Life Long Brain Health and DMT Comparative Effectiveness

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12 Month Disclosures

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MS Heresy (Vollmer)

- MS is not a disease of myelin. It is a disease of the CNS and its impact on neurons is the key driver of disability and long term outcomes.
- It is inflammation driven by B cells derived from deep cervical lymph nodes from factors coming from the CNS that are the key drivers of MS inflammation.
- The key impact of the adaptive immune attack on the CNS is activation of astrocytes leading to production NO and TNF and other toxic intermediates that lead to death of neurons and oligodendrocytes (the basis for add on therapies in the future).
- The only difference between RRMS and Progressive MS is the loss of Neurological Reserve in Progressive MS caused by subclinical and clinical disease in early MS.

Educational Objectives:

1) To introduce the concept of **First Generation First Line DMTs, Second Generation First Line DMTs and 5th Line DMTs.**

2) To review the concept of **Neurological Reserve** as it pertains to MS and its implications for maintaining Life Long Brain Health as a Key Goal in the treatment of MS.

3) To discuss the **relative safety and efficacy** of the 15 approved or about to be approved disease modifying therapies in multiple sclerosis and its implication for maintaining **Life Long Brain Health in MS.**

Natural History of Untreated MS:

- Rate of Brain Volume Loss in early MS is 7x greater in MS patients than age matched controls beginning at onset.[1]
- Median age of reaching DSS of 4 is 44.3 years.[2]
- Median age of reaching DSS of 6 is 54.7 years.[2]
- By 30 years of disease duration 75% of RRMS patients will have entered the secondary progressive phase of MS.[2]
- Life Expectancy reduced by 5 to 10 years.[2]
- **Rate of "Benign MS" (defined as EDSS< or = 4) at 30 years disease duration: 13%.[2]**

1. Vollmer T, et al; *J Neurol Sci* 357:1-2; 8—18 Oct. 2015
2.Confavreux, Compston, Chapter 4,
McAlpine"s Multiple Sclerosis, 4th edition, 2006

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Modern Classification of MS DMTs:

- **First Generation First Line DMTS (FirstGen DMTs):**
  - **Interferon Beta 1b**
  - **Interferon Beta 1a IM**
  - **Interferon Beta 1a Sub Q**
  - **Pegylated Interferon Beta 1a**
  - **Glatiramer Acetate**
  - **Teriflunomide**
- **Second Generation First Line DMTS (SecGen DMTs):**
  - **Natalizumab in Repetitively JC Ab Negative Patients**
  - **Fingolimod**
  - **Dimethyl Fumarate**
  - **Ocrelizumab/Rituximab**

Modern Classification of MS DMTs (cont.):

- Third **(Fifth)** Line Agents (not appropriate for first line use and will not be discussed today):
  - Mitoxantrone- Acute Leukemia, Congestive Heart failure,
    - Serious Infections
  - Alemtuzumab- Serious Autoimmune Diseases, Cancer,
    - Serious Infections
  - Daclizumab- Severe Liver Disease, Immune-mediated Disorders (skin, colitis)
  - Natalizumab in JCV Ab positive patients- PML
  - Bone Marrow Transplant- Infections, cancer, accelerated brain atrophy

Key Points for Discussion:

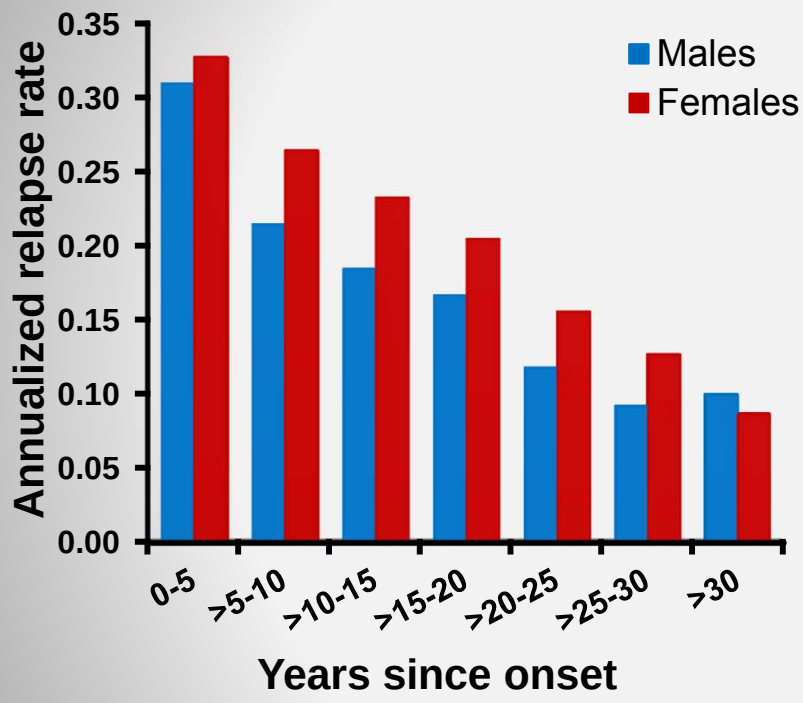
1) **MS disease activity is greatest at onset and declines beginning at age 35 on average.**

2) **The CNS has limited ability (Neurological Reserve) to buffer for subclinical new lesions and accelerated brain atrophy in early MS.**

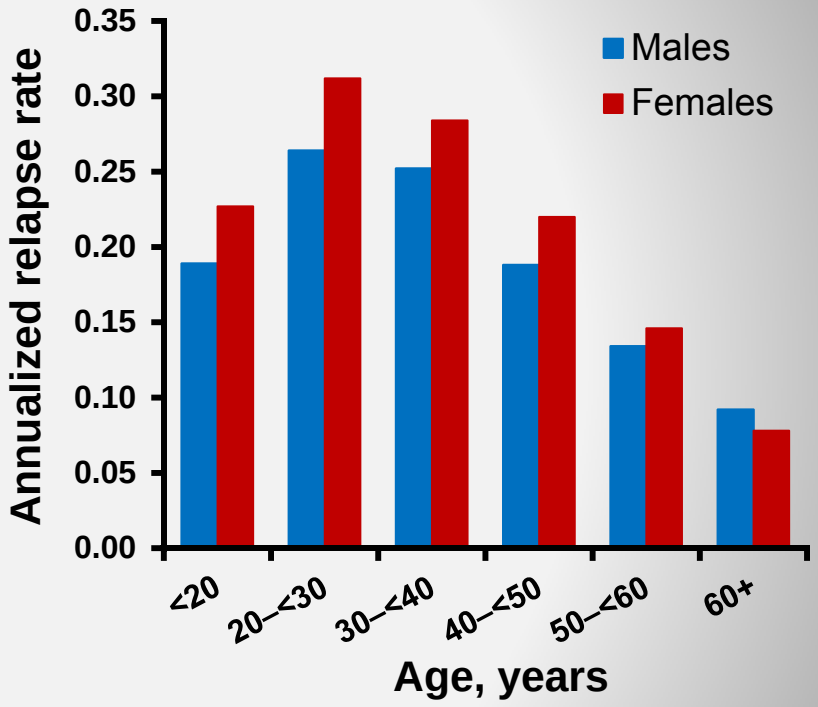
3) **All DMTs are not equal.**

Relapses in MS are Age and Time-Dependent[1]

Relapse rate from onset (N=2,477)



Relapse rate by patient age (N=2,477)



"From the population perspective, the impact of any therapeutic agent targeting the inflammatory processes in MS-- has the greatest potential during periods of high disease activity"

Adapted from: 1. Tremlett H et al. *J Neurol Neurosurg Psych.* 2008

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Most Newly Active MRI Lesions are Clinically Silent:

- Monthly MRI in seven patients over 1 year
  - 50 new brain lesions
  - Only five relapses

	Case number						
	1	2	3	4	5	6	7
Lesion score[a]	79	11	97	129	27	50	50
Number of new contrast-enhancing lesions							
Month 1	0	0	5	0	2	0	1
Month 2	0	1	10 (13)	3	1	0	0
Month 3	1	0	2 (6)	2	1	0	0
Month 4	0	0	2 (3)	2	0	0	1
Month 5	–	0	1 (2)	1	3	0	0
Month 6	–	0	2	1	1	0	0
Month 7	–	0	2	1	0	0	–
Month 8	–	0	0	0 (1)	0	–	–
Month 9	–	1	0	0	2	–	–
Month 10	–	0	1	–	0	–	–
Month 11	–	0	–	–	–	–	–
Month 12	–	0	–	–	–	–	–

MRI lesion associated with a clinical relapse

– No examination

-Lesion score was determined on unenhanced images by T2-weighting and a semiquantitative scoring system; the score represents the number of lesions on the initial scan

-Numbers in parentheses indicate the total number of new, persistently enhancing and re-enhancing lesions in cases where not all enhancing lesions were new lesions

Table adapted with permission from Barkhof F *et al. Am J Roentgenol* 1992;159:1041–7

Key Points for Discussion:

1) MS disease activity is greatest at onset.

2) The CNS has limited ability (Neurological Reserve) to buffer for subclinical new lesions and accelerated brain atrophy in early MS.

3) All DMTs are not equal.

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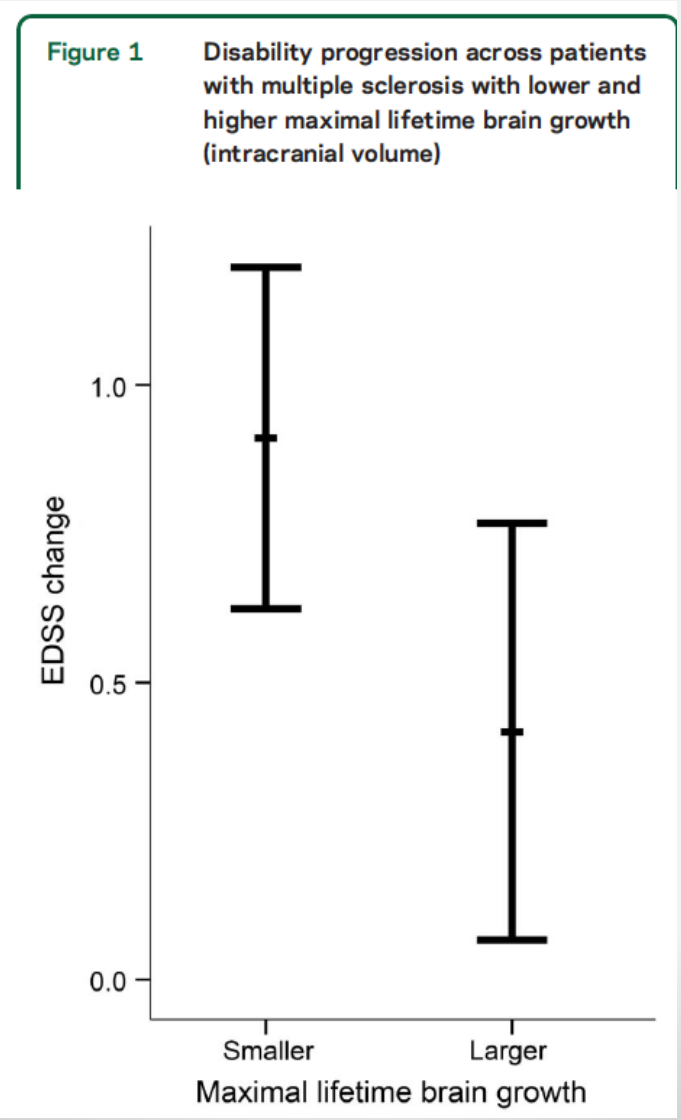
Concept: Neurological Reserve in MS

- **Brain (Neurological) Reserve** = capacity of the brain to compensate for subclinical MS lesions and recover from relapses.
- **Cognitive Reserve**= the increase in Brain Reserve that comes from intellectual and physical activity (Healthy Lifestyle)
- **Maintaining Brain and Cognitive Reserve (Neurological Reserve)** are key to minimizing the effects of normal ageing on neurological function.
- **Neurological Reserve** is, at least partially, related to **Brain and Spinal Cord Volume.**
- Maintaining **Neurolgical Reserve (Brain Volume)** in early MS is critical to maximizing **Neurological Function** in late life for MS patients.

1. Nithianantharajah J. Hannan, A; Progress in Neurobiology, (2009) 89 369-382
2. Rudrauf D, Adv in Neuroscience (2014) Article ID 462765, 28 pages

Larger Brains decrease risk of Disability Progression over 5 years:



Sumnowski, et al,
Neurology 86, 2006-2009
May 24, 2016

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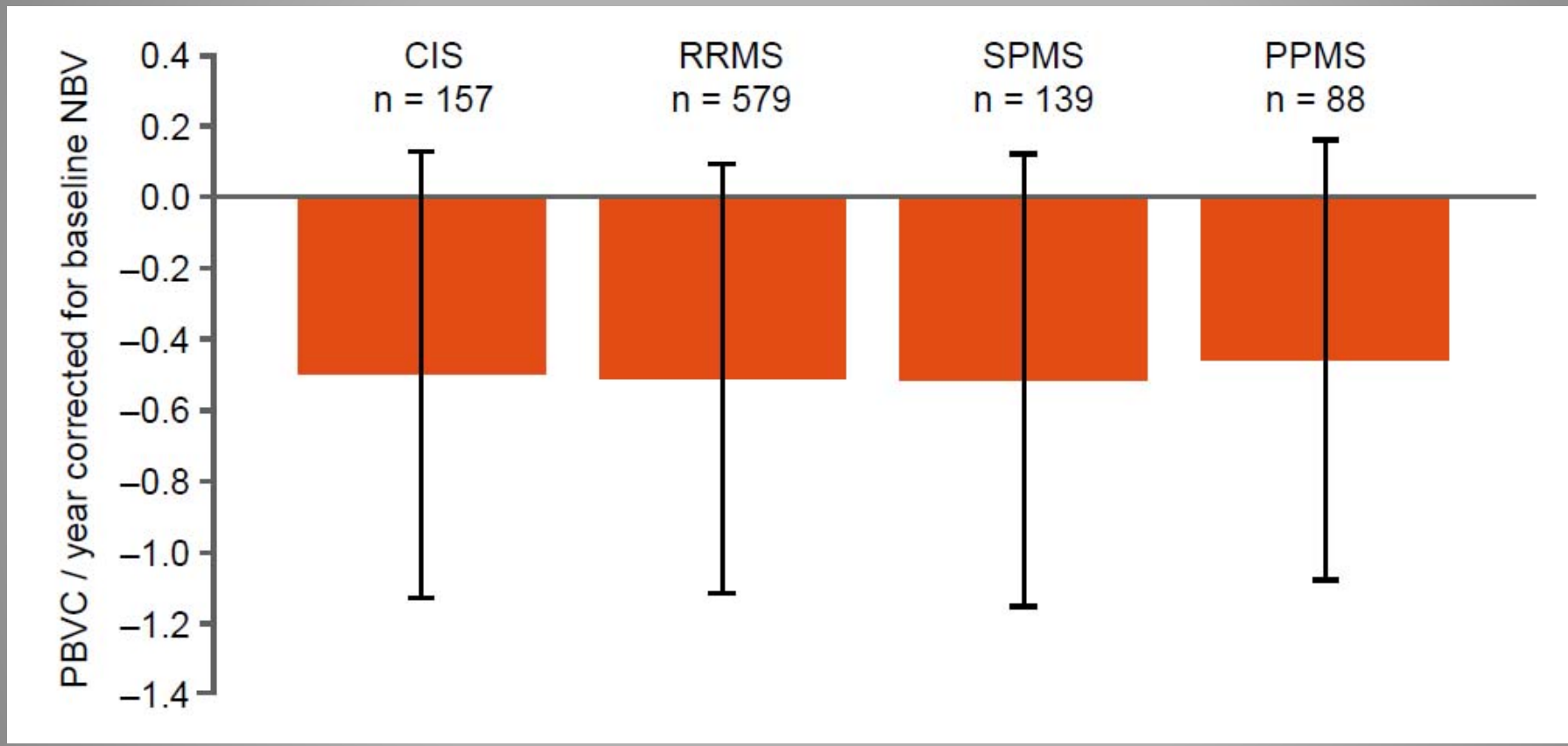
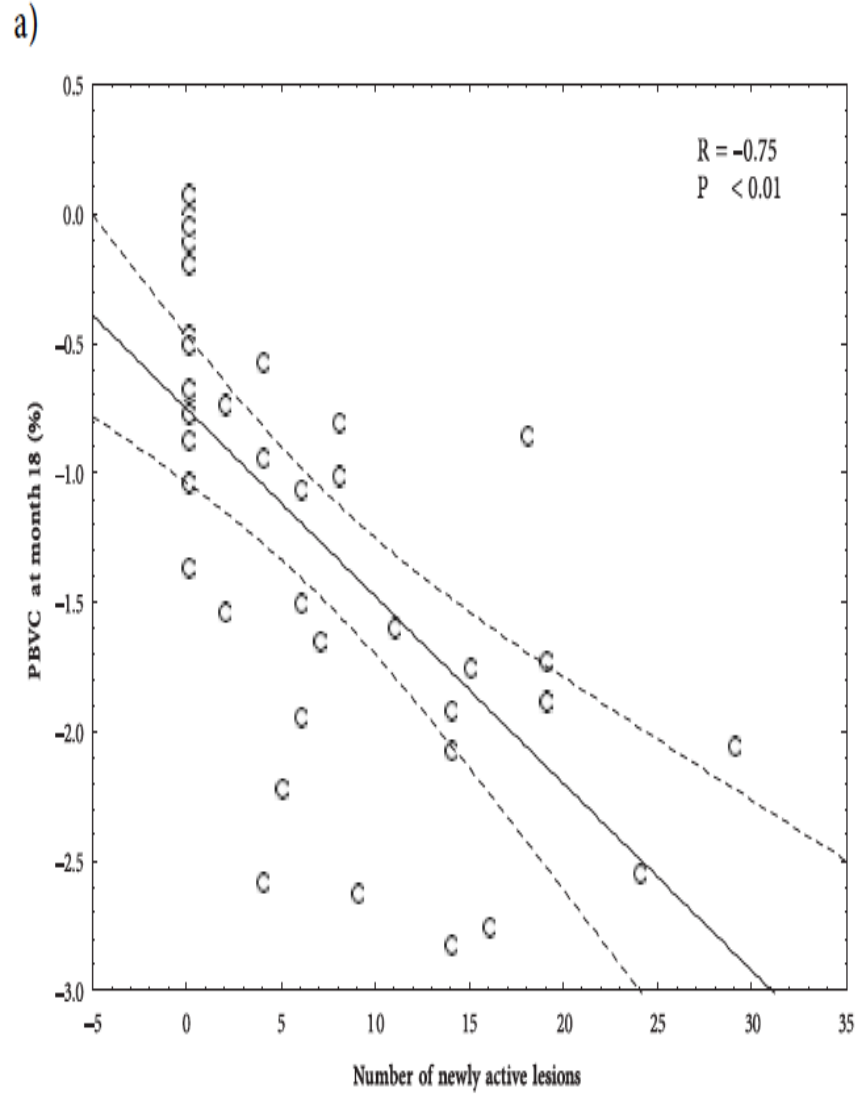
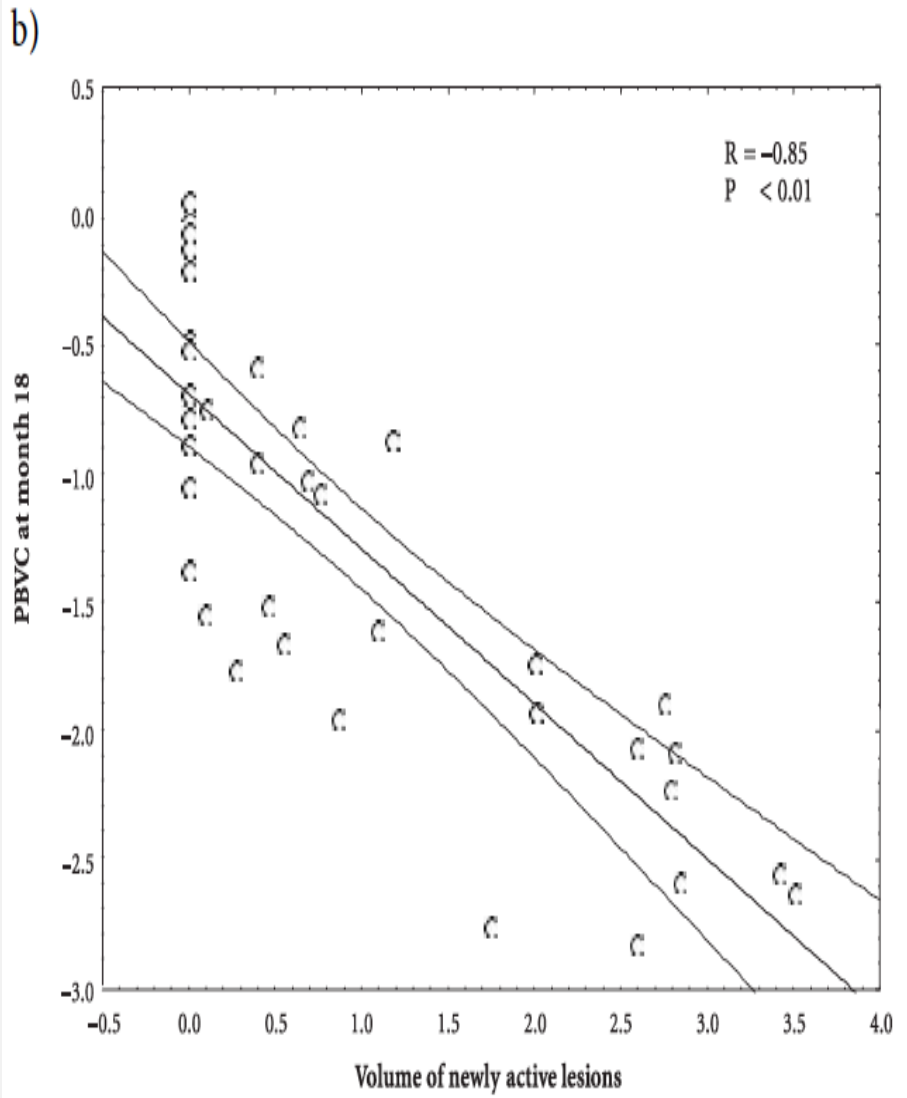
Brain atrophy occurs early in MS



Adapted from: De Stefano N et al. Neurology 2010; 74: 1868–76.

Newly Active MRI Lesions Drive Brain Atrophy in CIS (MS):





Paolillo, et al, J Neurol (2004)251: 432-439

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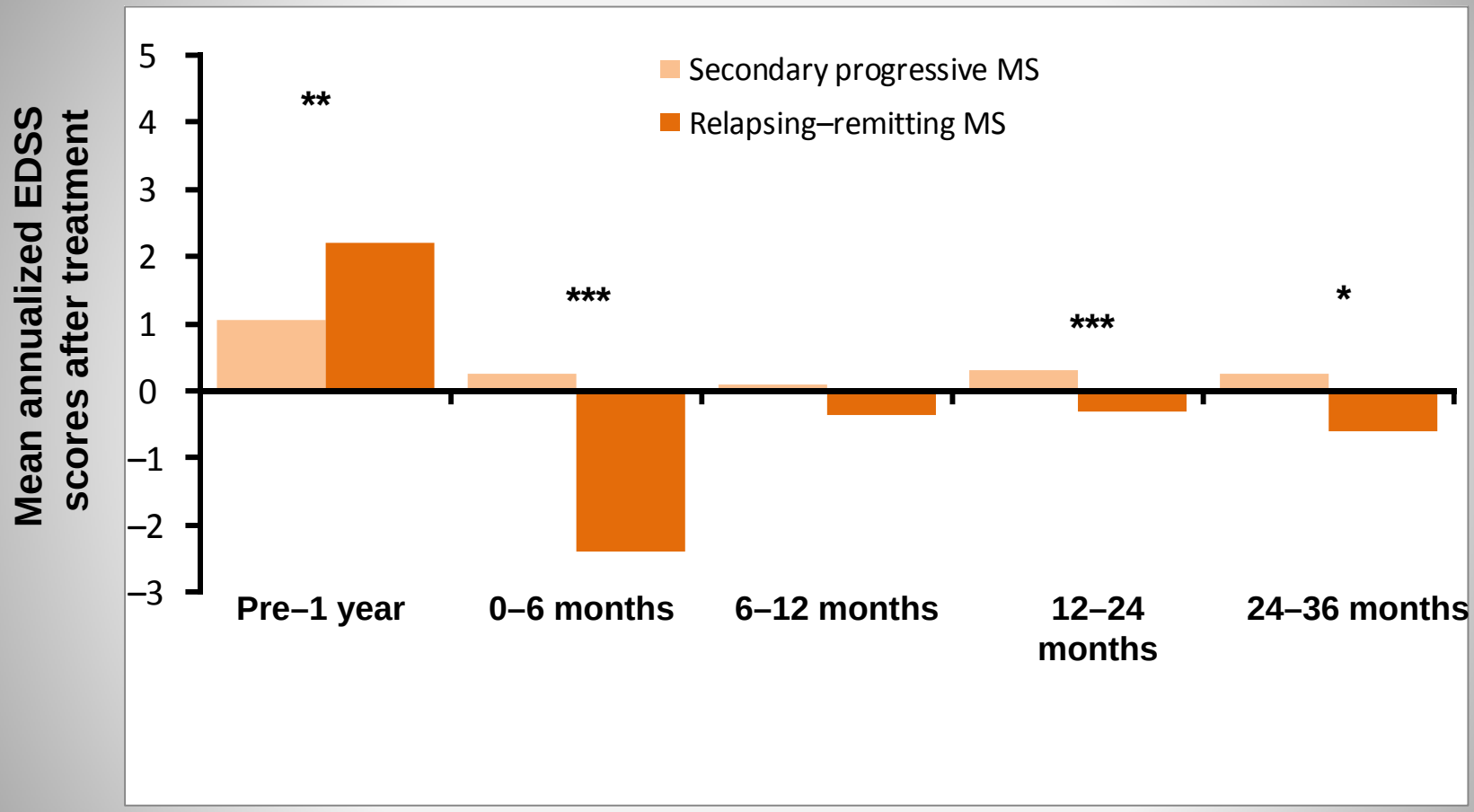
Brain Atrophy and New Lesion Formation Predict Disability:

TABLE 2. Sensitivity Analysis: Coefficients of Determination (R^2) Values according to Different Subgroups of Trials and Different Methods of Analysis

	R^2 Atrophy (p)	R^2 Lesions (p)	R^2 Atrophy + Lesions (p)
Trial excluded[a]			
MSCRG[13]	0.48 (0.001)	0.63 (<0.001)	0.76 (<0.001)
AFFIRM[14]	0.43 (0.004)	0.58 (<0.001)	0.72 (<0.001)
SENTINEL[15]	0.48 (0.001)	0.68 (<0.001)	0.79 (<0.001)
REGARD[16]	0.28 (0.016)	0.50 (0.001)	0.65 (0.001)
BEYOND[17]	0.61 (<0.001)	0.42 (0.003)	0.72 (<0.001)
FREEDOMS[18]	0.45 (0.002)	0.59 (<0.001)	0.74 (0.001)
CLARITY[19]	0.50 (0.001)	0.60 (<0.001)	0.75 (<0.001)
TEMSO[20]	0.58 (<0.001)	0.61 (<0.001)	0.80 (<0.001)
DEFINE[21]	0.49 (0.001)	0.60 (<0.001)	0.75 (<0.001)
CONFIRM[22]	0.52 (<0.001)	0.60 (<0.001)	0.76 (<0.001)
CARE-MSI[23]	0.50 (0.001)	0.71 (<0.001)	0.77 (<0.001)
CARE-MSII[24]	0.46 (0.002)	0.65 (<0.001)	0.77 (<0.001)
FREEDOMSII[25]	0.49 (0.001)	0.61 (<0.001)	0.79 (<0.001)

Sormani M, et al. Atrophy Surrogacy in MS; Ann Neurol. 2014; 75:43-49

The Window of Therapeutic Opportunity in MS[1]



1. Coles A, *et al. J Neurol* 2006; Comparison of change in disability between the relapsing–remitting and secondary progressive cohorts. The data are annualized to allow comparison between time epochs of different duration.* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Mann–Whitney U test)

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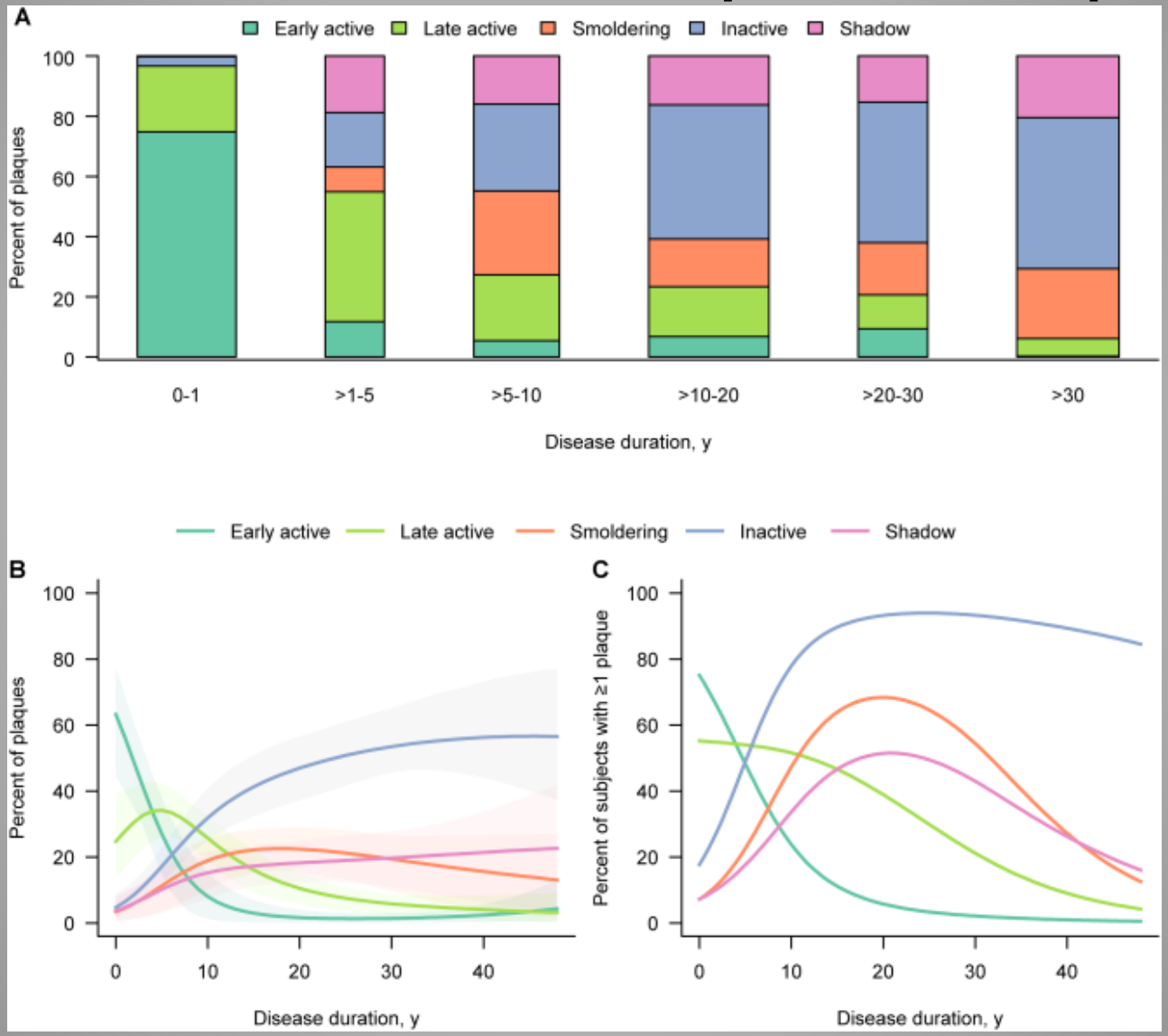
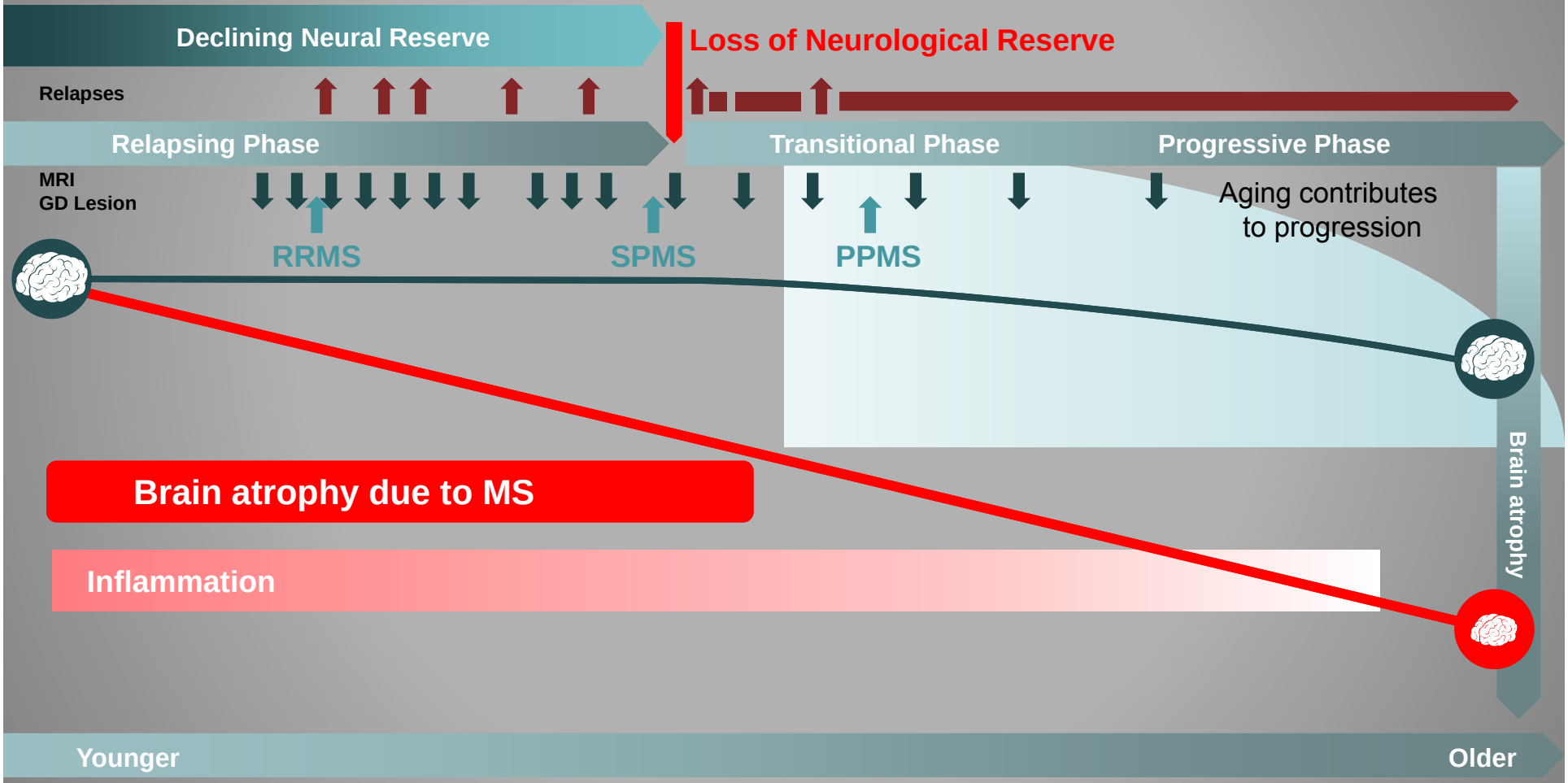
Clinical and pathological insights into the dynamic nature of the white matter multiple sclerosis plaque



Annals of Neurology
Volume 78, Issue 5, pages 710-721, 24 AUG 2015 DOI: 10.1002/ana.24497
http://onlinelibrary.wiley.com/doi/10.1002/ana.24497/full#ana24497-fig-0003

Loss of Neurological Reserve Explains Onset of and lack of Resilience in Progressive MS



BBB, blood-brain barrier; Gd, gadolinium enhancing;
PPMS, primary progressive multiple sclerosis;
SPMS, secondary progressive multiple sclerosis

THE PRIMARY GOAL IN THE TREATMENT OF MS WITH DMTS:

- **To maximize lifelong brain health** (Preserve brain volume in early MS in order to preserve Neurological Reserve to buffer for the effect of MS and normal ageing in late life.)
- **To accomplish this we need to:**

1. Diagnose MS as early as possible.

2. Help patients adopt a healthy, active lifestyle to avoid comorbidities that would also tax **Neuorological Reserve** and help them build **Reserve** through exercise/learning.

3. **Use the OPTIMAL DMT with an acceptable safety profile for the individual MS patient as early in the disease course as possible.**

Key Points for Discussion:

1) MS disease activity is greatest at onset.

2) The CNS has limited ability (Neurological Reserve) to buffer for subclinical new lesions and accelerated brain atrophy in early MS.

3) **All DMTs are not created equal.**

Key Question: Which Strategy Will Provide The Best Outcomes For MS Patients and Society?

- **Escalation Therapy-** In new onset MS start with **First Generation First Line DMTs** and wait for "treatment failure" before proceeding to Second Generation DMTs.

- **Optimized Therapy-** In new onset MS start with **Second Generation First Line DMTs** based on careful patient selection and monitor to maximize safety with the goal being to minimize CNS injury due to MS as much as possible in early disease in order to maximize life long brain health, minimize chance of entering SPMS and improve outcomes in later life.

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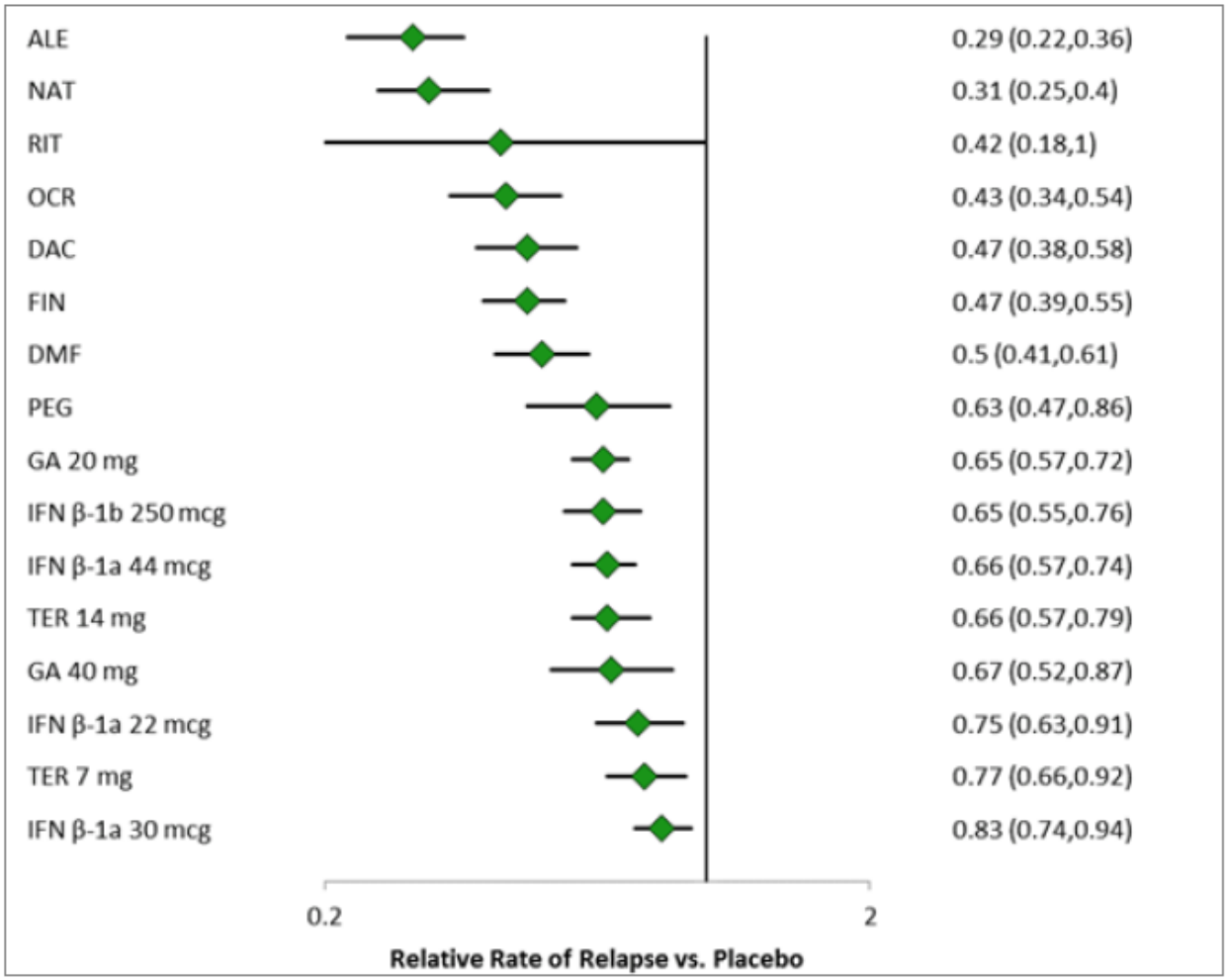
Myths Concerning FirstGen DMTs vs SecGen DMTs:

- FirstGen DMTs are cheaper than SecGen DMTs.- **False**
- FirstGen DMTs are safer than SecGen DMTs-not with appropriate patient selection.- **False**
- Some MS patients do perfectly well on FirstGen DMTs- Possibly, but can you identify them at onset with a high degree of certainty such that you don't let the poor responders accumulate unnecessary disability?- **No**
- We can identify treatment failure on FirstGen DMTs and can switch to SecGen DMTs then.- Continued Brain Atrophy will lead to increased late life disability?-**No**
- Use of SecGen DMTs is aggressive therapy- Wrong, it is **Optimized Therapy**.

MS DMT Comparative Effectiveness For ARR:

Figure 3. Forest Plot of DMTs vs. Placebo for Annualized Relapse Rate



Legend: The diamonds represent the point estimate from the NMA for the relative risk of relapse rate for each drug compared to placebo and the horizontal bars represent the 95% credible intervals. Any numbers less than 1 indicate a reduction in the relapse rate compared to placebo.

Comparative Safety for SAEs for MS DMTS:

Table 11. Harms of DMTs

Drug (Brand name)	Major safety concerns	D/C rates	SAEs
Subcutaneous injections			
Interferon β-1a 30 mcg (Avonex)	Depression, suicide, psychosis, liver toxicity, seizures, allergic reactions, CHF, ↓ peripheral blood counts, thrombotic microangiopathy, flu-like symptoms are common (49%)	4%	14%
Interferon β-1b 250 mcg (Betaseron, Extavia)	Liver toxicity, allergic reactions, depression, suicide, CHF, injection site necrosis (4%), leukopenia, thrombotic microangiopathy, flu-like symptoms are common (57%)	6%	11%
Glatiramer acetate (Copaxone, Glatopa)	Post-injection reaction (16%), transient chest pain (13%), lipoatrophy, skin necrosis, injection site reactions	3%	13%
Interferon β-1a 22/44 mcg (Rebif)	Depression, suicide, livery injury, allergic reactions, ↓ peripheral blood counts, thrombotic microangiopathy, seizures, injection site reactions common (~90%), injection site necrosis (3%), flu-like symptoms are common (59%)	5%	16%
Peginterferon β-1a (Plegridy)	Liver toxicity, depression, suicide, seizures, allergic reactions, CHF, ↓ peripheral blood counts, thrombotic microangiopathy, flu-like symptoms are common (47%)	5%	11%
Daclizumab (Zinbryta)	↑ risk of infection and skin reactions. Hypersensitivity reactions, depression, and suicide. Boxed warning: significant hepatic injury (0.7%), autoimmune hepatitis (0.3%), other immune mediated disorders. Serious immune-mediated reactions in 5% of patients. Only available through REMS.*	15%	22%

Draft Evidence Report: DMTs for RRMS and PPMS

Comparative Safety for SAEs for MS DMTS:

Drug (Brand name)	Major safety concerns	D/C rates	SAEs
Oral agents			
Fingolimod (Gilenya)	1st dose bradycardia, ↑ risk of serious infection, PML, macular edema, PRES, ↓ respiratory function (↓FEV1), liver toxicity, ↑BP, basal cell carcinoma (2%). Only available through REMS.*	12%	10%
Teriflunomide (Aubagio)	Boxed warning for hepatotoxicity (including fatal liver failure) and teratogenicity. ↓ WBC, ↑ risk of infection, peripheral neuropathy (1.4 – 1.9%); ↑ BP (3-4%). Hair thinning.	13%	13%
Dimethyl fumarate (Tecfidera)	Anaphylaxis, angioedema, PML, ↓ WBC, flushing (40%)	14%	18%
Intravenous infusions			
Natalizumab (Tysabri)	Boxed warning for PML. ↑ risk for herpes encephalitis and meningitis, liver toxicity, hypersensitivity (including anaphylaxis) reactions, ↑ risk of infection. Only available through REMS.*	6%	19%
Alemtuzumab (Lemtrada)	Boxed warning for serious (sometimes fatal) autoimmune conditions such as ITP, life-threatening infusion reactions, ↑ risk of malignancies. Infusion reactions (92%), rash (53%), lymphopenia (99.9%). Only available through REMS.*	2%	33%
Ocrelizumab (Ocrevus)	Risk of infection, possible ↑ risk for PML (due more to being related to rituximab and ofatumumab)[100]	3%	7%
Rituximab (Rituxan)	Boxed warning for fatal infusion reactions within 24 hours of infusion, severe mucocutaneous reactions (including fatalities), HBV reactivation, PML (all for non-MS indications). ↑ risk of infection, ↑ risk of cardiac arrhythmia, bowel obstruction, cytopenias	4%	13%

Draft Evidence Report: DMTs for RRMS and PPMS

Even SecGen DMTs May Not Be Equal:

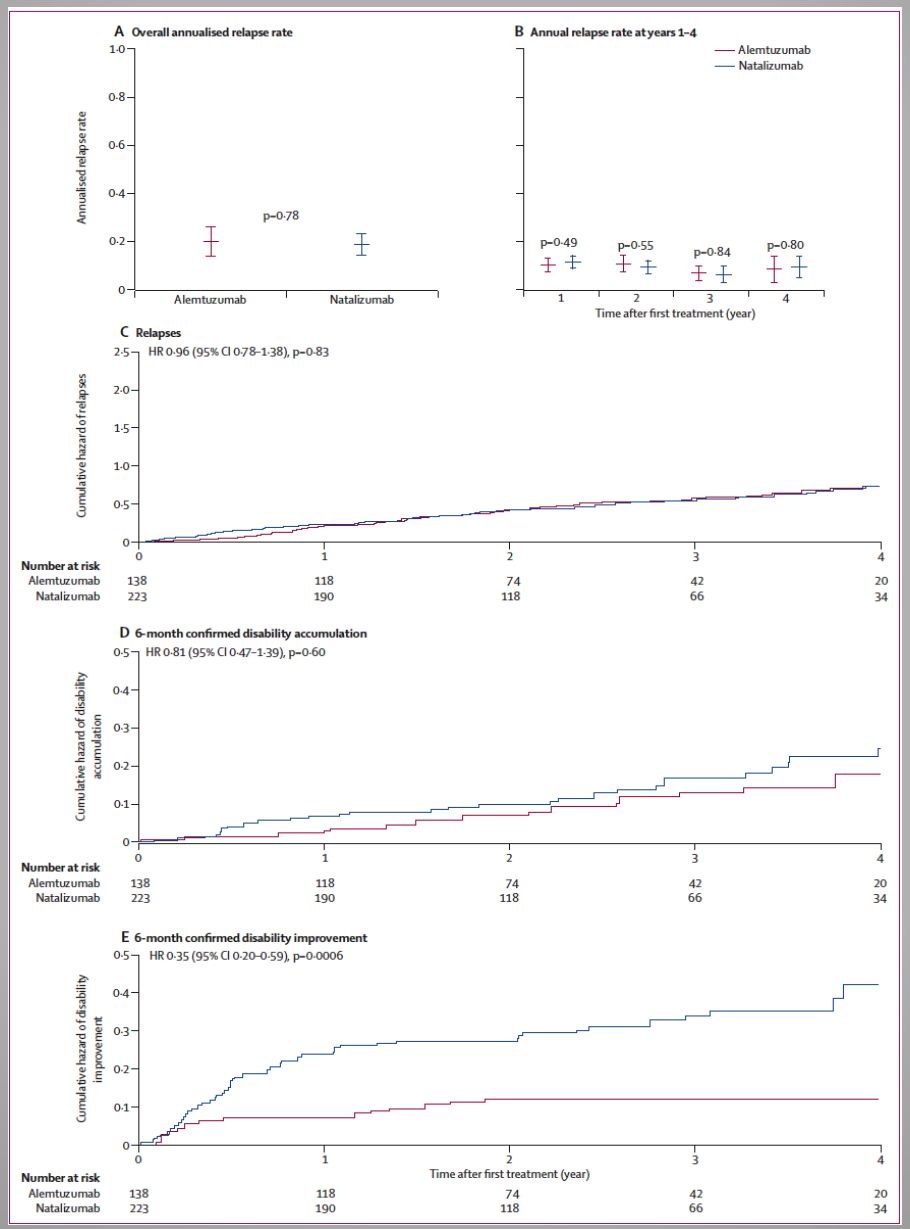
TABLE 2. Distribution of Outcomes for the RTX and FGL Groups

Result	Stockholm		Gothenburg		Umeå		Total	
	RTX, n = 77	FGL, n = 79	RTX, n = 8	FGL, n = 56	RTX, n = 29	FGL, n = 7	RTX, n = 114	FGL, n = 142
Gd^+ lesions, within 1.5 years								
Patients with positive scan	1	10	0	9	0	4	1	23
Patients with valid scan[a]	36	48	6	40	27	7	69	95
Patients with positive scan/ patients with valid scan	0.03	0.21	0.00	0.23	0.00	0.57	0.01	0.24
Gd^+/new T2 lesions, within 1.5 years								
Patients with positive scan	1	15	0	11	0	5	1	31
Patients with valid scan[b]	42	60	6	40	27	7	75	107
Patients with positive scan/ patients with valid scan	0.02	0.25	0.00	0.28	0.00	0.71	0.01	0.29
Clinical relapse, within 1.5 years								
Patients with clinical relapse	1	19	0	6	1	0	2	25
Person-years	67.85	83.63	11.56	62.17	42.03	8.50	121.44	154.30
Incidence of clinical relapse per year	0.01	0.23	0.00	0.10	0.02	0.00	0.02	0.16
AE, within 1.5 years								
Patients with AE	2	12	3	18	1	0	6	30
Person-years	67.45	91.22	9.17	48.32	42.09	8.50	118.71	148.04
Incidence of AE per year	0.03	0.16	0.33	0.37	0.02	0.00	0.05	0.20
First-dosing AEs								
Patients with first-dosing AE	22	5	3	5	5	0	30	10
First-dosing AEs/patient	0.29	0.06	0.38	0.09	0.17	0.00	0.26	0.07
Drug survival, within 1.5 years								
Patients who discontinued therapy	2	26	0	11	0	3	2	40
Person-years	67.87	94.82	11.56	66.15	42.31	8.50	121.74	169.47
Incidence of therapy discontinuation per year	0.03	0.27	0.00	0.17	0.00	0.35	0.02	0.24

[a]A scan done at least 3 months after treatment start and before treatment ended.
[b]A scan done at least 3 months after treatment start and before treatment ended, or a scan done after treatment start and before treatment ended, compared to a scan done after treatment start.
AE = adverse event; FGL = fingolimod; Gd^+ = gadolinium enhancing; RTX = rituximab.

Alping, et al; Rituximab vs Fingolimod; Ann Neurol; 2016;79: 950-958

Alemtuzumab vs Natalizumab in Key Outcomes



Kalinic, T; et al. Treatment effectiveness of alemtuzumab vs natlizumab, fingolimod and Inf Beta in RRMS: a cohort study. The Lancet.

Published Online
February 10, 2017
http://dx.doi.org/10.1016/S1474-4422(17)30007-8

Evolution of Therapeutic Goals In MS:

- 1993- Decrease annualized relapse rate **(ARR).**
- 1996- Improve tolerability and safety.
- 2006- Decrease AAR further, decrease sustained accumulation of disability **(SAD)** and decrease rate of brain volume loss.
- **2017-is no evidence of disease activity (NEDA) and for RRMS patients improvement in function and QOL by year 2 of treatment (NEDA+) and to preserve brain volume to maximize Life Long Brain Health.**

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The Future of Clinical Trials in MS: Add On Clinical Trials:

- **Unmet Need #1: Therapies that can enhance re-myelination of CNS axons. (Biotin?, Alpha Lipoic Acid?, Clobetazol?, Miconazole?, S1P antagonists?)**
- **Unmet Need #2: Therapies that can inhibit Type II astrocytes and decrease the up regulation of TNF, iNOS and other noxious intermediates. (Laquinimod?, S1P antagonists?, Dimethyl Fumarate?, Statins?)**
- **Unmet Need #3: Therapies that can enhance neurite sprouting and other mechanisms that support cortical re-organization. (S1P antagonists?)**
- **Unmet Need #4: Therapies that can minimize further neuronal loss and normalize rate of brain volume loss. (laquinimod?, S1P antagonists? Dimethyl Fumarate?, Statins?)**

Thank You