

Ascertaining the Role of the Primary Care Clinician in the Recognition and Management of Patients With Multiple Sclerosis in the Modern Era

Andrew Woo, MD, PhD

David Geffen School of Medicine at UCLA
Santa Monica Neurological Consultants
Santa Monica, California

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Disclosures

Andrew Woo, MD, PhD, has a financial interest/relationship or affiliation in the form of:

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Acorda Therapeutics; Biogen; Genentech; Mallinckrodt Pharmaceuticals; Multiple Sclerosis Association of America; Novartis Pharmaceuticals Corporation; and Sanofi Genzyme.

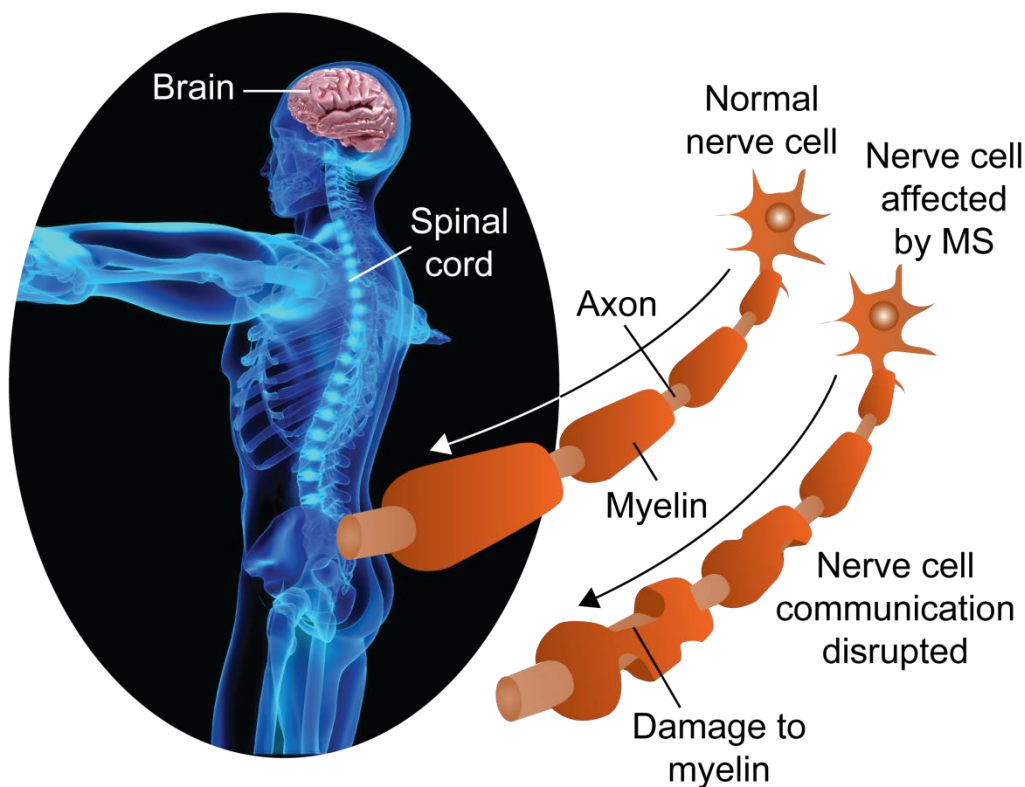
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Practical Considerations for Recognizing Patients With MS

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Multiple Sclerosis: What Is It?¹⁻³



- Acquired disorder to the CNS that is chronic, autoimmune, inflammatory, demyelinating, and progressive
- Over 400,000 patients with MS in United States; ~2.3 million worldwide
- 90% of patients who present are aged 15-50 y
 - 3:1 female-to-male ratio
- Highly variable disease course
 - Patients tend to experience a myriad of symptoms over the course of their disease

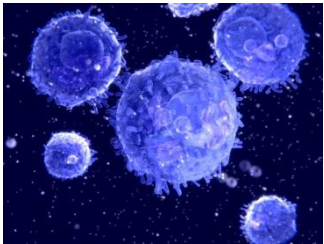
Etiology of Multiple Sclerosis Is Multi-Factorial¹⁻³



Genetics

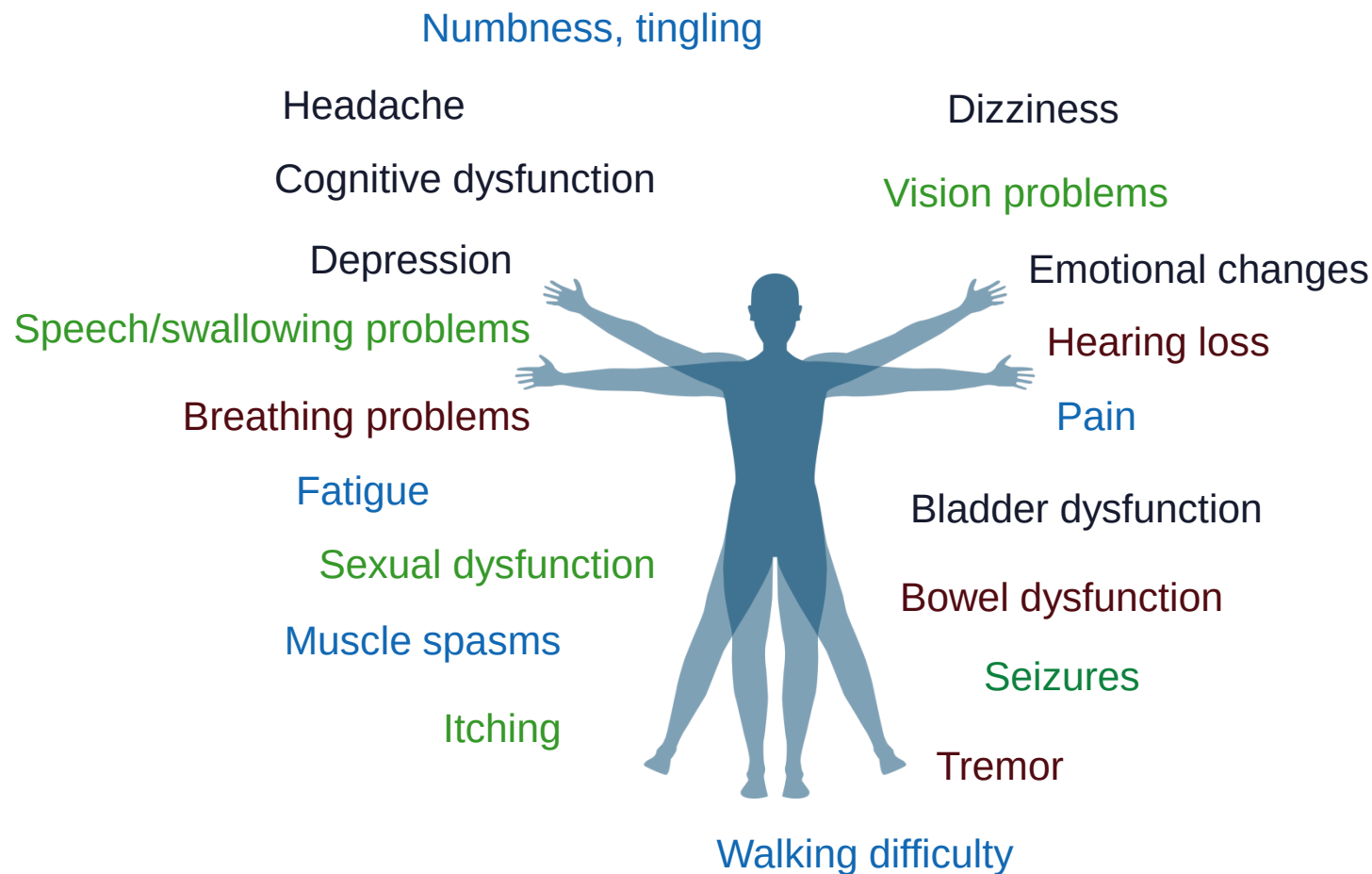


Environmental



Immune System

Common Symptoms Associated With MS^{1,2}



1. Toosy A et al. *Handb Clin Neurol*. 2014;122:513-562.

2. <http://moderndayms.com/2017/02/unusual-symptoms-multiple-sclerosis>. Accessed July 10, 2017.

MS Most Often Begins With an Initial Clinical Demyelinating Event¹⁻³

Initial demyelinating event typically referred to as a clinically isolated syndrome (or CIS), with common manifestations including:



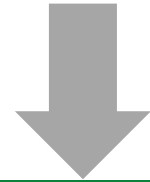
Optic Neuritis

- Sudden, subacute unilateral loss of VA
- Pain upon eye movement
- Decreased color perception



Transverse Myelitis

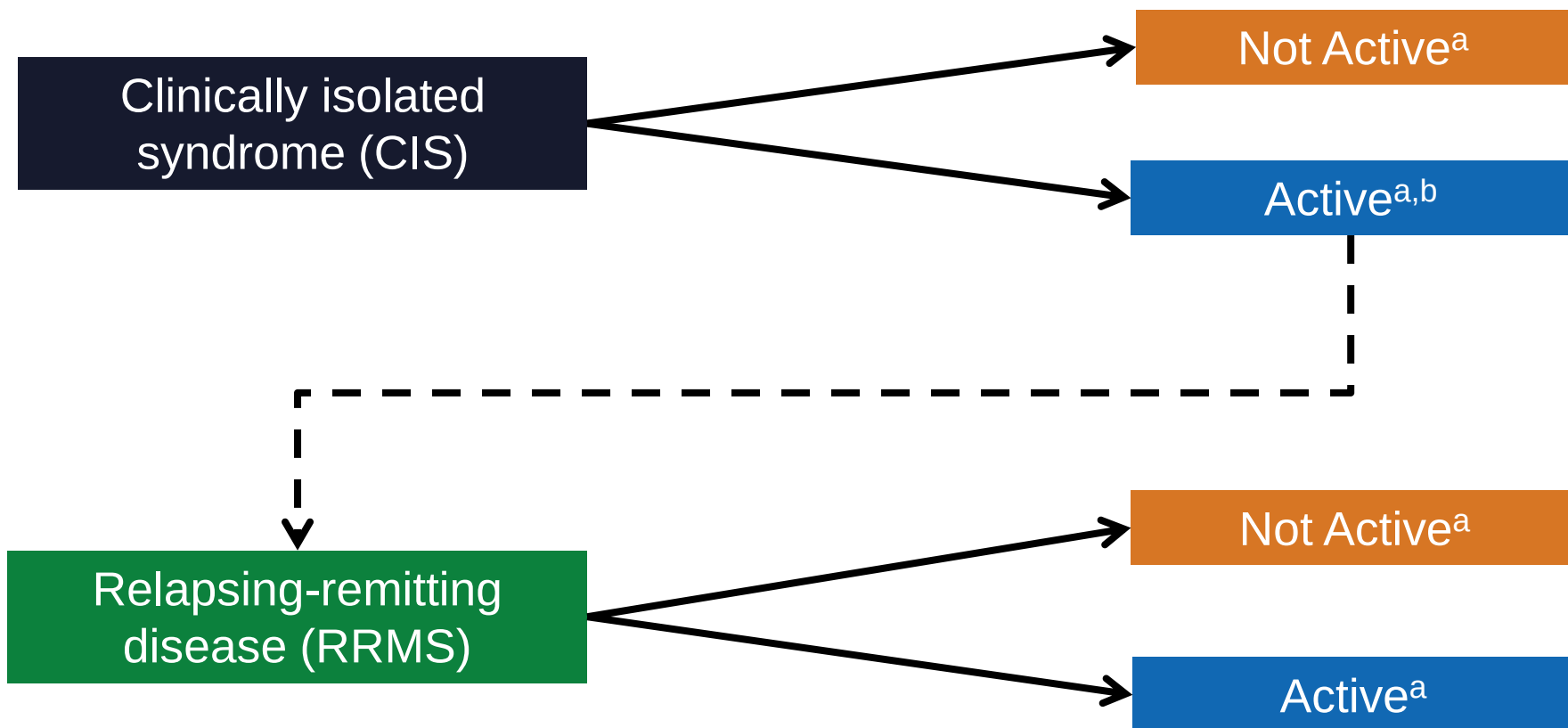
- Unilateral ascending numbness in leg
- Paresthesias
- Weakness
- Lhermitte's sign
- Torso tightness
- Bladder/bowel dysfunction



Brainstem syndromes

- Diplopia
- Facial numbness or weakness
- Vertigo
- Ataxia

2013 MS Phenotype Descriptions: Relapsing MS¹

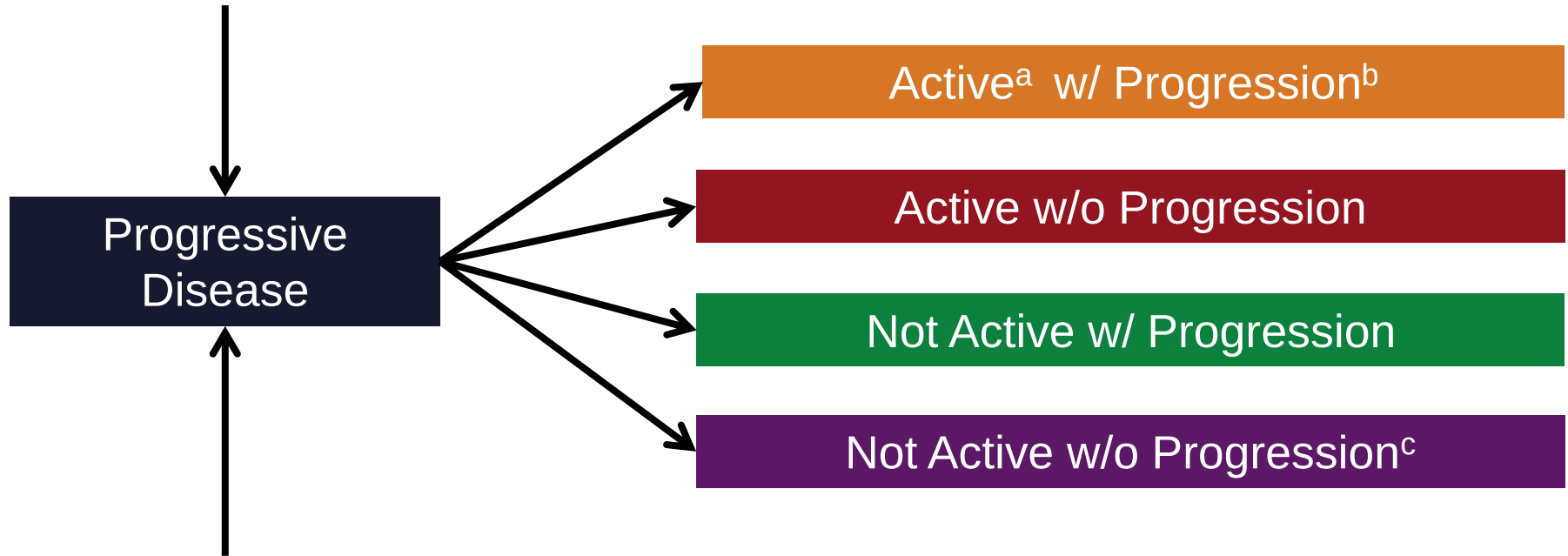


^a Activity determined by clinical relapse and/or MRI activity (GdE lesions; new/unequivocally enlarging T2 lesions) assessed at least annually; if assessments not available, activity "indeterminate." ^b CIS, if subsequently active fulfilling current MS diagnostic criteria, becomes RRMS.

1. Lublin FD et al. *Neurology*. 2014;83:1-9.

2013 MS Phenotype Descriptions: Progressive MS¹

Primary Progressive: Progressive accumulation of disability from onset



Secondary Progressive: Progressive disability accumulation after initial relapsing course

^a Activity determined by clinical relapse and/or MRI activity, assessed at least annually; if assessments not available, activity "indeterminate." ^b Progression measured by clinical evaluation, assessed at least annually. If assessments are not available, activity and progression "indeterminate." ^c Stable disease.

1. Lublin FD et al. *Neurology*. 2014;83:1-9.

Diagnosing MS^{1,2}

- ❑ Clinical findings supported by laboratory data
- ❑ Blood work → Rule out confounding diagnosis
- ❑ MRI ± contrast (gadolinium)
 - Brain
 - Cervical/thoracic spine
- ❑ CSF
 - Oligoclonal bands

Serologic Tests to Rule Out Conditions That Mimic MS¹

Performed Routinely

Test	Condition That May Mimic MS
ANA titer	- Rheumatologic disease - Systemic lupus erythematosus
<i>Borrelia</i> titer	Lyme disease
CBC	Infection, inflammation, neoplasm
ESR	Infection, inflammation
Rapid plasma reagin	Syphilis
TSH	Hypothyroidism
B ₁₂ level	Vitamin B ₁₂ deficiency

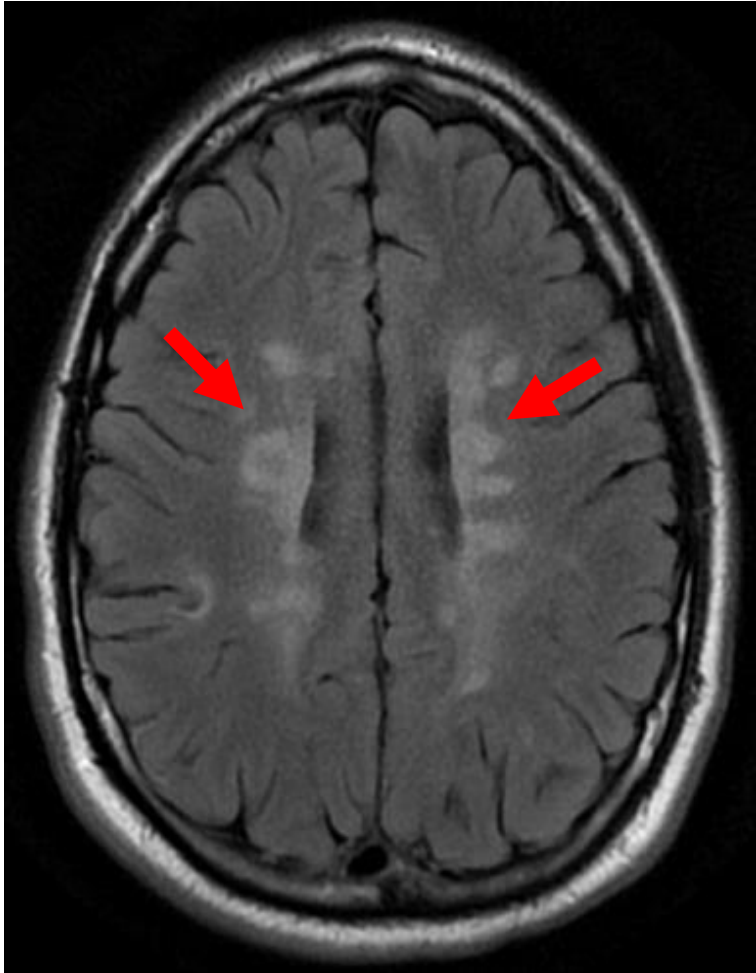
In Appropriate Clinical Situation

Test	Condition That May Mimic MS
Angiotensin-converting enzyme	Sarcoidosis
Autoantibody assays ^a	- Behçet syndrome, - Sjögren's syndrome - Systemic lupus erythematosus - Vasculitis
HIV screen	HIV infection
HTLV-1	HTLV-1 infection
Very long chain fatty acid levels	Adrenoleukodystrophy

^a Antineutrophil cytoplasmic, anticardiolipin, antiphospholipid, anti-SS-A, and anti-SS-B antibodies.

1. Saguil A et al. *Am Fam Physician*. 2014;90:644-652.

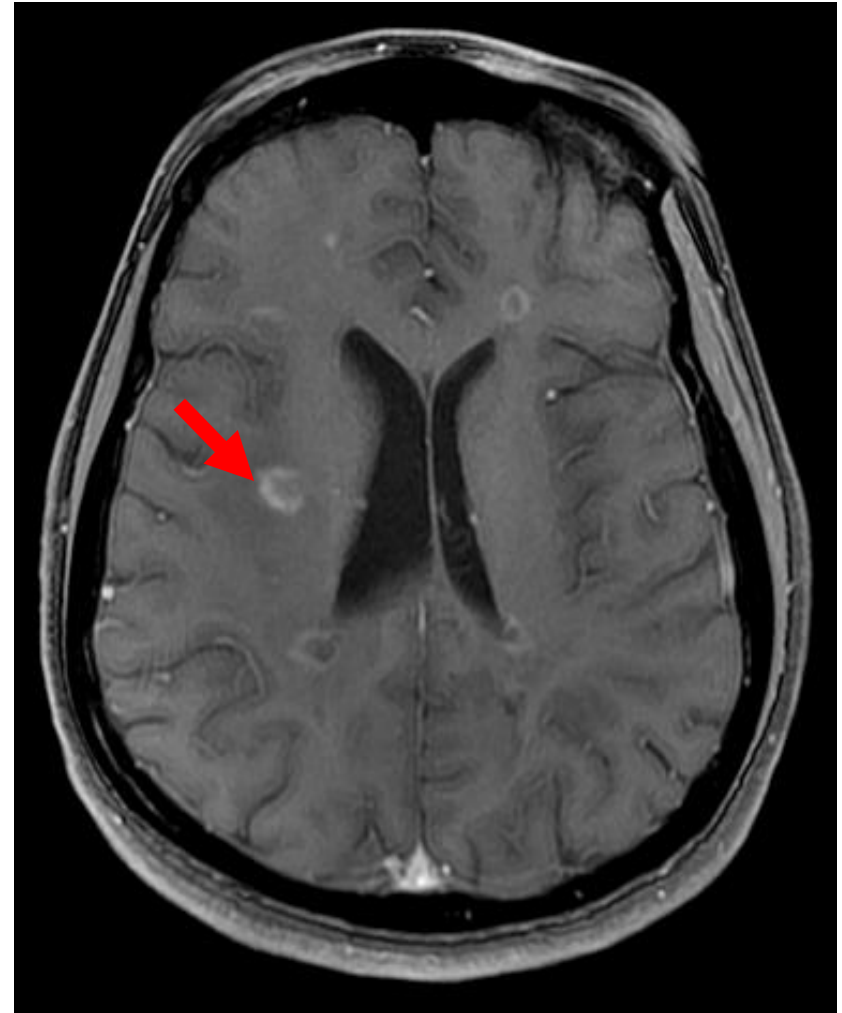
T2-Weighted Brain MRI^{1,2}



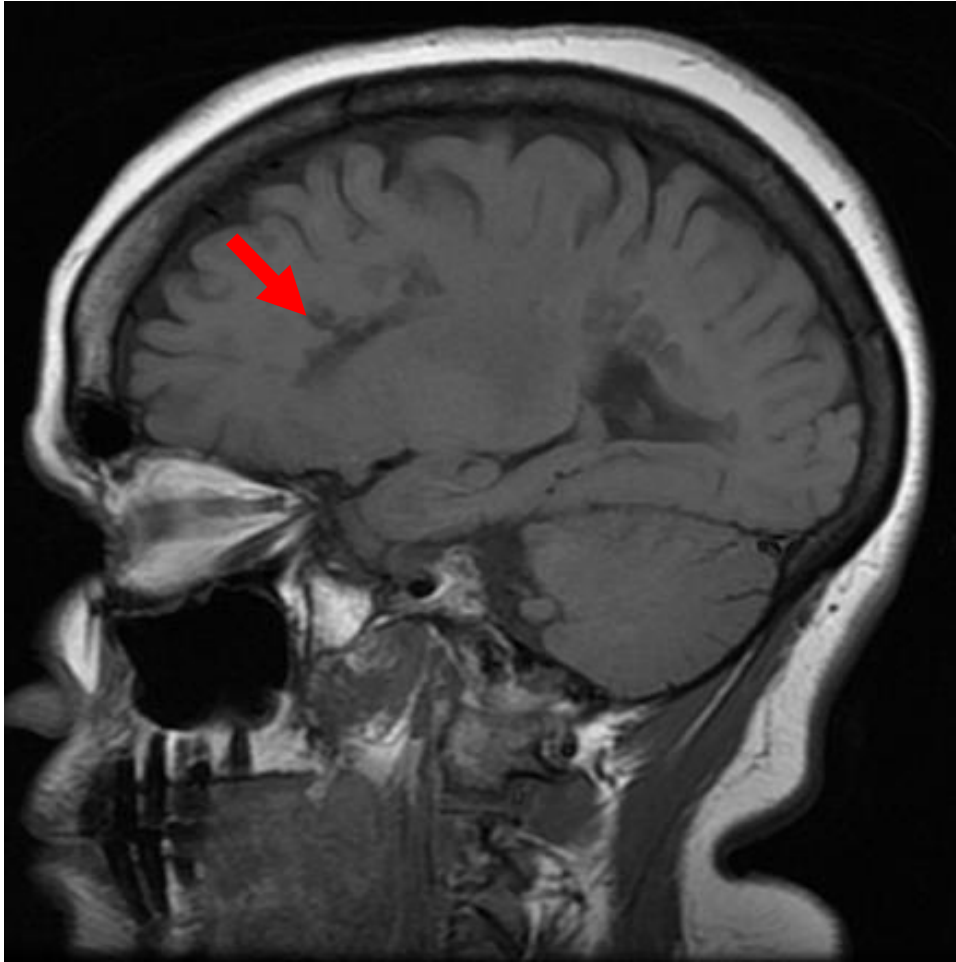
- Very sensitive for detecting supratentorial lesions
- Lesions typically 3-15 mm in diameter and round or ovoid
- Indicative of disease burden
- Lacks pathological specificity

T1-Weighted Brain MRI With Contrast¹⁻³

- Gadolinium enhancement reveals regions where blood-brain barrier has been disrupted, signifying active inflammation
- Enhancing lesions can persist from 2 weeks to 2 months

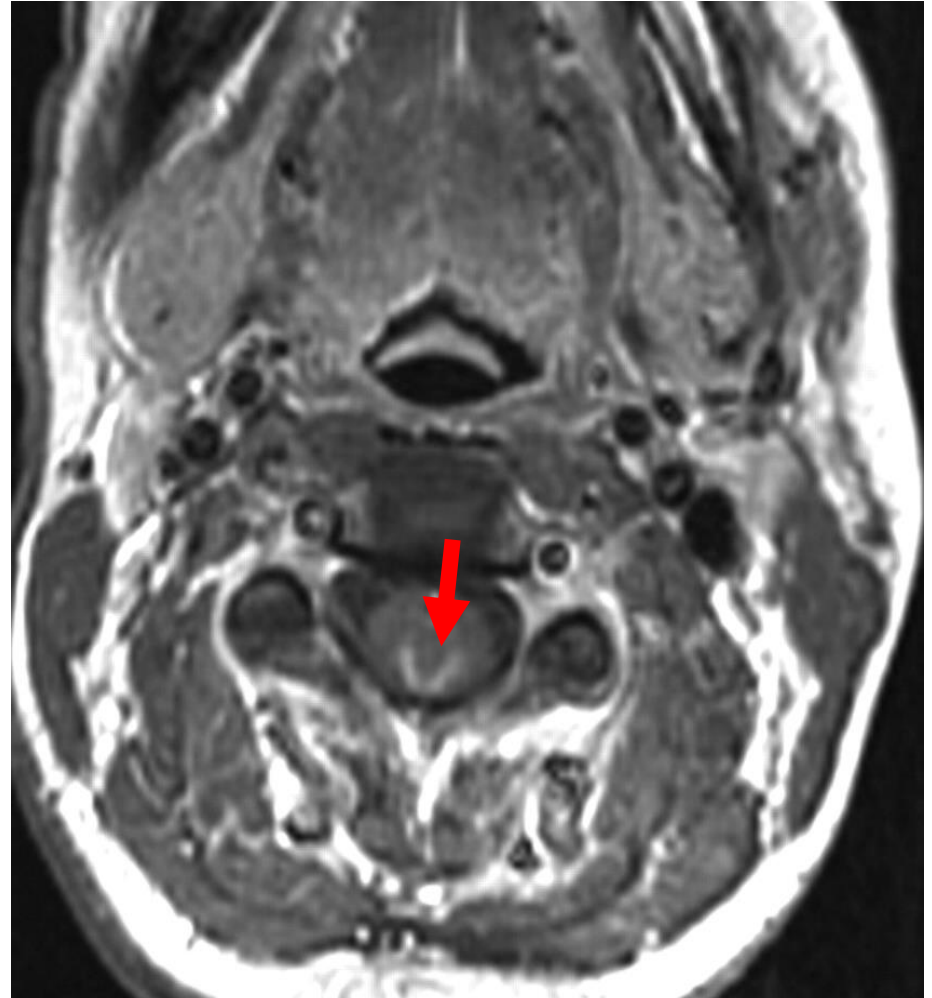
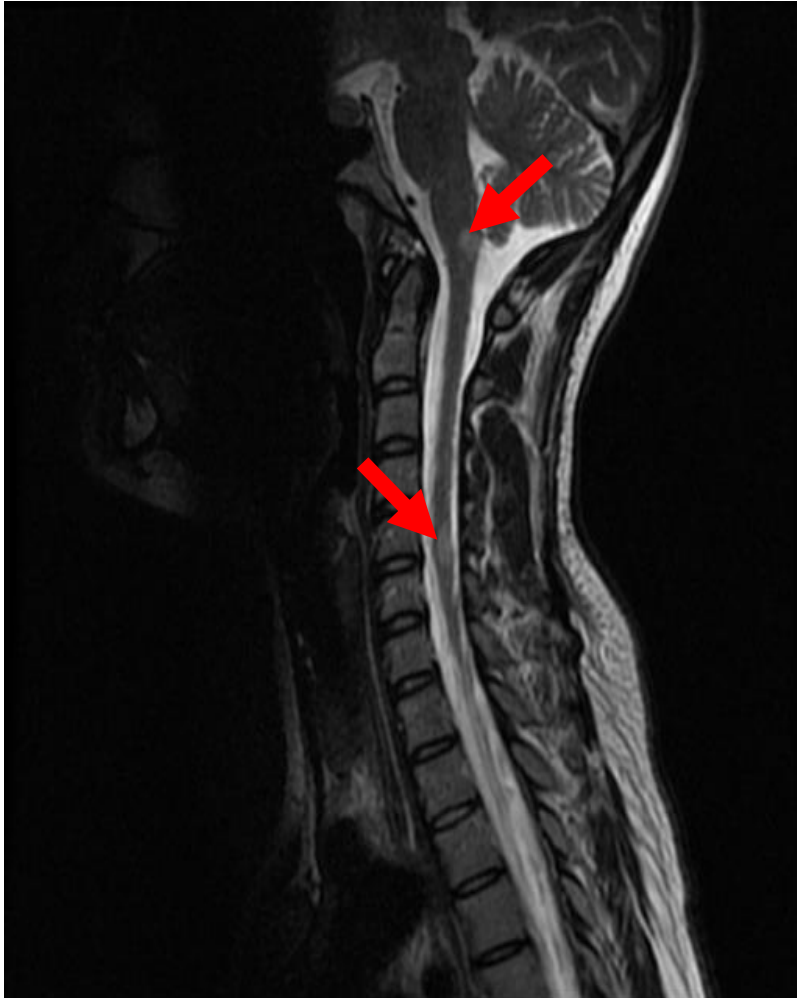


T1-Weighted Brain MRI Without Contrast^{1,2}



- Reveals hypointense lesions or “black holes”; areas of permanent axonal damage
- Lesions can also be areas of edema, which may disappear on subsequent scans
- Chronic hypointense lesions correlate better with disability

MRI of Spinal Cord



2017 Revisions of the McDonald MS Diagnostic Criteria¹

Dissemination in Space (DIS) Requirements

- ≥ 1 T2 lesion^a in ≥ 2 of 4 CNS locations:
 - Periventricular^b
 - Cortical or juxtacortical
 - Infratentorial
 - Spinal cord

Dissemination in Time (DIT) Requirements

Simultaneous presence of gadolinium-enhancing and non-enhancing lesions^a at any time, **or**

A new T2 or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of timing of baseline scan

Additional Recommendations

In a patient with a typical CIS and fulfilment of clinical or MRI criteria for DIS and no better explanation for the clinical presentation, demonstration of CSF-specific oligoclonal bands in absence of other CSF findings atypical of MS allows a diagnosis of MS to be made

At time of diagnosis, a provisional phenotype should be specified and whether the course is active or not, and progressive or not based on previous year's history; phenotype should be periodically re-evaluated based on accumulated information

^a No distinction between symptomatic and asymptomatic MRI lesions is required. ^b For some patients—eg, individuals older than 50 years or those with vascular risk factors—it might be prudent for the clinician to seek a higher number of periventricular lesions.

1. Thompson AJ et al. *Lancet Neurol*. 2018;17:162-173.

2017 Revisions of the McDonald MS Diagnostic Criteria¹ (Cont'd)

Progressive From Onset of MS

- ≥ 1 y of progression (retrospective or prospective) independent of clinical relapse
- 2 out of 3 of the following criteria:
 - ≥ 1 T2 lesion^a in ≥ 1 area (periventricular, cortical or juxtacortical, or infratentorial)
 - ≥ 2 T2 spinal cord lesions
 - Presence of CSF-specific oligoclonal bands

^a No distinction between symptomatic and asymptomatic MRI lesions is required.

1. Thompson AJ et al. *Lancet Neurol*. 2018;17:162-173.

Considerations for General Practitioners in Patients With Suspected MS¹

Talk to your patients

- In patients who present with signs and symptoms consistent with MS, it is important for them to understand that specific criteria must be met in order for MS to be diagnosed

Be proactive

- Send patients with suspected MS directly for an MRI and refer to neurology immediately, rather than waiting for an initial neurology referral and subsequent MRI

Disease-Modifying Therapy for MS Management

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FDA-Approved DMTs for RRMS Management

Approved Prior to 2010

GA 20 mg/d subQ	IFN β -1b 250 mcg, 1x/2 d subQ
IFN β -1a 30 mcg, 1x/wk IM	Natalizumab 300 mg, 1x/4 wk IV
IFN β -1a 22 mcg/44 mcg, 3x/wk, subQ	Mitoxantrone ^a 12 mg/m ² , ^b 1x/3 mo IV

Approved Since 2010

Teriflunomide 7 mg/14 mg, 1x/d PO	GA 40 mg, 3x/wk subQ
Dimethyl fumarate 240 mg, 2x/d PO	PEG-IFN β -1a 125 mcg, 1x/2 wk subQ
Fingolimod 0.5 mg/d PO	Daclizumab 150 mg, 1x/4 wk, subQ ^c

Alemtuzumab 12 mg 1x/d, 5 d IV → 12 mg 1x/3 d IV, 12 mo later

Ocrelizumab 300 mg IV starting dose → 300 mg IV, 2 wk later → 600 mg 1x/6 mo IV^d

^a Also approved for secondary progressive MS. ^b Maximum cumulative lifetime dose: 140 mg/m².

^c Voluntarily withdrawn from all markets in March 2018. ^d Also approved for treatment of primary progressive MS.

Goals of Treatment With DMT in RRMS

1

Reduce incidence and severity of relapses

2

Slow or delay disability progression

3

Decrease MRI disease activity

Efficacy of Approved Injectable DMTs for RRMS: Results From Separate PBO-Controlled Trials¹⁻¹⁰

DMT	↓ Relapses	↓ MRI Endpoints	Delay Conversion to CDMS	↓ Disability Progression ^a
GA 20 mg	✓	✓	✓	
GA 40 mg	✓	✓		
IFN β-1a 30 mcg	✓	✓	✓	✓
IFN β-1a 44 mcg	✓	✓	✓	✓
IFN β-1b 250 mcg	✓	✓	✓	
PEG-IFN β-1a 125 mcg	✓	✓		✓

^a Significant decrease in ≥1 phase 3 clinical trial.

1. Jacobs LD et al. *N Engl J Med*. 2000;343:898-904.
2. Kappos L et al. *Neurology*. 2006;67:1242-1249.
3. Comi G et al. *Lancet*. 2009;374:1503-1511.
4. Comi G et al. *Lancet Neurol*. 2012;11:33-41.
5. Johnson KP et al. *Neurology*. 1995;45:1268-1276.
6. Kahn O et al. *Ann Neurol*. 2013;73:705-713.
7. PRISMS Study Group. *Lancet*. 1998;352:1498-1504.
8. Jacobs LS et al. *Ann Neurol*. 1996;39:285-294.
9. IFNB Study Group. *Neurology*. 1993;43:655-661.
10. Calabresi PA et al. *Lancet Neurol*. 2014;13:657-665.

AEs and Monitoring Considerations for Glatiramer Acetate and IFN β Preparations

Glatiramer Acetate¹

- Common AEs
 - Injection-site and post-injection reactions, lipoatrophy
- Monitoring prior to treatment initiation and during treatment course
 - None

IFN β s²⁻⁵

- Common AEs
 - Injection-site reactions, flu-like symptoms, depression, LFT $\uparrow$, WBC $\downarrow$, hypothyroidism
- Monitoring prior to treatment initiation and during treatment course
 - LFT, CBC, TSH

1. Copaxone (glatiramer acetate) Prescribing Information. <http://copaxone.com/pdfs/PrescribingInformation.aspx>. Accessed February 13, 2018. 2. Plegriid (peginterferon beta-1a) Prescribing Information. https://www.plegriid.com/content/dam/commercial/multiple-sclerosis/plegridy/pat/en_us/pdf/november/plegridy-prescribing-information.pdf. Accessed February 13, 2018. 3. Rebif (interferon beta-1a) Prescribing Information. http://www.emdserono.com/ms.country.us/en/images/Rebif_PI_tcm115_140051.pdf?Version=. Accessed February 13, 2018. 4. Avonex (interferon beta-1a) Prescribing Information. http://www.avonex.com/pdfs/guides/Avonex_Prescribing_information.pdf. Accessed February 13, 2018. 5. Betaseron (interferon beta-1b) Prescribing Information. http://labeling.bayerhealthcare.com/html/products/pi/Betaseron_PI.pdf. Accessed February 13, 2018.

Efficacy Profiles of Approved Oral DMTs for RRMS: Results From Separate PBO-Controlled Trials

DMT	↓ Relapses	↓ MRI Endpoints	Delay Conversion to CDMS	↓ Disability Progression ^a
Fingolimod ^{1,2}	✓	✓		✓
Teriflunomide ³⁻⁵	✓	✓	✓	✓ ^b
Dimethyl fumarate ^{6,7}	✓	✓		✓

^a Significant decrease in ≥1 phase 3 clinical trial. ^b Significant decrease in 2 phase 3 clinical trials.

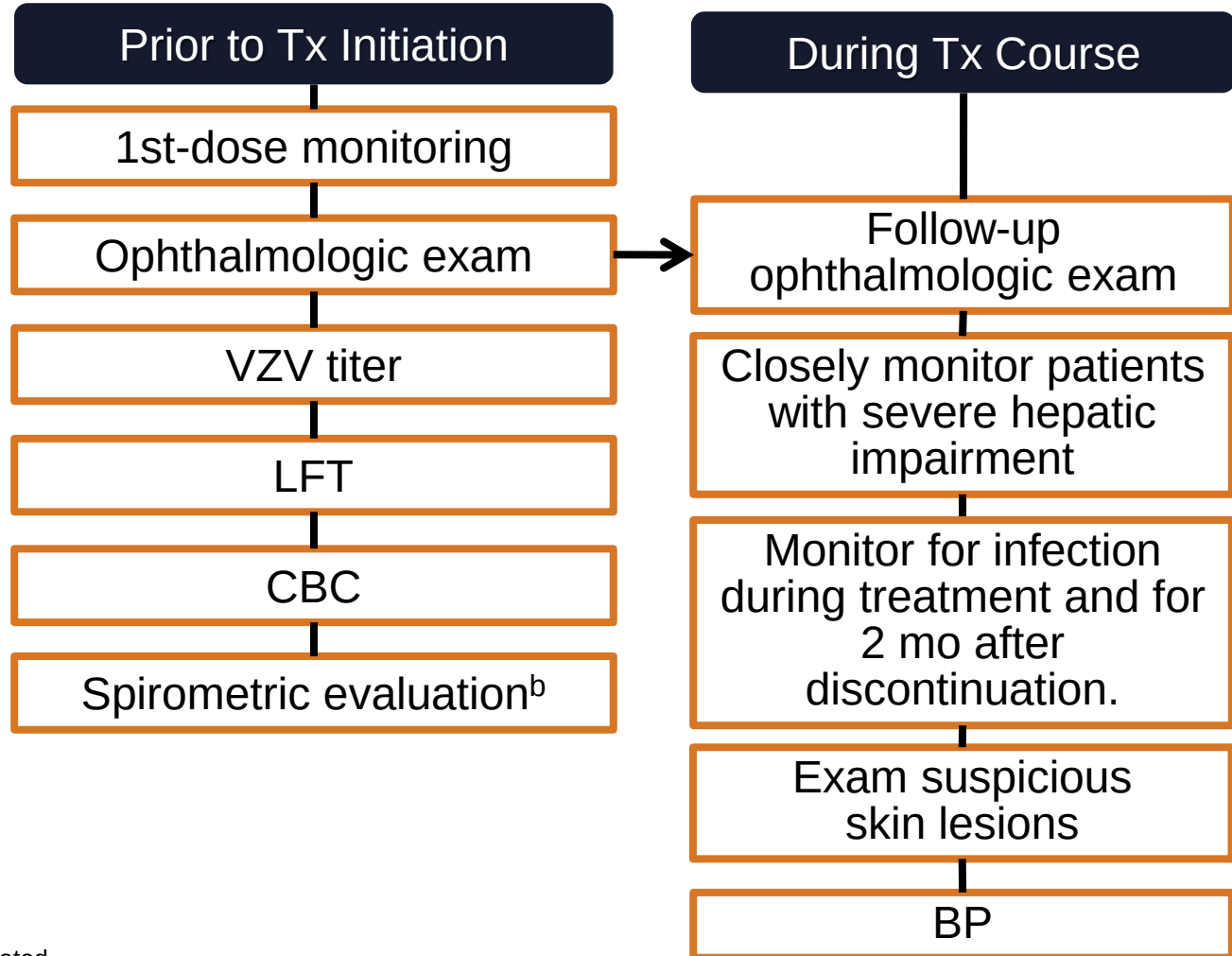
1. Kappos L et al. *N Engl J Med*. 2010;362:387-401.
2. Calabresi PA et al. *Lancet Neurol*. 2014;13:545-556.
3. Miller A et al. *Lancet Neurol*. 2014;13:977-986.
4. Confavreux C et al. *Lancet Neurol*. 2014;13:247-256.
5. O'Connor P et al. *N Engl J Med*. 2011;365:1293-1303.
6. Gold R et al. *N Engl J Med*. 2012;367:1098-1107.
7. Fox R et al. *N Engl J Med*. 2012;367:1087-1097.

Safety Profile and Monitoring Requirements for Fingolimod1

Most Common AEs^a (≥10% and >PBO)

- Headache
- LFT elevation
- Diarrhea
- Cough
- Influenza
- Sinusitis
- Back pain
- Abdominal pain
- Pain in extremity

Monitoring



^a As per prescribing information. ^b When indicated.

1. Gilenya (fingolimod) Prescribing Information. <http://www.pharma.us.novartis.com/product/pi/pdf/gilenya.pdf>. Accessed May 3, 2017.

Teriflunomide: AE and Monitoring Profile¹

Most Common AEs ($\geq 10\%$ and $\geq 2\%$ greater than PBO)^a

Headache
Diarrhea
ALT increase

Nausea
Alopecia

Monitoring

Prior to Tx Initiation

- Negative pregnancy test
- TB screen
- LFT (ALT, bilirubin)
- CBC
- BP

During Tx Course

- ALT, monthly for first 6 months
- BP

^a As per prescribing information.

1. Aubagio (teriflunomide) Prescribing Information. <http://products.sanofi.us/aubagio/aubagio.pdf>. Accessed February 13, 2018.

Dimethyl Fumarate: AE and Monitoring Profile¹

Most Common AEs ($\geq 10\%$ and $\geq 2\%$ PBO)^a

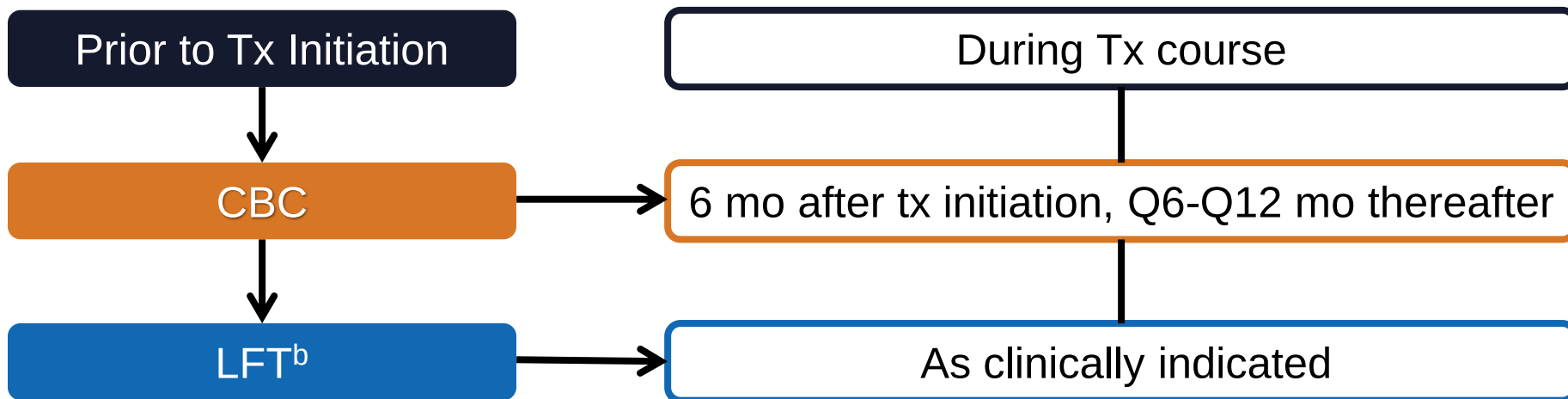
Flushing

Abdominal pain

Diarrhea

Nausea

Monitoring



^a As per prescribing information. ^b Serum aminotransferase, alkaline phosphatase, and total bilirubin.

1. Tecfidera (dimethyl fumarate) Prescribing Information. <http://www.tecfidera.com/pdfs/full-prescribing-information.pdf>.

Accessed May 3, 2017.

Efficacy Profiles of Monoclonal Antibodies Approved for RRMS After 2010: Results From Trials

Monoclonal Antibody	↓ Relapses	↓ MRI Endpoints	↓ Disability Progression (confirmed at 3 mo or 6 mo) ^a
Natalizumab ^{1b}	✓	✓	✓
Alemtuzumab ^{2,3c}	✓	✓	✓
Ocrelizumab ^{4c,d}	✓	✓	✓

^a Significant decrease in ≥ 1 phase 3 clinical trial. ^b Versus PBO. ^c Versus IFN β -1a 44 mcg 3x/wk subQ. ^d Positive outcomes also reported in patients with primary progressive MS when compared to PBO.⁵

1. Polman CH et al. *N Engl J Med*. 2006;354:899-910. 2. Cohen JA et al. *Lancet*. 2012;380:1819-1828. 3. Coles AJ et al. *Lancet*. 2012;380:1829-1839. 4. Hauser S et al. *N Engl J Med*. 2017;376:221-334. 5. Montalbon X et al. *N Engl J Med*. 2017;376:209-220.

The Need for Ongoing Monitoring With Natalizumab¹

Most Common AEs (incidence $\geq 10\%$)^a

Headache
Fatigue
UTI
Arthralgia
LRTI
Gastroenteritis
Vaginitis
Depression
Extremity pain
Abdominal discomfort
Diarrhea NOS
Rash

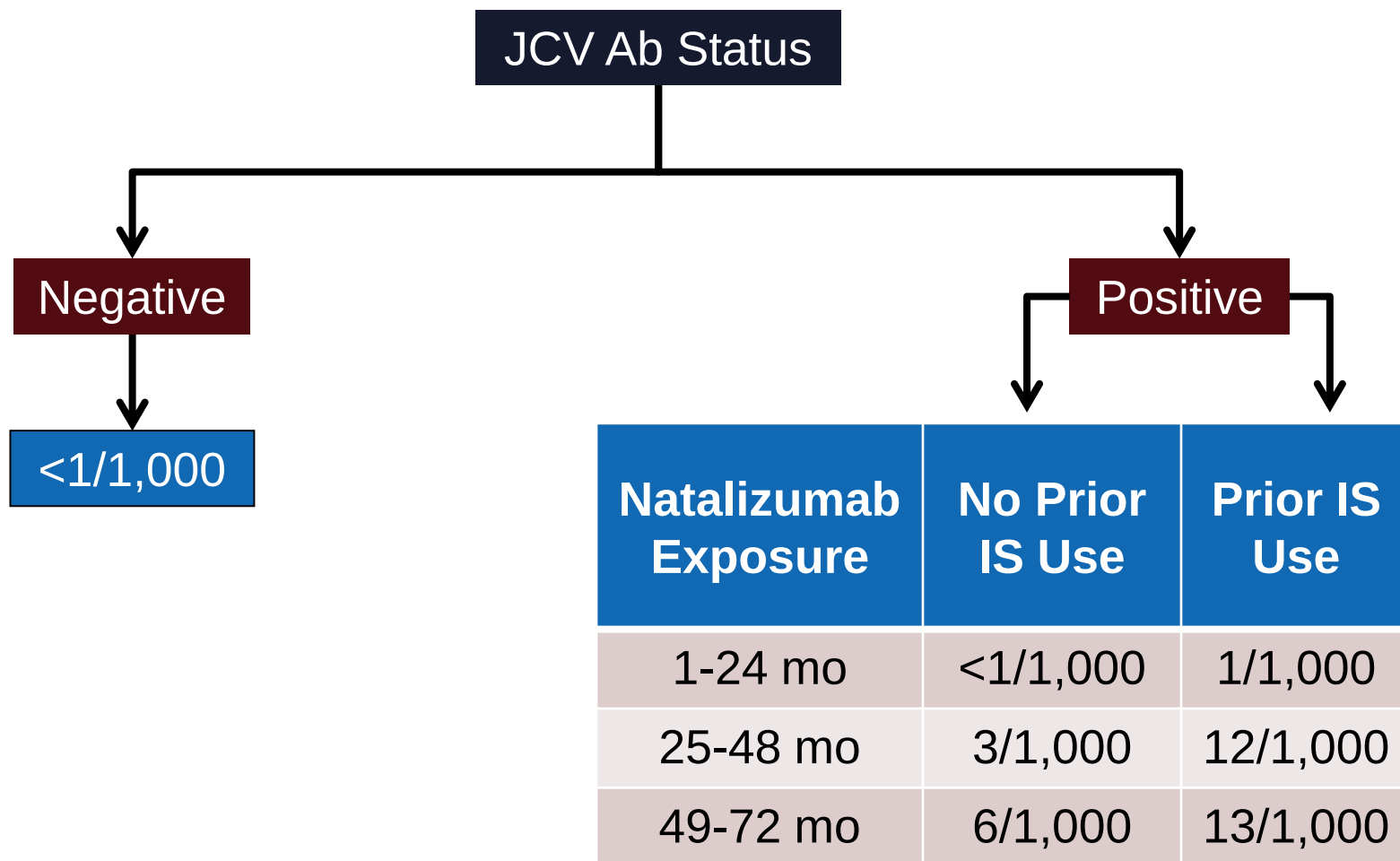
Monitoring

Parameter	Prior to Tx Initiation	During Tx
LFT	✓	✓
CBC	✓	✓
MRI ^b	✓	✓
JCV status	✓	✓

^a As per prescribing information. ^b May help differentiate subsequent MS symptoms from PML.

1. Tysabri (natalizumab) Prescribing Information. <http://www.tysabri.com/prescribingInfo>. Accessed February 13, 2018.

Natalizumab: PML Risk Stratification¹



Alemtuzumab: AE Profile¹

Potential AEs (incidence ≥10% and >IFN β-1a) ^a				
Rash	Headache	Pyrexia	Nasopharyngitis	Nausea
UTI	Fatigue	Insomnia	URTI	Herpes viral infection
Urticaria	Pruritus	Thyroid gland disorders	Fungal infection	Arthralgia
Extremity pain	Back pain	Diarrhea	Sinusitis	Oropharyngeal pain
Paresthesia	Dizziness	Abdominal pain	Flushing	Vomiting

^a As per prescribing information.

1. Lemtrada (alemtuzumab) Prescribing Information. <http://products.sanofi.us/lemtrada/lemtrada.pdf>. Accessed February 13, 2018.

Alemtuzumab: Monitoring During and After Treatment¹

Parameter	During Treatment	48 Months After Last Dose
CBC with differential	Monthly	Monthly
Serum creatinine	Monthly	Monthly
Urinalysis with urine cell count	Monthly	Monthly
Thyroid function	1x/3 mo	1x/3 mo
Skin examination	Annually	

Ocrelizumab: AE and Monitoring Profile¹

Most Common AEs ($\geq 10\%$ and $> \text{IFN } \beta\text{-1a subQ}$)^{a,b}

URTI

Infusion reactions

Prior to Tx Initiation

HBV screen

Before Each Infusion

- Infection assessment
- 100 mg IVMP ~30 min prior to infusion
- Antihistamine ~30-60 min prior to each infusion
- Consider adding antipyretic
- Monitor ≥ 1 h after each infusion

Ongoing

Patients should follow standard breast cancer screening guidelines

^a As per prescribing information. ^b In patients with relapsing MS.

1. Ocrevus (ocrelizumab) Prescribing Information. https://www.gene.com/download/pdf/ocrevus_prescribing.pdf.

Accessed February 13, 2018.

Selected Emerging DMTs for the Treatment of MS

Agent	MOA	Status
Siponimod	S1P receptor modulator	Positive phase 3 data in patients with secondary progressive MS¹
Ozanimod	S1P receptor modulator	Positive results in patients with relapsing MS recently announced from phase 3 Radiance Part B and SUNBEAM trials^{2,3}
Ponesimod	S1P receptor modulator	- Phase 3 trial comparing ponesimod with teriflunomide in relapsing MS, active but no longer recruiting patients⁴ - Phase 3 trial evaluating ponesimod as an adjunct to dimethyl fumarate is active and recruiting⁵
Ofatumumab	Anti CD20 MAb	ASCLEPIOS I and ASCLEPIOS II are ongoing phase 3 clinical trials comparing ofatumumab to teriflunomide⁶

1. Kappos L et al. 69th Annual American Academy of Neurology Annual Meeting (AAN 2017). Abstract CT.002.
2. Cohen JA et al. 7th Joint European Committee for Treatment and Research in Multiple Sclerosis–Americas Committee for Treatment and Research in Multiple Sclerosis Meeting (MSParis2017). Abstract 280 3. Comi G et al. MSParis2017. Abstract 232.
4. <https://clinicaltrials.gov/ct2/show/NCT02425644>. Accessed February 13, 2018. 5. <https://clinicaltrials.gov/ct2/show/NCT02907177>. Accessed February 13, 2018. 6. Hauser S et al. AAN 2017. Abstract S16.005.

Current Challenges Associated With Treatment Selection in Patients With MS

No consensus algorithm for MS treatment



Individualized treatment based on many patient- and disease-specific factors



Involves careful consideration of benefits vs risks of individual therapies, as well as patient preferences and laboratory testing results

Importance of Treatment Adherence in Patients With MS

Adherence^{1,2}

The ongoing active, voluntary, and collaborative involvement of the patient, resulting in a mutually acceptable course of behavior that helps maintain a desired, preventive, or therapeutic outcome

- Although disease course remains highly variable and unpredictable among individuals with MS, DMTs have significantly altered and improved its natural history
- Early and continuous use of DMTs in RRMS been associated with improved long-term outcomes³⁻⁵
- Delayed or discontinued treatment has been shown to deliver less benefit than continuous therapy in long-term studies of original patients in pivotal randomized-controlled trials of DMTs⁵
- Empowering patients to remain adherent to therapy is critical for successful outcomes

1. Saunders C et al. *J Neurosci. Nursing*. 2010;42:S10-S17. 2. Namey MA. Promoting adherence to complex protocols. In: Halper J, ed. *Advanced Concepts in Multiple Sclerosis Nursing Care*. 2nd ed. New York, NY: Demos Medical Publishing; 2007:91-100.
3. Baumhackl U. *Neurology*. 2008;255(Suppl 1);75-83. 4. Goodin DS and Bates D. *Mult Scler*. 2009;15:1175-1182.
5. Carroll WM. *Mult Scler*. 2009;15:951-958.

Conclusions¹

- The diagnosis and treatment of MS has evolved considerably and rapidly over the last several years, with many patients initially presenting to their family or general practitioner

Become the eyes and ears for the neurologist

- Neurologists may see patients once or twice a year vs the patient's more frequent office visits and calls to their family practitioner
- Understand the difference between expected changes and true AEs

Work in concert with neurologists

- Manage patients' symptoms and treatment-related AEs, as well as maintain their quality of life as much as possible and empower them to adhere to therapy long term

Audience Q&A



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