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CONTINUING MEDICAL EDUCATION

Finding Your Footing in the Shifting Landscape of Multiple Sclerosis

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- Actively participate by responding to ARS questions and/or asking the faculty questions
- Complete the activity post-test and evaluation at the link provided
- Over the next 90 days, actively work to incorporate improvements in your clinical practice from this presentation
- Complete the follow-up survey from CME Outfitters in approximately 3 months

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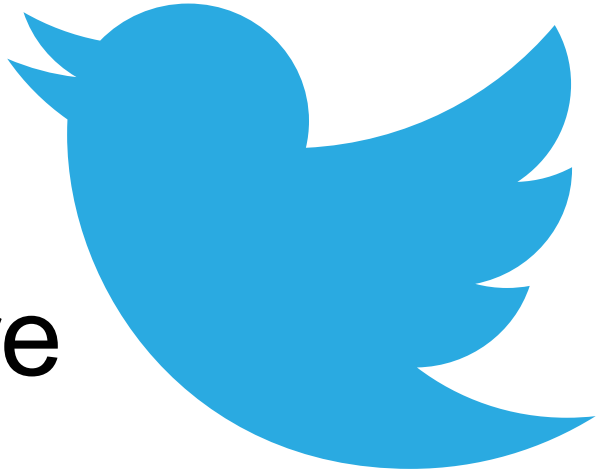
#MSupdate



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Learning Objective 1

Identify the immunological mechanisms that contribute to MS.

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Learning Objective 2

Assess clinical data supporting the efficacy and safety of novel and emerging immune-directed therapies for MS.

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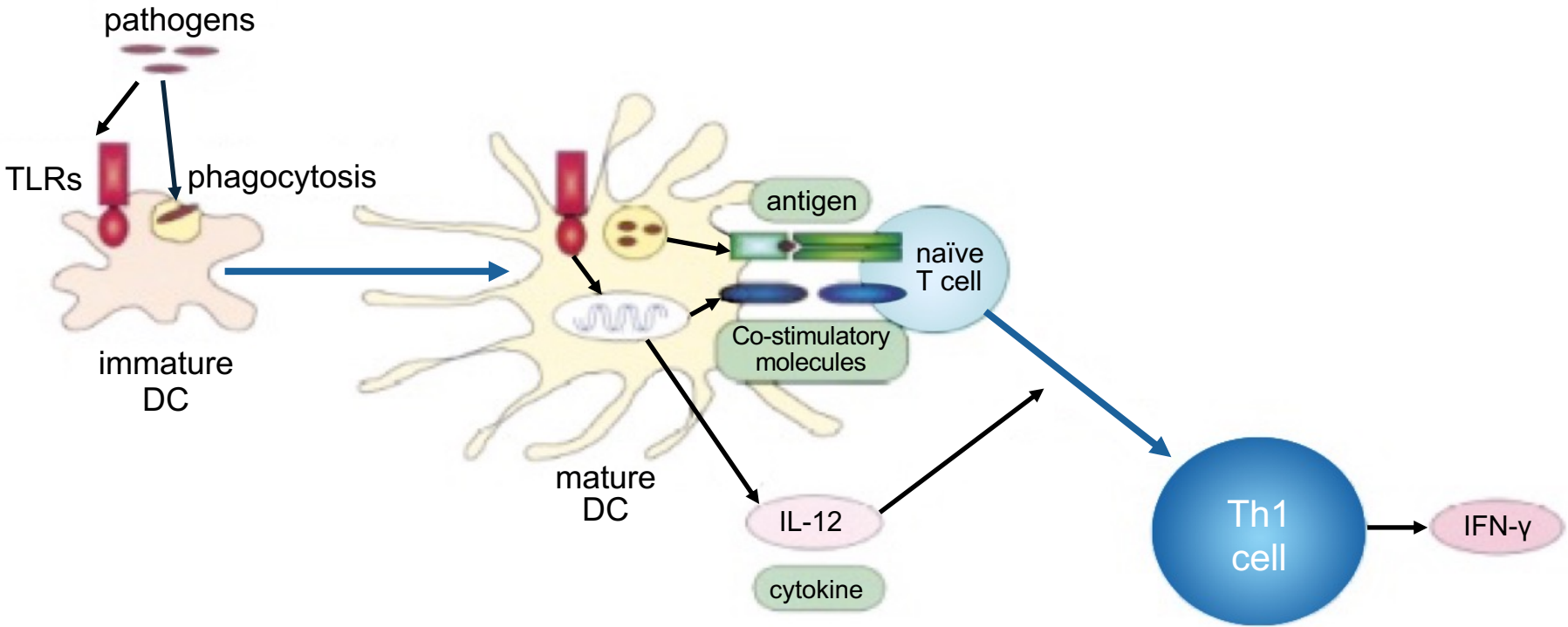
Learning Objective 3

Integrate biomarkers and imaging techniques to assess disease progression in patients with MS.

Disease Progression

- Clinical course is variable
- Much of the disease is clinically silent
- We do not fully understand the pathogenesis of multiple sclerosis (MS) or know whether MS is a single disease or a common end point of multiple disease etiologies

Triggers of Inflammation



DC = dendritic cells; IL = interleukin; IFN- γ = interferon gamma; Th = T helper; TLRs = toll-like receptors

Akira S, et al. *Nat Immunol.* 2001;2(8):675-680.
Schaeffer J, et al. Multiple sclerosis. In: *Neurobiology of Brain Disorders.* 2015.

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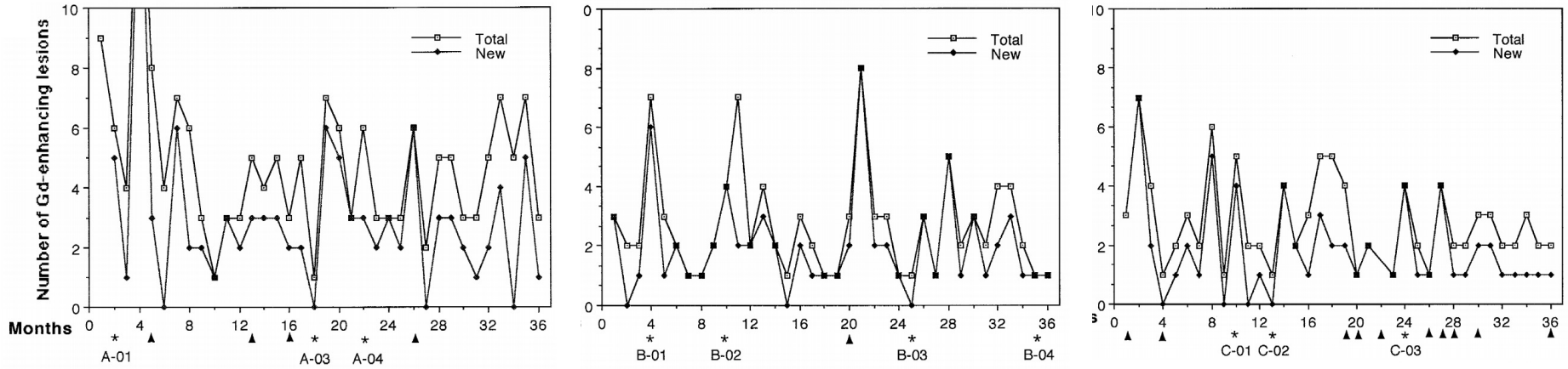
Pathophysiology of Multiple Sclerosis

An Animated Tour

Chapter 1: Gross Anatomy

MRI Lesions Come and Go in RRMS

The number of Gd-enhancing lesions in the brains of 3 MS patients over a 3 year period as determined by monthly MRI



- Arrowheads indicate occurrence of clinical exacerbations
- Asterisks indicate generation of T-cell lines

Gd = gadolinium; MRI = magnetic resonance imaging; RRMS = relapsing-remitting MS

Lovett-Racke AE, et al. *J Neuroimmunol.* 1997;78(1-2):162-171.

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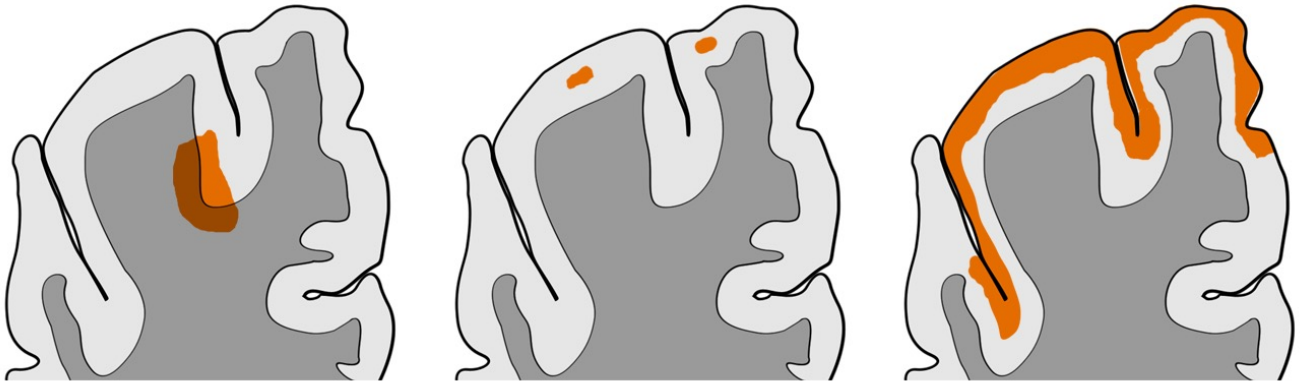
Pathophysiology of Multiple Sclerosis

An Animated Tour

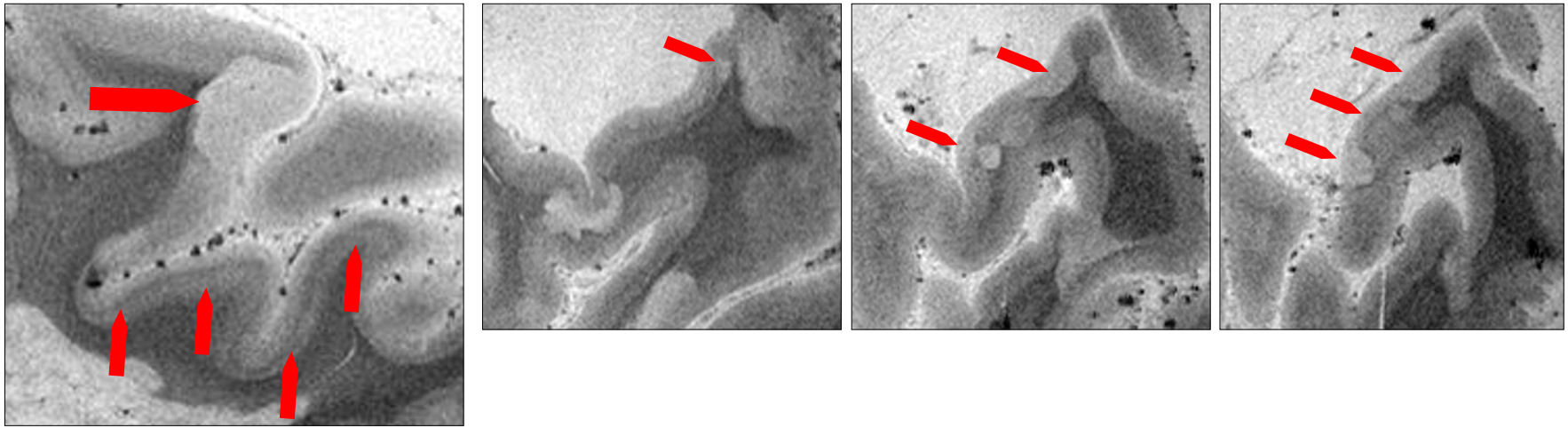
Chapter 2: Lesion Formation

Cortical Lesions in MS



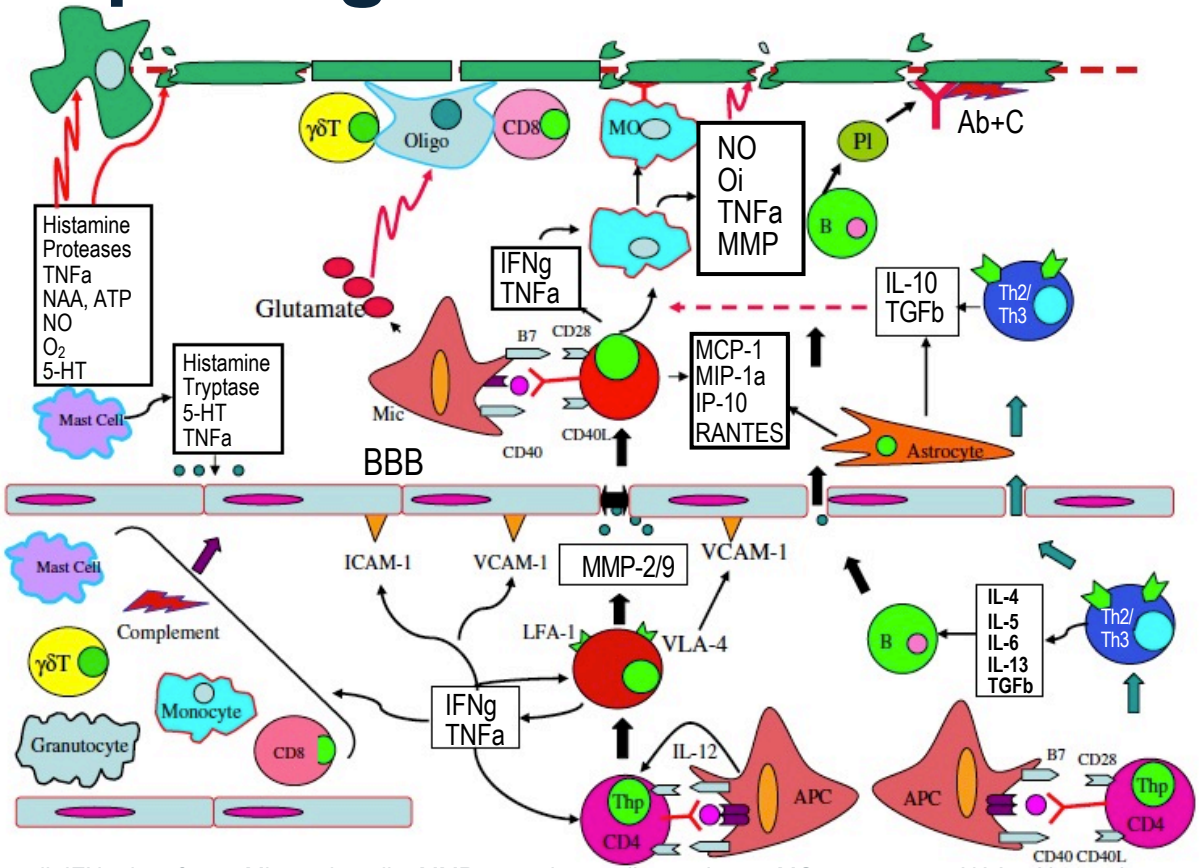
Trapp BD, Nave KA. *Annu Rev Neurosci*. 2008;31:247-269.

Imaging Cortical lesions



Pitt D, et al. *Arch Neurol.* 2010;67(7):812-818.

Immunopathogenesis of the MS Lesion



APC = antigen presenting cell; IFN = interferon; Mic = microglia; MMP = matrix metalloproteinase; MO = monocyte; NAA = N-acetylaspartate; NO = nitric oxide; PI = plasma; TNFa = tumor necrosis factor alpha; VCAM = vascular cell adhesion molecule

Dhib-Jalbut S, et al. *J Neuroimmunol*. 2006;176(1-2):198-215.

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Pathophysiology of Multiple Sclerosis

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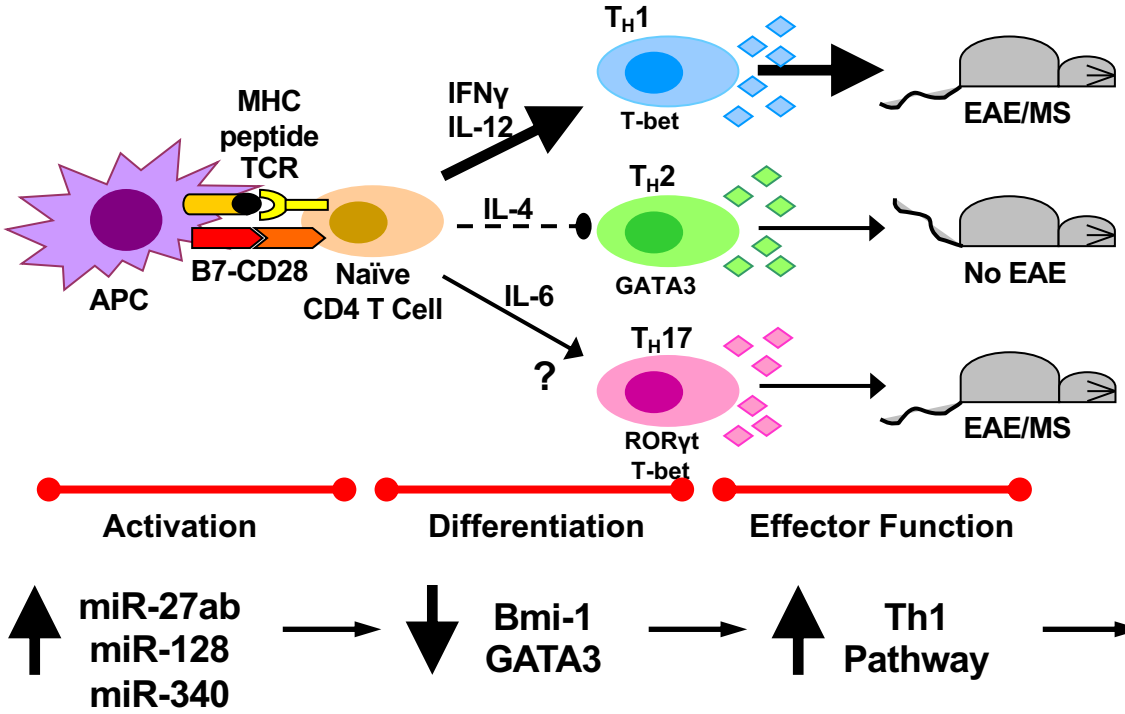
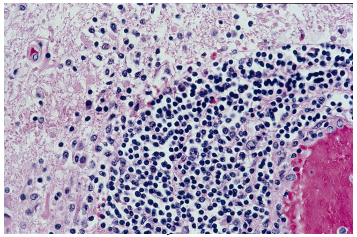
Chapter 3: Lymphocyte Activation

T-Cells in Multiple Sclerosis



Perivascular Inflammation in MS brain



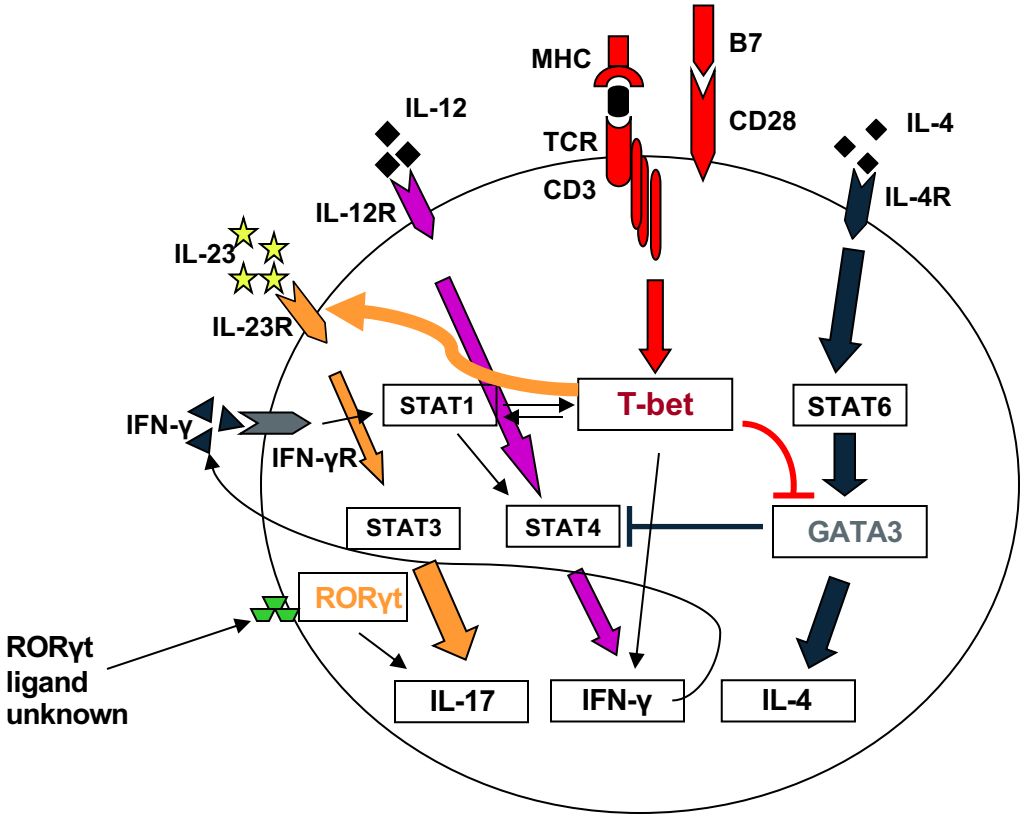
Sclerotic plaques in MS brain

miR-27ab, miR-128, miR-340 → ↓ **Bmi-1, GATA3** → ↑ **Th1 Pathway** → ↑ **Susceptibility to EAE/MS**

APC = antigen presenting cell; EAE = experimental autoimmune encephalomyelitis; MHC = major histocompatibility complex; TCR = T-cell receptor

Guerau-de-Arellano et al. *Brain.* 2011;134(Pt 12):3578-3589. Lovett-Racke AE, et al. B*iochim Biophys Acta.* 2011;1812(2):246-251.

Transcriptional Regulation of T-Cell Differentiation



Lovett-Racke AE, et al. B*iochim Biophys Acta.* 2011;1812(2):246-251.

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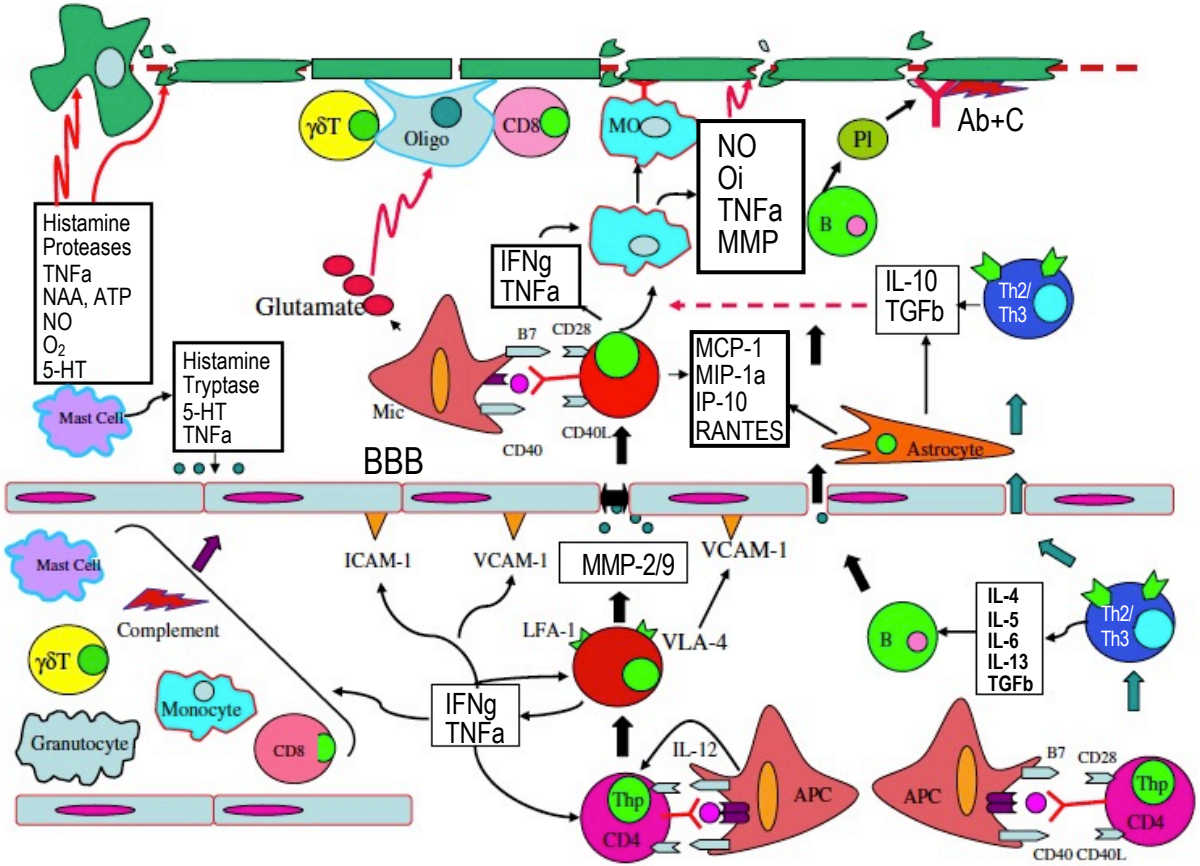
Pathophysiology of Multiple Sclerosis

An Animated Tour

Chapter 4: T Cell Differentiation

Immunopathogenesis of the MS Lesion



Dhib-Jalbut S, et al. *J Neuroimmunol*. 2006;176(1-2):198-215.

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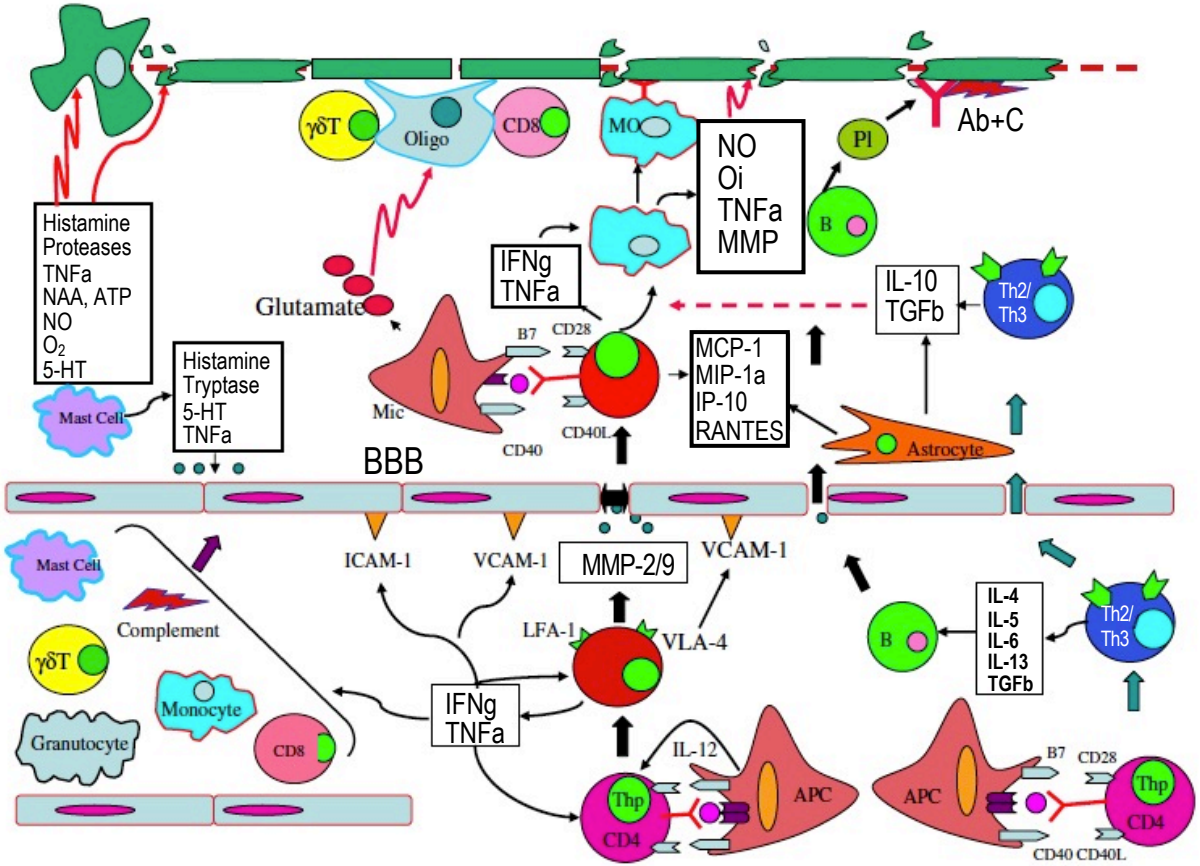
Chapter 5: Axon Demyelination

Immunopathogenesis of the MS Lesion



Dhib-Jalbut S, et al. *J Neuroimmunol*. 2006;176(1-2):198-215.

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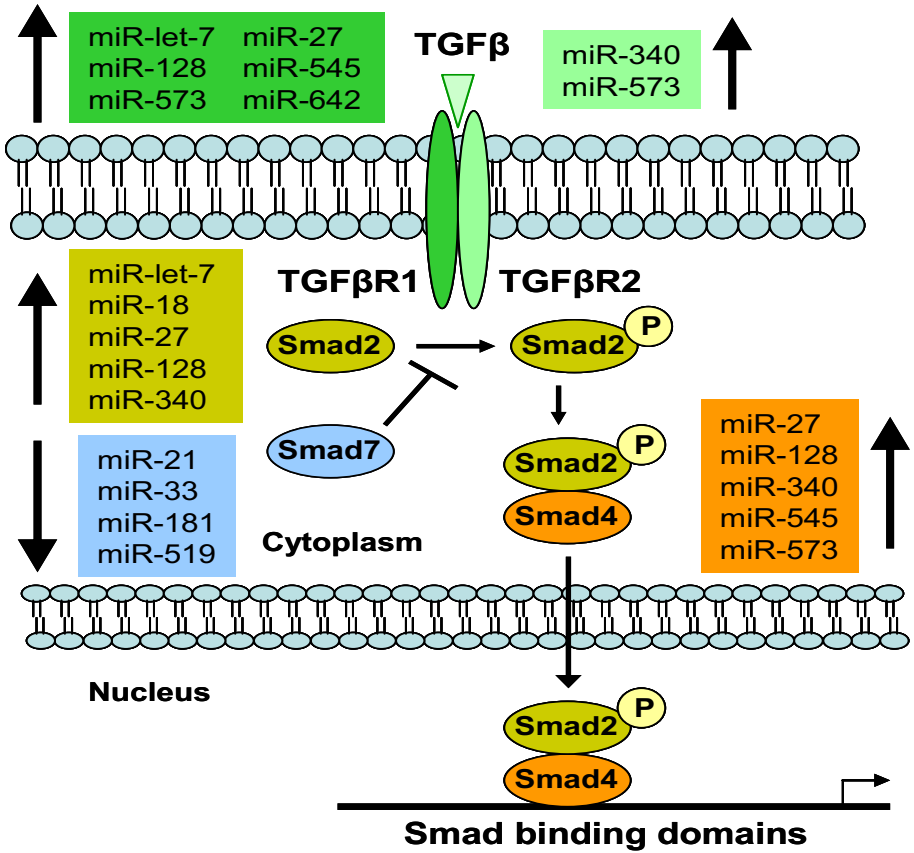
An Animated Tour

Chapter 6: Remission

miRNAs in MS target TGF-β signaling



Severin ME, et al. *Brain.* 2016;139(Pt 6):1747-1761.

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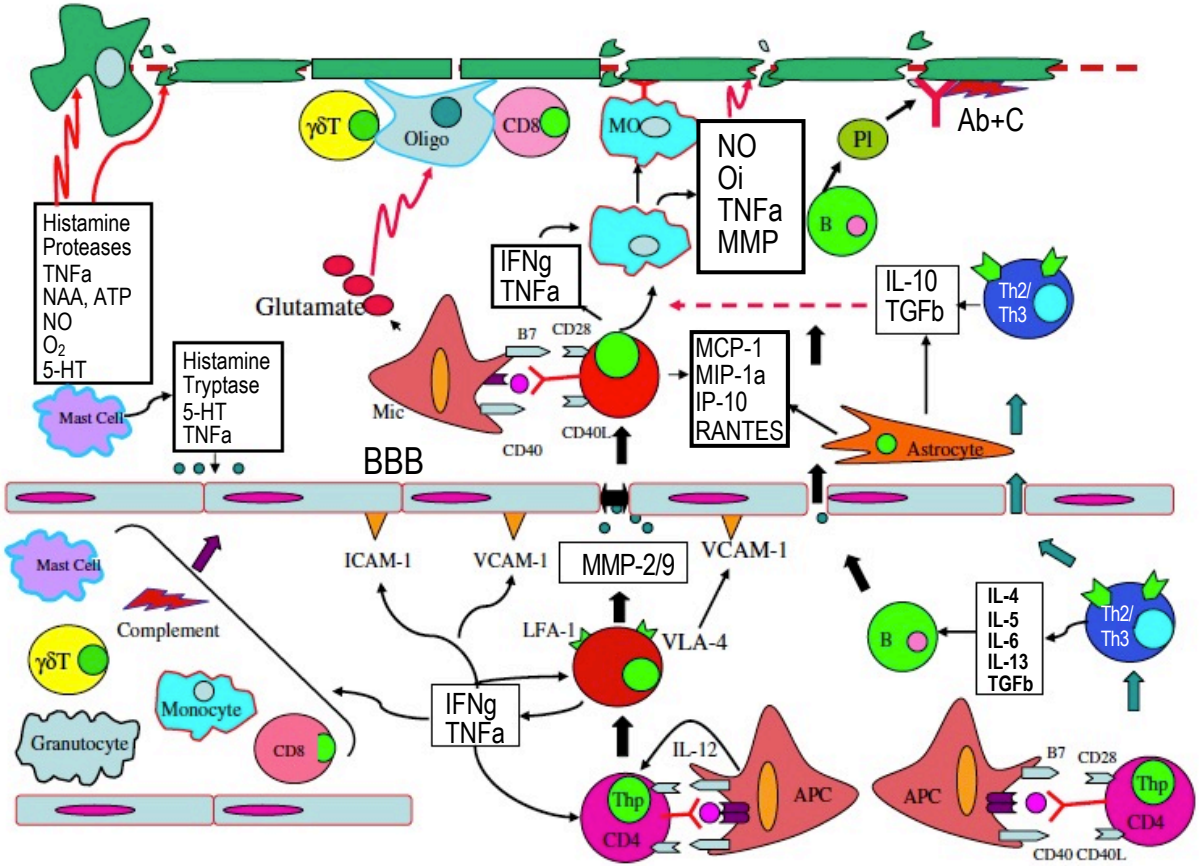
Pathophysiology of Multiple Sclerosis

An Animated Tour

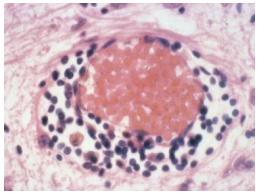
Chapter 7: Relapse

Immunopathogenesis of the MS Lesion

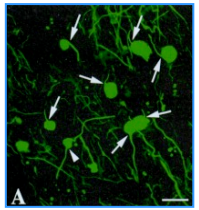


Dhib-Jalbut S, et al. *J Neuroimmunol*. 2006;176(1-2):198-215.

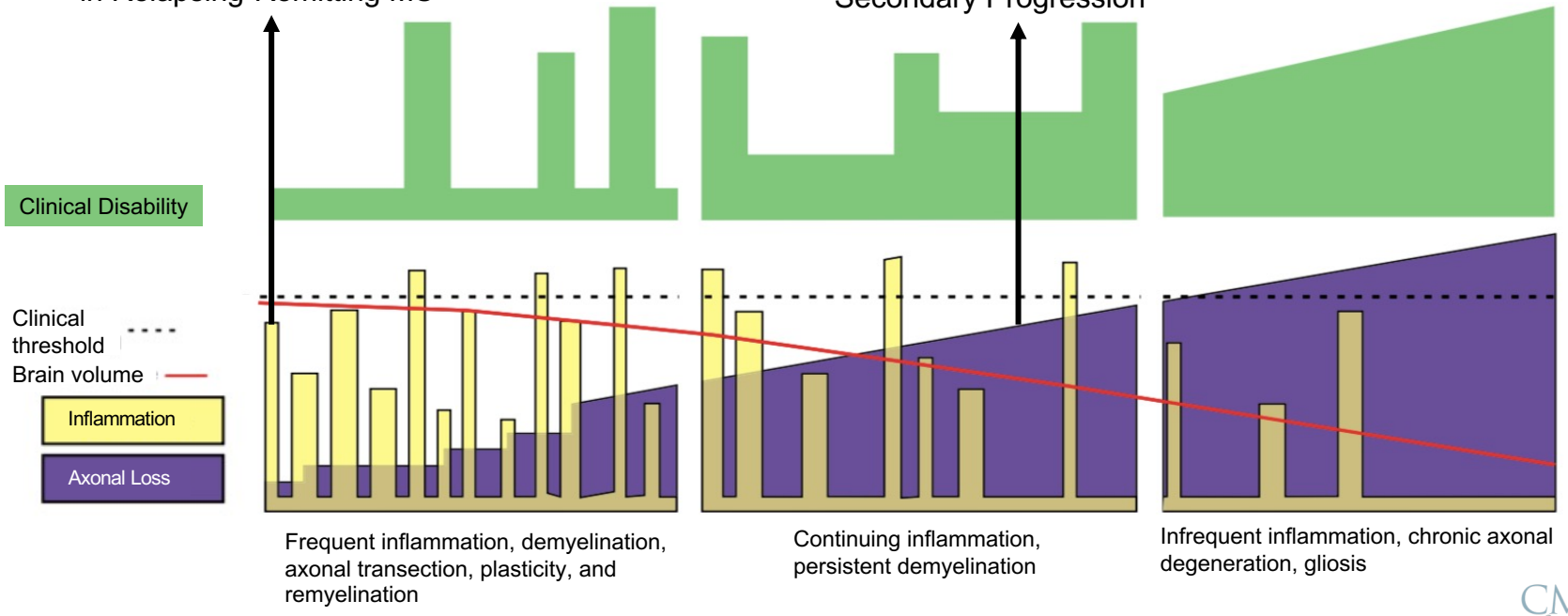
Inflammation and Axonal Loss in MS



Perivascular inflammation
in Relapsing-Remitting MS



Active MS lesions in
Secondary Progression



Compston A, Coles A. *Lancet*. 2002;359(9313):1221-1231. Trapp BD, et al. *N Engl J Med.* 1998;338(5):278-285.

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Pathophysiology of Multiple Sclerosis

An Animated Tour

Chapter 8: Progressive MS

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Learning Objective 2

Assess clinical data supporting the efficacy and safety of novel and emerging immune-directed therapies for MS.

Patient Presentation

- Laura is a 26-year-old woman who woke up 2 weeks ago with visual loss in the left eye. She felt like she had a “film” over her eye. She was seen by her optometrist who suspected optic neuritis and referred her to an ophthalmologist.
- Optic neuritis diagnosis was confirmed, and she was treated with 3 days of IVMP with about 80% improvement of symptoms and referred to neurology for evaluation.
- She is married with 2 small children and works as a middle school teacher. She hopes to expand her family in the future.

IVMP = intravenous methylprednisolone

History and Physical

- Upon taking further history, patient recalls an episode 5 months ago when she had foot drop and mild weakness in her right leg, which improved but did not completely resolve after 4 weeks. She did not have brain MRI performed at that time.
- Exam vision was 20/20 in the left eye and 20/40 in the right eye, +hyperreflexia in right lower extremity with 4+/5 dorsiflexion
- Exam otherwise unremarkable
- Imaging: MRI showed > 10 supratentorial brain lesions with 3 Gd+ lesions and cervical spine showed multifocal, patchy increased signal without enhancement.
- Other Tests: LP showed > 5 OCBs; Aquaporin 4 Ab negative

Gd+ = gadolinium-enhancing; LP = lumbar puncture; OCB = oligoclonal bands

Audience Response

How would you treat this patient?

A. Wait for another clinical episode before starting treatment
B. Start treatment with an immunomodulator
C. Start treatment with a cell-trafficking inhibition agent
D. Start treatment with a cell-depleting therapy
E. I don’t know

Predictors of Poor Prognosis in MS

Demographic and environmental factors

- Older age at onset
- Male sex
- Not of European descent
- Low vitamin D levels
- Smoking (recently questioned)
- Comorbid conditions

Clinical factors

- Primary progressive disease subtype
- High relapse rate
- Shorter interval between the 1st and 2nd relapses
- Brainstem, cerebellar, or spinal cord onset
- Poor recovery from the first relapse
- Higher EDSS score at diagnosis
- Polysymptomatic onset
- Early cognitive deficits

MRI observations

- High number of T2 lesions
- High T2 lesion volume
- Presence of Gd-enhancing lesions
- Presence of infratentorial lesions
- Presence of spinal cord lesions
- Whole brain atrophy
- Grey matter atrophy

Biomarkers

- High number of T2 lesions
- Presence of IgG and IgM oligoclonal bands in CSF
- High serum or CSF levels of neurofilament light chain
  High levels of chitinase in the CSF
- Retinal nerve fiber layer thinning detected with OCT

CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; IgG = immunoglobulin G; IgM = immunoglobulin M; OCT = optic coherence tomography

Rotstein D, Montalban X. *Nat Rev Neurol*. 2019;15(5):287-300.

Racial Disparities in MS Incidence and Outcomes

In the US, the incidence of MS was found to be

- 47% greater among Black vs. White individuals
- 59% greater in Black women vs. White women

Langer-Gould A, et al. *Neurology.* 2013;80(19):1734-1739.

Clinical Characteristics of MS in Black Patients

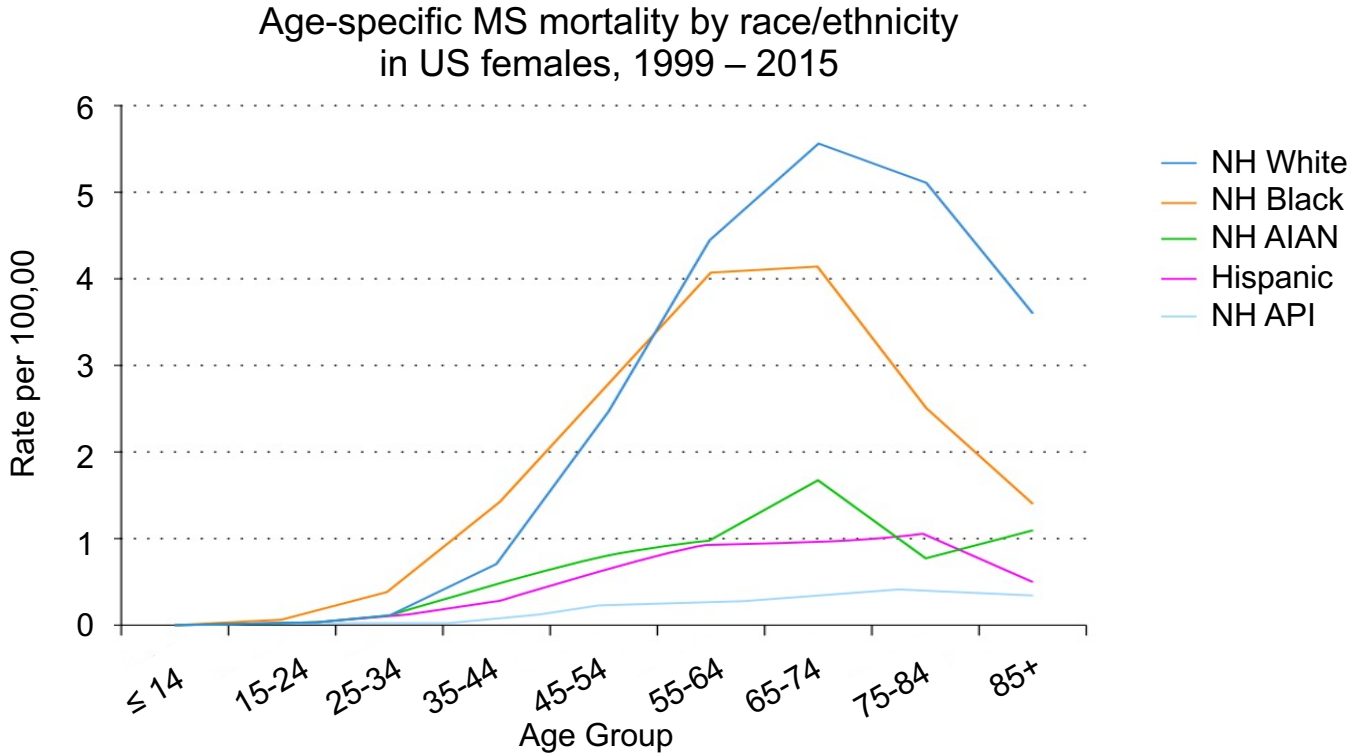
Disease progression is significantly faster in Black patients in both brain and retinal measures.[1]

MRI analysis found whole brain, gray matter, and white matter atrophy to occur twice as fast in Black patients compared with White patients.[1]

Black patients also show faster atrophy of the thalamus, which could be linked to cognitive impairment.[1,2]

1. Caldito NG, et al. *Brain.* 2018;141(11):3115-3129. 2. Weinstock-Guttman B, et al. *Mult Scler.* 2003;9(3):293-298.

Mortality in MS Varies With Race, Age, and Sex



NH = non-Hispanic; AIAN = American Indian or Alaska Native; API = Asian or Pacific Islander

Amezcua L, et al. *Neuroepidemiology.* 2018;50(1-2):35-40.

AAN Guidelines for DMT Initiation in Adults with MS

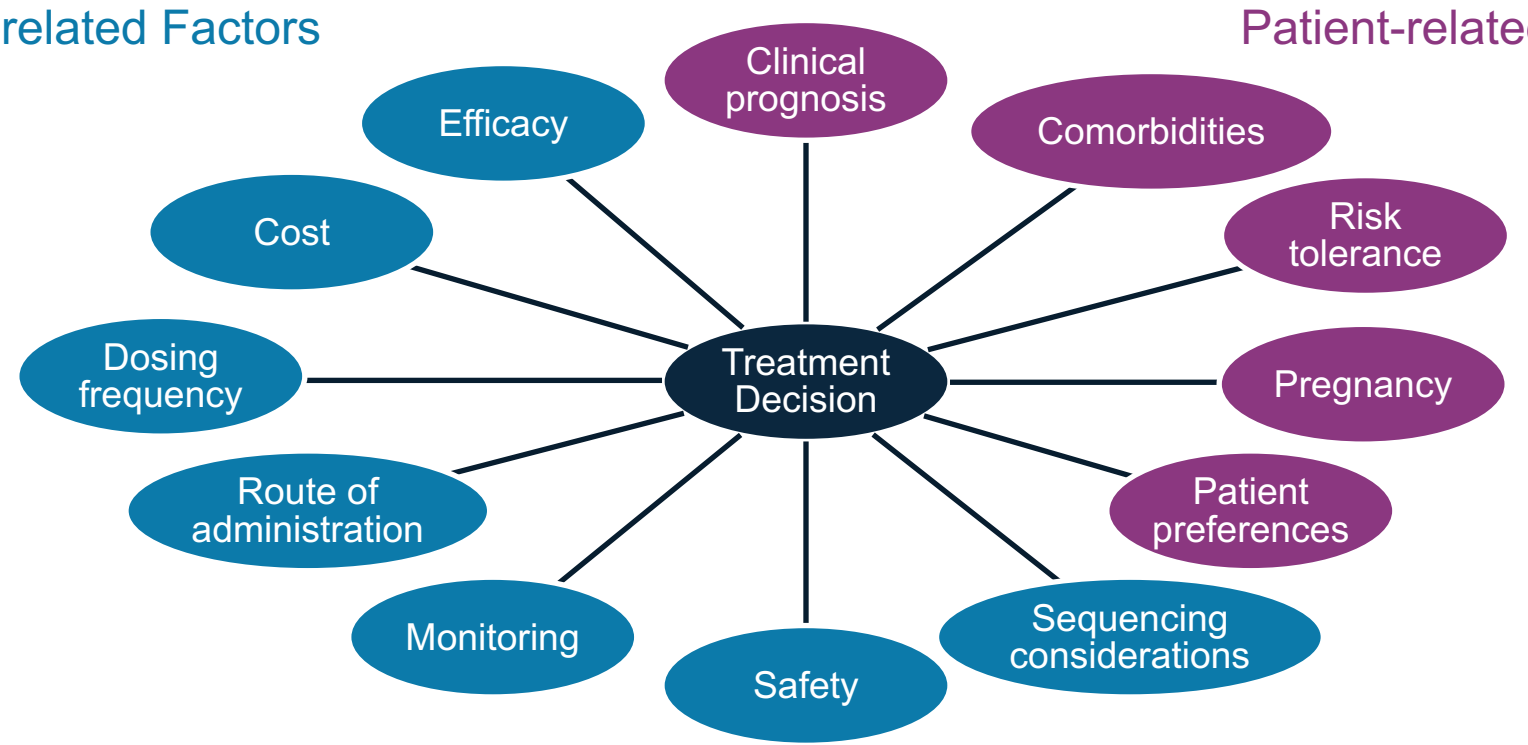
Level A Recommendations:

- Clinicians must ascertain and incorporate/review preferences in terms of safety, route of administration, lifestyle, cost, efficacy, common adverse effects (AEs), and tolerability in the choice of disease modifying therapies (DMT) in people with MS being considered for DMT.
- Clinicians must engage in an ongoing dialogue regarding treatment decisions throughout the disease course with people with MS.
- Clinicians must counsel people with MS on DMTs to notify the clinicians of new or worsening symptoms.

AAN = American Academy of Neurology

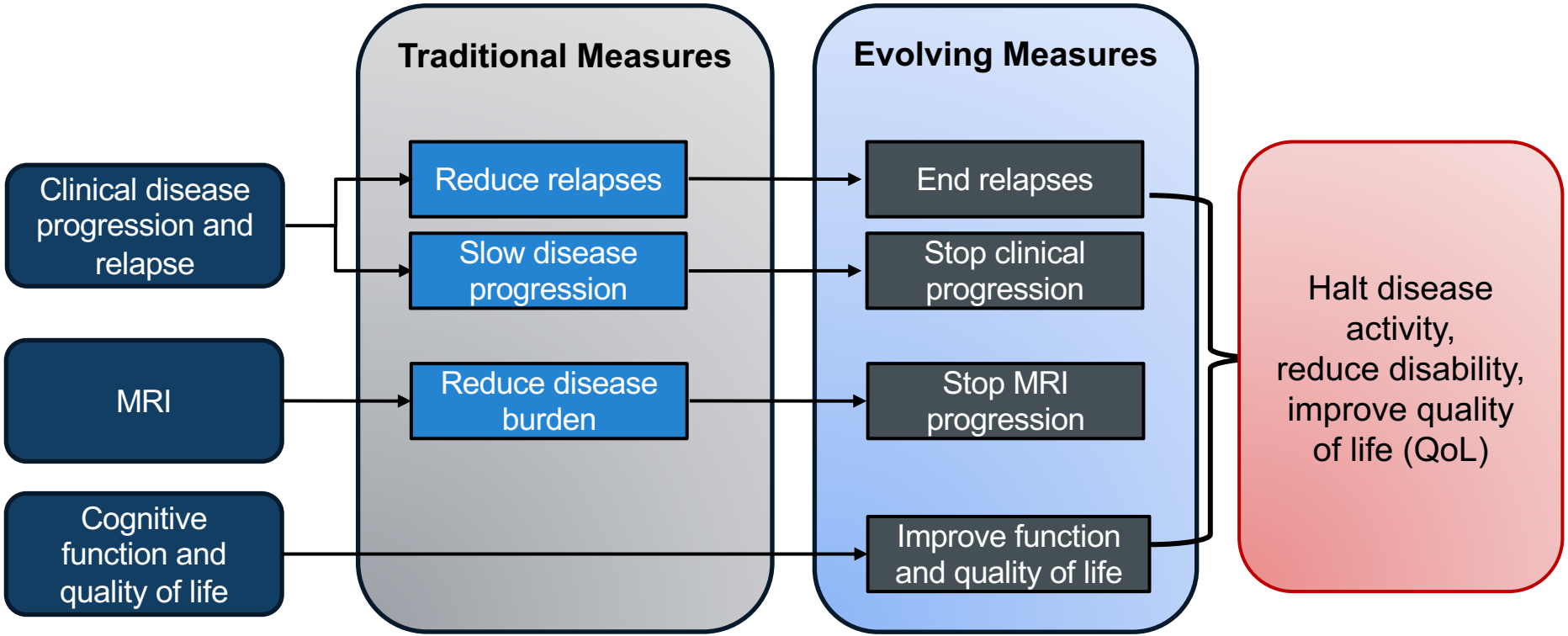
Rae-Grant A, et al. *Neurology*. 2018;90(17):789-800. Erratum in: *Neurology*. 2019;93(17):769.

Making Treatment Decisions: Considering the Benefits and Risks



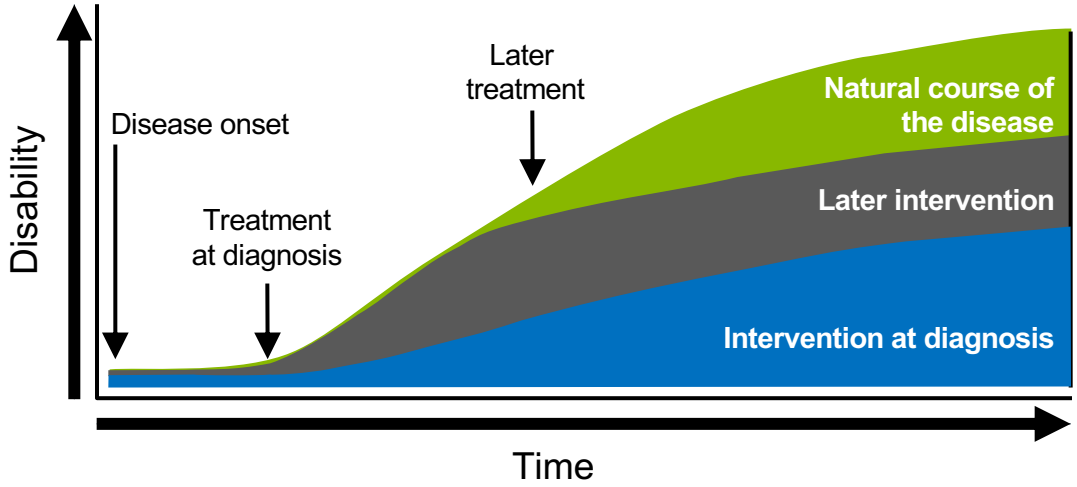
Rotstein D, Montalban X. *Nat Rev Neurol.* 2019;15(5):287-300.

Treatment Goals in MS



Smith AL, et al. *Neurotherapeutics.* 2017;14:952-960. Rotstein DL, et al. *JAMA Neurol.* 2015;72(2):152-8.
Lazibat I, et al. *Acta Clin Croat.* 2016;55(1):125-33.

Early Intervention in MS: Maximizing the Use of the Therapeutic Window



- The therapeutic window in MS offers the greatest opportunity for long term benefit
- Finding the most appropriate intervention as early as possible is key

Miller JR. *J Manag Care Pharm* 2004;10(3 Suppl B):S4-11.

Treatment Initiation Choices

Induction (Higher Risk)

- Start with a higher efficacy agent
  - Obtain a treatment response for a given period
- Monitor for safety

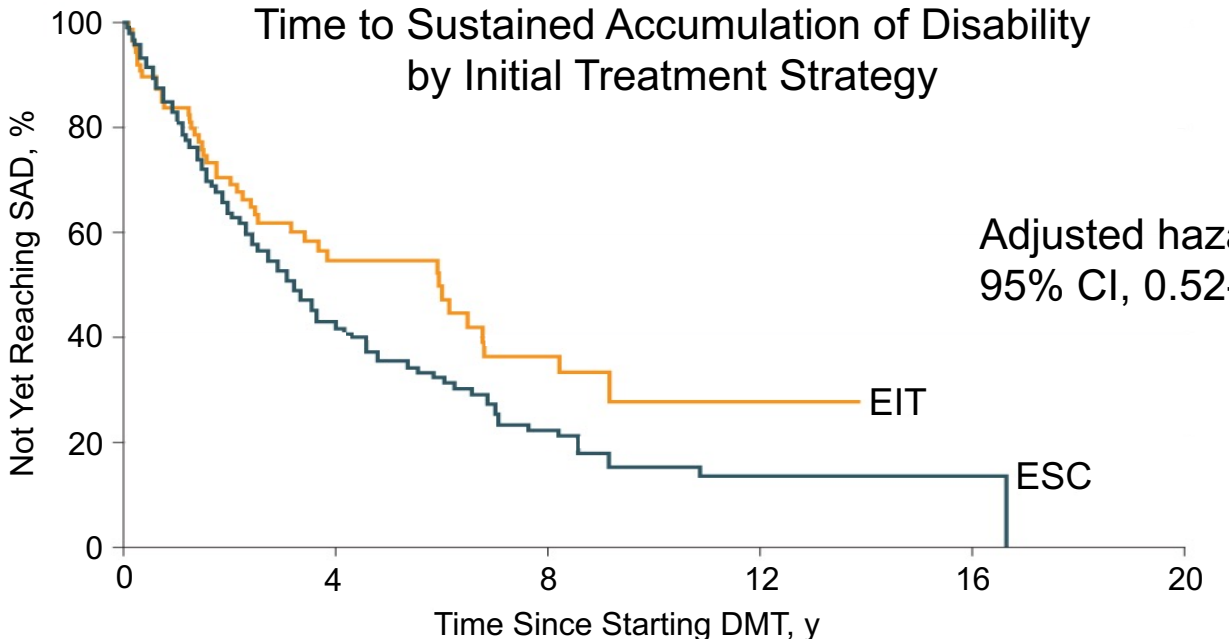
VS.

Escalation (Lower Risk)

- Start with a 1st line agent (“platform therapy”)
- Monitor treatment “response”
- If sub-optimal response, move to a higher efficacy agent
- Monitor treatment “response”

Lazibat I, et al. *Coll Antropol*. 2014;38(1):385-393.

Early Initiation of DMTs Leads to Improved Disease Control and Long-term Outcomes



EIT = early intensive treatment; ESC = escalation approach; SAD = sustained accumulation of disability

Harding K, et al. *JAMA Neurol.* 2019;76(5):536-541. Merkel B, et al. *Autoimmun Rev*. 2017;16(6):658-665.

Disease Modifying Medications: Categories

Immunomodulators

Interferon-beta
Glatiramer Acetate
Dimethyl Fumarate
Diroximel Fumarate
Teriflunomide

Pros
- Safety
- Long term experience

Cons
- Modest efficacy
- Many injectable

Cell-Trafficking Inhibition Agents

Natalizumab
Fingolimod
Siponimod
Ozanimod

Pros
- Greater efficacy
- Onset of action quick
- Well tolerated

Cons
- Opportunistic infections (PML)
- Cells still in body
- Rebound disease
- Long term safety unclear

Cell-Depleting Therapies

Alemtuzumab
Cladribine
Ocrelizumab
Rituximab*
Ofatumumab
AHSCT (BMT)

Pros
- Definitive in depleting disease-causing cells
- Some are IRT
- No rebound disease

Cons
- Opportunistic infections
- Secondary autoimmunity (alemtuzumab)
- Most cumbersome

* Not approved by the FDA for treatment of MS

AHSCT = autologous hematopoietic stem cell transplantation; BMT = bone marrow transplant; IRT = immune reconstitution therapy; PML = progressive multifocal leukoencephalopathy

Rizvi SA, et al. *Clinical Neuroimmunology*. 2nd ed. 2020.

Matching DMT Selection to Likely Progression of MS

Diagnosis of CIS or RRMS

Poor prognostic factors **absent**

Injectables
- GA
- IM IFN-β1a
- SC IFN-β1a
- SC PEG-IFN-β1a
- SC IFN-β1b

Oral agents
- Dimethyl fumarate
- Diroximel fumarate
- TER

Factors that influence drug selection	Favored drug(s)
Needle phobia	TER, DMF
Monitoring	GA
Pregnancy	GA, IFN-beta
Safety	GA

Poor prognostic factors **present**

Infusions
- Alemtuzumab
- Natalizumab
- Ocrelizumab

Oral agents
- Cladribine
- Fingolimod
- Ozanimod
- Siponimod

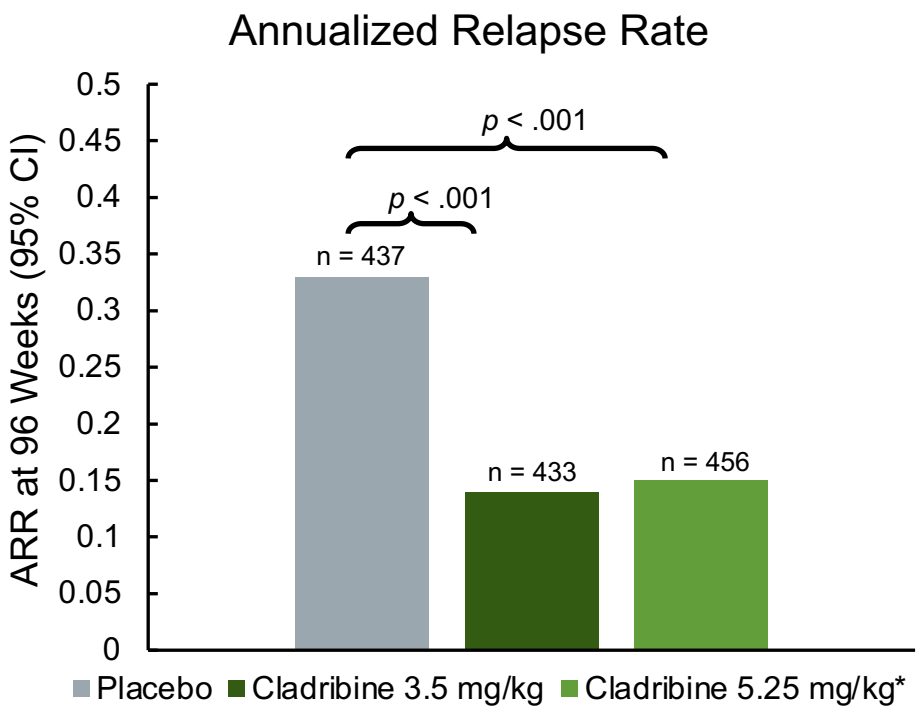
Factors that influence drug selection	Favored drug(s)
JCV positivity	All but NTZ
History of poor adherence	NTZ, OCR
Monitoring	CLAD, OCR
Efficacy	ALEM, NTZ, OCR
Pregnancy (with planning)	ALEM, CLAD, NTZ
Prefer oral route	CLAD, FNG
Prefer induction	ALEM, CLAD

ALEM = alemtuzumab; CLAD = cladribine; CIS = clinically isolated syndrome; PEG = pegylated; DMF = dimethyl fumarate; FNG = fingolomod; GA = glatiramer acetate; IM = intramuscular, JCV = John Cunningham virus; NTZ = natalizumab; OCR = ocrelizumab; SC = subcutaneous; TER = teriflunomide

Rotstein D, Montalban X. *Nat Rev Neurol.* 2019;15(5):287-300.

Cladribine: Efficacy and Safety

- CLARITY trial (N = 1326) of cladribine 3.5 mg/kg and 5.25 mg/kg* vs placebo:
  - 58% and 55% ARR reduction
  - 80% and 79% relapse-free vs. 61% with placebo
  - 86% and 88% reduction in Gd+ lesions
  - Increased rate of lymphocytopenia
- ORACLE trial:
  - In patients with first clinical demyelinating event, cladribine delayed conversion to clinically definite MS

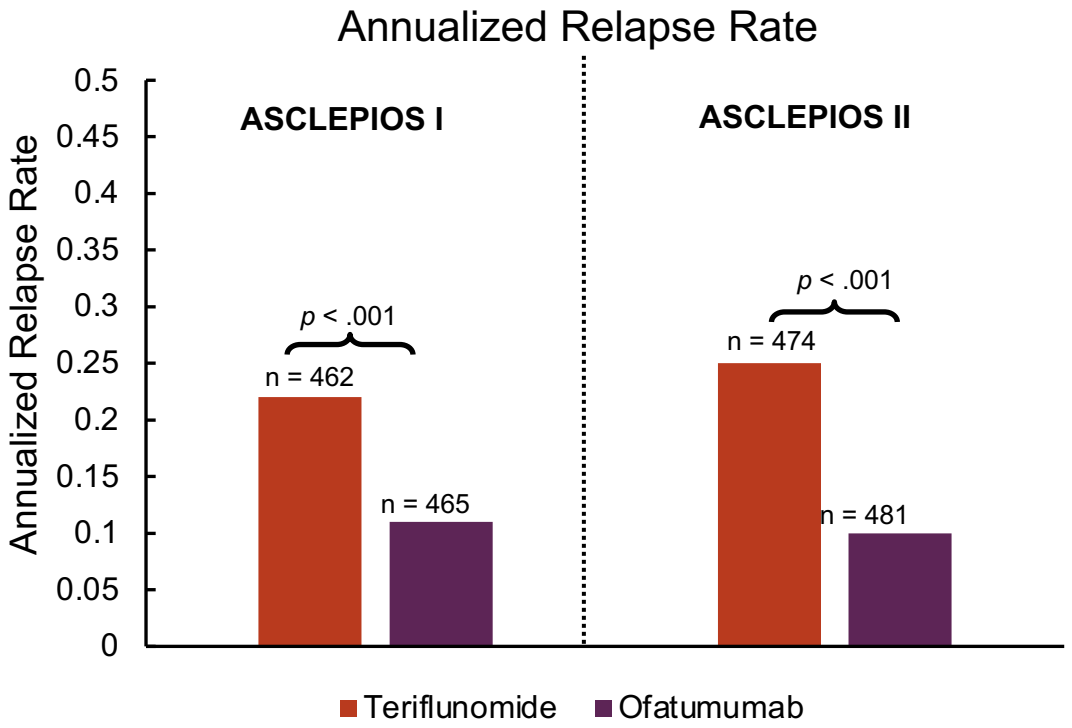


*5.25 mg/kg dose is not FDA-approved; FDA-recommended cumulative dose is 3.5 mg/kg.
ARR = annualized relapse rate.

Giovannoni G, et al. *N Engl J Med*. 2010;362(5):416-426. Leist TP, et al. *Lancet Neurol.* 2014;13(3):257-267.

Ofatumumab: Efficacy and Safety

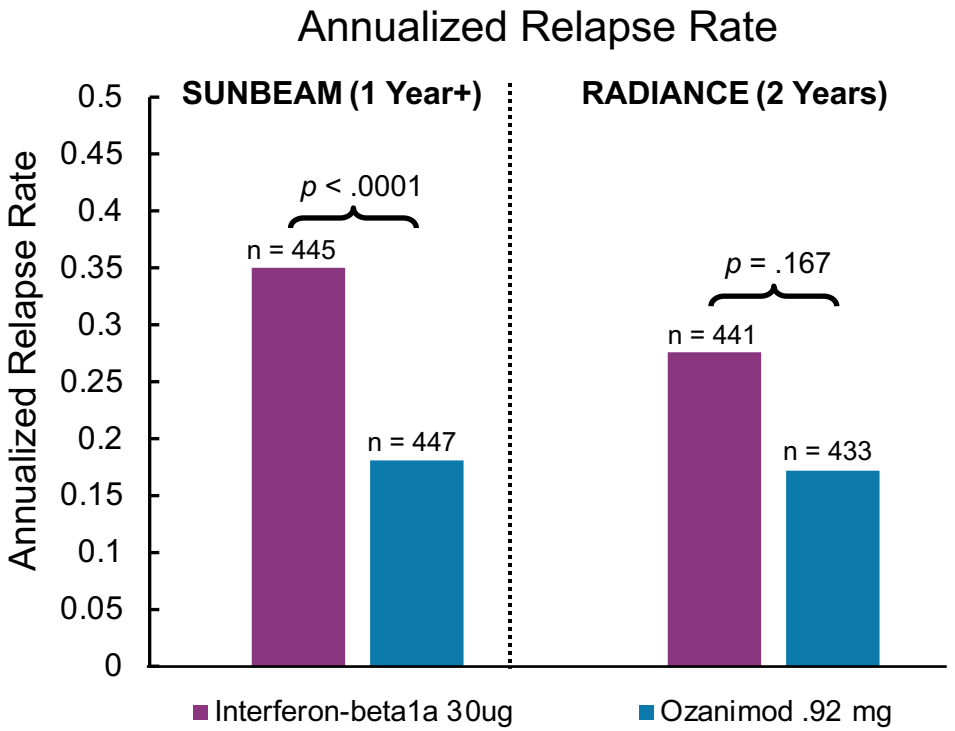
- ASCLEPIOS I and II
  - N = 927, N = 954 respectively
- 97% and 93% reduction in Gd+ lesions in ofatumumab group vs teriflunomide
- 51% and 59% reduction in ARR in ofatumumab group compared to teriflunomide
- Demonstrated safety and tolerability profile with infection rates similar to teriflunomide



Hauser SL, et al. *N Engl J Med*. 2020;383(6):546-557.

Ozanimod: Efficacy and Safety

- SUNBEAM and RADIANCE trials
  - N = 1346, N = 1313 respectively[1,2]
- 63% and 53% reduction in Gd+ lesions in ozanimod group versus interferon-beta 1a[1,2]
- 48% and 38% reduction in ARR in patients receiving ozanimod vs interferon-beta 1a[1,2]
- No clinically significant cardiac adverse effects, lymphopenia and macular edema in patients receiving ozanimod[1,2]



1. Cohen JA, et al. *Lancet Neurol.* 2019;18(11):1021-1033. 2. Comi G, et al. *Lancet Neurol.* 2019;18(11):1009-1020.

Diroximel Fumarate: Efficacy and Safety

EVOLVE-MS-1

- Phase III, open-label, single-arm, 96-week trial (n = 696)
- Primary endpoint: safety and tolerability
- Week 48 Adjusted ARR: 0.16 (95% CI: 0.13–0.20), similar to prior observations with DMF

EVOLVE-MS-2

- Phase III, randomized, double-blind, 5-week trial vs DMF (n = 504)
- 46% reduction in number of days with an IGISIS symptom intensity score ≥ 2 vs DMF (RR [95% confidence interval]: 0.54 [0.39-0.75]; *p* = 0.0003)
- Lower rates of GI AEs: 34.8% with DRF vs 49.0% with DMF

AE = adverse event; DMF = dimethyl fumarate; DRF = diroximel fumarate; GI = gastrointestinal; IGISIS = Individual Gastrointestinal Symptom and Impact Scale

Naismith RT, et al. *Mult Scler.* 2020;26(13):1729-1739. Naismith RT, et al. *CNS Drugs.* 2020;34(2):185-196.

Emerging Therapies: BTK inhibitors

Agent	Clinical Trial Status
Evobrutinib	Phase III trials recruiting • EvolutionRMS 1 & 2 trials vs teriflunomide for RMS
Tolebrutinib (SAR442168)	Phase III trials recruiting • GEMINI 1 and 2 vs teriflunomide for RMS • PERSUES vs placebo for PPMS • HERCULES vs placebo for SPMS
Fenebrutinib	Phase III trial commencing
BIIB091	Phase I trial recruiting

BTK = Bruton's tyrosine kinase; PPMS = primary progressive multiple sclerosis; RMS = relapsing multiple sclerosis

ClinicalTrials.gov Identifiers: NCT04411641, NCT04458051, NCT04410978, NCT04410991, NCT04544449, NCT04564612.

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CONTINUING MEDICAL EDUCATION

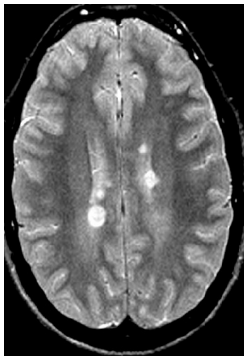
Learning Objective 3

Integrate biomarkers and imaging techniques to assess disease progression in patients with MS

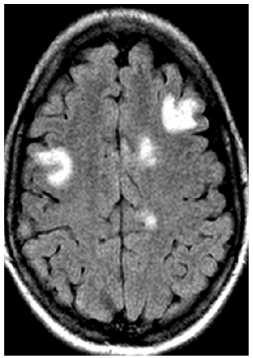
2017 Diagnostic Criteria: MRI

DIS: ≥ 1 T2 lesions in ≥ 2 locations

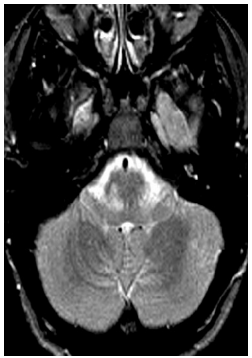
Periventricular



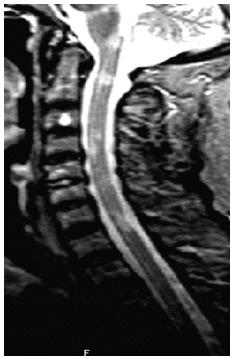
Cortical / Juxtacortical



Infratentorial



Short segment Spinal cord



Changes from the 2010 McDonald Criteria:

- No distinction between symptomatic and asymptomatic lesions
- Both cortical* and juxtacortical lesions can be utilized

*Recommend cortical lesions only be utilized by centers experienced in identifying them

DIS = dissemination in space

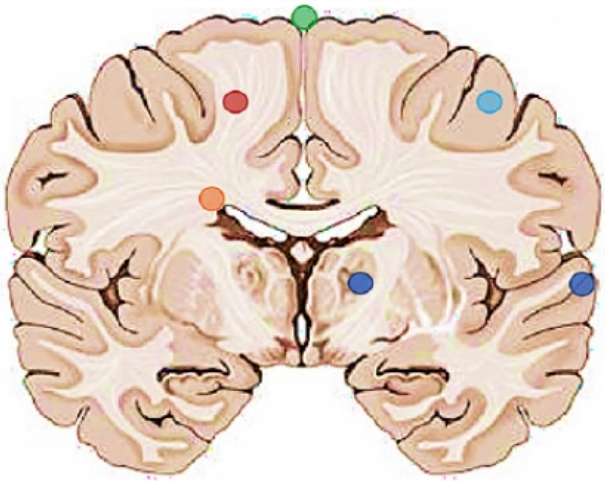
Thompson AJ, et al. *Lancet Neurol.* 2017;17(2):162-173. Solomon AJ, Naismith RT, Cross AH. *Neurology*. 2019;92(1):26-33.

Emerging Imaging Biomarkers

Normal Appearing White Matter
- New techniques to detect subtle pathological changes
- MTR used to monitor changes in myelin in clinical trials

White Matter Lesions
- Distinctive lesion features (i.e., CVS and peripheral rim)
- Methods to detect SEL on conventional MRI

Leptomeningeal Infiltrates:
- Visible at ultra-high and high field MRI on post-contrast 3D T2-FLAIR
- Used as biomarker for MS inflammation
- Differences in MS phenotypes
- Role in Cortical lesions' development



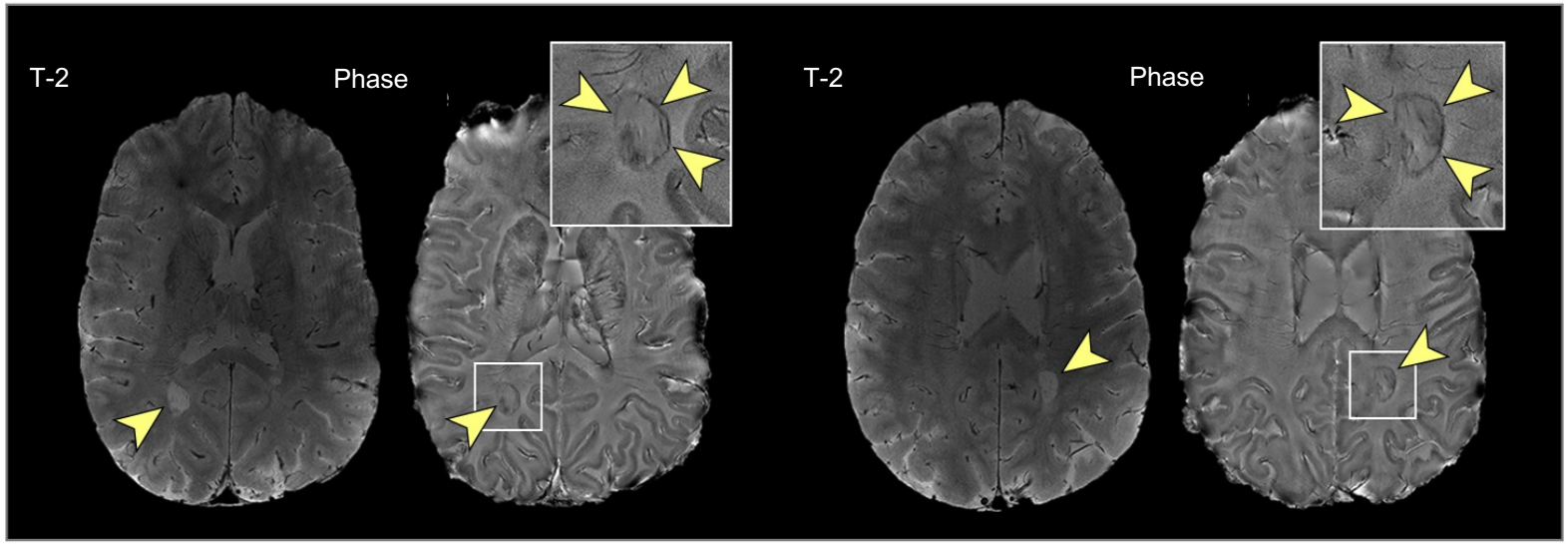
Cortical Lesions:
- Inclusion in 2017 McDonald criteria
- New MRI techniques to improve their detection
- Association with clinical disability and cognitive impairment
- Association with meningeal inflammation
- Used to test the neuroprotective effect of DMD
- Network based approaches applied to explore abnormalities within the principal brain networks

Normal Appearing Grey Matter
- Differences in regional GM atrophy development between phenotypes
- Role of DGM and thalamus volume loss in MS pathogenesis
- Relationship between cortical atrophy and motor cognitive impairment

CVS = central vein sign; GM = gray matter; DGM = deep gray matter; DMD = Duchenne muscular dystrophy; MTR = magnetization transfer ratio; SEL = spinal epidural lipomatosis

Cortese R, et al. *Ther Adv Neurol Disord.* 2019;12:1756286419859722. Elliott C, et al. *Mult Scler J.* 2019, 25(14) 1915-1925.

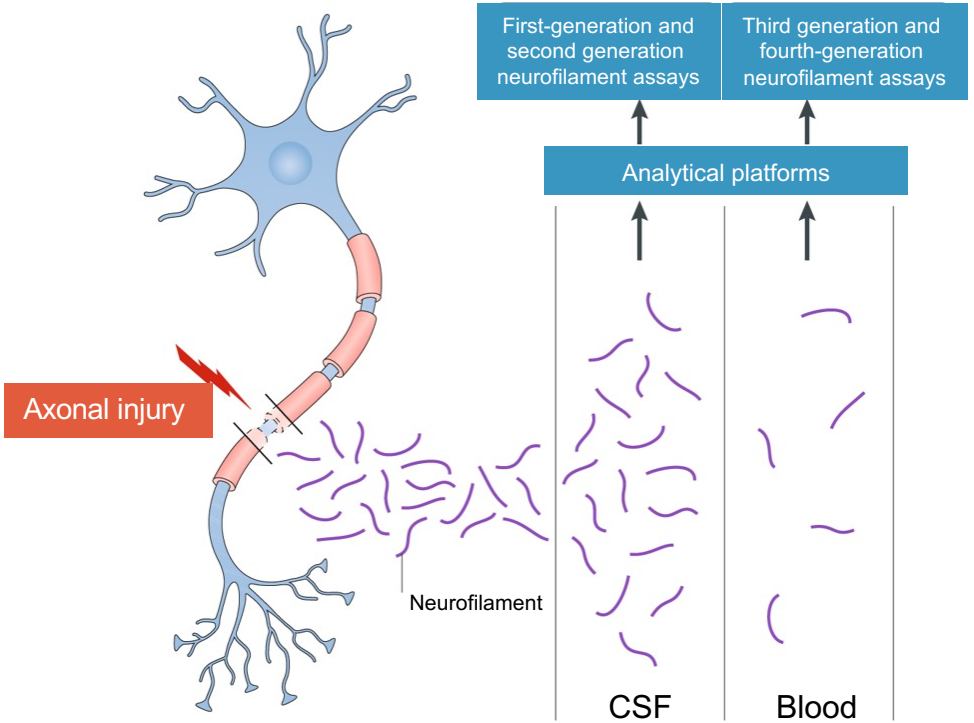
Advances in Brain Imaging: Phase Rims



Absinta M, et al. *JAMA Neurol.* 2019;76(12):1474-1483.

Biomarkers: Neurofilament

- Three major neurofilament protein subunits, light (NfL), medium and heavy (NfH), form the backbone of the axonal cytoskeleton
- Following axonal damage NfL and NfH are released
- Traditionally NfL and NfH were measured in the CSF by ELISA
- Newer, more sensitive technologies, like single molecule array (Simoa), reliably measure NfL in the blood.
- Correlation between paired CSF and serum NfL with Simoa: r = 0.88



Teunissen CE, et al. *Mult Scler.* 2012;18(5):552-556. Kuhle J, et al. *Clin Chem Lab Med.* 2016;54(10):1655-1661.

NfL Is Not Specific to MS

- NfL is elevated in other neurodegenerative diseases, including:
  - Alzheimer's disease
  - Amyotrophic lateral sclerosis
  - Traumatic brain injury
- Serum NfL levels increase 2.2% per year with age in healthy controls

1. Kapoor R, et al. *Neurology.* 2020;95(10):436-444. 2. Jeromin A, Bowser R. *Adv Neurobiol.* 2017;15:491-528.

NfL in Patients with MS

- CSF NfL concentration predicts long-term disability (up to 14 years)[1]
- Serum NfL (sNfL) concentration predicts progression of degeneration and clinical disability[2,3]
  - Higher sNfL concentrations predicted brain volume loss over 2 and 5 years[3,4]
  - Higher sNfL concentrations associated with worse later clinical outcomes including worsening in EDSS, walking speed, manual dexterity, and cognitive processing speed[3,5,6]
- NfL concentration was found to decrease after treatment with rituximab[7], natalizumab[8], fingolimod[9], ocrelizumab[10], ofatumumab[11], or cladribine[12]

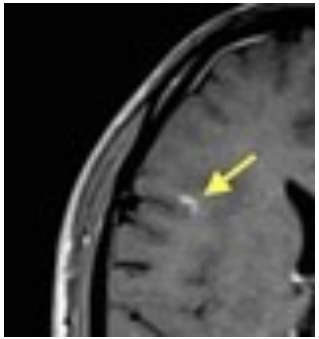
1. Salzer J, et al. *Mult Scler.* 2010;16(3):287-292. 2. Kapoor R, et al. *Neurology.* 2020;95(10):436-444. 3. Barro C, et al. *Brain.* 2018;141(8):2382-2391.
4. Siller N, et al. *Mult Scler.* 2019;25(5):678-686. 5. Disanto G, et al. *Ann Neurol.* 2017;81(6):857-870. 6. Jakimovski D, et al. *Mult Scler.* 2020;26(13):1670-1681.
7. Alvarez E, et al. *Mult Scler J Exp Transl Clin*. 2015;1:2055217315623800. 8. Gunnarsson M, et al. *Ann Neurol.* 2011;69(1):83-89.
9. Kuhle J, et al. *Neurology.* 2015;84(16):1639-1643. 10. Bar-Or A, et al. ECTRIMS 2019 Congress; 2019. Abstract No. 152.
11. Hauser SL, et al. *N Engl J Med.* 2020;383(6):546-557. 12. Yildiz O, et al. *Mult Scler Relat Disord.* 2018;24:20-27.

Lorene

- 35-year-old right-handed woman of Hispanic ethnicity who developed subacute weakness in right hand along with an electrical sensation in her spine upon flexing her neck. MRI of brain and spinal cord showed 5 supratentorial and one posterior C2 hyperintensities, suggestive of demyelination.
- Lumbar puncture (LP) showed: 9 CSF-restricted oligoclonal bands (OCBs), IgG Index 1.08 (high), normal glucose, sl high protein at 45. Six nucleated cells (no diff), 0 red blood cells (RBCs).
- Lorene works as a clerk in a department store, and her main complaints are fatigue, and right-hand clumsiness, which is intermittently worse and better.
- She was diagnosed with RRMS and began interferon beta-1b given every other day subcutaneously.
- She is monitored annually per AAN guidelines

Lorene, continued

- She continued to take beta-interferon for 2 years, adherently, despite continued flu-like symptoms but without any clinical worsening or relapses.
- She underwent her yearly surveillance MRI which showed a single Gd-enhancing juxtacortical lesion, which was asymptomatic, in addition to her already-known brain and spinal cord lesions which were unchanged.
- She denies missing any doses of subcutaneous beta-interferon therapy.



Audience Response

Which is *least likely* to be an effective strategy for treating Lorene, who has been taking IFN beta-1b for 2 years since her initial MS diagnosis, with no clinical relapses during that time, and now presents with a single new asymptomatic Gd-enhancing lesion?

A. Remain on IFN beta-1b
B. Cell-trafficking inhibition agents
C. Cell-depleting therapies
D. Dimethyl fumarate
E. I don't know

Lorene

- Lorene has a new, asymptomatic, Gd-enhancing lesion that looks typical of demyelination.
- Studies suggest that she will not do well over the long-term with an enhancing lesion if stays on beta-IFN therapy.
- A follow-up study of the pivotal beta-IFN1a study found that new enhancing lesions predicted EDSS worsening (OR 8.96).

Bermel RA, et al. *Ann Neurol.* 2013;73(1):95-103.

Guidelines for Monitoring Disease Progression and Treatment Response

AAN Level B recommendations in people with MS on DMTs:

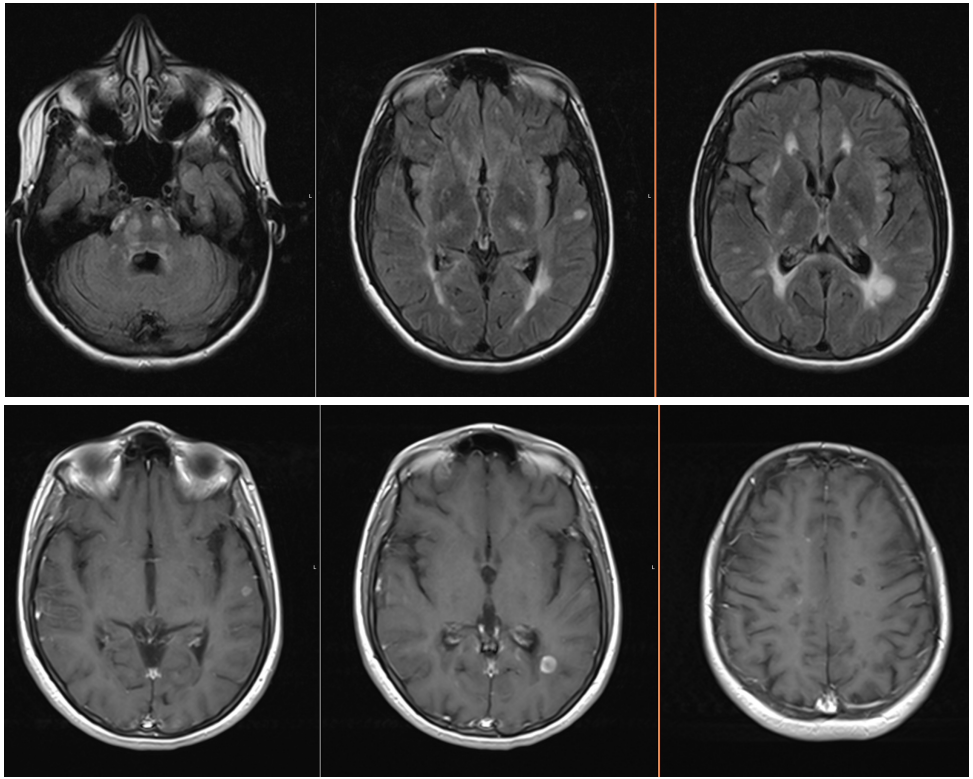
- Monitor MRI disease activity from the clinical onset of disease to detect the accumulation of new lesions in order to inform treatment decisions.
  - Optimal interval for monitoring is uncertain and may vary among DMTs
- Follow up either annually or according to medication-specific risk evaluation and mitigation strategy (REMS)
- Monitor for medication adherence, AEs, tolerability
- Monitor reproductive plans of women of childbearing potential
- Discuss switching DMT in people using a DMT long enough for the treatment to take full effect and are adherent to therapy with: 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT.

Rae-Grant A, et al. *Neurology.* 2018;90(17):777-788.

Clinical Case - Jacob

- 46-year-old attorney
- Tremor and incoordination that was first noticed 3 weeks earlier
- Paresthesia of both legs lasting 3 days occurring 1 year earlier
- Urinary frequency and urgency

Clinical Case – Jacob's MRI Findings



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Clinical Case - Jacob

- Discussion of potential DMT ensues
- Jason is very concerned about his potential exposure to SARS-CoV-2 and the effects of DMTs

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Jacob's Questions About COVID-19 and MS

- Will immunosuppressants make him more susceptible to COVID-19 complications?
- If he gets COVID-19, is it likely to provoke an MS relapse?
- How will DMTs affect his response to the SARS-CoV-2 vaccines?

COViMS Voluntary Registry

Patient Characteristics (n = 1944)

	N	%
Confirmed MS	1837	94.5%
Laboratory positive COVID-19	1657	82.2
Recovered	1204	61.9
Recovering	537	27.6
Death	62	3.2
Symptoms never developed	70	3.6
Unknown	71	3.7

Mortality

	Deceased (N = 62)	Alive (N = 1811)
Female	58%	76%
Age, mean (SD)	60.8 (13.2)	47.0 (13.0)
No DMT	19 (34%)	256 (14%)
Dimethyl fumarate	4 (11%)	229 (15%)
Ocrelizumab	12 (32%)	522 (35%)
Natalizumab	3 (8%)	196 (13%)
Fingolimod	0 (0%)	119 (8%)

If you have a patient with MS who has developed suspected or definite COVID-19, you can enter their clinical data at COViMS.org.

COViMS = COVID-19 Infections in MS & Related Diseases

COViMS Registry. The COViMS Database Public Data Update. www.COViMS.org. Accessed January 11, 2021.

MS DMT	Effects on Vaccine Responses (EL = Evidence Level)	Expected Effect on SARS-CoV-2 Vaccine Response
Beta-IFNs	8 EL3 studies. Overall, beta-IFNs appear to have no adverse effects on vaccine responses.[1-4]	Expect normal responses
Glatiramer Acetate	4 EL3 studies. Two studies found reduced response rates vs IFN-beta; two found no difference vs IFN-beta or untreated controls.[1,2,5]	Likely near normal responses, depending on vaccination type.
Teriflunomide	2 EL3 studies. Reduced but sufficient responses to seasonal influenza and rabies vaccines.[6,7]	
Dimethyl fumarate	1 EL3 study. No effects on vaccine responses.[8]	
Natalizumab	6 EL3 studies. Reduced response rates vs IFN-beta and glatiramer acetate.[5,9,10]	Probable reduced response
Fingolimod	1 EL2 study and 2 EL3 studies found fingolomod reduced vaccine responder rates.[11,12]	Probable reduced response
Siponimod	1 EL2 study in healthy subjects found reduced but sufficient titers after influenza vaccination concomitant with siponimod and no effect on pneumococcal vaccine response.[13]	
B-cell depleting agents	1 EL2 study found attenuated but protective response to nonlive vaccines given >12 weeks after ocrelizumab.[14] 1 EL3 study found blunted response to vaccinations administered within 6 months of alemtuzumab dosing.[15]	Expect significantly reduced humoral vaccine response; > 6 months after cladribine or alemtuzumab treatment, response may be normal.

1. Olberg HK, et al. *Eur J Neurol*. 2018;25(3):527-534. 2. Olberg HK, et al. *Mult Scler J*. 2014;20(8):1074-1080. 3. Schwid SR, et al. *Neurology*. 2005;65:1964-1966. 4. Olberg HK, et al. *Mult Scler J*. 2014;20(8):1074-1080. 6. Bar-Or A, et al. *Neurology*. 2013;81(6):552-558. 7. Bar-Or A, et al. *Neurol Neuroimmunol NeuroInflammation*. 2015;2(2):e70. 8. Von Hehn C, et al. *Neurol Neuroimmunol NeuroInflammation*. 2018;5(1). 9. Vågberg M, et al. *Neurol Res*. 2012;34:730-733. 10. Kaufman M, et al. *J Neurol Sci*. 2014;341(1-2):22-27. 11. Mehling M, et al. *Ann Neurol*. 2011;69(2):408-413. 12. Kappos L, et al. *Neurology*. 2015;84(9):872-879. 13. Ufer M, et al. *Neurol Neuroimmunol Neuroinflamm*. 2017;4:e398. 14. Stokmaier D, et al. *Neurology*. 2018;90(15 Suppl). 15. McCarthy CL, et al. *Neurology*. 2013;81(10):872-876.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Consider prognostic factors and patient- and drug-specific factors to determine the therapeutic approach to RRMS
- Partner with patients to discuss treatment goals to optimize outcomes
- Integrate most recent clinical data into the treatment paradigm of patients with RRMS

To Ask a Question

Please click on the *Ask Question* tab and type your question. Please include the faculty member's name if the question is specifically for him/her.

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AFTER THE SHOW

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CME for MIPS
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