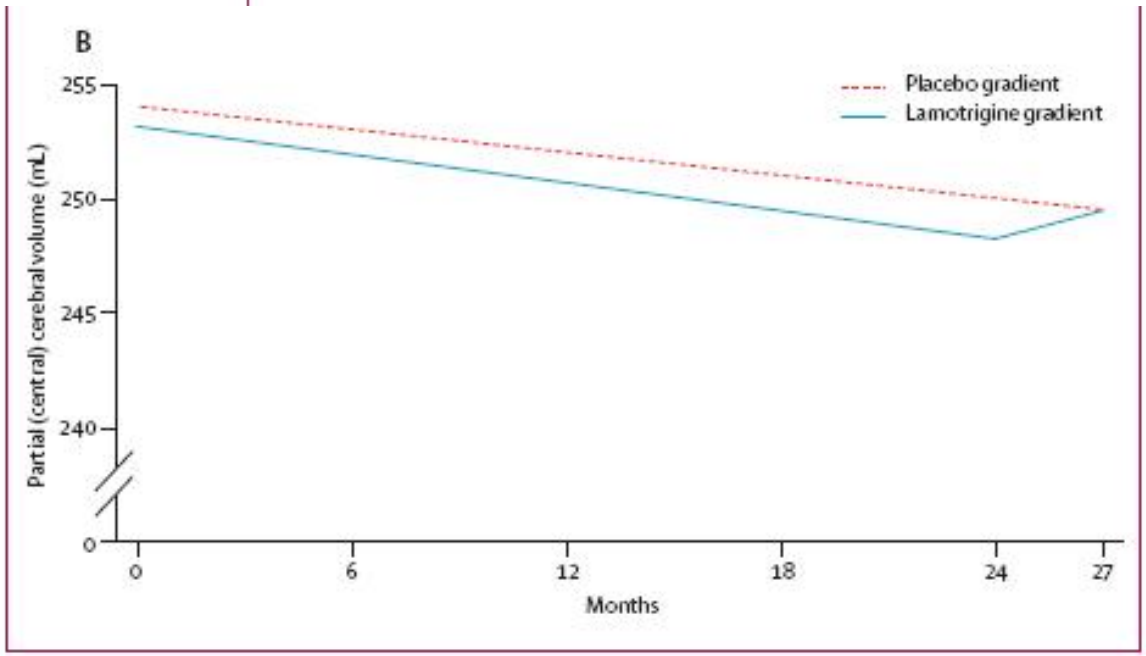

Figure 3: Exploratory analyses of change of partial (central) cerebral volume using longitudinal models (A) Analysis of change of linear gradient with pivot set at 12 months and of curvature. (B) Analysis of change of linear gradient with pivot set at 24 months.

What is on the horizon ?

- MS: new measures to monitor the disease
  (M. Filippi and M.A.Rocca, The Lancet Neurology, 2013;12:12 – 13)
  - Cortical lesions
  - Cortical thickness
  - Tract specific analyses
  - Remyelination
- Spinal cord

Canadian treatment optimization recommendations

Table 1 Recommendations for determining level of concern during the first year of treatment, based on number of relapses, confirmed[a] disease progression, and the combined criteria for relapses and disease progression

Level of concern	Relapse	Disease progression		Combined relapse/disability criteria
		Baseline EDSS score ≤3.5	Baseline EDSS score ≥4.0	
High	1 severe attack >1 moderate attack	>2 points	>1 point	≥1 parameters "high" or 2 parameters "medium"
Medium	1 moderate attack >1 mild attack	2 points	1 point	1 parameter "medium", or 2 parameters "low"
Low	1 mild attack	<2 points	<1 point	1 parameter "low"
None	No attacks	0 points	0 points	2 parameters "none"

Attacks starting within 30 days of each other were classified as the same attack with the maximum severity and the relapse assigned to the earlier period. When the severity was missing, the attack was classed as severe. For combinations of scores listed, the worst case was taken.

EDSS = Expanded Disability Status Scale.

[a]Disease progression confirmed at a 6-month interval.

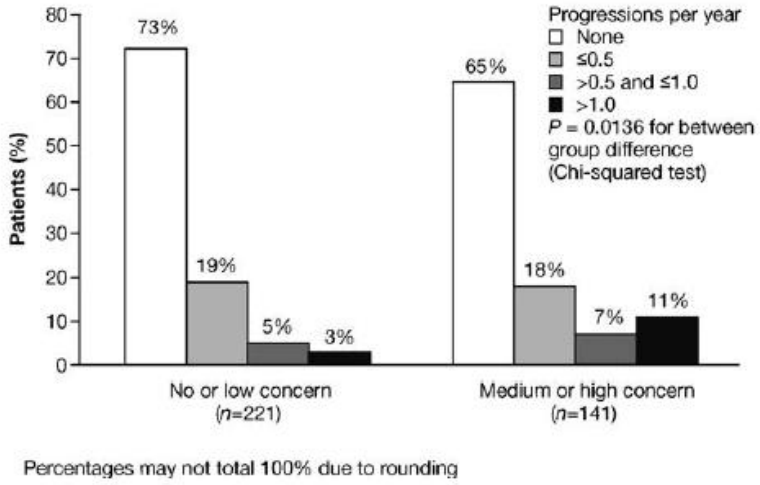

Figure 6 Proportions of patients receiving either dose of interferon (IFN) β-1a who had different levels of disease progression during years 2–4 of the PRISMS study by their assigned level of concern based on year 1.

Freedman MS et al.,
Mult Scler 2008;14:1234-1241)

Canadian treatment optimization recommendations

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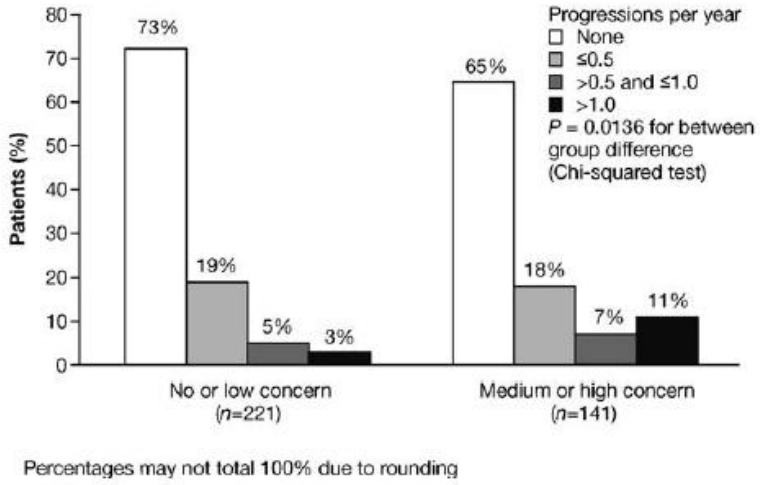

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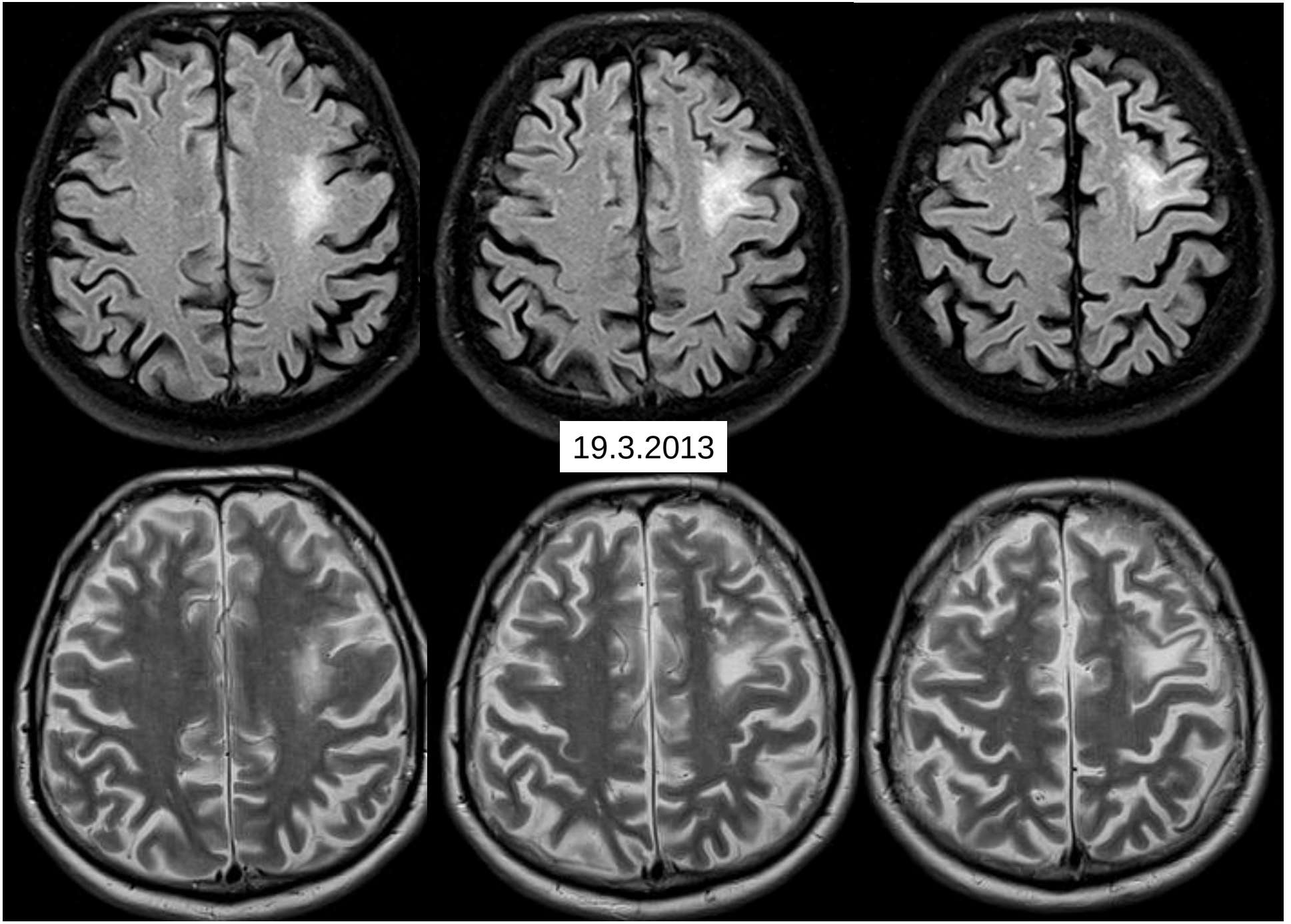
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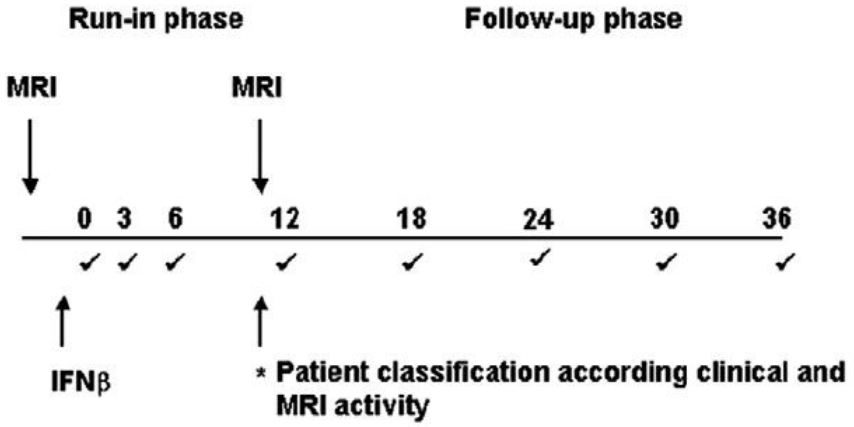
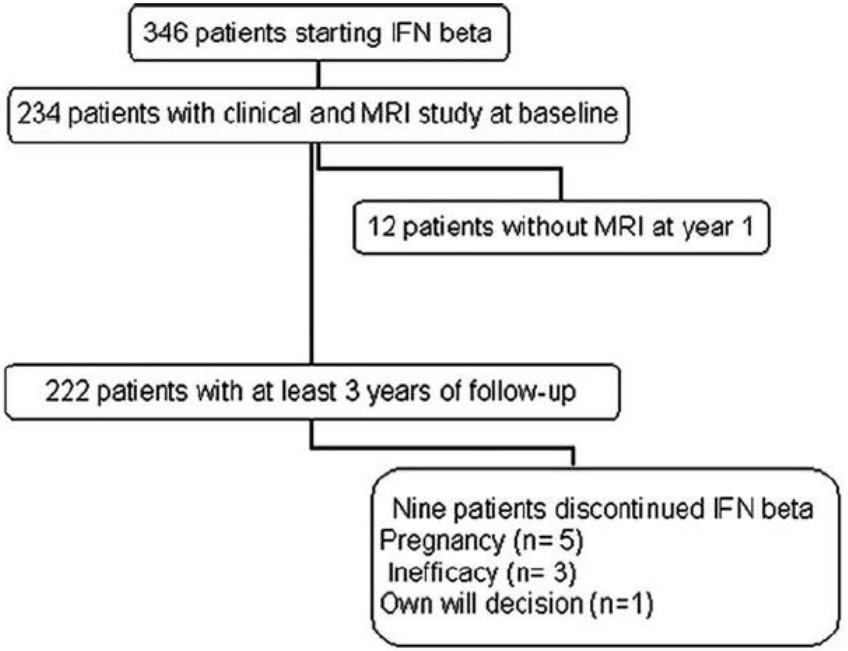
RESEARCH PAPER

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]





Outcome variables

Definition of inadequate treatment response during 24 months of follow-up

- Presence of relapses
- Disease progression ; increase in EDSS ?Q 1 point sustained for ?Ž6 months

Predictor variables

R+ = ? 1 relapse within first year

P+ = increase of ?ë1 EDSS point within first year

MRI+ = > 2 active lesions (new or enlarging T2 or Gd+ lesions)

Table 2 Risk of activity during the period of follow-up (months 12–36) according the positivity for the different variables after 12 months of therapy

	Odds ratio (CI)	Significance
One positive variable	1.4 (0.7–2.6)	0.3
Two positive variables	5.9 (2.5–15.6)	<0.0001
Three positive variables	13.2 (2.9–125.7)	0.0003

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

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Scoring treatment response in patients with relapsing multiple sclerosis

Multiple Sclerosis Journal
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Abstract

Background: We employed clinical and magnetic resonance imaging (MRI) measures in combination, to assess patient responses to interferon in multiple sclerosis.

Objective: To optimize and validate a scoring system able to discriminate responses to interferon treatment in patients with relapsing–remitting multiple sclerosis (RRMS).

Methods: Our analysis included two large, independent datasets of RRMS patients who were treated with interferons that included 4-year follow-up data. The first dataset ("training set") comprised of 373 RRMS patients from a randomized clinical trial of subcutaneous interferon beta-1a. The second ("validation set") included an observational cohort of 222 RRMS patients treated with different interferons. The new scoring system, a modified version of that previously proposed by Rio et al., was first tested on the training set, then validated using the validation set. The association between disability progression and risk group, as defined by the score, was evaluated by Kaplan Meier survival curves and Cox regression, and quantified by hazard ratios (HRs).

Results: The score (0–3) was based on the number of new T2 lesions (>5) and clinical relapses (0,1 or 2) during the first year of therapy. The risk of disability progression increased with higher scores. In the validation set, patients with score of 0 showed a 3-year progression probability of 24%, while those with a score of 1 increased to 33% (HR = 1.56; $p = 0.13$), and those with score greater than or equal to 2 increased to 65% (HR = 4.60; $p < 0.001$).

Conclusions: We report development of a simple, quantitative and complementary tool for predicting responses in interferon-treated patients that could help clinicians make treatment decisions.

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**

ABSTRACT: The Canadian Multiple Sclerosis Working Group (CMSWG) developed practical recommendations in 2004 to assist clinicians in optimizing the use of disease-modifying therapies (DMT) in patients with relapsing multiple sclerosis. The CMSWG convened to review how disease activity is assessed, propose a more current approach for assessing suboptimal response, and to suggest a scheme for switching or escalating treatment. Practical criteria for relapses, Expanded Disability Status Scale (EDSS) progression and MRI were developed to classify the clinical level of concern as Low, Medium and High. The group concluded that a change in treatment may be considered in any RRMS patient if there is a high level of concern in any one domain (relapses, progression or MRI), a medium level of concern in any two domains, or a low level of concern in all three domains. These recommendations for assessing treatment response should assist clinicians in making more rational choices in their management of relapsing MS patients.

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Preventing brain atrophy should be the gold standard of effective therapy in MS (after the first year of treatment): Yes

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