Brain Volume Loss negli studi registrativi delle nuove terapie in Sclerosi Multipla

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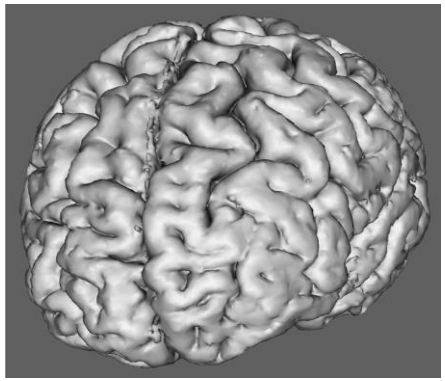
Introduction

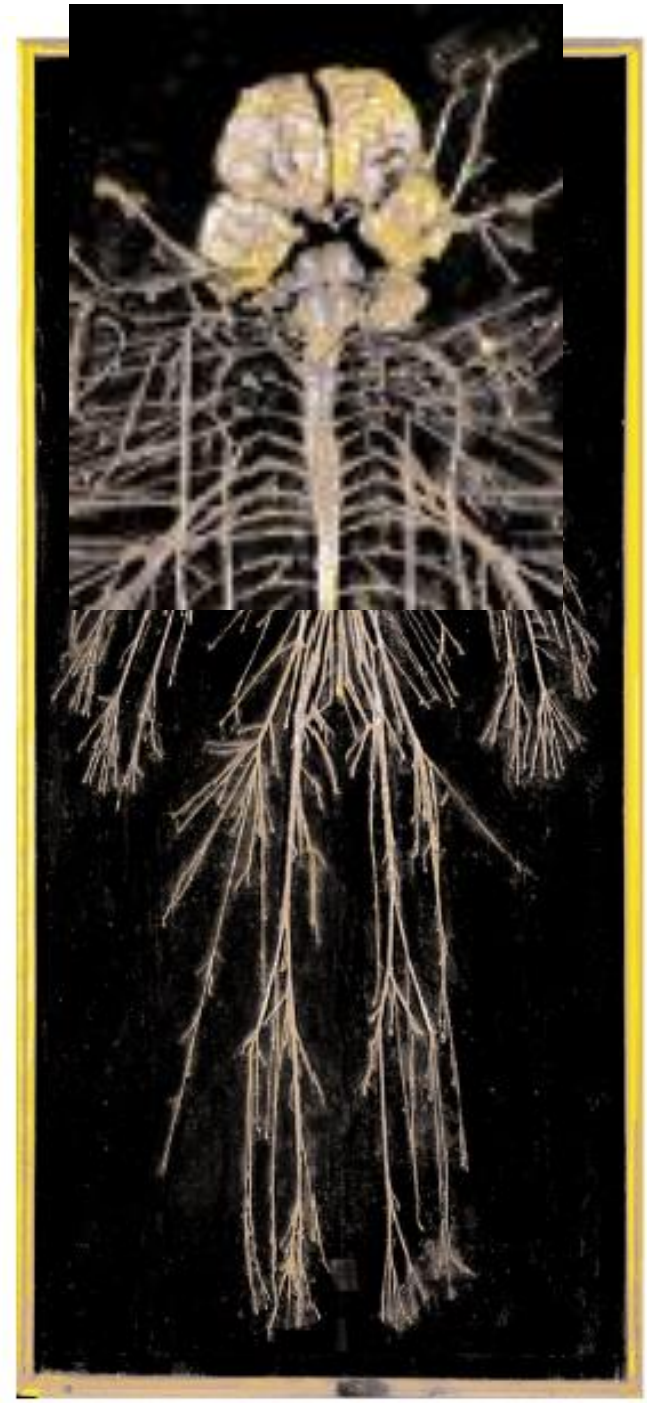
- Brain atrophy is considered an important marker of disease progression in MS. However, most longitudinal studies have assessed brain atrophy over short-to-moderate time periods

- The clinical relevance of long-term brain atrophy in MS patients has been assessed recently (Zivadinov et al 2014)

Brain Atrophy in MS-Outline

- What is Brain Atrophy?
- How can brain atrophy be measured
- Brain Atrophy as endpoint in clinical studies
- Interpreting Brain Atrophy
- Can Brain Atrophy be used in the clinic?





Central and peripheral nervous system (dry prepared of a human being, 1883)
Anatomic Museum of Dept. of Medicine, Surgery & Neuroscience, University of Siena

Definition and Causes of Atrophy

- “Ατροφία”: ἀ "not” Τροφή "nourishment”

Wasting of tissue

Causes of atrophy

- poor nourishment
- poor circulation
- loss of hormonal support
- poor development
- disuse or lack of exercise
- apoptosis of cells
- disease intrinsic to the tissue itself

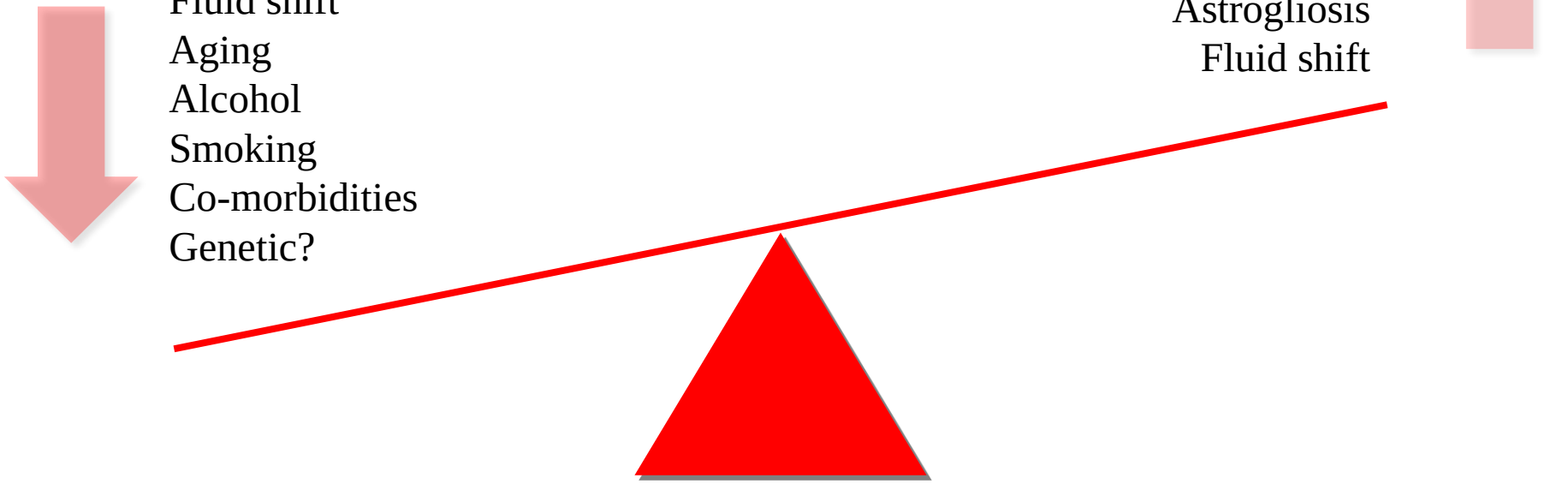
Brain Volume Change:
A Composite of Multiple Pathophysiological Mechanisms

Factors causing brain volume reduction:

Tissue loss (such as myelin, axons, and possibly also astrocytes)
Fluid shift
Aging
Alcohol
Smoking
Co-morbidities
Genetic?

Factors causing brain volume increase:

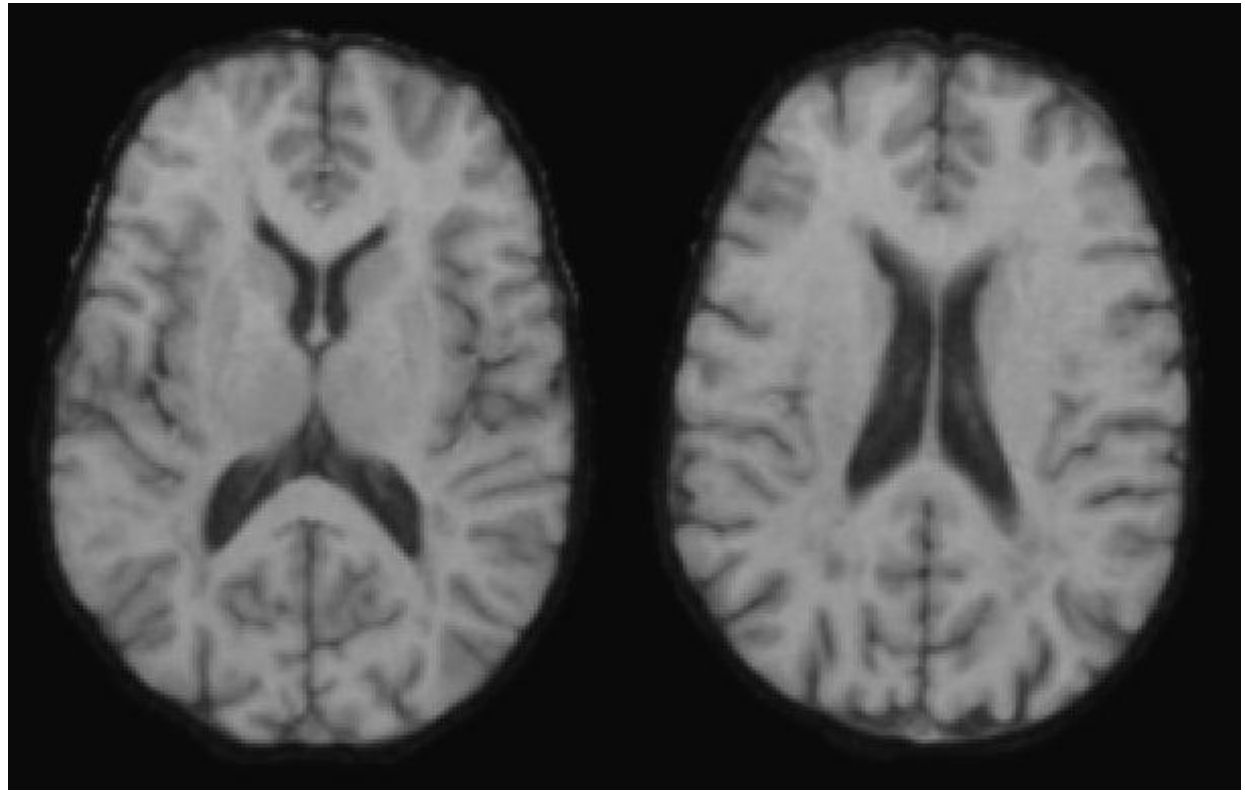
Neuronal repair
Remyelination
Astrogliosis
Fluid shift



ApoE=apolipoprotein E.

Simon JH. Mult Scler. 2006;12:679-687; Barkhof F et al. Nat Rev Neurol. 2009 ;5:256-266; De Stefano N et al. CNS Drugs. 2014;28:147-156.

Example of Atrophy in Action



- *Changes in 1 year in normal control ~0.2-0.4%*
- *Changes in 1 year in MS patients: ~0.5-1%*

Brain Atrophy as predictor of long-term disability in MS

Brain atrophy and lesion load predict long term disability in multiple sclerosis

Veronica Popescu,[1] Federica Agosta,[2] Hanneke E Hulst,[1,3] Ingrid C Sluimer,[1] Dirk L Knol,[4] Maria Pia Sormani,[5] Christian Enzinger,[6] Stefan Ropele,[6] Julio Alonso,[7] Jaume Sastre-Garriga,[8] Alex Rovira,[8] Xavier Montalban,[7] Benedetta Bodini,[9] Olga Ciccarelli,[9,10] Zhaleh Khaleeli,[9] Declan T Chard,[9,10] Lucy Matthews,[11] Jaqueline Palace,[12] Antonio Giorgio,[13] Nicola De Stefano,[13] Philipp Eisele,[14] Achim Gass,[14,15] Chris H Polman,[16] Bernard M J Uitdehaag,[4] Maria Jose Messina,[17] Giancarlo Comi,[17] Massimo Filippi,[2,17] Frederik Barkhof,[1] Hugo Vrenken,[1,18] on behalf of the MAGNIMS Study Group[19]

Clinical and magnetic resonance imaging predictors of disease progression in multiple sclerosis: a nine-year follow-up study

L Lavorgna[1], S Bonavita[1,2], D Ippolito[1], R Lanzillo[3], G Salemi[4], F Patti[5], P Valentino[6], G Coniglio[7], M Buccafusca[8], D Paolicelli[9], A d'Ambrosio[1], V Bresciamorra[3], G Savettieri[4], M Zappia[5], B Alfano[10], A Gallo[1], IL Simone[9] and G Tedeschi[1,2]

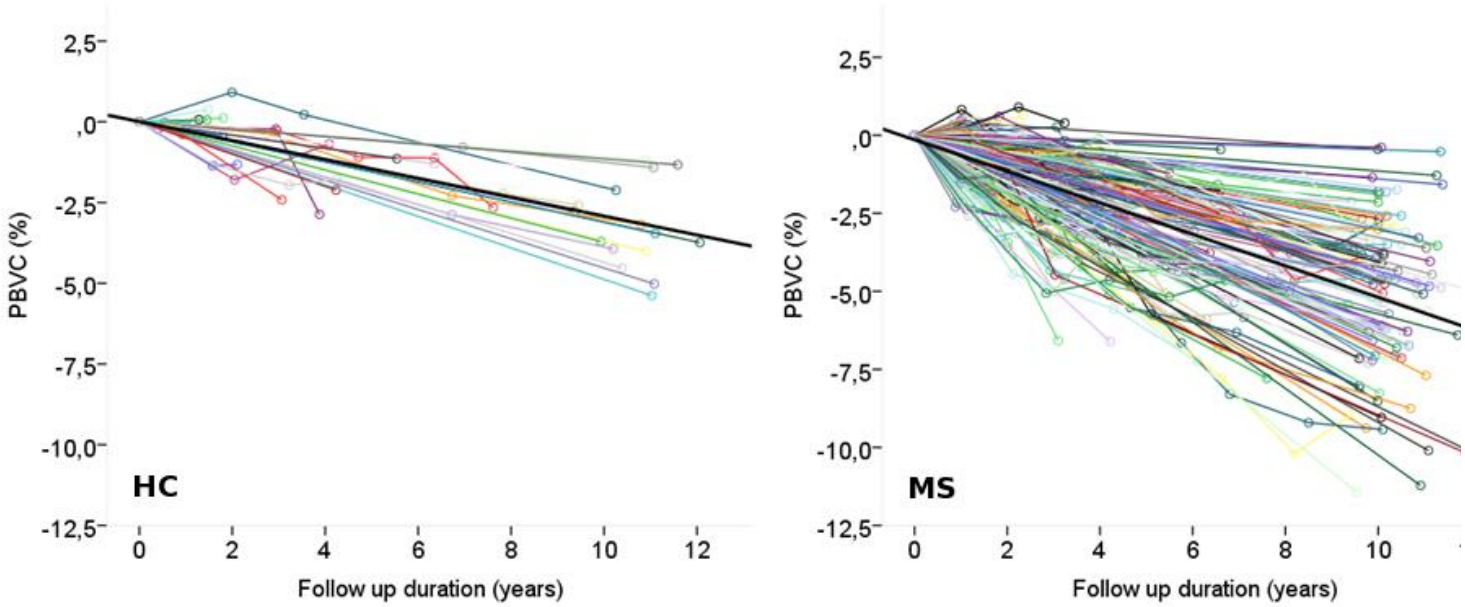
Gray matter damage predicts the accumulation of disability 13 years later in MS

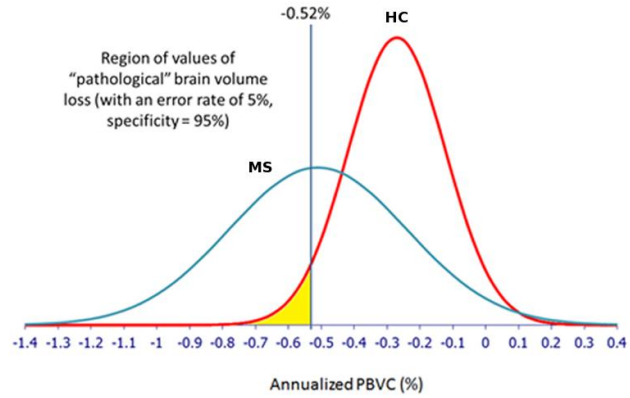
Neurology® 2013;81:1759-1767

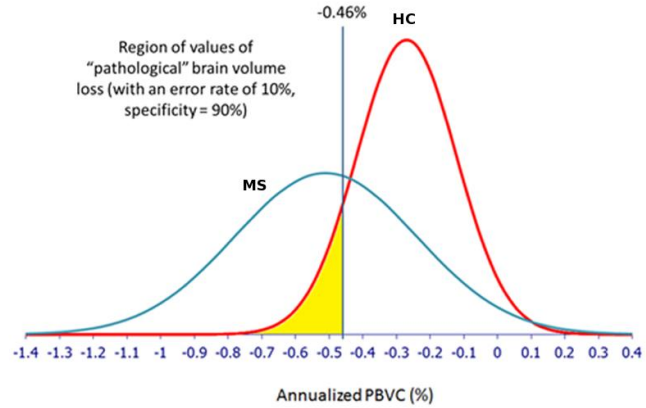
Massimo Filippi, MD
Paolo Preziosa, MD
Massimiliano Copetti, PhD
Gianna Riccitelli, PhD
Mark A. Horsfield, PhD
Vittorio Martinelli, MD
Giancarlo Comi, MD
Maria A. Rocca, MD

Pathological Cutoffs of Brain Atrophy Rates in MS

SIENA Method



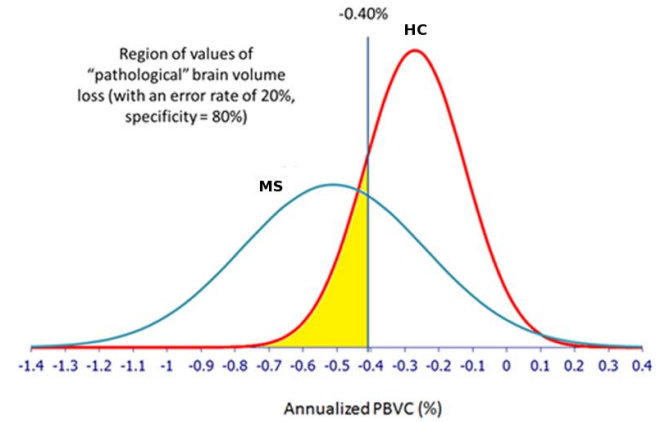




SM: 206, 87% RR, 7% SP, 6% PP
HC: 35

Follow up: 7.5 y (1-12 y)

PBVC cutoffs	Specificity	Sensitivity
-0.52%	95% (observed 97%)	49% (observed 44%)
-0.46%	90% (observed 91%)	56% (observed 48%)
-0.40%	80% (observed 86%)	65% (observed 61%)



Specificity= probability of being below the cutoff for an HC
Sensitivity= probability of being above the cutoff for a MS patient

De Stefano et al JNNP 2016

Normative Data of Brain Atrophy Rates

SIENA Method

MAGNIMS Study

Annualised PBVC

1.5 T

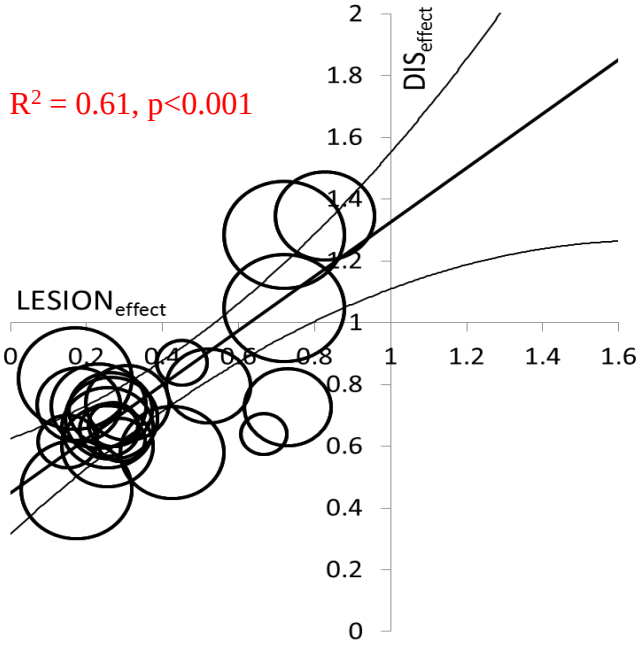
Age range (y)	Predicted PBVC/y	Follow-up time	80° N.P	95°N.P
20-30	-0.17	1 year	-0.48	-0.87
		2 years	-0.37	-0.58
30-40	-0.23	1 year	-0.55	-0.98
		2 years	-0.44	-0.67
40-50	-0.29	1 year	-0.64	-1.10
		2 years	-0.51	-0.76
50-60	-0.36	1 year	-0.72	-1.24
		2 years	-0.59	-0.86
60-70	-0.43	1 year	-0.82	-1.41
		2 years	-0.67	-0.96
70-80	-0.50	1 year	-0.92	-1.60
		2 years	-0.76	-1.09

3 T

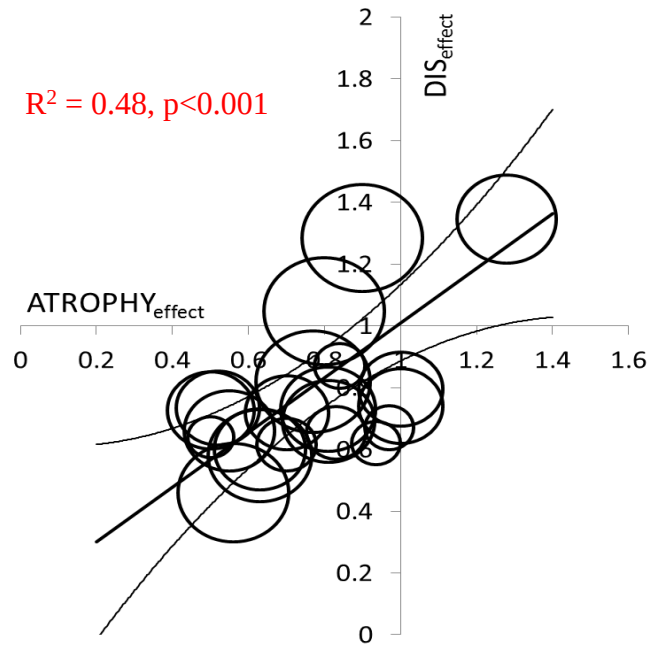
Age range (y)	Predicted PBVC/y	Follow-up time	80°N.P	95°N.P
20-30	-0.05	1 year	-0.34	-0.68
		2 years	-0.24	-0.44
30-40	-0.11	1 year	-0.41	-0.77
		2 years	-0.30	-0.51
40-50	-0.17	1 year	-0.48	-0.87
		2 years	-0.37	-0.59
50-60	-0.23	1 year	-0.56	-0.99
		2 years	-0.44	-0.67
60-70	-0.30	1 year	-0.64	-1.11
		2 years	-0.51	-0.76
70-80	-0.36	1 year	-0.73	-1.25
		2 years	-0.59	-0.86

Battaglini et al in preparation

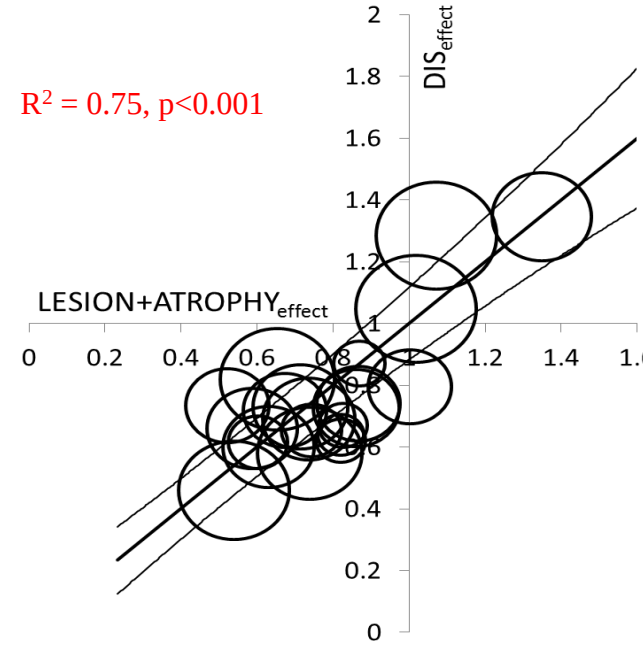
Meta-analysis of Randomised Clinical Trials in RRMS: lesions, brain atrophy and clinical disability



Lesion effect



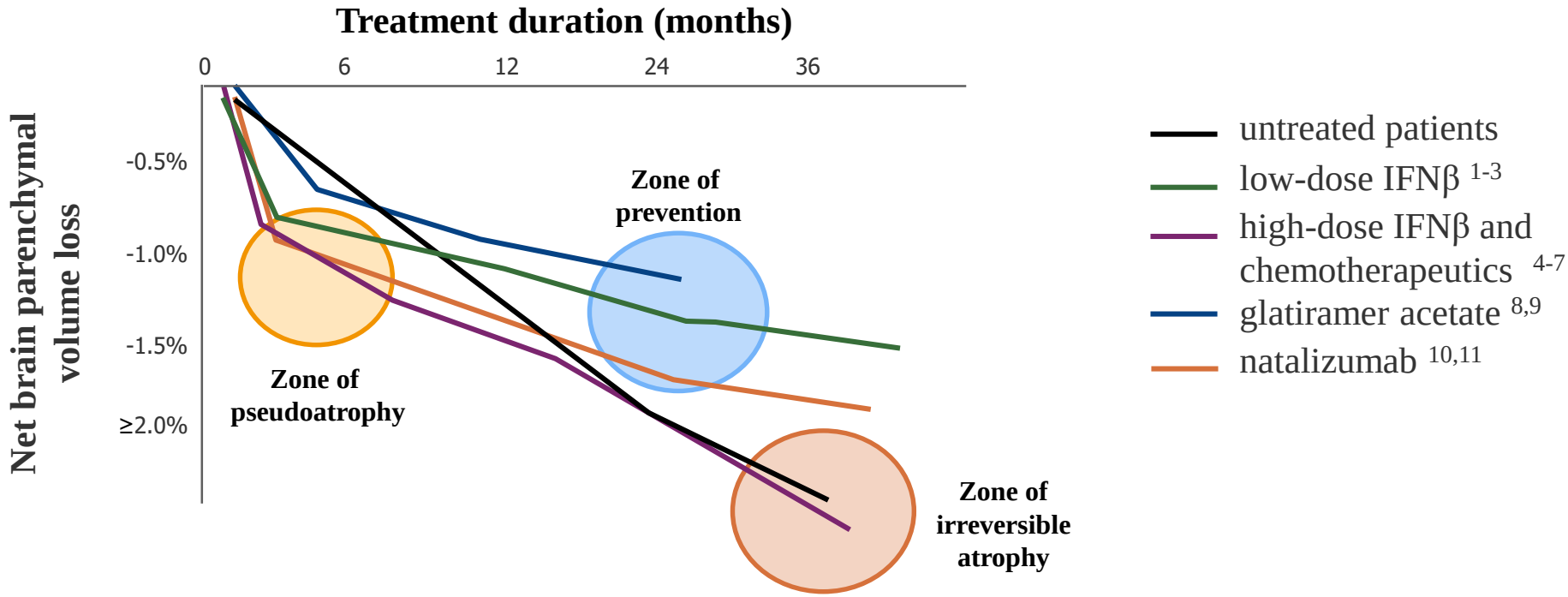
Atrophy effect



Lesion + Atrophy effect

Sormani MP, Arnold DL and De Stefano N, Annals of Neurology 2013

Pseudoatrophy is observed in the first 6-9 months of treatment with the majority of DMTs



- Pseudoatrophy mimics brain volume changes caused by tissue loss
- Possible causes include:
  - resolution of inflammation and oedema
  - changes in electrolyte balance and vascular permeability or dehydration

From: Zivadinov R, et al. J Neurol. 2008;255 Suppl 1:61-74; 1. Filippi M, et al. Lancet 2004; 364:1489–1496; 2. Hardmeier M, et al. Neurology 2005;64:236–240; 3. Rudick RA, et al. Neurology 1999;53:1698–1704; 4. Jones C, et al. Neurology 2001;56(Suppl 3):A379; 5. Chen JT, et al. Neurology 2006;66:1935-1937; 6. Inglese M, et al. J Neurol Neurosurg Psychiatry 2004;75:643–644; 7. Roccatagliata L, et al. Mult Scler 2007; 13:1068-1070; 8. Ge Y, et al. Neurology 2000;54:813–817; 9. Sormani MP, et al. Neurology 2004;62:1432–1434; 10. Fisher E, et al. J Neurol 2005;149 ;
11. O' Connor PW, et al. Abstract persented at ANN 2006

Clinical Relevance of Brain Volume Measures in MS

Brain Volume Outcomes from Placebo-Controlled Trials

Treatment	Phase, duration	Disease type, study population (N)	Reduction in brain volume loss vs placebo
IFNβ-1a IM	Phase 3, 2 years post hoc	RRMS (172)	Year 1 vs baseline: NS Year 2 vs Year 1: Significant Year 2 vs baseline: NS
IFNβ-1a SC	Phase 3, 2 years	CIS suggestive of MS (309)	Year 1 vs baseline: NS Year 2 vs Year 1: NS Year 2 vs baseline: Significant
IFNβ-1b SC	Phase 3, 5-year extension	CIS suggestive of MS (468)	Year 5 vs baseline: NS
IFNβ-1b SC	Phase 3, 3 years	SPMS (718)	Year 3 vs baseline: NS
GA	Phase 3, 1.5 years	RRMS (207)	Year 1.5 vs baseline: Significant
GA	Phase 3, 5 years (3 years placebo-controlled, 2 years open label)	CIS suggestive of MS (409)	Early vs delayed treatment (baseline to last observed value: Significant

IM=intramuscular; SC=subcutaneous; NS=not significant; GA=glatiramer acetate; SPMS=secondary progressive MS.

De Stefano N et al. *CNS Drugs* 2014;28:147-156.

Treatment	Phase, duration	Disease type, study population (N)	Reduction in brain volume loss vs placebo
Natalizumab	Observational, 2 years	MS (39)	Year 1 vs baseline: Significant (WM) Rate in Year 1 vs Year 2: Significant
Natalizumab	Phase 3, 2 years	RRMS (942)	Year 1 vs baseline: NS Year 2 vs Year 1: Significant Year 2 vs baseline: NS
Fingolimod	Phase 3, 2 years	RRMS (1272)	6 months vs baseline: Significant Year 1 vs baseline: Significant Year 2 vs Year 1: Significant Year 2 vs baseline: Significant
Teriflunomide	Phase 3, 2 years	RRMS (1088)	Year 2 vs baseline (global volume): NS Year 2 vs baseline (WM): Significant
Laquinimod	Phase 3, 2 years	RRMS (1,106)	Year 2 vs baseline (global volume, WM, GM):Significant Year 1 vs baseline (global volume, WM, GM): Significant
Laquinimod	Phase 3, 2 years	RRMS (1,331)	Year 2 vs baseline (global volume, WM, GM):Significant
Dimethyl fumarate (bid)	Phase 3, 2 years	RRMS (540)	Year 2 vs baseline: Significant
Dimethyl fumarate (bid)	Phase 3, 2 years	RRMS (681)	Year 2 vs baseline: NS

De Stefano N et al. *CNS Drugs* 2014;28:147-156.

Clinical Relevance of Brain Volume Measures in MS

Brain Volume Outcomes from Active Comparator-Controlled Trials

Treatment	Comparator	Phase, duration	Disease type, study population (N)	Reduction in brain volume loss vs placebo
IFNβ-1b SC	GA	Phase 3, 2-3.5 years	RRMS (2244)	Year 1 vs baseline: NS Year 2 vs Year 1: NS Year 3 vs Year 2: NS
IFNβ-1a IM	Dose comparison	Phase 3, 3 years	RRMS (189)	Year 3 vs baseline: Significant
GA	IFNβ	Post hoc, 2 years	RRMS (86)	Year 2 vs baseline (gray matter): Significant
GA	IFNβ	Retrospective, 5 years	RRMS (275)	Year 5 vs baseline: Significant
Natalizumab	IFNβ	Pilot, 1.5 years	RRMS (26)	Year 1.5 vs baseline: Significant
Alemtuzumab	IFNβ-1b SC	Phase 2, 3 years	RRMS (334)	Year 3 vs Year 1: Significant Year 3 vs baseline: Significant
Alemtuzumab	IFNβ-1b SC	Phase 3, 2 years	RRMS (840)	Year 2 vs baseline: Significant
Alemtuzumab	IFNβ-1b SC	Phase 3, 2 years	RRMS (581)	Year 2 vs baseline: Significant
Fingolimod	IFNβ-1a IM	Phase 3, 1 year	RRMS (1292)	Year 1 vs baseline: Significant

De Stefano N et al. *CNS Drugs.* 2014;28:147-156.

Effect of intramuscular interferon beta-1a on gray matter atrophy in relapsing–remitting multiple sclerosis: A retrospective analysis

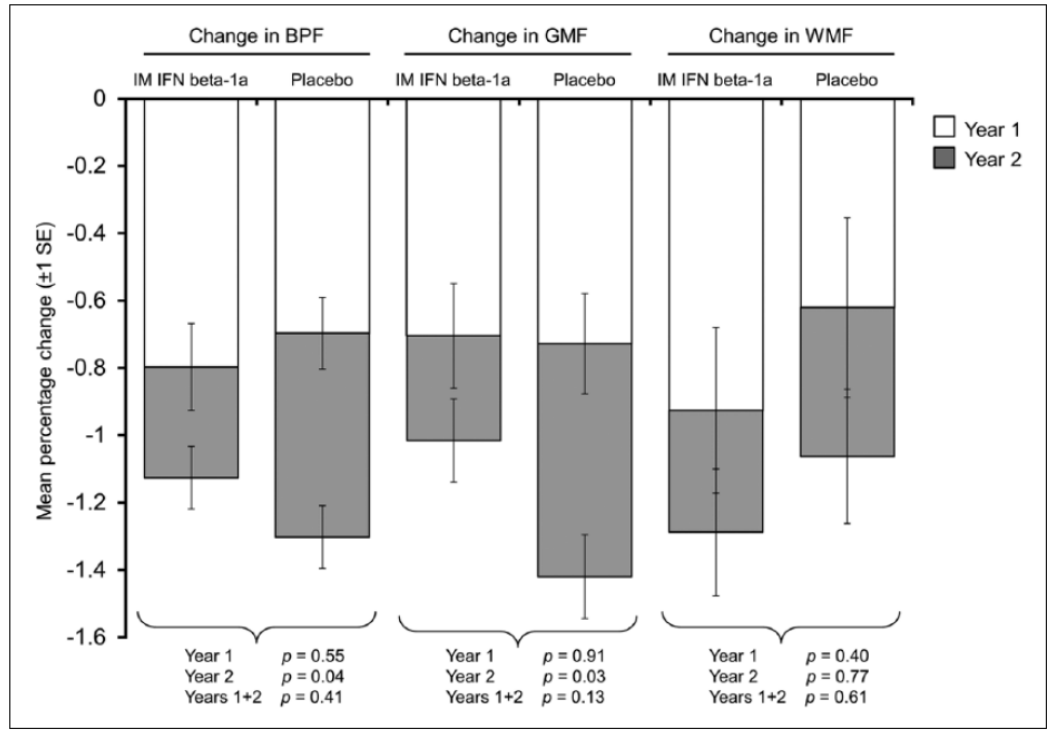
E Fisher, K Nakamura, J-C Lee, X You, B Sperling and RA Rudick

Multiple Sclerosis Journal
2016, Vol. 22(5) 668–676
DOI: 10.1177/
1352458515599072

Multiple Sclerosis Collaborative Research Group Phase 3 IM IFN β-1a vs placebo in RRMS

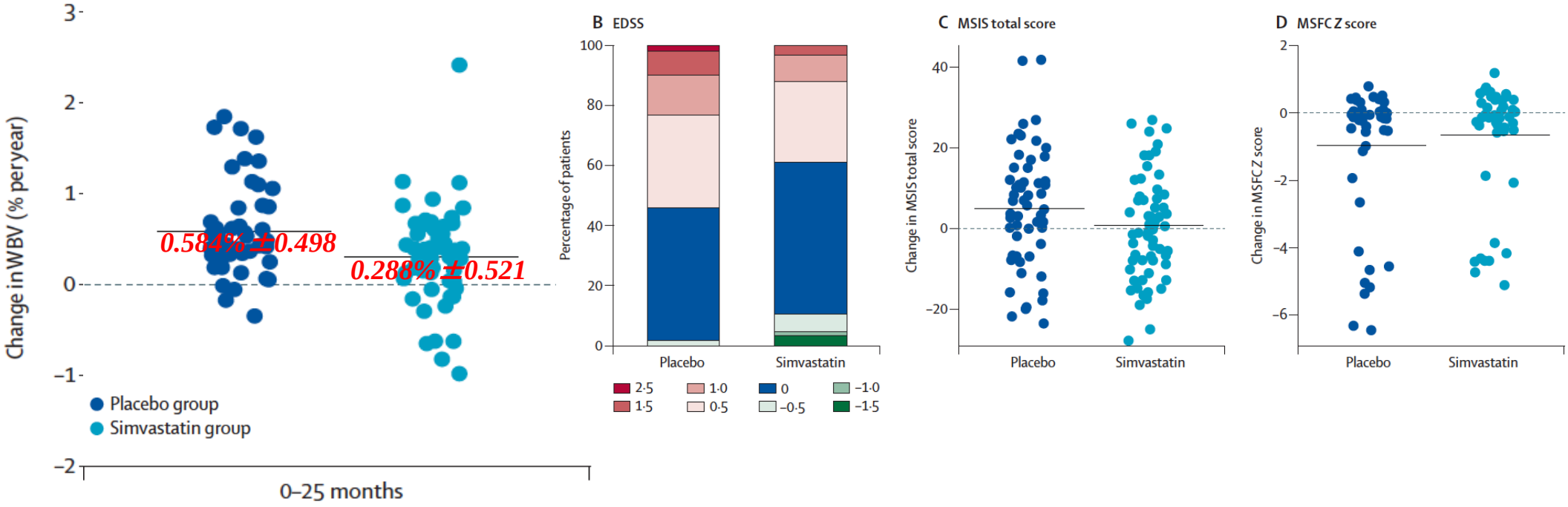
Brain atrophy variable, mean (SD)	IM IFN beta-1a (*n*=62)	Placebo (*n*=69)	*p* value
BPF % change			
Year 1	−0.80 (1.01)	−0.70 (0.89)	.55
Year 2	−0.33 (0.74)	−0.61 (0.77)	.04
Years 1 and 2	−1.12 (1.23)	−1.30 (1.18)	.41
GMF % change			
Year 1	−0.70 (1.22)	−0.73 (1.23)	.91
Year 2	−0.31 (0.97)	−0.69 (1.03)	.03
Years 1 and 2	−1.02 (1.41)	−1.42 (1.57)	.13
WMF % change			
Year 1	−0.93 (1.94)	−0.62 (2.21)	.40
Year 2	−0.36 (1.48)	−0.44 (1.66)	.77
Years 1 and 2	−1.29 (2.31)	−1.06 (2.66)	.61

BPF: brain parenchymal fraction; GMF: gray matter fraction; IM IFN beta-1a: intramuscular interferon beta-1a; SD: standard deviation; WMF: white matter fraction.



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

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



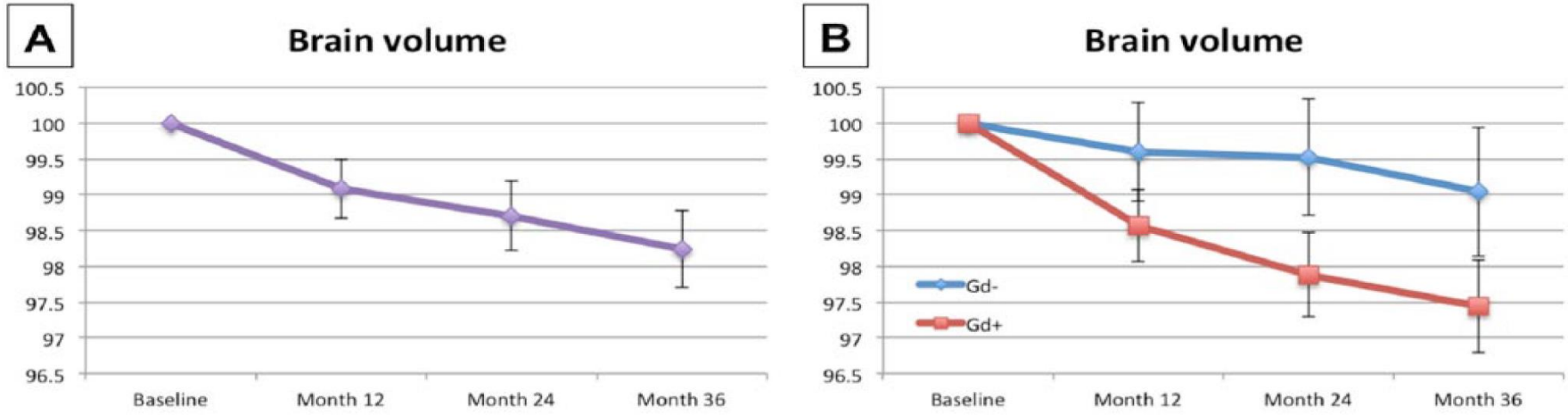
Chataway, Lancet 2014

Brain atrophy in natalizumab-treated patients: A 3-year follow-up

J Sastre-Garriga, C Tur, D Pareto, A Vidal-Jordana, C Auger, J Río, E Huerga, M Tintoré, A Rovira and X Montalban

BVL is different in MS patients with/without baseline Gd activity

n=62, 3 years follow up

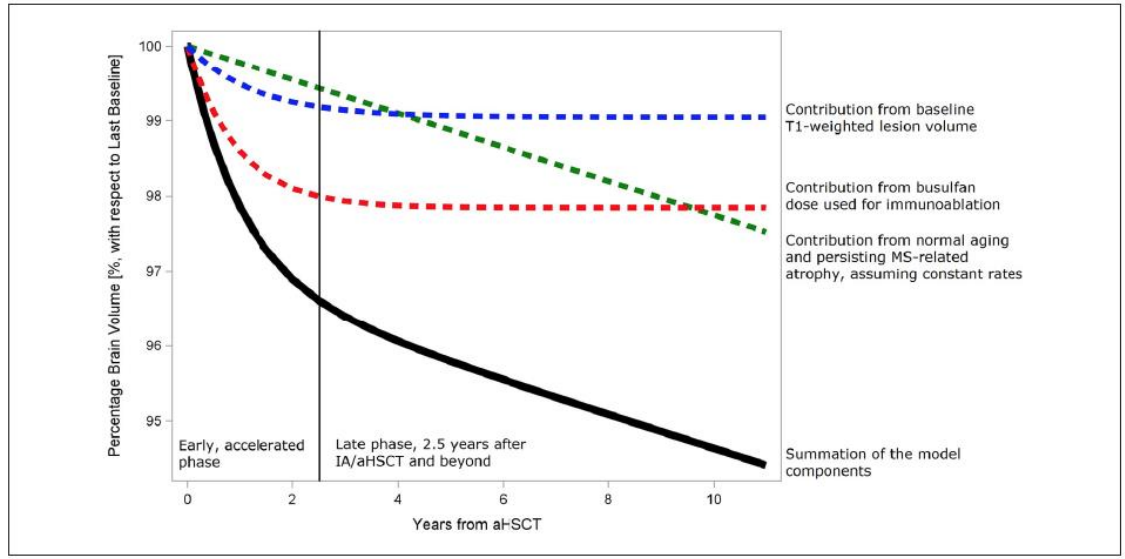


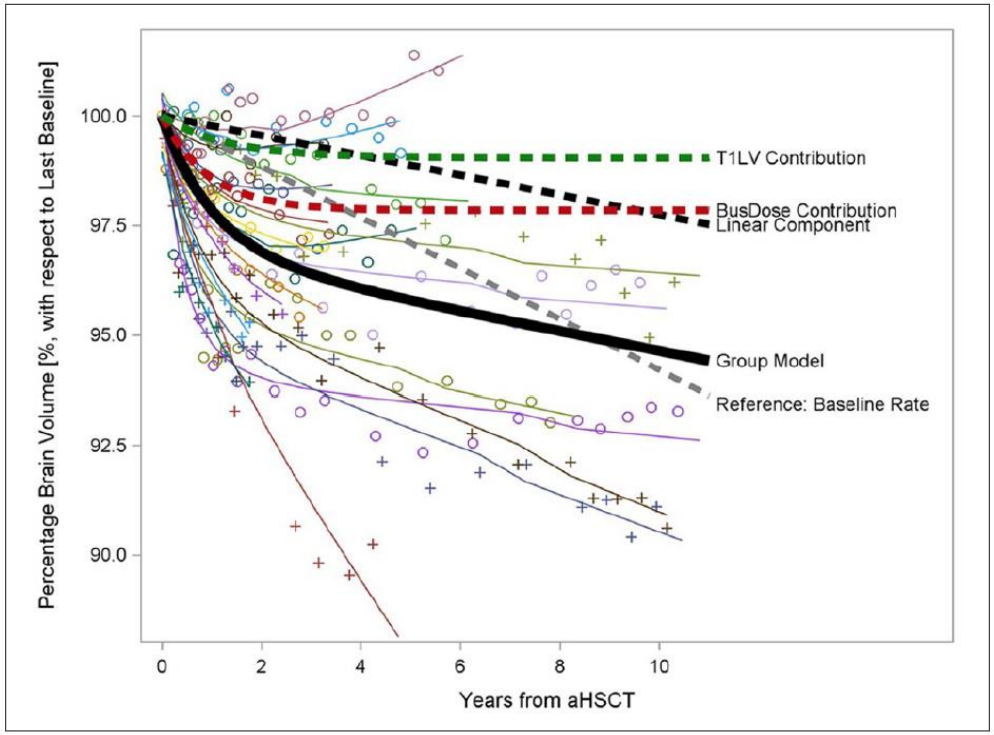
Gd activity predicts a higher rate of PBVC in Natalizumab treated patients

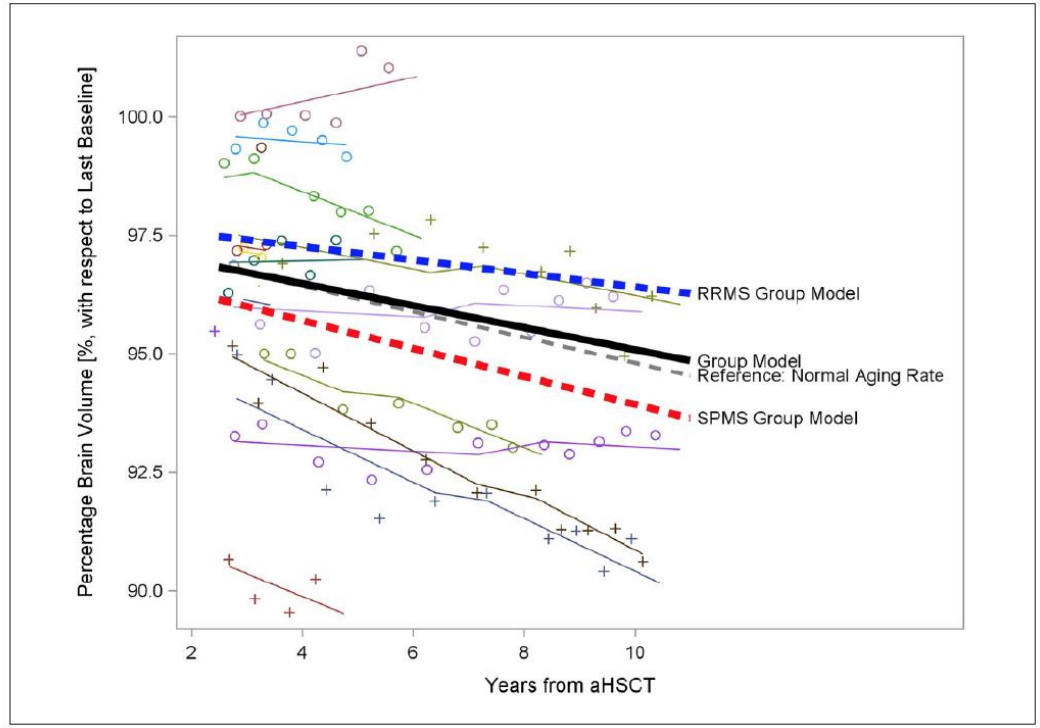
Brain atrophy after bone marrow transplantation for treatment of multiple sclerosis

Hyunwoo Lee, Sridar Narayanan, Robert A Brown, Jacqueline T Chen, Harold L Atkins, Mark S Freedman and Douglas L Arnold

Multiple Sclerosis Journal . 2016.







Cladribine significantly reduced the rate of brain atrophy vs placebo[a,b]

Percentage brain volume change (Months 6–24)[1]

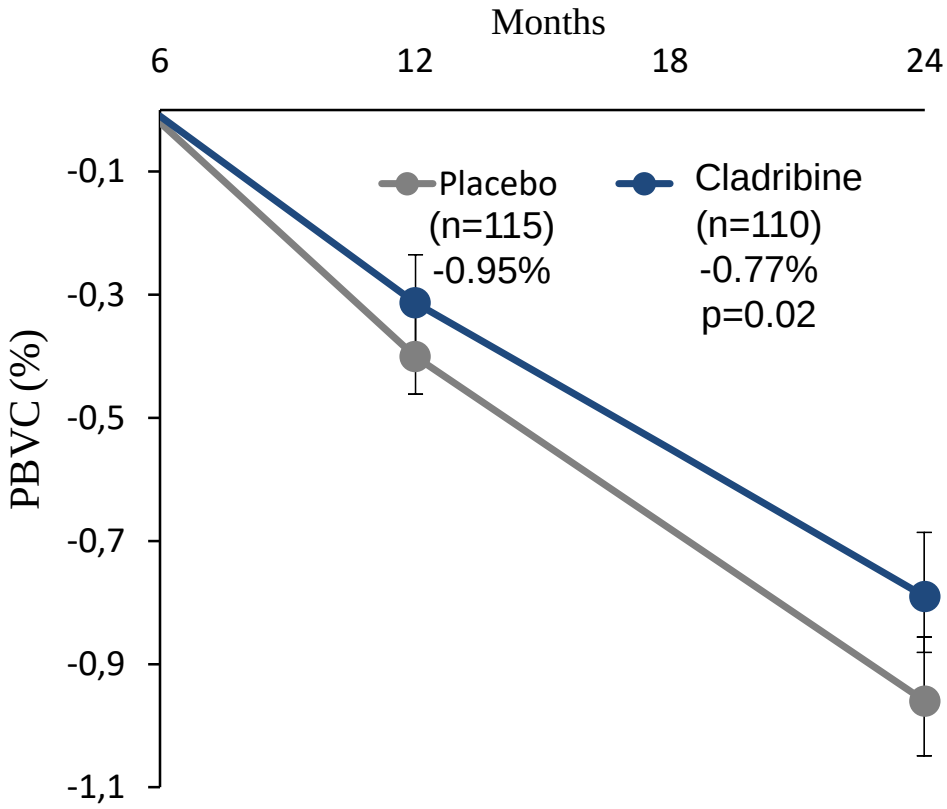


Figure adapted from De Stefano N et al. Mult Scler 2017;

Annualized brain volume change (Months 6–24)[c,1]

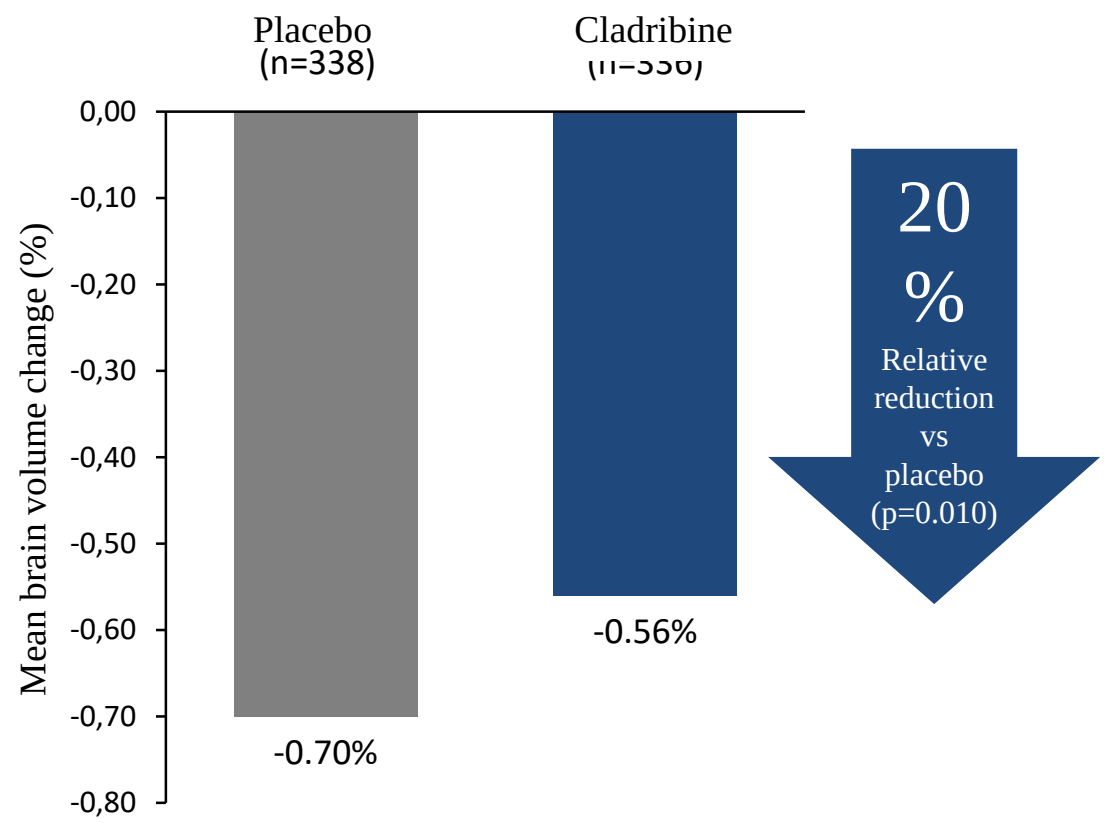


Figure created from data presented in De Stefano N et al. Mult Scler 2017;

[a]As these are data from a *post hoc* analysis, no conclusions can be drawn with regards to clinical outcome. Further randomised, controlled clinical trials will be necessary to corroborate these findings;

[b]Data from the 2-year CLARITY trial. Brain atrophy was assessed from Months 6 to 24 to avoid confounding influence of pseudoatrophy in the first 6 months[2]; [c]Measured by structural image evaluation using normalization of atrophy (SIENA), which measures change in brain volume based on pre-gadolinium T1-weighted MRI scans. MRI, magnetic resonance imaging; PBVC, percentage of brain volume changes.

1. De Stefano N et al. Mult Scler 2017;; 2. De Stefano N and Arnold D. Mult Scler 2015;

Slowing of Cortical Gray Matter Atrophy With Teriflunomide Is Associated With Delayed Conversion to Clinically Definite MS

TOPIC study (NCT00622700)

Table 1. Demographics and Baseline Disease Characteristics for the ITT TOPIC Population

	Placebo (n=197)	Teriflunomide 7 mg (n=203)	Teriflunomide 14 mg (n=214)
Female, n (%)	135 (68.5)	128 (63.1)	153 (71.5)
Age, mean (SD), y	32.0 (8.4)	31.5 (9.0)	32.7 (8.1)
Time since first symptom of MS, mean (SD), mo	1.88 (0.52)	1.89 (0.56)	1.80 (0.56)
EDSS score			
Mean (SD)	1.71 (1.00)	1.50 (1.02)	1.78 (0.95)[a]
Median (min, max)	1.50 (0.0, 5.5)	1.50 (0.0, 6.0)	1.50 (0.0, 5.0)[a]
Total lesion volume,[b] mean (SD), mL	9.15 (10.69)[c]	8.07 (9.98)[d]	8.78 (9.36)[e]
Number of Gd-enhancing lesions, mean (SD)	1.4 (4.1)[c]	1.1 (3.0)[d]	1.4 (3.7)[f]

[a]n=213; [b]total volumes of hyperintense lesions on T2 plus hypointense lesions on T1 as measured by MRI scan; [c]n=177; [d]n=187; [e]n=200; [f]n=199. EDSS, Expanded Disability Status Scale; Gd, gadolinium; ITT, intent-to-treat.

Zivadinov R, et al. Poster P671: ECTRIMS/ACTRIMS 2017

Slowing of Cortical Gray Matter Atrophy With Teriflunomide Is Associated With Delayed Conversion to Clinically Definite MS

TOPIC study (NCT00622700)

Table 2. Baseline Characteristics by Group for the ITT Population With Nonmissing Annualized Percentage Change From Baseline in CGMV[a]

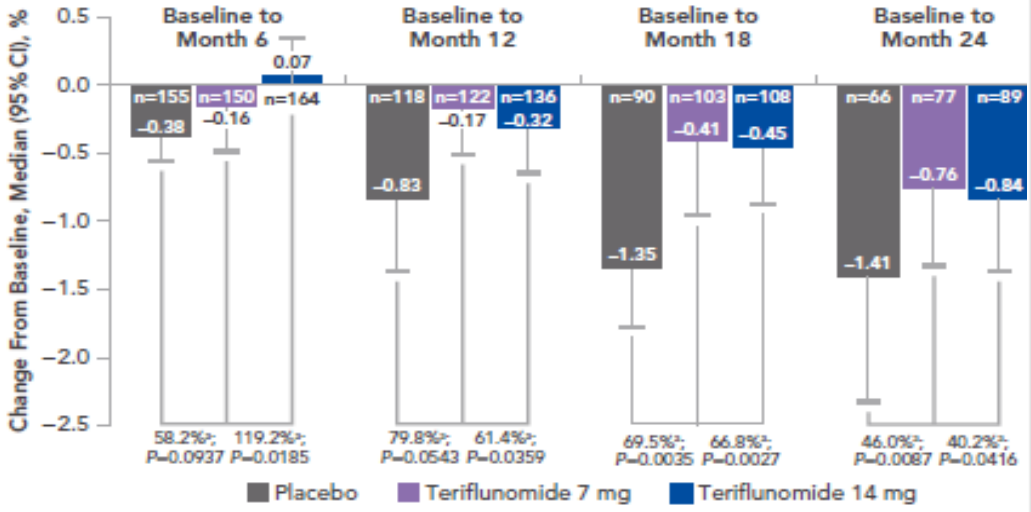
	Least CGMV loss → Most CGMV loss		
	Group 1 (≥0.206% change)	**Group 2 (≥−1.879 to <0.206% change)**	**Group 3 (<−1.879% change)**
Patients, n	140	251	94
Female, n (%)	94 (67.1)	173 (68.9)	59 (62.8)
Age, mean (SD), y	31.6 (8.8)	32.9 (8.3)	32.0 (8.8)
Time since first symptom of MS, mean (SD), mo	1.86 (0.54)	1.75 (0.51)	2.02 (0.55)
EDSS score			
Mean (SD)	1.61 (1.02)[b]	1.63 (0.96)[c]	1.65 (1.07)
Median (min, max)	1.5 (0.0, 5.5)[b]	1.5 (0.0, 5.5)[c]	1.5 (0.0, 6.0)
Total lesion volume,[d] mean (SD), mL	7.91 (8.05)[e]	8.02 (9.36)[f]	10.36 (13.06)[g]
Number of Gd-enhancing lesions, mean (SD)	1.25 (3.49)[e]	1.11 (3.37)[f]	2.09 (5.28)[g]

[a]The intent-to-treat (ITT) population represents pooled data from placebo and active treatment groups; [b]n=139; [c]n=250; [d]total volume of lesions on T_2- and T_1-weighted scans; [e]n=122; [f]n=231; [g]n=89. CGMV, cortical gray matter volume; EDSS, Expanded Disability Status Scale; Gd, gadolinium.

Zivadinov R, et al. Poster P671: ECTRIMS/ACTRIMS 2017

MRI Outcomes

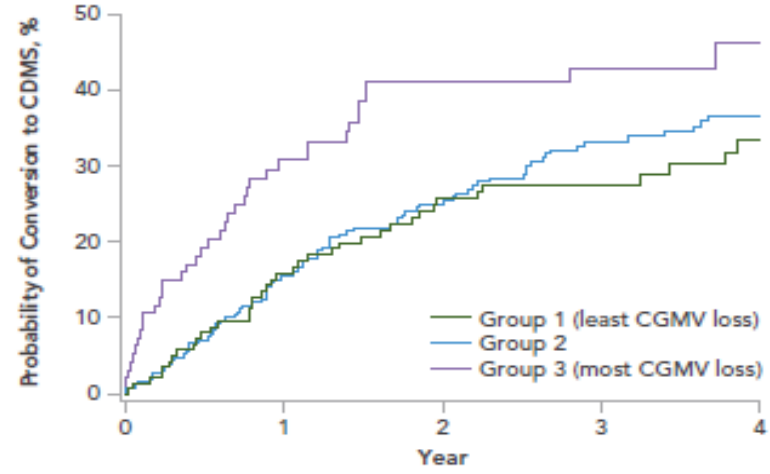
Figure 1. Change From Baseline in Cortical Gray Matter Volume Over 2 Years[15]



ᵃRelative change vs placebo.
CI, confidence interval.

CDMS Conversion According to CGMV Loss

Figure 3. Time to Relapse Determining Conversion to CDMS Up to Year 4ᵃ



Number at risk					
Group 1 (least CGMV loss)	140	104	87	63	34
Group 2	251	199	164	117	82
Group 3 (most CGMV loss)	94	56	42	28	13

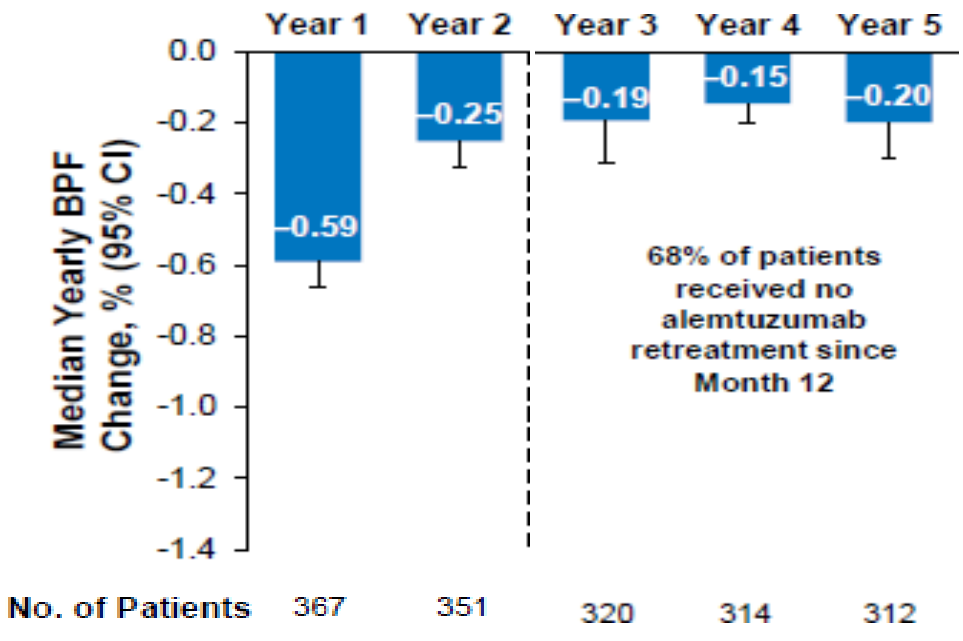
ᵃAnalyses based on pooled data from placebo and active treatment groups (total population).
CDMS, clinically definite MS; CGMV, cortical gray matter volume.

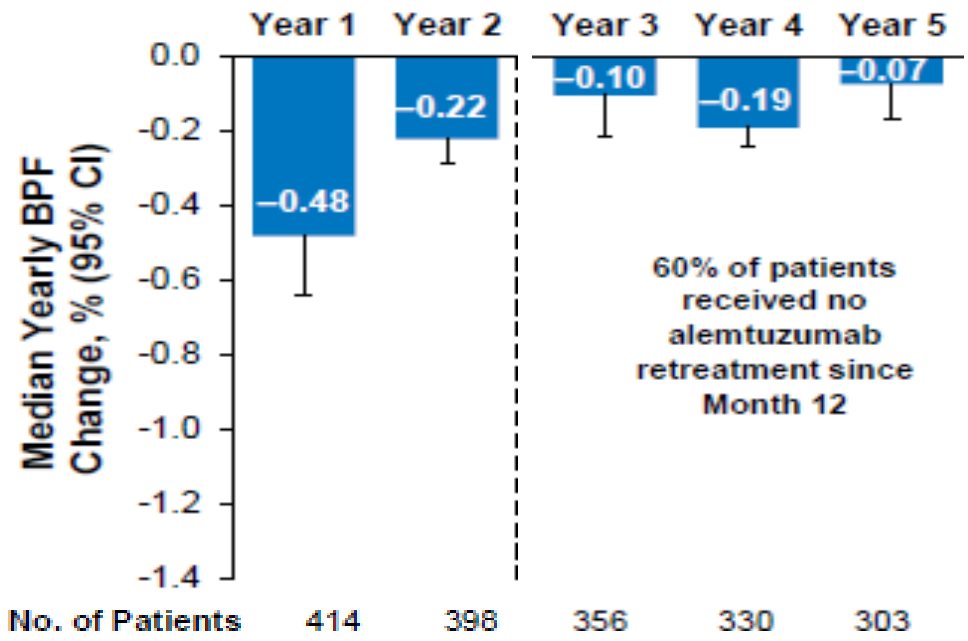
CGMV variation (%)	CDMS conversion risk (%)			
	6M	12M	18M	24M
1%	17.5% (P=0.0007)	12.4% (P=0.0099)	14.2% (P=0.0009)	14.5% (P=0.0005)

* Teriflunomide 7mg vs placebo, P = 0.0089
* Teriflunomide 14 mg vs placebo, P = 0.0052

Durable slowing of BVL with Alemtuzumab: Care MS I & II

Median Annual Brain Volume Changes



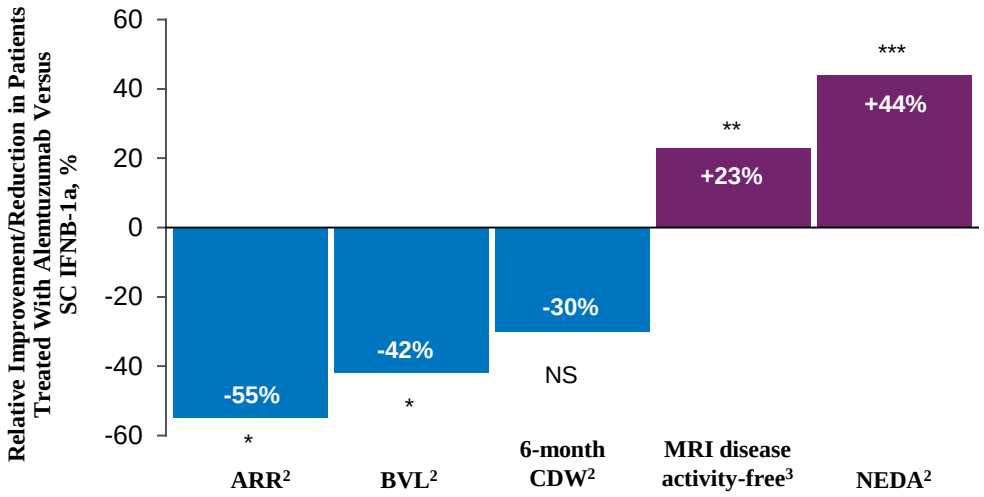


Shippling S. et al. S51.001, AAN 2016

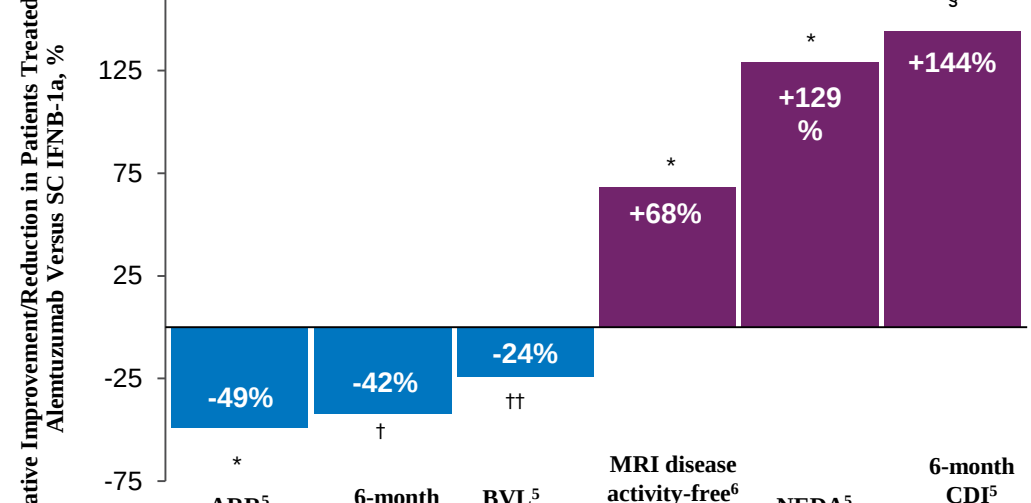
CARE-MS Core

Efficacy Summary Relative to SC IFNB-1a at 2 Years

CARE-MS I[1]



CARE-MS II[4]



*P<0.0001; **P=0.0388 ***P=0.006; †P=0.0084; ††P=0.01; §P=0.0002.

ARR=annualized relapse rate; BVL=brain volume loss; CDI=confirmed disability improvement defined as a reduction in the EDSS score of ≥1.0 (or 0.5, for baseline EDSS scores >5.5) sustained for at least 6 months. Analysis for CDI was restricted to those with a baseline EDSS ≥2.0; CDW=confirmed disability worsening defined as ≥1.0-point EDSS increase from baseline (or ≥1.5 points if baseline EDSS=0); NEDA=no evidence of disease activity; NS=not significant; SC IFNB-1a=subcutaneous interferon beta-1a

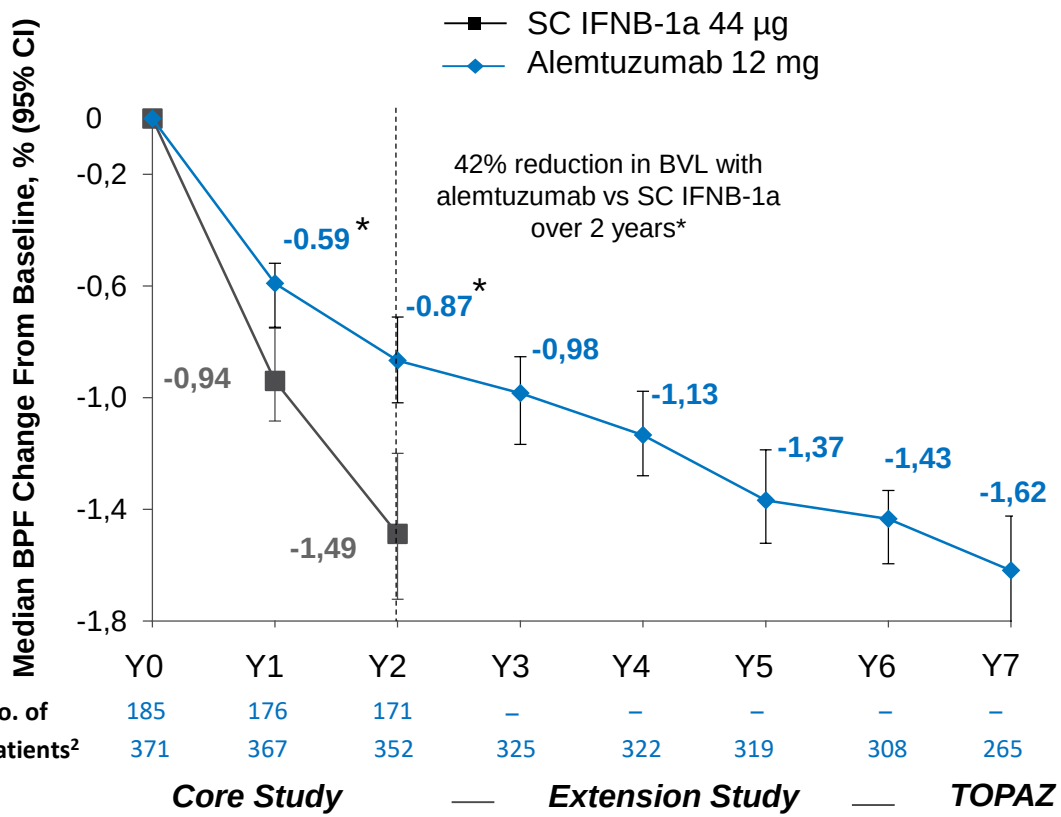
1. Singer B et al. AAN 2017, Platform S24.005; 2. Cohen JA et al. *Lancet* 2012;380:1819-28; 3. Giovannoni G et al. ENS 2012, 0288; 4. Fox E et al. AAN 2017, Platform S24.006; 5. Coles AJ et al. *Lancet* 2012;380:1829-39; 6. Hartung HP et al. AAN 2013, P07.093.

CARE-MS I Core/Extension/TOPAZ

Slowing of Brain Volume Loss Through Year 7 in Patients Who Received Alemtuzumab 12 mg in the CARE-MS I Core Study

BPF Change From Baseline[1]

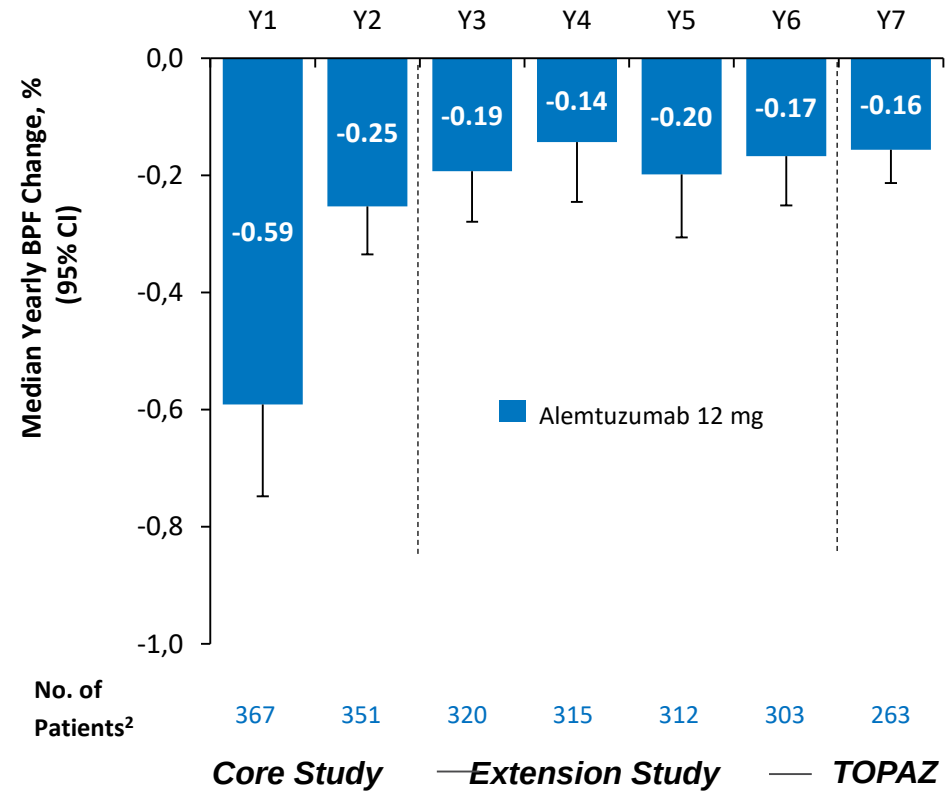
(Core: Tertiary Endpoint; Extension: Pre-specified Endpoint)[2]



*Alemtuzumab vs SC IFNB-1a, $P<0.0001$.

Median Yearly BPF Change[1]

(Core: Tertiary Endpoint; Extension: Pre-specified Endpoint)[2]



- Through 7 years, brain volume loss slowed in the absence of continuous treatment in patients who were treatment-naive at baseline
  - 61% of patients received no alemtuzumab retreatment

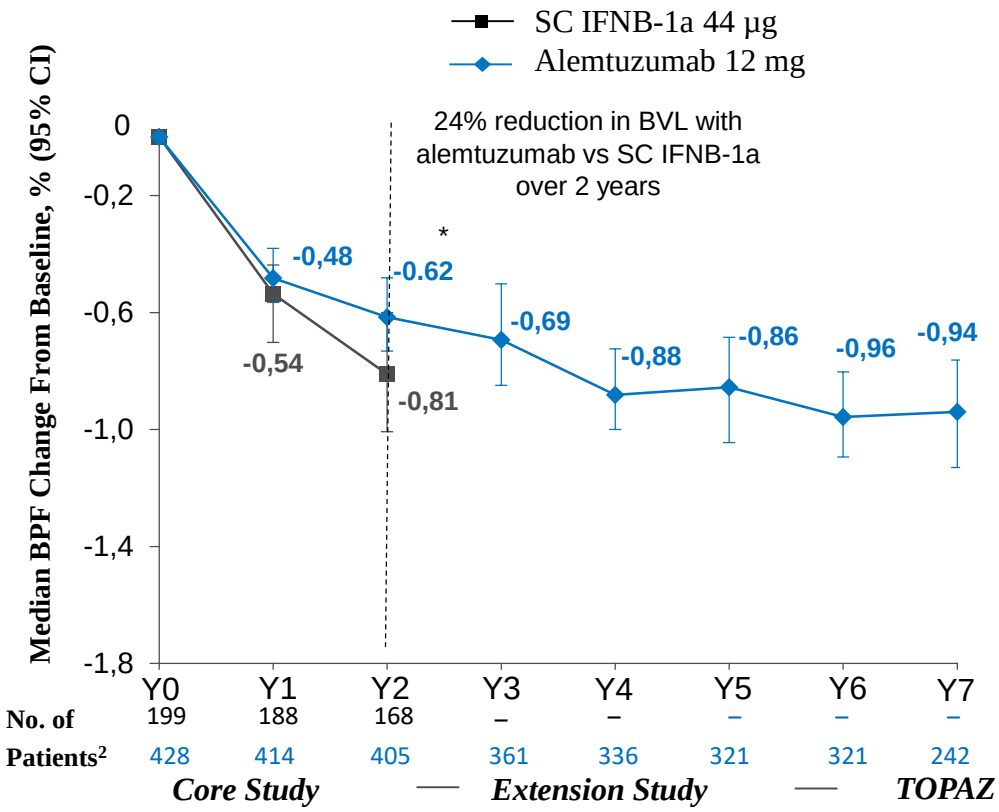
BPF=brain parenchymal fraction; BVL=brain volume loss. 1. Arnold DL et al. ACTRIMS-ECTRIMS 2017, P1189;

CARE-MS II Core/Extension/TOPAZ

Slowing of Brain Volume Loss Through Year 7 in Patients Who Received Alemtuzumab 12 mg in the CARE-MS I Core Study

BPF Change From Baseline[1]

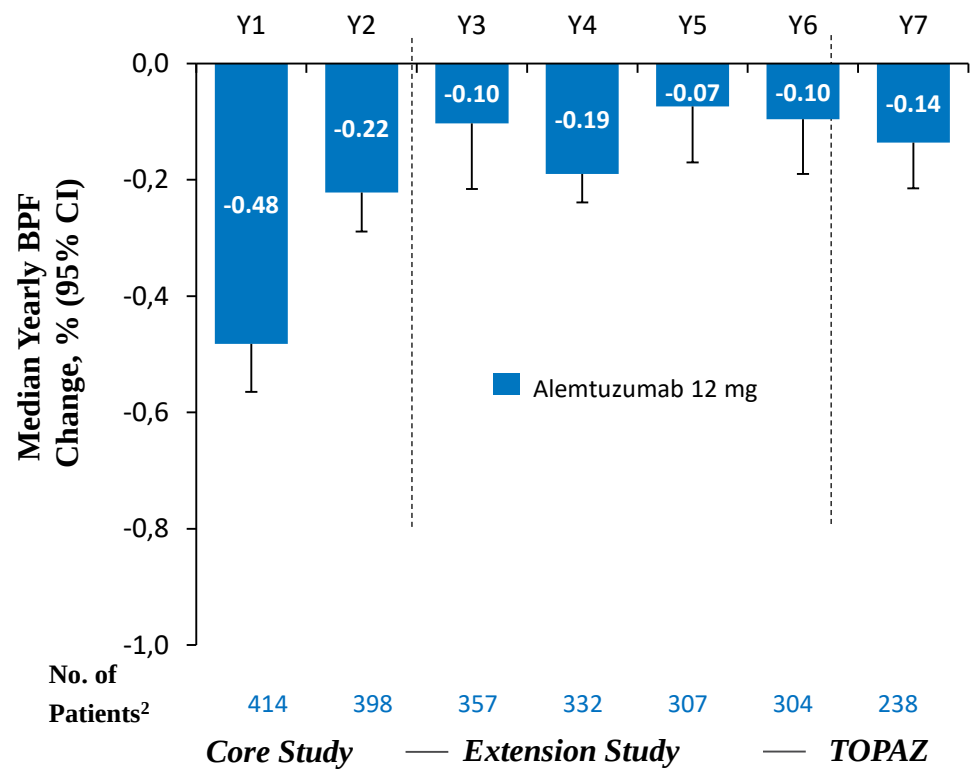
(Core: Tertiary Endpoint; Extension: Pre-specified Endpoint)[2]



*Alemtuzumab vs SC IFNB-1a, *P*=0.0121

Median Yearly BPF Change[1]

(Core: Tertiary Endpoint; Extension: Pre-specified Endpoint)[2]



- Through 7 years, brain volume loss slowed in the absence of continuous treatment in patients who were treatment-naive at baseline
  - 52% of patients received no alemtuzumab retreatment

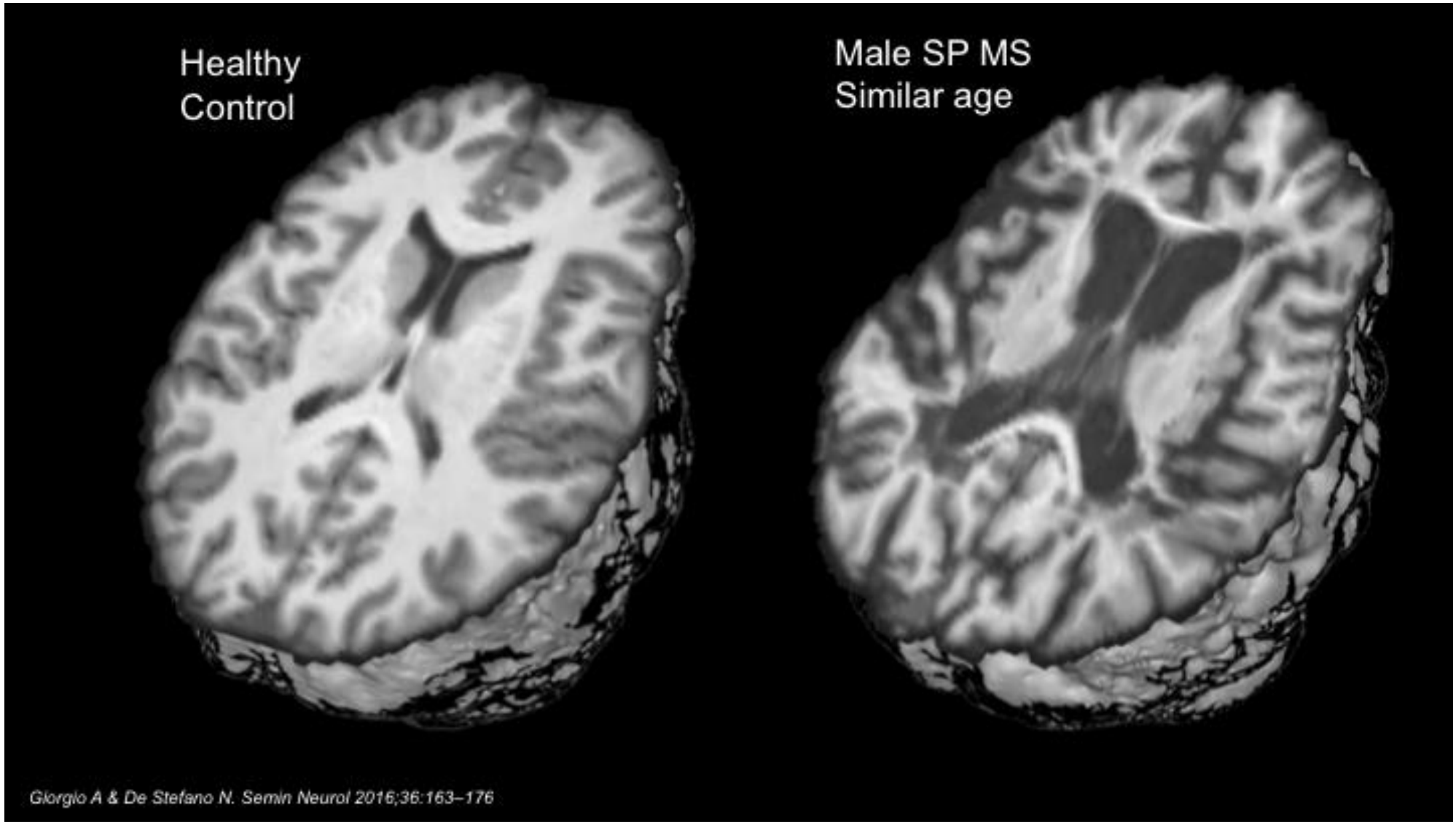
1. Pelletier D et al. ACTRIMS-ECTRIMS 2017, P741

Conclusions

- Global MRI-derived measures of brain volumes are feasible, sensitive to changes and clinically relevant.
- Measures of MRI-derived brain volumes have been extensively used in clinical studies as end points in clinical trials
- Whole brain atrophy measures can reliably monitoring therapeutic intervention in clinical trials.


Grazie per la vostra attenzione

Brain Atrophy in MS



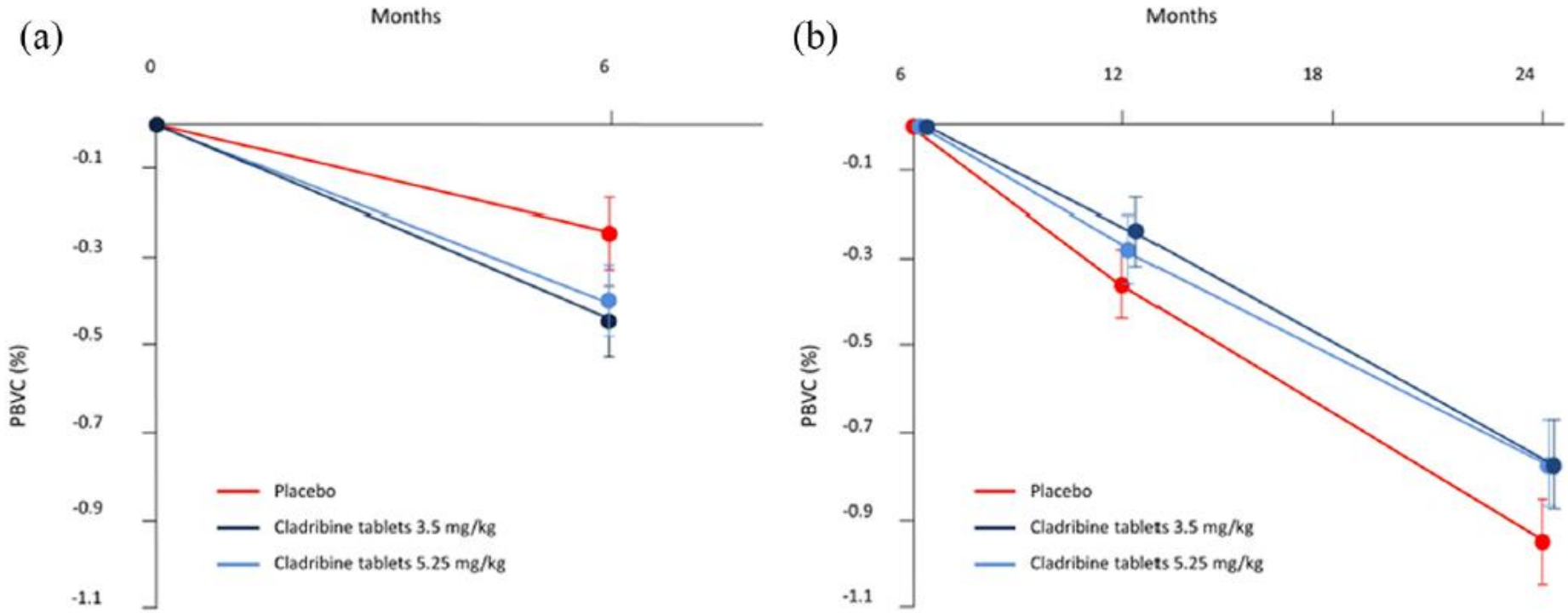
MULTIPLE SCLEROSIS JOURNAL | MSJ

Short Report

Reduced brain atrophy rates are associated with lower risk of disability progression in patients with relapsing multiple sclerosis treated with cladribine tablets

Multiple Sclerosis Journal
1–5
DOI: 10.1177/1352458516690269

Nicola De Stefano, Antonio Giorgio, Marco Battaglini, Alessandro De Leucio, Christine Hicking, Fernando Dangond, Gavin Giovannoni and Maria Pia Sormani



Data from CLARITY suggest that Cladribine can significantly reduce brain atrophy vs placebo[a]

Cladribine significantly reduces brain atrophy vs placebo[1]

Residual rates in treated patients were close to the physiological rates[1]

Brain atrophy reduction correlates with a reduced risk of disability progression[1]

[a]As these are data from a *post hoc* analysis, no conclusions can be drawn with regards to clinical outcome. Further randomised, controlled clinical trials will be necessary to corroborate these findings

CLARITY, Cladribine Tablets Treating Multiple Sclerosis Orally; RMS, relapsing MS

1. De Stefano N et al. Mult Scler 2017.