Individualizing Therapy and Optimizing Treatments in MS

A CME-certified **Neurology Exchange** Activity

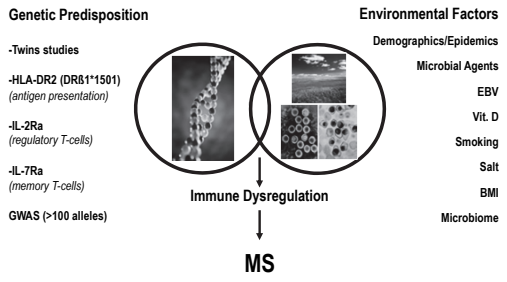
Jointly provided by Potomac Center for Medical Education and Rockpointe
This program is supported by an educational grant from EMD Serono

Educational Objectives

- Incorporate the latest MRI criteria and other prognostic measures to improve diagnosis and initiate DMD therapy earlier in the course of MS
- Assess the mechanisms of action and efficacy and safety profiles of current and emerging DMD therapies to develop individualized MS therapies that optimize adherence and improve patient outcomes
- Utilize evidence from recent diagnostic and prognostic biomarker studies to improve monitoring of disease activity and response to DMD therapy in MS

Multiple Sclerosis

An Immuno-genetic Disease



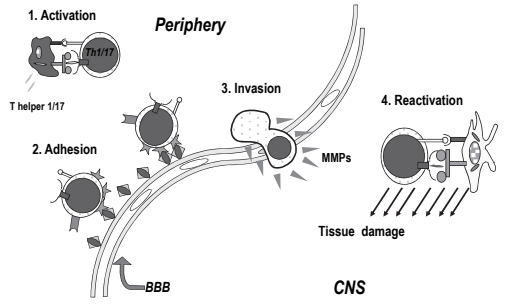
Images courtesy of Dhib-Jalbut S; 2013.

Additional Disease Modifiers

- Poly unsaturated fatty acids diet (PUFAs)[1]
- Body mass index and role of adipokines[2]
- Melatonin[3]

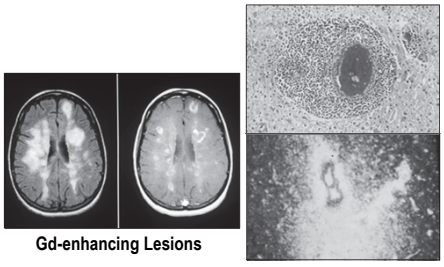
1. Bjornevik et al. Presented at: ECTRIMS 2015, abstract #1054.
2. Hagman et al. Presented at: ECTRIMS 2015, P725.
3. Farez et al. Presented at: ECTRIMS 2015, abstract #46.

A View of MS Immunopathogenesis



Courtesy of Amit Bar-Or.

Pathology of MRI Gd-enhancing Lesion

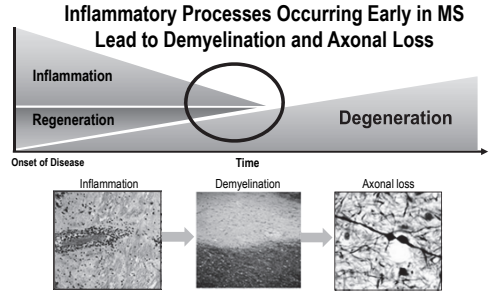


Gd-enhancing Lesions

Perivascular inflammation and demyelination

Images courtesy of Dhib-Jalbut S.

Immunopathogenesis of MS



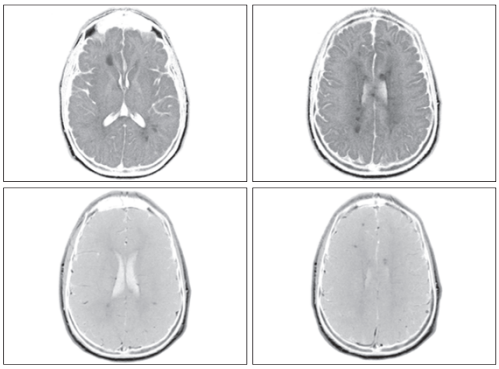
Compston A et al. *Lancet*. 2008;372:1502-1517.
Paolillo A et al. *J Neurol*. 2004;251:432-439.
Kuhlmann T et al. *Brain*. 2002;125:2202-2212.
Trapp BD et al. *Curr Opin Neurol*. 1999;12:295-302.

Case Presentation

- 27-year-old man previously healthy develops weakness and tingling in both legs, imbalance and impaired bladder emptying two weeks after upper respiratory infection and possible fever
- PMH positive for Lyme disease (erythema chronicum migrans) at age 12, treated with antibiotics
- FH positive for MS in paternal grandmother

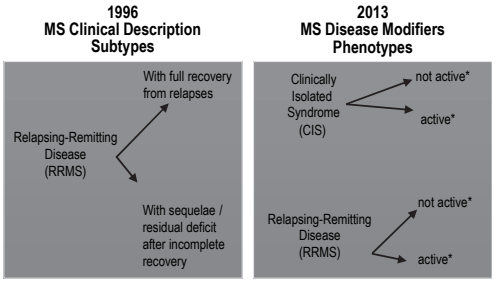
Case Presentation *(continued)*

- Brain MRI shows multiple T2H, including periventricular ovoid lesions, juxtacortical lesions, and cerebellar lesion; also, multiple very small gadolinium-enhancing lesions
- Cervical spine MRI shows multiple T2H
- CSF positive for oligoclonal bands, not present in serum, and elevated IgG index



1996 vs 2013 MS Phenotype Descriptions

Relapsing-Remitting Disease

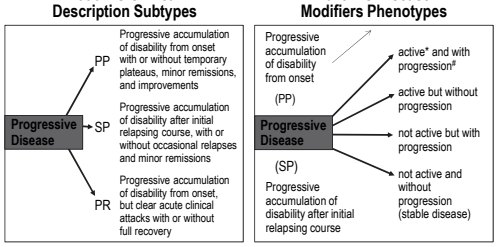


*activity = clinical relapses and/or MRI (Gd-enhancing MRI lesions; new/enlarging T2 lesions)

International Advisory Committee on Clinical Trials in MS. National Multiple Sclerosis Society (NMSS) and European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); 2013.

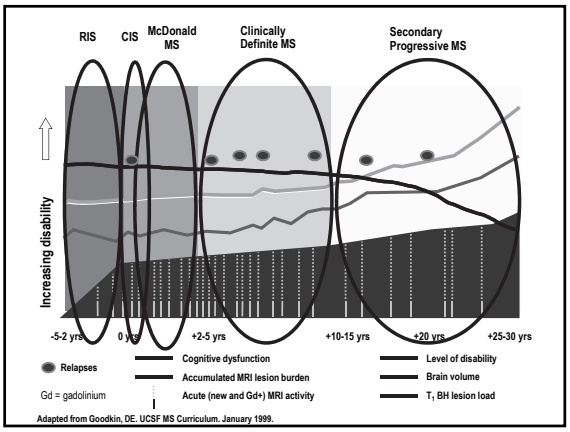
1996 vs 2013 MS Phenotype Descriptions

Progressive Disease

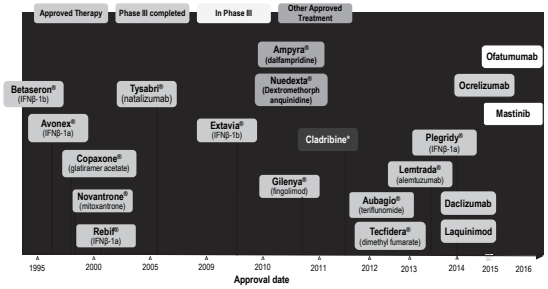


*activity = clinical relapses and/or MRI (Gd-enhancing MRI lesions; new/enlarging T2 lesions)
#progression measured by clinical evaluation at least annually

International Advisory Committee on Clinical Trials in MS. National Multiple Sclerosis Society (NMSS) and European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); 2013.



Existing and Emerging MS Therapies



*In March 2011, the FDA did not approve cladribine and requested Merck KGaA provide an improved understanding of its safety risks and overall benefit-risk profile.

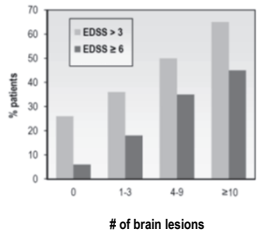
Predicting the Course of MS

- Clinical features of onset bout
  - Motor worse than sensory
  - Polyregional worse than monosymptomatic
  - Early bladder involvement poor prognosis
- Incomplete recovery from initial attack
- Short interval between attacks

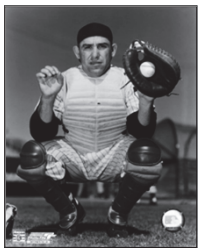
Prognosis

Initial MRI

- T2 lesion numbers
- Median EDSS at 20 years = 6 for ≥10 T2 lesions
- 3 or 4 Barkhof criteria moderate correlation with EDSS at 5 years



Fisniku LK. *Brain*. 2008;131:808-817.



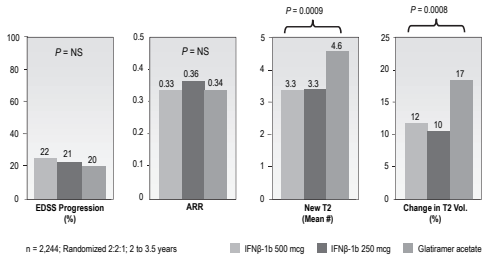
"The future ain't what it used to be."

— Lawrence Peter "Yogi" Berra

Making Treatment Decisions

Considering the Benefits and Risks

BEYOND: IFNβ-1b 250 or 500 µg vs Glatiramer Acetate



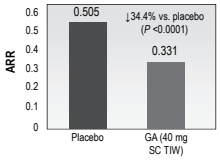
O'Connor P et al. *Lancet Neurol.* 2009;8:889-897.

Interferon Beta

INTERFERON	ADVERSE EVENTS	ROUTE AND FREQUENCY	COMMENTS
IFNB-1b (Betaseron)	Flu-like sx; depression, ISRs	SC every other day	No pre-filled syringe
IFNB-1a (Avonex)	Same but no ISRs	IM weekly	Flu-like sx may persist
IFNB-1a (Rebif)	Same as IFNB-1b	SC 3 times weekly	
IFNB-1a pegylated (Plegridy)	Same as IFNB-1b	SC every other week	Flu-like sx may persist and possibly be more intense

Glatiramer Acetate

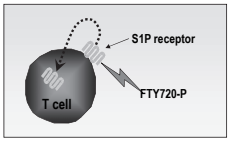
GA PREPARATION	DOSAGE	AEs	COMMENTS
Copaxone	20 mg daily	ISRs; Post-injection systemic reaction, lipoatrophy	1st available prep; ~30% ARR reduction
Copaxone	40 mg tiw	Same	~34% ARR reduction
Glatopa	20 mg daily	?Same	Pharmcologically equivalent; no human studies



Outcome	GA vs. Placebo	*P*-value
Cumulative no. of gd-enhancing lesions	44.8% ↓	<0.0001
Cumulative no. of new or enlarging T2 lesions	34.7% ↓	<0.0001

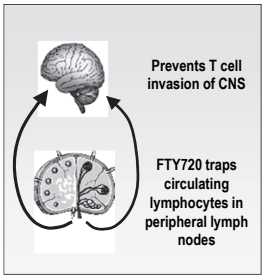
Kahn O et al. Presented at: European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) 2012; Lyon, France. Abstract 166.

Fingolimod (FTY720): Mode of Action



FTY720 results in internalization of the S1P1 receptor

This blocks lymphocyte egress from lymph nodes while sparing immune surveillance by circulating memory T cells



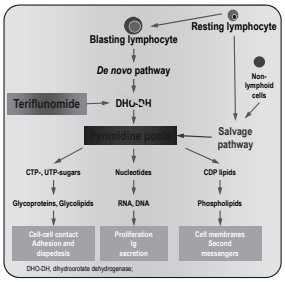
Cohen JA, Chun J. *Ann Neurol.* 2011;69:759-777.

Managing Patients on Fingolimod

- **Before Initiation of Treatment**
  - Baseline CBC and liver panel
  - Cardiac status and ECG
  - Baseline ophthalmological exam
  - Baseline dermatological exam
  - Varicella immune status
- **Baseline 6-hour monitoring because of potential bradycardia**
- **On Treatment Monitoring**
  - Follow CBC, liver panel
  - Ophthalmological f/u at 3-4 months and annually
  - Annual dermatological exam
  - Check BP
- **Infections**
  - 5 reported cases of PML
  - Rare cases of cryptococcal meningitis
  - Increased risk of shingles or VZV

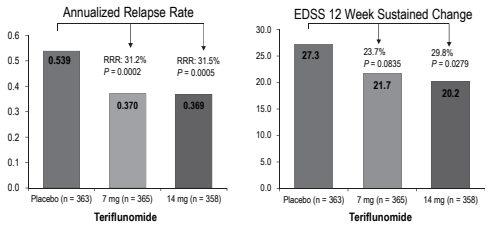
Teriflunomide: *A Selective Dihydroorotate Dehydrogenase Inhibitor*

- A newly approved oral disease-modifier for relapsing forms of MS (RMS)
- Blocks *de novo* pyrimidine synthesis, reducing T- and B-cell proliferation and function in response to autoantigens
- Preserves replication and function of cells (e.g. hemopoietic cells, memory T-cells) living on the existing pyrimidine pool (salvage pathway)



Miller A et al. Presented at: American Academy of Neurology (AAN) 2011, April 9-16; Honolulu, HI.

Teriflunomide for RRMS (Phase III TEMSO Study): Key Clinical Outcomes



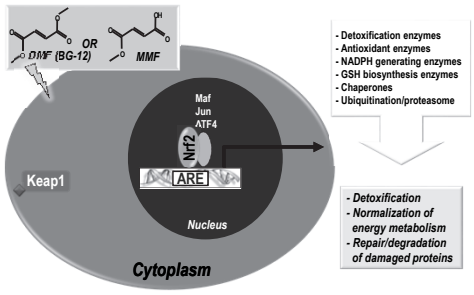
RRR = relative risk reduction

O'Connor P et al. *N Engl J Med*. 2011;365:1293-1303.

Tolerability Issues with Teriflunomide

- Low incidence of GI symptoms, particularly diarrhea
- Mild hair thinning
- Monthly liver panel x 6 months
- Occasional neutropenia – check CBC periodically
- Check BP
- Category X pregnancy rating
  - Accelerated elimination procedure

DMF Has Shown Nrf2 Pathway Activation



DMF = dimethyl fumarate; MMF = monomethyl fumarate

Scannevin R et al. Poster presented at ECTRIMS, October 13-16, 2010. Gothenburg, Sweden. P887.
Feinstein D et al. Poster presented at ECTRIMS, October 13-16, 2010. Gothenburg, Sweden. P879.

DMF: Integrated Efficacy Analysis of DEFINE and CONFIRM

Endpoint (at 2 years)	Placebo (n = 771)	DMF BID (n = 769)
Annualized relapse rate (ARR) Reduction vs placebo	0.37	0.19* 49%
Proportion of patients relapsed HR vs placebo		0.57*
Time to 12-week confirmed disability progression HR vs placebo		0.68*
Time to 24-week confirmed disability progression HR vs placebo		0.71*

* Statistically significant vs placebo

Fox RJ et al. Presented at: American Academy of Neurology (AAN) 2013, March 16-23; San Diego, CA. Abstract P07.097.

Safety and Tolerability Issues with Dimethyl Fumarate

- Gastrointestinal symptoms
- Flushing
- Occasional lymphopenia – follow CBC
  - 4 cases of PML reported*
- Infrequent liver enzyme elevations (follow LFTs)
- Adherence to twice-a-day regimen
- Category C pregnancy rating

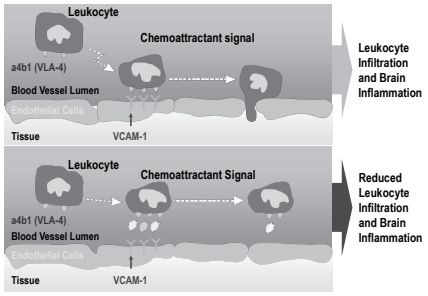
*All PML cases reported in patients with severe and prolonged lymphopenia (lymphocyte counts <500/µl and >6 months)

Tecfidera SPC; EU: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002601/human_med_001657.jsp&mid=WC0b01ac058001d124.

Tecfidera SPC; US: http://google2.fda.gov/search?q=Tecfidera&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&requiredfields=-archive%3AYes&output=xml_no_dtd&getfields=*.

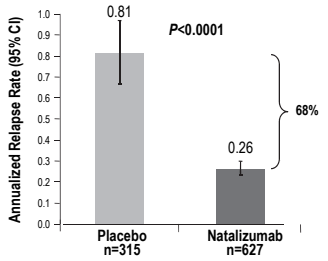
Real-life data.

Natalizumab Mechanism of Action



O'Connor P. *Expert Opin Biol Ther*. 2007;7:123-136.

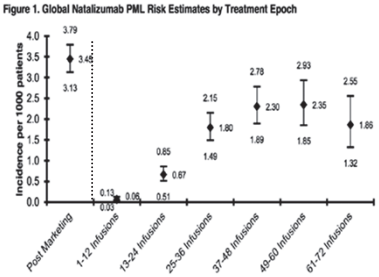
Natalizumab vs Placebo Affirm Study (1801)



Polman C et al. *N Engl J Med*. 2006;354:899-910.

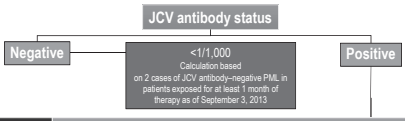
Natalizumab-associated PML

Overall Incidence by Treatment Epoch



430 (428 MS, 2 CD) confirmed PML cases as of January 6, 2014; (141 US, 252 EEA, 37 ROW).

JCV Antibody Status and Risk for PML



Natalizumab exposure	PML risk estimate per 1000 pts (No prior IS use)					Prior IS use
	Index Result ≤0.9	Index Result ≤1.1	Index Result ≤1.3	Index Result ≤1.5	Index Result >1.5	
1-24 months	0.1 (0-0.41)	0.1 (0-0.34)	0.1 (0.01-0.39)	0.1 (0.03-0.42)	1.0 (0.64-1.41)	1/1,000
25-48 months	0.3 (0.04-1.13)	0.7 (0.21-1.53)	1.0 (0.48-1.98)	1.2 (0.64-2.15)	8.1 (6.64-9.8)	13/1,000
49-72 months	0.4 (0-0.41)	0.7 (0.08-2.34)	1.2 (0.31-2.94)	1.3 (0.41-2.96)	8.5 (6.22-11.38)	9/1,000

IS = immunosuppressant

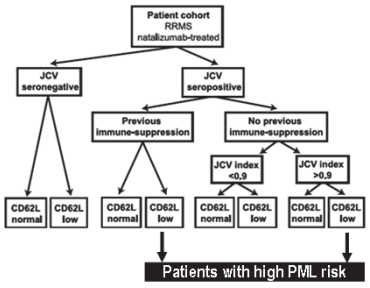
Tysabri (natalizumab) Prescribing Information. www.tysabri.com/en_US/tysb/site/pdfs/TYSABRI-pi.pdf. Accessed: April 7, 2014.

PML Risk Stratification Using Anti-JCV Antibody Index and L-selectin

- Low CD62L in natalizumab-treated patients was prospectively validated as a biomarker for increasing a patient's relative risk 55-fold.
- 86% sensitivity / 91% specificity for CD62L and 100% sensitivity / 59% specificity for JCV index as predictors of PML.
- CD62L values inversely correlated with JCV seropositivity, so the lower the CD62L value of a patient was, the higher the probability that they were JCV+, culminating in the finding that 26/27 (96%) of CD62L low patients were JCV+.
- CD62L values negatively correlated with JCV index values.

Schwab et al. *Mult Scler*. 2015;1352458515607651.

L-Selectin and Risk of PML



Schwab et al. *Mult Scler*. 2015;1352458515607651.

Choosing Therapy

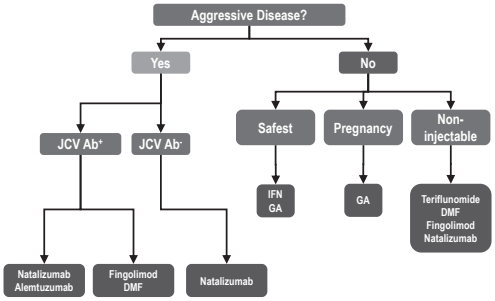


Image courtesy of Aaron Miller.

Are Stable MS Patients Who Stop DMT at Risk for Increased Relapses and Disability

- 36% of stoppers experienced relapses within 5 years
- More likely in young, less-disabled patients
- Relapse rate for stoppers and stayers was similar but stoppers showed more disability progression
- Stopping DMT in patients with no relapses for 5 years does not appear to put them at risk for relapse

Kister et al. Presented at: ECTRIMS 2015; poster #261.

Ocrelizumab: Results of Opera 1 and Opera 2 Phase III Trials in Relapsing-remitting MS

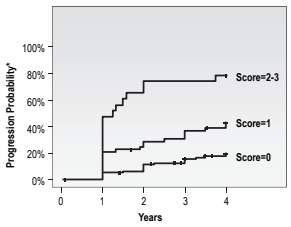
- Ocrelizumab 600 mg q 6 months vs subcutaneous IFNB-1a 3X weekly
- Primary endpoint: 46% and 47% reduction in ARR compared to INFB
- Secondary endpoints:
  - 43% and 37% reduction in confirmed disability progression (12 weeks) vs IFNB
  - 43% and 37% reduction in confirmed disability progression (24 weeks) vs IFNB
  - 94% and 95% reduction in total no. of T1 gadolinium enhancing lesions vs IFNB
  - 77% and 83% reduction in total no. of new and/or enlarging T2H lesions vs IFNB
- Adverse events: Most common was infusion reactions (34.3% vs 9.7%)
  - SAEs, including infection, similar in both groups (6.9% vs 8.7%)

Case Presentation *(continued)*

- The patient began subcutaneous interferon beta-1a three times weekly
- Examination 8 months later is normal and the patient feels well
- About one year after beginning IFNB, patient is doing fine
- Repeat MRI shows two tiny new T2 hyperintense lesions compared to his initial MRI

Modified Rio Score

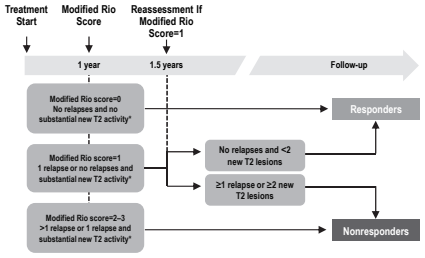
The modified Rio score, after 1 year of treatment, was able to predict the probability of disability progression at 4 years in RRMS patients with 69% accuracy



Modified Rio Score:	After 1 Year on Treatment: New T2 Lesions	After 1 Year on Treatment: Relapses
0	≤4	0
1	≤4	1
	>4	0
2	≤4	≥2
	>4	1
3	>4	≥2

* Probability of disability progression from the first year since treatment started and over the follow-up period (4 years), according to application of the modified Rio score on the "validation set" (observational cohort study, n=222).
Figure adapted from Sormani MP et al. *Mult Scler.* 2013;19:605-612.

Algorithm for Identifying Nonresponders Based on the Modified Rio Score



* Substantial new T2 activity is defined as >4–5 new T2 lesions in 1 year of treatment, or >1–2 new T2 lesions if the reference MRI scan to assess new T2 lesion formation is obtained at least 6 months after initiating therapy.

Figure adapted from Sormani MP et al. *Nat Rev Neurol.* 2013;9:504-512.

Case Presentation *(continued)*

- Patient returns 6 months later with double vision and facial numbness.
- Brain MRI shows a new Gd-enhancing pontine lesion.
- He was treated with a 5-day course of steroids with significant improvement in his vision.
- **Would you switch therapy at this point? And what are reasonable alternative therapies?**

Case Presentation

- A 25-year-old white female was diagnosed with MS 2 years earlier when she presented with optic neuritis and numbness below the mid-thoracic area. She was placed on interferon-beta 1a IM weekly injections.
- She continues to have relapses and worsening symptoms.

Case Presentation *(continued)*

- NAB Ab titer was low
- Is this treatment failure?
- Would you place the patient on a higher dose of IFN-B or would you switch therapy?

Defining Interferon ß Response Status in MS

- 15-year follow-up of pivotal MSCRG trial for weekly interferon
- 172 patients in placebo-controlled IFN-ß1a trial x 2 years
- In IFNb-1a group, disease activity predicted EDSS worsening:
  - Gadolinium-enhancing lesions (OR, 8.96; *P*<0.001)
  - Relapses (OR, 4.44; *P*=0.01)
  - New T2 lesions (OR, 2.90; *P*=0.08)
  - Conclusion: new MRI activity during IFN-ß1a treatment correlates with suboptimal response

Rudick RA et al. *Ann Neurol.* 2004;56:546-555.
Bermel RA et al. *Ann Neurol.* 2013;73:95-103.

MRI as a Surrogate of Future Disease Activity

- 370 patients underwent MRI at baseline and 1 year after beginning IFN
- Followed for relapse or disability progression in years 1-4
- At year 1: ≥1 Gd-enhancing lesion or ≥2 T2 lesions had same risk for worsening disease in years 1-4 and for a clinical relapse within the first year
- MRI activity after starting IFN has similar implication as a relapse

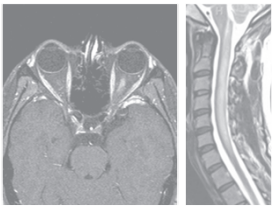
Prosperini L et al. *Mult Scler.* 2013;PMID:23999607.

Case Presentation *(continued)*

- Follow-up MRI showed 2 non-enhancing brain T2 lesions and a new enhancing spinal cord lesion between T1 and T4.
- Serum NMO Ab test was positive.

Neuromyelitis Optica

- Inflammatory demyelination of the optic nerves and spinal cord
- Characterized by a specific IgG antibody marker (NMO antibody)
- Target antigen is aquaporin-4, a water channel abundant in the CNS
- Role of NMO-Ab in pathogenesis remains uncertain



Pittock SJ. *Semin Neurol.* 2008;28:95-104.
Lennon VA et al. *Lancet.* 2004;364:2106-2112.

NMO Pre- and Post-treatment Median Annualized Relapse Rates

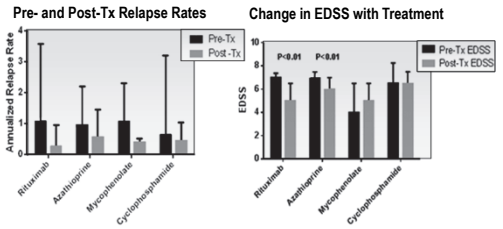
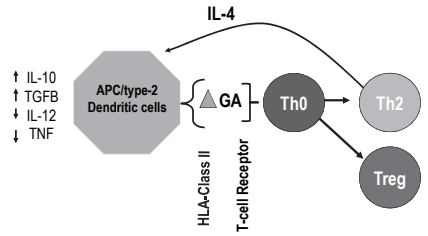


Fig. 1 Pre- and post-treatment median annualized relapse rates (ARR). The median ARR decreased from 1.17 to 0.25 on rituximab (P<0.01), 0.92 to 0.56 on azathioprine (P=0.475), 1.06 to 0.39 on mycophenolate (P<0.05), and 1.30 to 0.92 on cyclophosphamide (P=0.021).

Torres J et al. *J Neurol Sci.* 2015;351:31-35.

Promising Future Biomarkers

Glatiramer Acetate Binds to HLA Class II on Antigen Presenting Cells and induces Type-2 APCs



Weber MS et al. *Nat Med.* 2007;13:935-943.

DR and DQ Haplotypes Predictors of Clinical Response to GA

PROGNOSTIC PROFILE	HAPLOTYPES	NR / R (%R)
Poor prognostic profile	DR15 - DQ6 absent DR17 - DQ2 present	10 / 2 (16.7%)
Neutral prognostic profile	DR15 – DQ6 present & DR17 – DQ2 present DR15 – DQ6 absent & DR17 – DQ2 absent	17 / 11 (39.5%)
Good prognostic profile	DR15 – DQ6 present DR17 - DQ2 absent	7 / 17 (70.8%)

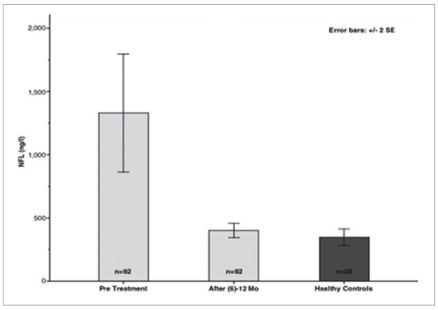
Dhib-Jalbut S et al. *MSARD.* 2013;2:340-348.

Potential IFN-β Serum Biomarkers

Responders	Non-responders
Increase in IL-10	Decrease in IL-10
IL-7 high/Il-17 low T cells	IL-17F levels >200pg/mL
Reduction in Th1 cytokines	High baseline IFN-β levels
Increased in neurotrophic factors	NAB
MicroRNA 26a-5p	SNPs (IRF8, IRF5)
Increased monocytes IFN-I secretion in response to TLR	Increase PSTAT1 and IFNR1 on monocytes at baseline

Dhib-Jalbut S et al. *J Neuroimmunology.* 2013;254:131-140.
Comabella M et al. *Brain.* 2009;132:3353-3365.

Axonal Damage Markedly Reduced by Natalizumab



Gunnarsson M et al. *Ann Neurol.* 2011;69:83-89.

Exploratory Biomarkers of Newer MS Therapies

Treatment	Tissue	Biomarker
Natalizumab	PB	VLA-4, CD34 cells
	CSF	NFL, Fetuin-A, Osteopontin, CHI3L1
Fingolimod	PB	Decreased Naïve and Tcm, Decreased CD4:CD8 ratio, Decreased Th17, Decreased B-cells
	CSF	Decreased T-cells and CD4:CD8 ratio
Rituximab	CSF	Decreased T and B cells, CXCL13
Daclizumab	PB/CSF	Increased NKreg cells, CD56 bright cells
BMT	PB	Decreased TH17

PB = peripheral blood; BMT = bone marrow transplant; CSF = cerebrospinal fluid

Safety Biomarkers

Treatment	Complication	Biomarker
Natalizumab	PML	JCV assay, L-Selectin, mir320b
Alemtuzumab	Autoimmune thyroiditis	IL-21

Plavina T et al. *Ann Neurol.* 2014;76:802-812.
Schwab N et al. *Neurology.* 2013;81:865-871.
Munoz-Culla M et al. *Mult Scler.* 2014;20:1851-1859.
Azzopardi L et al. *J Neurol Neurosurg Psychiatry.* 2014;85:795-798.

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  - Your answers are important and will help us identify remaining educational gaps and shape future CME activities
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  - Return all forms to on-site CME staff

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