Updates in Multiple Sclerosis

Aaron M. Carlson, MD
Assistant Professor, Department of Neurology
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Presentation Goals

Goals

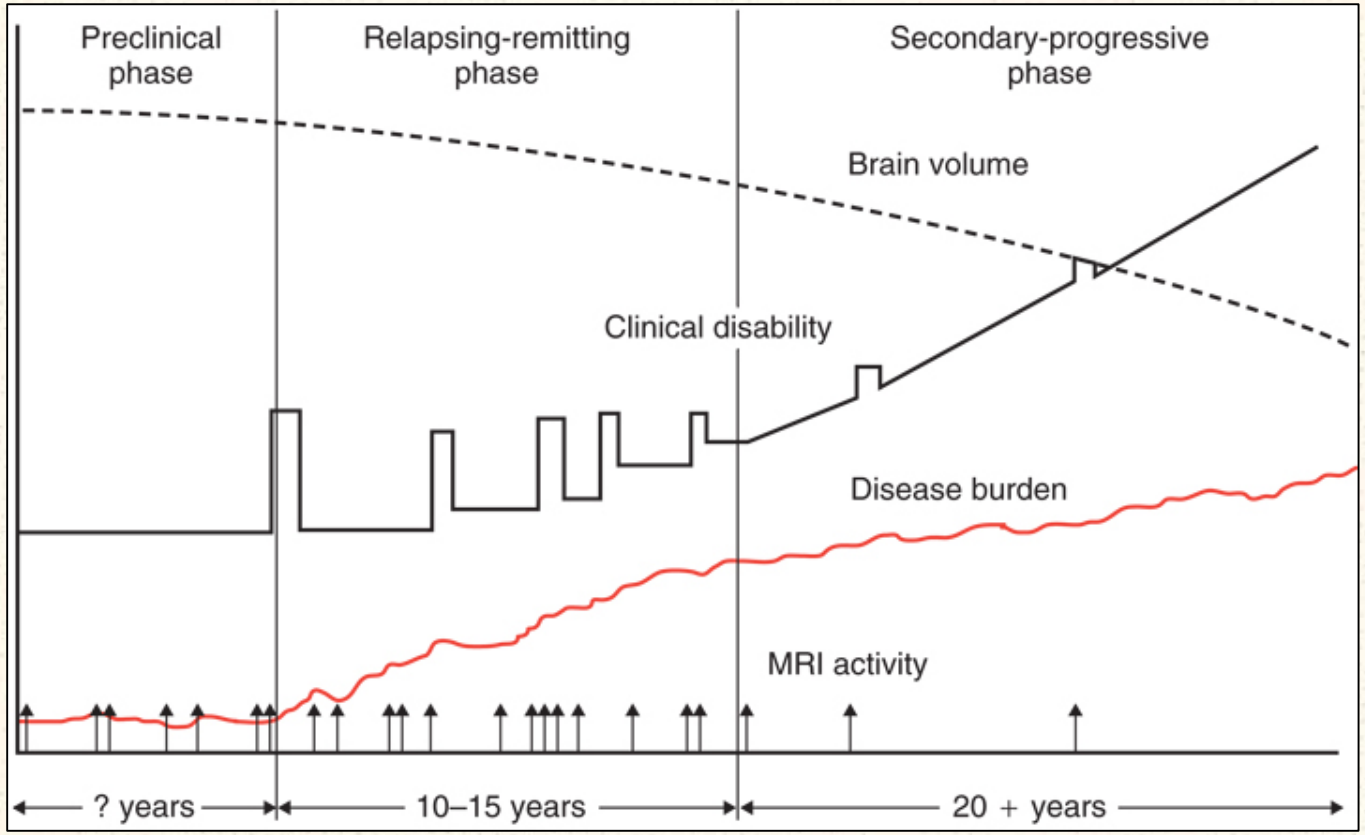
- Review the basic pathophysiology, course, and treatment of multiple sclerosis
- Specific focus on early forms of disease
  - So called ‘radiographically-isolated syndrome’ and clinically-isolated syndrome
- Role of newer, and generally more efficacious treatments
- Review of JC virus, progressive multifocal leukoencephalopathy (PML), and the risk in our medications

Review of Multiple Sclerosis

What is Multiple Sclerosis?

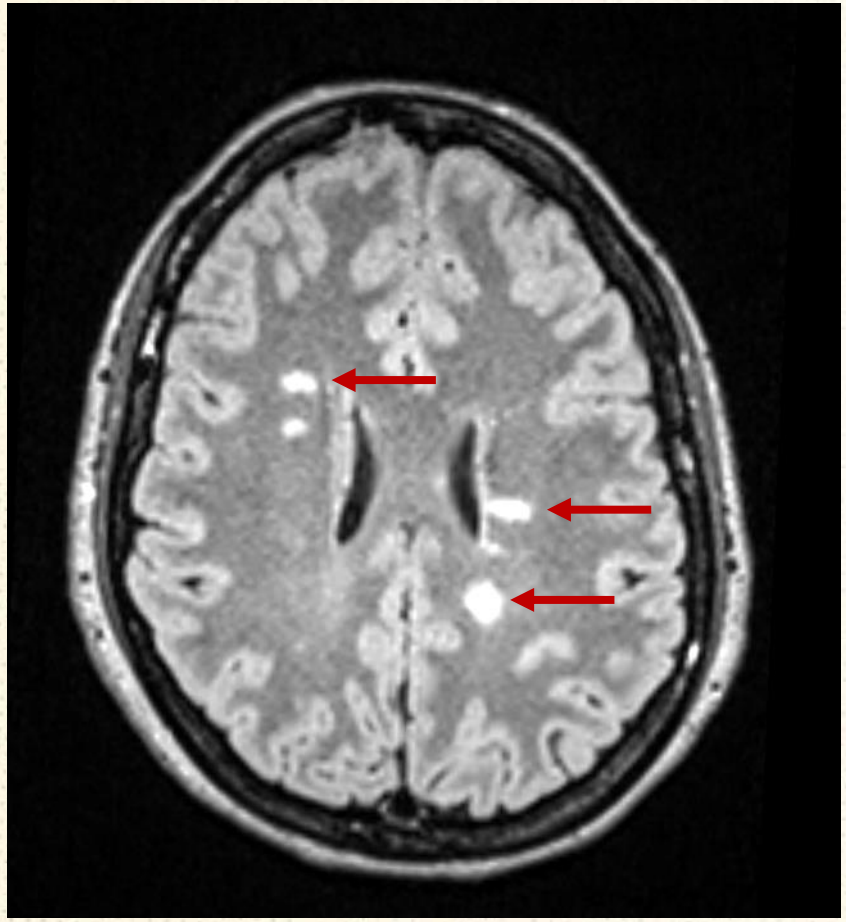
- A demyelinating disease causing relapses of focal neurological dysfunction, most commonly with improvement or resolution of symptoms
- Progressive disease develops in a minority of patients
- A common cause of neurological disability in young adults
- **One of the most treatable neurological conditions**

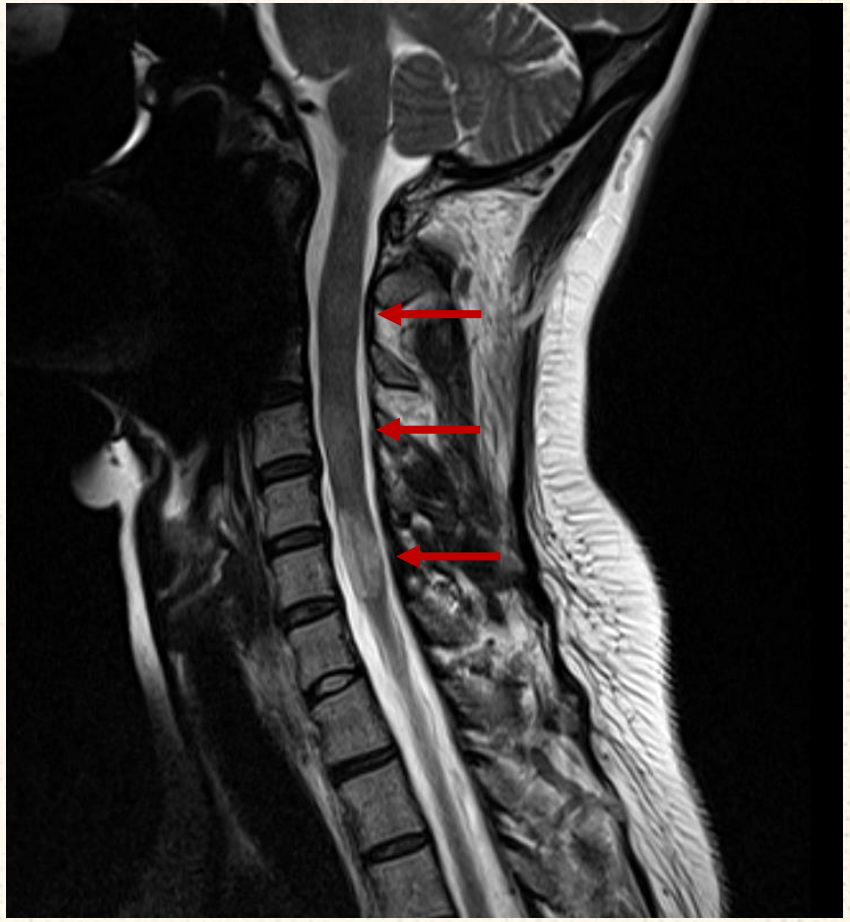
MS natural history



Fox, R. J. & Cohen, J. A. Multiple sclerosis: the importance of early recognition and treatment. Cleve. Clin. J. Med. 68, 157-171 (2001)

Multiple Sclerosis Typical MRI



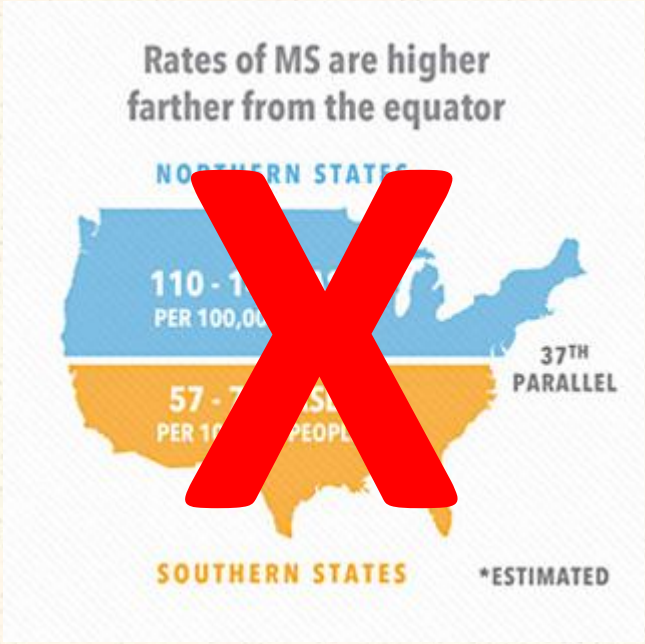


Risk factors

- HLA DRB*1501 is the best established genetic risk factor
- Family history (up to ~20% for twins, 1-3% with affected sibling, 2-3% with affected parent)
- Low vitamin D levels
- High latitude for first 16 years of life*

Westerlind, H. *et al*. Modest familial risks for multiple sclerosis: a registry-based study of the population of Sweden. *Brain* **137**, 770-778 (2014).

Epidemiology of MS



Imaging from http://wwwmsviewsandrelatednews.blogspot.com/2014/06/multiple-sclerosis-by-numbers-facts.html. Accessed 2/4/2019.

Epidemiology of MS

- Recent studies suggest latitude gradient is less clear
- US Prevalence is now estimated at > 200 per 100,000
  - *~1 million patients with MS in the US*
- Suggestion that African Americans, particularly women, are more frequently affected than previous estimates

Langer-Gould, A., Brara, S. M., Beaber, B. E. & Zhang, J. L. Incidence of multiple sclerosis in multiple racial and ethnic groups. *Neurology* **80**, 1734-1739 (2013).
Wallin, M. T. et al. *The prevalence of multiple sclerosis in the united states: a population-based healthcare database approach* (MULTIPLE SCLEROSIS, 2017).

Diagnosis of MS

- The diagnosis is based on dissemination in *time* and *space*

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶

Thompson, A. J. *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology* **17**, 162-173 (2018).

Diagnosis of MS

- Practically, we use MRI, CSF, and clinical information to make the diagnosis
- Patients are seen frequently early on, with serial imaging to allow for an expedited diagnosis and treatment

Diagnosis of MS

- **Mis**diagnosis remains a large issue
- MS referrals to subspecialists accurate 30% of the time
  - Usually based on MRI findings
- Alternative etiologies: migraine, hypertensive changes, psychiatric illness, pain disorders
- A single diagnosis code for MS has low sensitivity and specificity for a true diagnosis

Carmosino, M. J., Brousseau, K. M., Arciniegas, D. B. & Corboy, J. R. Initial evaluations for multiple sclerosis in a university multiple sclerosis center: outcomes and role of magnetic resonance imaging in referral. Arch. Neurol. 62, 585-590 (2005).
Wallin, M. T. et al. *The prevalence of multiple sclerosis in the united states: a population-based healthcare database approach* (MULTIPLE SCLEROSIS, 2017).

Early Forms of Disease

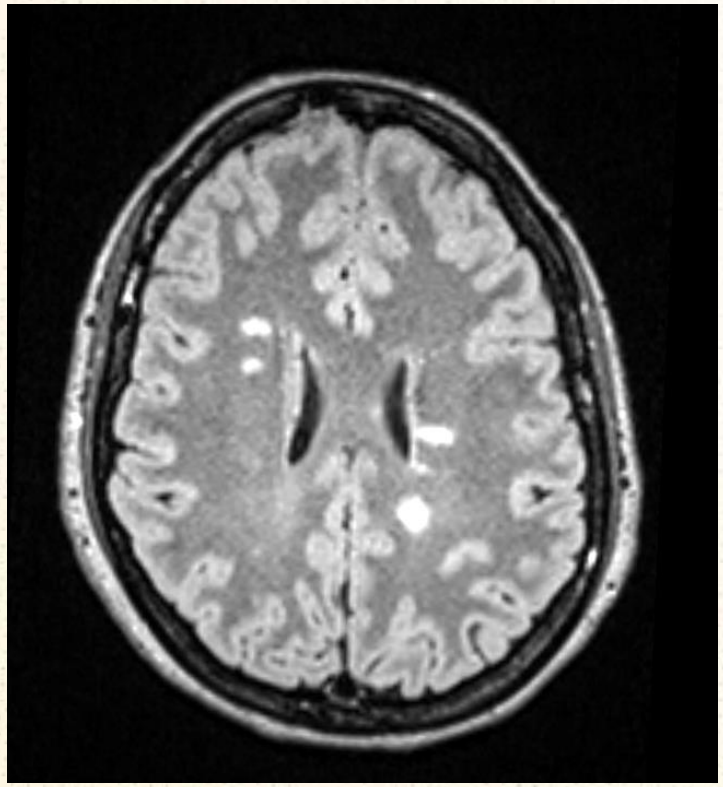
Radiographically isolated syndrome (RIS)

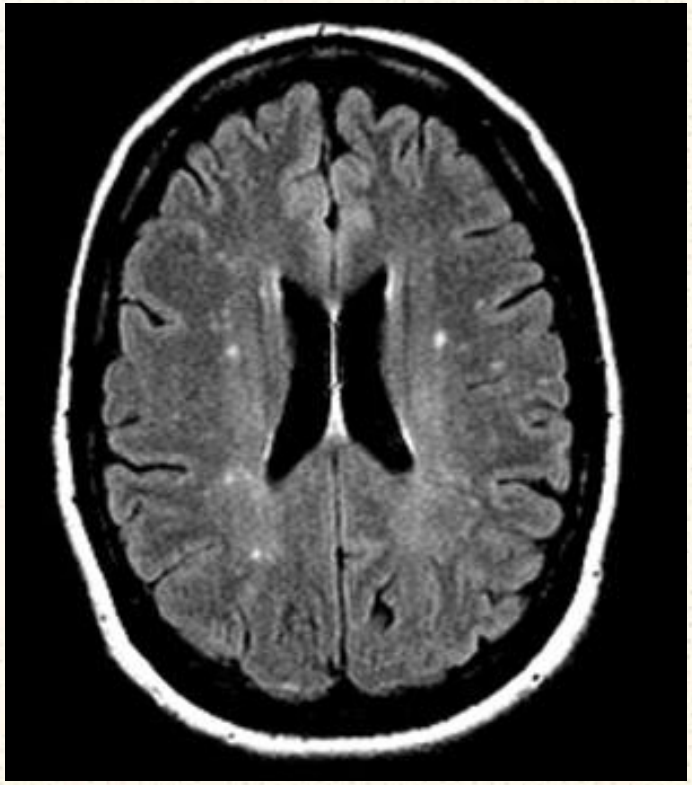
- **Used to describe MS typical lesions in a patient with no attacks and normal exam**
- Not a formal diagnosis
- Proposed criteria:
  - MS-like lesions in 3 of 4 typical areas (juxtacortical, periventricular, brainstem, and spinal cord)
  - Not a vascular pattern
  - No clinical symptoms or localizing exam findings
  - Not substance-related
  - Other processes excluded

Okuda, D. T. et al. Incidental MRI anomalies suggestive of multiple sclerosis The radiologically isolated syndrome. Neurology 72, 800-805 (2009).

Radiographically isolated syndrome (RIS)

Compare and Contrast





MRI of migraine accessed from https://www.medimaging.net/mri/articles/294764232/mri-study-shows-migraines-with-aura-unrelated-to-brain-anomalies.html on 2/4/2019

Radiographically isolated syndrome (RIS)

- Risk of conversion to a clinical syndrome at 5 years:
  - **34%**
- Predictors of conversion:
  - Male sex
  - Age < 37 years
  - Spinal cord lesions

Okuda, D. T. et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. PloS one 9, e90509 (2014).

Clinically Isolated Syndrome (CIS)

- MS-like clinical presentation that either lacks dissemination in *time* or *space*
- Typical clinical syndromes:
  - **Optic neuritis**, focal supratentorial syndrome, **focal brainstem syndrome**, partial myelopathy
- With our new criteria, less patients will have clinically isolated syndrome
  - Easier to make diagnosis of MS
  - MRI can provide time and space
  - Positive CSF can provide time

Clinically Isolated Syndrome (CIS)

- **How much of CIS is ultimately MS?**
  - In the largest analysis to date, 72% met criteria for a diagnosis of multiple sclerosis over a median of ~ 7 years
  - MRI findings were the greatest predictor
- **Can we delay or prevent the onset of MS with treatment?**
  - Possibly
  - 3 medications have been studied in CIS in clinical trials

Tintore, M. et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 138, 1863-1874 (2015).

Clinically Isolated Syndrome (CIS)

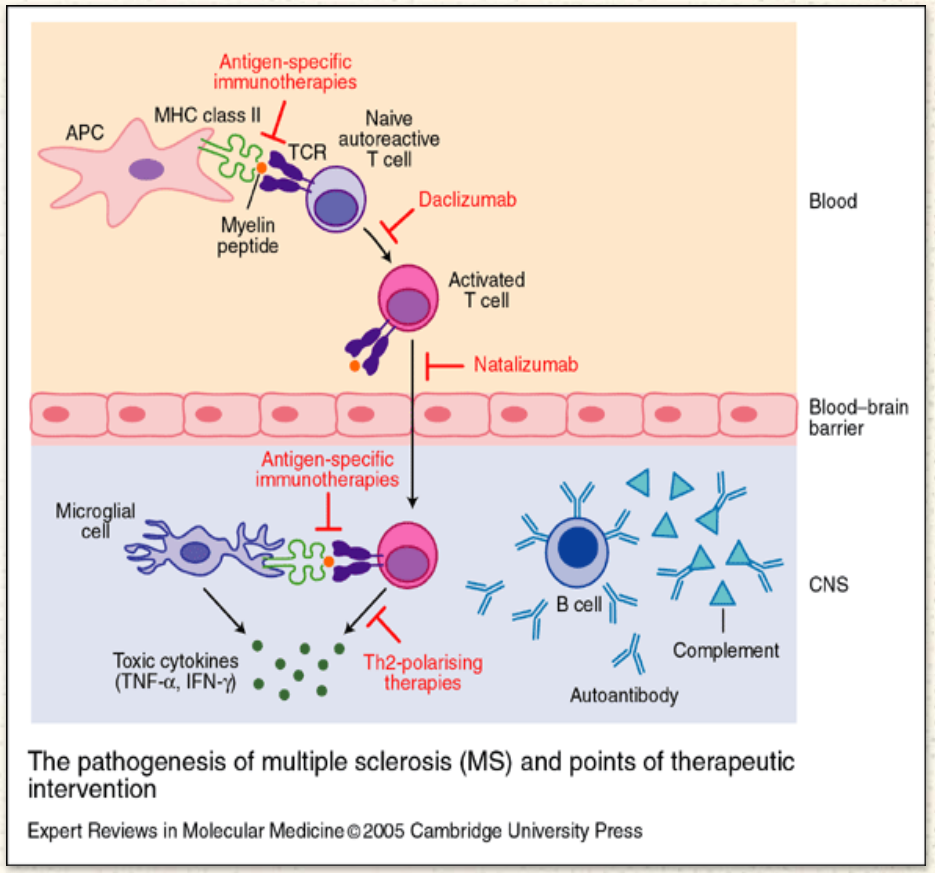
- **Interferon beta-1a**
  - Various formulations employed
  - Reduced risk of progression to MS by 40-50% over 2-3 years
- **Glatiramer acetate**
  - Reduced risk of progression to MS by 45% over roughly 3 years
- **Teriflunomide**
  - Reduced risk of progression to MS by ~40% over roughly 2 years

Comi, G. et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial. The Lancet 374, 1503-1511 (2009).
Miller, A. E. et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Neurology 13, 977-986 (2014).
Jacobs, L. D. et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. N. Engl. J. Med. 343, 898-904 (2000).
Kappos, L. et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 67, 1242-1249 (2006).

Evolution of treatment

Evolution of treatment

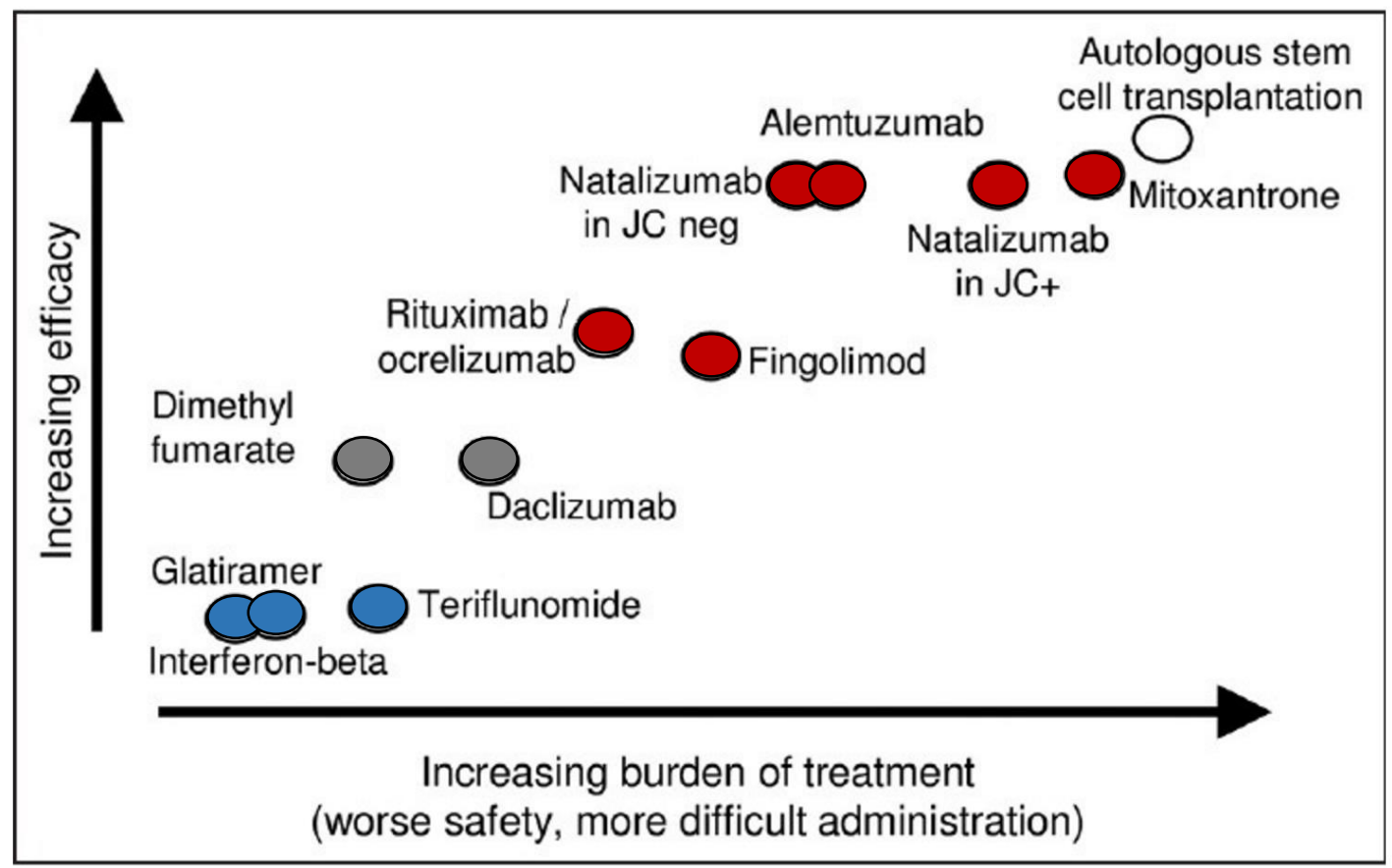
- Betaseron 1993 (interferon beta-1b)
- Avonex 1996 (interferon beta-1a)
- Copaxone 1997 (glatiramer acetate)
- Novantrone 2000 (mitoxantrone)
- Rebif 2002 (interferon beta-1a)
- Tysabri 2006 (natalizumab)
- Extavia 2009 (interferon beta-1b)
- Gilenya 2010 (fingolimod)
- Aubagio 2012 (teriflunomide)
- Tecfidera 2013 (dimethyl fumarate)
- Plegridy 2014 (peginterferon beta-1a)
- Lemtrada 2014 (alemtuzumab)
- Glatopa 2015 (generic glatiramer acetate)
- ~~Zinbryta 2016 (daclizumab)~~
- Ocrevus 2017 (ocrelizumab)*



The pathogenesis of multiple sclerosis (MS) and points of therapeutic intervention

Expert Reviews in Molecular Medicine ©2005 Cambridge University Press

Evolution of treatment



Coles, A. Newer therapies for multiple sclerosis. Annals of Indian Academy of Neurology 18, S30 (2015).

Approach to therapy

- **‘Escalation’ versus ‘Induction’**
  - Two groups, one favoring highly effective medication early, one escalating therapy if breakthrough disease occurs early
  - Data is growing for use of highly effective medications early
  - Definition of aggressive disease is somewhat opaque
    - Most physicians would consider 2 or more relapses a year ‘aggressive’
  - Our goal is to obtain ‘NEDA’, or no evidence of disease activity.
    - No relapses, no new lesions on MRI, and no increase in disability

Natalizumab

- Humanized antibody to a4 integrins, prevents lymphocytes from crossing blood-brain barrier
- Highly effective in reducing multiple pertinent outcome measures.
- May have some benefit in secondary progressive disease
- Dosed at 300mg every 4 weeks, *although alternative regimens are employed*
- Side effects: **PML**

Kapoor, R. et al. Effect of natalizumab on disease progression in secondary progressive multiple sclerosis (ASCEND): a phase 3, randomised, double-blind, placebo-controlled trial with an open-label extension. The Lancet Neurology 17, 405-415 (2018).
Polman, C. H. et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N. Engl. J. Med. 354, 899-910 (2006).
Miller, D. H. et al. A controlled trial of natalizumab for relapsing multiple sclerosis. N. Engl. J. Med. 348, 15-23 (2003).1

Alemtuzumab

- Humanized monoclonal antibody versus CD52, a marker widely expressed on leukocytes
- Highly effective in multiple outcome measures, both clinical and radiographic
- Given as two short courses of therapy one-year apart, referred to as ‘interrupted immunotherapy’
- Side effects: Autoimmune disease (**thyroid disease**, ITP, glomerulonephropathy), infections (listeria, **herpes-related**), serious infusion reactions.

Tintore, M. et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 138, 1863-1874 (2015).

Ocrelizumab

- Humanized monoclonal antibody versus CD20, a marker of a wide lineage of B cells
- Effective for relapsing-remitting and **primary progressive MS**
  - Reduces relapses by ~50% compared to interferon beta-1a
  - Reduces risk of disability progression in PPMS by 25%
- Dosed every 6 months (first dose split over two weeks)
- Side effects: increased URIs, herpetic infections, possible increase in serious infections, PML, and cancer*

Montalban, X. et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N. Engl. J. Med. 376, 209-220 (2017).
Hauser, S. L. et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N. Engl. J. Med. 376, 221-234 (2017).

PML risk in MS Medications

Risk of progressive multifocal leukoencephalopathy (PML)

- What is PML?
  - Caused by JC virus, a DNA virus ubiquitous in the environment
  - 60% of the population is exposed
  - Rarely causes disease in immunocompetent hosts, best described in patients with AIDS
  - Risk in MS was first discovered in trials of natalizumab with multiple sclerosis
  - No proven effective treatment (treat immunosuppressive condition and supportive care)

Risk of PML in MS Medications

ORIGINAL ARTICLE BRIEF REPORT

Progressive Multifocal Leukoencephalopathy in a Patient Treated with Natalizumab

Annette Langer-Gould, M.D., Scott W. Atlas, M.D., Ari J. Green, M.D., Andrew W. Bollen, M.D., and Daniel Pelletier, M.D.

ORIGINAL ARTICLE BRIEF REPORT

Progressive Multifocal Leukoencephalopathy after Natalizumab Therapy for Crohn's Disease

Gert Van Assche, M.D., Ph.D., Marc Van Ranst, M.D., Ph.D., Raf Sciot, M.D., Ph.D., Bénédicte Dubois, M.D., Ph.D., Séverine Vermeire, M.D., Ph.D., Maja Noman, M.D., Jannick Verbeeck, M.Sc., Karel Geboes, M.D., Ph.D., Wim Robberecht, M.D., Ph.D., and Paul Rutgeerts, M.D., Ph.D.

ORIGINAL ARTICLE BRIEF REPORT

Progressive Multifocal Leukoencephalopathy Complicating Treatment with Natalizumab and Interferon Beta-1a for Multiple Sclerosis

B.K. Kleinschmidt-DeMasters, M.D., and Kenneth L. Tyler, M.D.

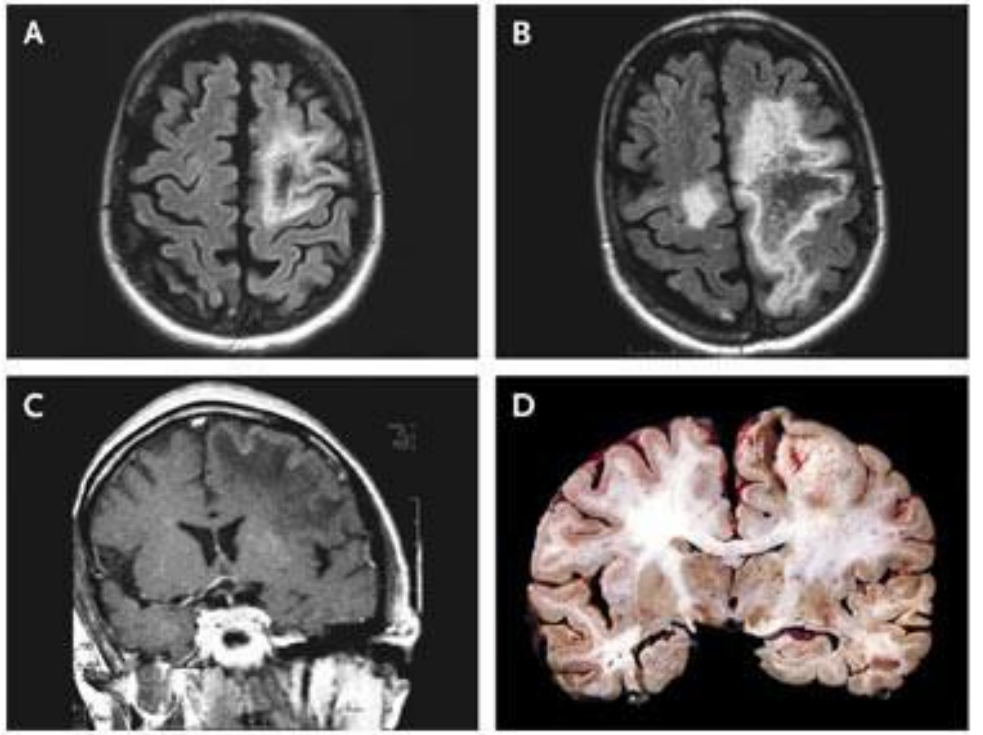


Image from: Kleinschmidt-DeMasters, B. K. & Tyler, K. L. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N. Engl. J. Med. 353, 369-374 (2005).

Risk of PML in MS Medications

- A risk of PML has now been seen in multiple medications
- Gilenya (fingolimod)
  - ~20 cases, <1/10000 risk
  - Risk factors not clearly established, many older patients
- Tecfidera (dimethyl fumarate)
  - <10 cases, <1/10000 risk
  - Possible risks of decreased lymphocyte counts (ALC < 500), older age
- Natalizumab
  - Risk stratification possible

Risk of PML in Natalizumab

- A viral titer assay was developed as part of the REMS program
- Titer is checked every 6 months (some centers every 3 months)
- Allows for a stratification of risk
  - Negative or low-titer = low risk
  - Medium-high titer and > 24 months of exposure = high risk
  - Prior immunosuppression increases risk, and is a relative contraindication

Risk of PML in Natalizumab

	PML risk estimate (per 1000)*	Monitoring steps	
		Anti-JCV antibody	MRI
			Frequency
Immunomodulatory drug treatment, including natalizumab	..	..	Annually
Natalizumab treatment, anti-JCV negative	..	Every 6 months	Annually
Natalizumab treatment, anti-JCV positive, no prior immunosuppression			
Anti-JCV antibody index <0·9			
Treatment duration 1–72 months	0·1–0·6	Every 6 months	Annually
Anti-JCV antibody index 0·9–1·5			
Treatment duration 1–36 months	0·1–0·8	Every 6 months	Annually
Treatment duration 37–72 months	2–3	..	Every 3–4 months
Anti-JCV antibody index >1·5			
Treatment duration 1–24 months	0·2–0·9	..	Annually
Treatment duration 25–72 months	3–10	..	Every 3–4 months
Natalizumab treatment, anti-JCV positive, prior immunosuppression			
Treatment duration 1–24 months	0·3–0·4	..	Annually
Treatment duration 25–72 months	4–8	..	Every 3–4 months

Major, E. O., Yousry, T. A. & Clifford, D. B. Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. The Lancet Neurology 17, 467-480 (2018)

Management of PML in Natalizumab

- Care is generally supportive
- Many practioners will employe plasma exchange to remove circulating natalizumab, but this is not proven helpful
- A positive note:
  - Introduction of a JC virus monitoring protocol in Sweden led to total prevention of natalizumab-associated PML (2012-present)

Kagstrom, S. et al. Reduction of the risk of PML in natalizumab treated MS patients in Sweden: an effect of JCV ab index surveillance (MULTIPLE SCLEROSIS JOURNAL, 2018)

Questions?