A 3D VIRTUAL SYMPOSIUM

PATIENT CONSIDERATIONS IN MS:

Achieving Optimal Outcomes Through an Individualized, Comprehensive Approach

Wednesday, February 16, 2022

FACULTY

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PROGRAM OVERVIEW

This symposium is designed to review early identification strategies for MS; assess the variety of treatments available to treat the condition; and discuss ways to improve adherence, engagement, and clinician/patient communication.

TARGET AUDIENCE

This activity is designed to meet the educational needs of neurologists, physician assistants, nurse practitioners, and all other healthcare practitioners that treat multiple sclerosis patients.

Learning Objectives

- Implement strategies to identify MS earlier in the disease course to initiate prompt treatment
- Review the safety and efficacy of current and emerging agents used for MS
- Assess patient barriers to MS medication adherence and implement shared decision-making to improve adherence
- Improve clinician/patient communication and patient engagement for a more holistic approach to MS treatment

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- **Research support:** Actelion, Alkermes, Celgene, CorEvitas LLC, Genentech/Roche, Genzyme/Sanofi, MedDay, NINDS, Novartis

Ulrike W. Kaunzner MD reports the following:

- **Salary:** AAN/Biogen MS Fellowship grant, 7/2019 to 6/2021

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CNE Content Review
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Douglas Cox, MSN, MHA, RN
Ultimate Medical Academy/CCM – Lead Nurse Planner

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AGENDA

I. **Overview; Identification; Disease Course; Comorbidities**
   a. Epidemiology, Pathophysiology, Phenotypes
   b. MS in the COVID-19 era
   c. Etiology/triggers; environmental factors; biomarkers
   d. Diagnostic criteria
   e. Disease course/prognosis
   f. Comorbidities

II. **Current and Novel Treatment Options**
   a. MS treatment options
      i. Established conventional treatments (interferon, glatiramer acetate)
      ii. Newer agents – recent monoclonal antibodies/orals (e.g., diroximel fumarate, siponimod, ozanimod, cladribine, etc.)
      iii. Ongoing clinical trials
   b. Treatment guidelines and safety considerations
   c. Emerging treatments/classes: purine nucleoside analogs; CD20/CD25 antagonists; S1P-R modulators; vaccine-based therapies; remyelinating agents; anti-LINGO; stem cells; etc.
   d. Results of recent and ongoing clinical trials of agents in late-stage development

III. **A Holistic, Personalized Approach to MS**
   a. The patient focus versus the symptom focus
   b. Encouraging engagement in long-term care
   c. Barriers/gaps/unmet needs in MS management from the patient standpoint
   d. Adherence to MS therapy
   e. Case Study(s)

IV. **Questions and Answers**

WEDNESDAY, FEBRUARY 16, 2022

Patient Considerations in MS

Achieving Optimal Outcomes Through an Individualized, Comprehensive Approach

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1

Disclosures

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2

Learning Objectives

- Implement strategies to identify multiple sclerosis (MS) earlier in the disease course to initiate prompt treatment
- Review the safety and efficacy of current and emerging agents used for MS
- Assess patient barriers to MS medication adherence and implement shared decision-making to improve adherence
- Improve clinician/patient communication and patient engagement for a more holistic approach to MS treatment

3

Part I: Overview; Identification; Disease Course; Comorbidities

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7

MS: Definition and Demographics

- MS is the major acquired CNS disorder of young adults, often causing disability
- 2017 estimate: 913,925 individuals with MS in the United States; >2.5 million affected worldwide
  - Autopsy studies suggest 25% of MS may be silent
  - MS varies in frequency worldwide, with a latitudinal impact
- 90% of cases present in people aged 15 to 50 years
  - Pediatric MS accounts for 2% to 5% of cases; <1% occurs before age 11 years
- 10% or less over age 50 years (late onset); <1% is ≥60 years (very late onset)

MS = multiple sclerosis; CNS = central nervous system.

Ma VY, et al. *Arch Phys Med Rehabil*. 2014;95:986-995,.e1. National Multiple Sclerosis Society. MS prevalence FAQs (www.nationalmssociety.org/About-the-Society/MS-Prevalence-FAQ). Accessed 2/11/2020. Wallin MT, et al. *Neurology*. 2019;92:e1029-e1040.

8

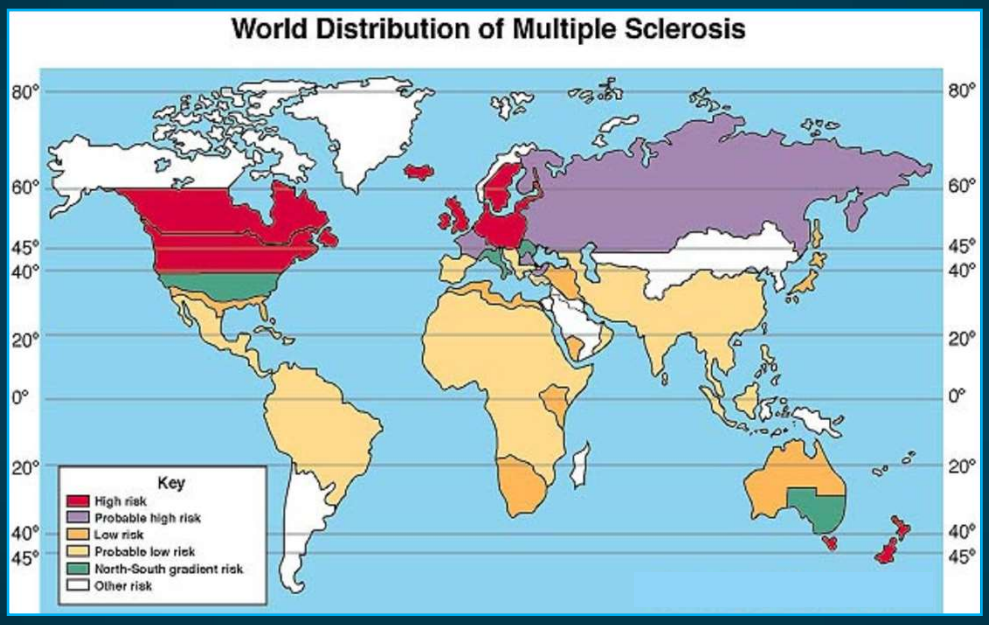
MS: Definition and Demographics

- Highly variable course (silent, "benign," malignant)
- Female-to-male ratio is 3:1; MS is increasing in women; a study in Denmark noted 114% ↑ in women, especially ages 50 to 64 years, vs 30% ↑ in men
- MS predominantly affects Caucasians (>90%) but now is increasing in other populations, and different disease courses within different populations
- Lifespan is shortened by about 6 to 12 years (7.5 years, most frequently stated) due to complications in disabled MS, brainstem involvement, and suicide

National Multiple Sclerosis Society (www.nationalmssociety.org/About-the-Society/MS-Prevalence-FAQs). Accessed 2/11/2020. Koch-Henriksen N, et al. *Neurology*. 2018;90:e1954-e1963.

9

Geographic Distribution and Inheritance of MS in Migrants



Adapted from McAlpine D, Lumadan CE, Acheson ED. *Multiple sclerosis: a reappraisal*. Livingstone Ltd., London, 1967.

10

3D Video 1: MS Pathophysiology

11

MS Neuropathology

- Focus is on inflammation (focal and diffuse), demyelination, and neurodegeneration (axonal/neuronal/synapse injury)
- Macroscopic (plaques)
  - Form around venules (central vein sign), close to CSF
  - Edema, inflammation, demyelination, axonal injury, neuronal/oligo loss, astrocytosis, and remyelination (70%-80%)

CSF = cerebrospinal fluid.

Dal-Bianco A, et al. *Eur Radiol*. 2015;25:2913-2920.

12

MS Neuropathology
(continued)

- Microscopic changes
  - Ion channel changes
  - Synapse loss
  - Axoglial unit injury
- Myelocortical MS (swollen axons)
  - 12% of MS
- Circuit/network disruption

- Ongoing injury occurs in untreated patients, even when they appear stable.

Dal-Bianco A, et al. *Eur Radiol*. 2015;25:2913-2920. Trapp BD, et al. *Lancet Neurol*. 2018; 17:870-884.

13

MS Genetics

- Lifetime risk of MS in the US is 3.5/1000 (0.35%)
- Lifetime risk in first degree relatives of MS cases is estimated at 3% (4% for siblings, 2% for parents, 2% for children), 10- to 30-fold greater than general population (0.1%-0.3%)
- Twin studies reveal 20% to 30% concordance rate in monozygotic pairs vs 2% to 5% for dizygotic pairs
- Family history of MS has been reported in 15% to 20% of patients with MS
- Risk for step-siblings of MS index cases and for individuals adopted by families with MS are similar to the general population
- Genome-wide association studies (GWAS) identified more than 200 single nucleotide polymorphism (SNPs) with MS susceptibility to date, 50% discovered since 2013

MSAA. *Who Gets Multiple Sclerosis*. Available at: https://mymsaa.org/ms-information/overview/who-gets-ms/. Baranzini SE, Oksenberg JR. *Trends Genet*. 2017;33(12):960-970.

14

MS Pathophysiology

- Outside-in hypothesis
  - Relapsing MS
  - Unknown trigger in the periphery; potential combination of genetics plus environmental factor (eg, EBV)
  - Focal inflammation
  - Systemic immune system attacks the CNS (involves adaptive immunity)
  - Most DMTs succeed, based on systemic impact
- Inside-out hypothesis
  - Progressive MS
  - Neurodegeneration
  - Intra-CNS changes with damage (involves innate immunity)
  - Role for glia: Altered oligo heterogeneity, regional microglial activation and heterogeneity, astrocyte metabolism implicated in progressive MS damage

DMT = disease-modifying therapy.

van der Poel M, et al. *Nat Commun*. 2019;10:1139. Bjornevik K, et al. *Science*. 2022;375(6578):296-301.

15

MS Endophenotypes

- Asymptomatic MS
  - Radiologically isolated syndrome (RIS): Not officially recognized yet as MS clinical phenotype
- Symptomatic MS
  - Prodromal MS: Not officially recognized yet as MS phenotype
  - Clinically isolated syndrome (CIS)
    - Categorized as high/low risk for MS based on MRI
    - High risk now recognized by FDA as a relapsing form of MS
  - Relapsing-remitting MS (RRMS)
  - Secondary progressive MS (SPMS)
    - Active SPMS now recognized by FDA as a relapsing form of MS
  - Primary progressive MS

Lublin FD, et al. *Neurology.* 2014;83:278-286. Okuda DT, et al, *Neurology.* 2009;72(9):800-805. Goodin D, et al. *PLoS ONE.* 2021;16(3):e0246157.

16

Prodromal MS

- Matched cohort study from linked health administrative/clinical databases from 4 Canadian provinces[1,2]
  - For 14,428 patients with MS vs 72,059 matched controls, annual healthcare use (ie, hospital admissions, physician claims, prescriptions) went up steadily from years 5 to 1 prior to clinically isolated syndrome (CIS)
  - More nervous, sensory, musculoskeletal, and genitourinary issues and psychiatry/urology encounters
- UK nested case-control study of 10,204 patients with MS vs 39,448 controls[3]
  - Primary care use in prior 10 years showed ↑ gastric, urinary, anorectal, anxiety/depression; headache/pain; and fatigue/insomnia
  - ↑ risk of MS with ↑ complaints

1. Wijnands JMA, et al. *Lancet Neurol*. 2017;16:445-451. 2. Wijnands JM, et al. *Mult Scler*. 2019;25:1092-1101. 3. Disanto G, et al. *Ann Neurol*. 2018;83:1162-1173.

17

MS Prodrome

- N=4,862 patients with MS vs N=22,649 UK controls: In 5 years pre-MS vs controls, ↑ use of specific drugs (antivertigo, antiepileptic, glucocorticoids, urinary antispasmodics, muscle relaxants)[1]
- N=8,669 patients with MS and N=40,867 Canadian controls: Hospitalizations related to urinary system/spinal cord and urinary antispasmodics/antivertigo prescriptions carried 2 to 3 times ↑ risk of MS[2]
- N=60 patients with MS, N=60 controls: Department of Defense (DoD) serum repository; serum NfL protein levels elevated in pre-MS vs controls a median of 6 years (4-10 years) before onset of MS[3]
  - Levels ↑ closer to MS presentation

NfL = neurofilament light chain.

1. Zhao Y, et al. *Neuroepidemiology*. 2020;54:140-147. 2. Högg T, et al. *Mult Scler Relat Disord*. 2018;25:232-240. 3. Bjornevik K, et al. *JAMA Neurol*. 2020;77:58-64.

18

MS Prodrome

- N=8 non-declared MS monozygotic twins of patients with MS
  - All showed either MRI lesions consistent with subclinical neuroinflammation (N=6) and/or +CSF OCBs (N=4)
  - Only N=2 met RIS criteria
  - Single cell RNA sequencing of CSF cells showed clonal activation and expansion of CD8+ T cells (activated tissue, resident memory T cells); small proportion of clonally expanded CD4+ T cells; expanded plasmablasts only with +OCBs
- Conclusion: very early activation of adaptive immunity in prodromal MS (especially CD8+ T cells)

MRI = magnetic resonance imaging; CSF = Cerebrospinal fluid; RNA = ribonucleic acid; CD = cluster of differentiation; OCB = oligoclonal bands.

Beltrán E et al. *J Clin Invest*. 2019;129:4758-4768.

19

MS Disease Activity

- 2 modifiers specified, considered over a defined timeframe (eg, 1 year)
- Active or not active
  - Involves clinical and MRI measures
  - Applies to all phenotypes
  - Determined by clinical relapse or by new/enlarging T2 or contrast + MRI lesion
- Progressing or not progressing
  - Applies to progressive phenotypes
  - Determined by presence/absence of gradual clinical worsening, independent of relapses
  - No MRI measure

Lublin FD, et al. *Neurology*. 2014;83:278-286.

20

MS Prognostic Profile

	Good	Poor
Race	White	Black
Age at onset	younger (<35 years)	older (≥35 years)
Sex	female	male
Smoker	no	yes
Vascular risk factors/comorbidities	absent	present
Cognitive dysfunction	absent	present
Phenotype	relapsing	progressive
First attack	optic neuritis, sensory, unifocal	motor, cerebellar, sphincter, multifocal
Recovery	complete	incomplete
Attack rate	low	high (≥2 in 1 year)

Bergamaschi R, et al. *Int Rev Neurobiol.* 2007;79:423-447.

21

Prognostic Factors

	Good	Poor
Disability at 5 years	no	yes
MRI: Lesion location	cerebral	posterior fossa; spinal cord; cortical
Number	low	high (≥9)
Enhancement	0-2	>2
Chronic T1 hypointense lesions	absent	present
Early discernable atrophy	no	yes
Cortical lesions	no	yes
CSF OCBs (IgG; IgM)	absent	positive
OCT RNFL	normal	thin
NFL levels	normal	elevated
Multimodal EP abnormalities	low score	high score

IgG = immunoglobulin G; IgM = immunoglobulin M; OCT = optical coherence tomography; RNFL = retinal nerve fiber layer; NFL = nerve fiber layer; EP = evoked potential.

Haider L, et al. *Brain*. 2021;144:1384-1395. Tintore M, et al. *Brain*. 2015;138:1863-1874.

22

2017 Revised McDonald Diagnostic Criteria

- 2017 revisions amplify to simplify and facilitate early diagnosis, and preserve specificity, to reduce misdiagnosis
- Reemphasize that criteria were developed for typical CIS; not for nonspecific symptoms
- Clarify MRI lesion size (≥3 mm); periventricular lesions must abut ventricles; juxtacortical lesions abut cortex
- Caution in attribution of historical events without corroborating objective evidence
- Criteria require exclusion of better alternate explanations
- Guidelines still allow diagnosis of MS on purely clinical grounds, but MRI is recommended in all patients; caution is urged in the absence of typical MRI lesions
- Determination of a provisional disease phenotype is recommended

CIS = clinically isolated syndrome.

Polman CH, et al. *Ann Neurol.* 2011;69:292-302. Thompson AJ, et al. *Lancet Neurol.* 2018;17:162-173.

23

2017 Revised McDonald Diagnostic Criteria: CSF

- CSF reemphasized in the 2017 revisions; threshold for CSF should be low
- Demonstration of unique CSF oligoclonal bands is the most reliable test of intrathecal antibody production; use appropriate standardized technology
- CSF particularly recommended when
  - Clinical and MRI evidence insufficient (second time point is needed) or atypical
  - Presentation other than typical CIS (including a progressive course)
  - Populations in which MS is less common (eg, non-Whites, older age groups)

CSF = cerebrospinal fluid.

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

24

2017 Revised McDonald Diagnostic Criteria
DIS and DIT

Dissemination in space (DIS)

- Lesions in 2 characteristic locations
  - Periventricular
  - Juxtacortical/cortical
  - Infratentorial
  - Spinal cord
- Symptomatic and asymptomatic lesions count

Dissemination in time (DIT)

- Simultaneous enhancing and nonenhancing lesions
- New lesions on subsequent MRI at any time point
- With typical CIS meeting DIS criteria and no better explanation, CSF oligoclonal bands can substitute for DIT

Polman CH, et al. *Ann Neurol.* 2011;69:292-302. Thompson AJ, et al. *Lancet Neurol.* 2018;17:162-173.

25

2017 Revised McDonald Diagnostic Criteria

Progressive form onset MS
• ≥1-year progression of neurologic impairment (prospective, retrospective) **plus**
• 2 of 3 criteria – ≥1 T2 lesions in characteristic brain area (periventricular, juxtacortical/cortical, infratentorial) – ≥2 T2 cord lesions – CSF oligoclonal bands

Polman CH, et al. *Ann Neurol*. 2011;69:292-302. Thompson AJ, et al. *Lancet Neurol*. 2018;17:162-173.

26

2017 Revised McDonald Diagnostic Criteria Misdiagnosis

- Misdiagnosis remains a clinical issue (at least 5%-10%; up to 20% reported)
- Several factors identified
  - MS heterogeneity
  - No single pathognomonic clinical feature/diagnostic biomarker
  - Nonspecific MRI findings; MRI lesions seen in other diseases
  - Increasing focus on early diagnosis

Thompson AJ, et al. *Lancet Neurol*. 2018;17:162-173. Toledano M, et al. *Curr Neurol Neurosci Rep*. 2015;15:57. Kaisey M, et al. *Mult Scler Relat Disord*. 2019;30:51-56.

27

Diagnostic Evaluation

- Clinical findings supported by laboratory data
- Blood work (to rule out confounding diagnoses)
  - IgG to aquaporin 4, MOG; other autoantibodies
  - Vitamin B12, 25 hydroxy vitamin D
  - TSH, Lyme, ACE, etc
- MRI
  - Brain MRI ± contrast
  - Cervical/thoracic MRI (include conus)
- CSF
  - Oligoclonal bands
  - IgG index/intrathecal IgG antibody production
  - Cell count, protein
  - Myelin basic protein is nonspecific injury marker
- Central vein sign potential future diagnostic biomarker
  - T2 echoplanar/SWI

Thompson AJ, et al. *Lancet Neurol.* 2018;17:162-173. Toledano M, et al. *Curr Neurol Neurosci Rep.* 2015;15:57.

28

Problem of MS Misdiagnosis
Study of 110 Misdiagnosed Patients

Contributors to MS misdiagnosis

- Inappropriate application of MS diagnostic criteria to atypical symptoms
- Inappropriate application of diagnostic criteria to historical episode without corroborating objective evidence
- Overreliance on MRI abnormalities in patients with nonspecific symptoms
- Erroneous determination of juxtacortical or periventricular lesion location
- Erroneous determination of DIT due to variability of slice orientation on serial images

Most common alternate diagnoses

- Migraine with MRI abnormalities
- Fibromyalgia
- Nonspecific/nonlocalizing symptoms with MRI abnormalities
- Psychogenic or conversion disorders
- NMOSD

Authors note that strict adherence to clinical and radiographic MS diagnostic criteria may have prevented misdiagnosis in many patients and that atypical symptoms for a demyelinating attack contributed to misdiagnosis in almost 2 of 3 patients.

NMOSD = neuromyelitis optica spectrum disorder.

Solomon AJ, et al. *Neurology.* 2016;87:1393-1399.

29

MS and Comorbidities

- Depression is the most frequent comorbidity in MS
  - 21% to 24% at any given time point
  - Associated with ↑ disability, ↓ health-related quality of life (QoL)
- English population-based retrospective matched cohort study
  - January 1987 to September 2018
- N=12,251 individuals with MS vs N=72,572 matched controls
- 21% of patients with MS had baseline depression vs 9% of controls (females, younger, >40% smokers)

Palladino R, et al. *Neurology*. 2021;97:e1322-e1333.

30

MS and Comorbidities

- Patient with MS vs controls had ↑ risk of incident vascular disease (regardless of depression), but highest in depressed patients with MS (significant in women with MS)
- All-cause 10-year mortality 1.75 times ↑ in controls with depression; 3.88 times ↑ in patients with MS without depression, 5.43 times ↑ in patients with MS with depression
- MS status and depression synergistic
  - 14% of observed mortality effect attributable to interaction (21% when restricted to men)
- Conclusion: Depression in MS is associated with ↑ vascular disease and ↑ mortality
  - Could treating depression make a difference?

Palladino R, et al. *Neurology*. 2021;97:e1322-e1333.

31

MS and COVID-19

- MS at increased risk for infections (especially urinary, pulmonary)
- No major concerns with COVID-19
  - Except for independent risk factors: ↑ age, male, Black, obese, vascular risk factors, ↑ disability, progressive MS
  - Immunosuppressive therapy
- Anti-CD20s have been associated with ↑ risk of COVID-19, more severe infection
  - In MuSC-19 registry, MS Global Data Sharing Initiative (but not COVISEP registry)
  - ↑ disability, male, and time on prescriptions are additional factors
- Anti-CD20s, S1P-R modulators interfere with vaccination (especially antibody response)
  - Vaccine response includes antibody response, virus specificCD4+/CD8+ T cell response
  - Recent data support excellent anti-CD20 cell vaccine response, and antibodies may increase with booster
  - X-linked hypogammaglobulinemia can recover from COVID-19
- mRNA vaccines not associated with ↑ short-term relapse risk
  - N=324 in Italian study; Pfizer vaccine
  - N=435 in Israeli study; Pfizer vaccine

Wolf A, Alvarez E. *Neurol Clin Pract*. 2021;11(4):358-361. Di Filippo M, et al. *J Neurol Neurosurg Psychiatry*. 2021 (doi:10.1136/jnnp-2021-327200). Achiron A, et al. *Mult Scler*. 2021;27(6):864-870.

32

Part II: Current and Novel Treatment Options

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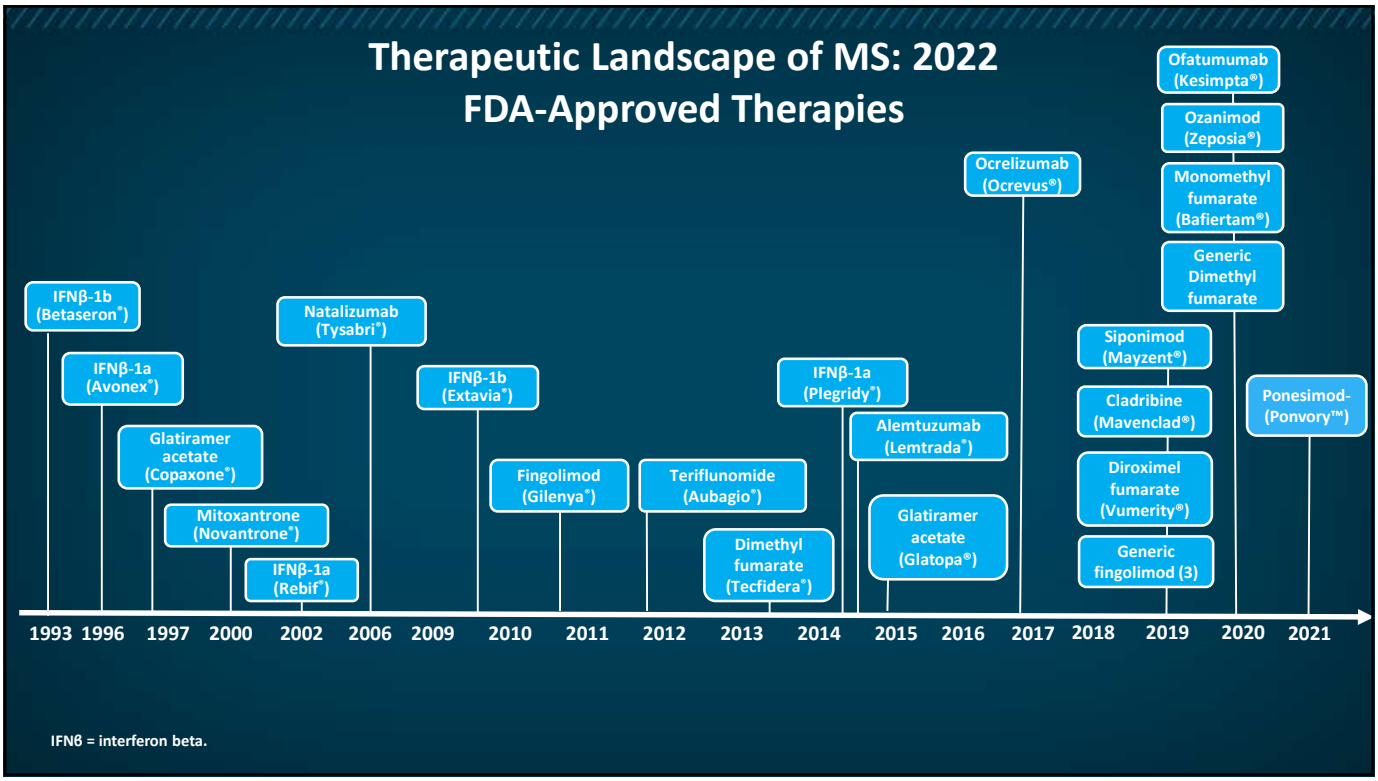
33



34

3D Video 2: MS Treatments

35

MS DMTS

- Injectables
- Orals
- Monoclonal antibodies

36

Injectable DMTs

- Interferonβ (IFNβ)
  - INFβ-1b 250 mcg SC QOD
  - INFβ-1a 30 mcg IM weekly
  - INFβ-1a 44 (22) mcg SC TIW
  - Pegylated INFβ-1a 125 mcg SC or IM every 2 weeks
- Glatiramer acetate (GA)
  - 20 mg SC QD and 40 mg SC TIW formulations
  - 3 products in United States (brand and generics)
- Key Features
  - Immunomodulatory (not immunosuppressive); no PML
  - Long-term experience
  - Minimal safety and modest tolerability concerns
  - Safest DMTs for pregnancy
  - GA requires no blood monitoring

DMTs = disease-modifying therapies; SC = subcutaneous; IM = intramuscular; QD = once a day; TIW = three times a week; RCT = randomized controlled trial; PML=progressive multifocal leukoencephalopathy

Cocco E, et al. *Mult Scler.* 2015;21:433-441. Jokubaitis VG, et al. *Ann Neurol.* 2016:80:89-100. Cree BA, et al. *Ann Neurol.* 2016;80:499-510. Comi G, et al. *Lancet.* 2017;389:1347-1356.

37

Oral DMTs

- Key features
  - Convenient delivery (no needle): ↑ adherence, no injection AEs
  - Efficacy as good or somewhat better than injectables
- S1P-receptor modulators
  - Fingolimod
  - Second generation (siponimod, ozanimod, ponesimod)
- Fumarates
  - Dimethyl fumarate (DMF)
  - Generic DMFs
  - Diroximel fumarate (DRF)
  - Monomethyl fumarate (MMF)
- Teriflunomide
- Cladribine

38

S1P-R Modulators

- <u>Fingolimod</u>
  - 0.5 mg by mouth daily; prodrug; S1P-R1, and 3,4,5
  - Loss of S1P-R1 traps ~70% of lymphocytes in lymphoid tissue; also penetrates CNS
  - FDA-approved for pediatric MS (PARADIGMS trial) and adult MS, relapsing forms (0.25 mg for ≤40 kg pediatric MS)
  - Concerns with hypertension, cardiac/bradycardia, pulmonary, diabetes/uveitis/cataract (macular edema) issues
- Prescreening
  - Prescreen with CBC+diff, hepatic panel, VZV-IgG, EKG/cardiology, OCT
  - Requires 6-hour first dose monitoring
  - Review vaccinations
- Safety
  - Risk for infection: PML (N=37 cases), *Cryptococcus*, herpes infections
  - Risk for rebound: Washes out by 6 to 8 weeks
  - Interference in vaccine response
  - Consider periodic skin examinations (basal cell carcinoma, melanoma)

Fingolimod (Gilenya®) PI 2019 (https://www.novartis.us/sites/www.novartis.us/files/gilenya.pdf). Accessed 1.11.2022.

39

S1P-R Modulators: Second Generation

- Goals
  - Limit receptor specificity (to remove first dose monitoring)
  - Shorter T ½, shorter washout
  - Remove prodrug issues
- Prescreening, safety concerns similar
- Siponimod
  - 2 mg by mouth daily; S1P-R1 and 5
  - Most do not require first dose monitoring (dose escalate over 5-6 days)
  - Positive phase 3 EXPAND SPMS trial (but FDA-approved for relapsing forms of MS)
  - Requires CYP2C9 genotyping (C*3/*3 contraindicated; C*3 heterozygotes limited to 1 mg)
- Ozanimod
  - 0.92 mg (1 mg) by mouth daily; S1P-R1 and 5
  - Most do not require first dose monitoring (dose escalate over 7 days)
  - 2 major metabolites have T ½= 11 days (vs ozanimod T ½ = 21 hours); T ½ washout longer than fingolimod
  - Concerns with MAO inhibitors, CYP2C8 inducers/inhibitors, BCRP inhibitors, adrenergic/serotonergic drugs
- Ponesimod
  - 20 mg by mouth daily; S1P-R1
  - Most do not require first dose monitoring (escalate over 2 weeks)

McGinley MP, Cohen JA. *Lancet.* 2021;398:1184-1194. Roy R, et al. *CNS Drugs.* 2021;35(4):385-402. Ozanimod (Zeposia®) PI 2021 (https://packageinserts.bms.com/pi/pi_zeposia.pdf). Accessed 1.10.2022. Siponimod (Mayzent®) PI 2021 (https://www.novartis.us/sites/www.novartis.us/files/mayzent.pdf). Accessed 1.11.2022. Ponesimod (Ponvory®) PI 2021 (https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/PONVORY-pi.pdf). Accessed 1.10.2022.

40

Fumarates

- Nrf2 activators (antiinflammatory, antioxidant)
- Dimethyl fumarate: Prodrug, parent compound; 240 mg by mouth 2 times daily (dose escalate over 1 week)
  - At least 12 generics; take with or without food
- Prescreening
  -Prescreen with CBC+diff, hepatic panel
- Safety
  - Early GI issues, flushing
  - Small risk of PML (N=11) linked to unusual lymphopenia (6%); check periodically 1-2 times annually)
  - VZV, rare other infections
- Diroximel fumarate: another prodrug packaged differently
  - 462 mg twice daily (dose escalate over 1 week)
  - Significant ↓ in GI side effects; avoid taking with high fat meal
- Monomethyl fumarate contains active agent
  - 190 mg twice daily (dose escalate over 1 week)
  - With or without food; improved GI tolerability (HC)

Valencia-Sanchez C, et al. *Expert Opin Pharmacother.* 2020;21(12):1399-1405. Paik J. *CNS Drugs.* 2021;35(6):691-700. Berger AA, et al. *Neurol Int.* 2021;13(2):207. Dimethyl fumarate (Tecfidera®) PI 2021 (https://www.tecfidera.com/content/dam/commercial/tecfidera/pat/en_us/pdf/full-prescribing-info.pdf). Accessed 1.10.2022. Winn et al. *Mult Scler Relat Disord.* 2020;45:102335.

41

Teriflunomide

- Inhibits mitochondrial enzyme DHDOD (critical for de novo pyrimidine pathway; spares salvage pathway)
- 14 mg and 7 mg daily
- Cytostatic for rapidly dividing lymphocytes
- Prescreening
  - Baseline CBC+diff, hepatic panel (then ALT monthly x 6), TB gold test, blood pressure, pregnancy test
  - Assess for hypertension
- Safety
  - Hair thinning (first 6 months)
  - Black boxes for liver toxicity (RA), embryofetal toxicity (animal models)
  - Drug can persist up to 24 months; accelerated elimination involves 11 days of cholestyramine or activated charcoal (until blood level <0.02 mcg/ml)
  - No PML cases to date

Miller AE. *Neurodegener Dis Manag*. 2021;11(5):387-409. Teriflunomide (Aubagio®) PI 2021 (https://products.sanofi.us/Aubagio/Aubagio.pdf). Accessed 1.10.2022.

42

Cladribine

- Synthetic purine analog; antimetabolite; selective lymphocyte depletor
- Induction strategy
  - 3.5 mg/kg total given as annual course over 5 days in 2 successive months, annually over 2 years (no treatment in Years 3 and 4)
- Recommended as second line choice
- Prescreening
  - CBC+diff, metabolic panel, pregnancy, TB, HIV, hepatitis B and C, IgG to VZV (vaccinate)
  - Follow standard cancer screening
  - Review vaccinations
  - MRI within 3 months
- Safety
  - Black box warning on malignancies (theoretic), teratogenicity
  - Lymphopenia: Monitor at 3 and 7 months after prescribed
  - Infections; herpes prophylaxis for lymphocyte count <200 cells per microliter

Cabrero FR, Morrison EH. *StatPearls* [internet]. 2021 (https://www.ncbi.nlm.nih.gov/books/NBK507717/). Cladribine (Mavenclad®) PI 2019 (https://www.emdserono.com/us-en/pi/mavenclad-pi.pdf). Accessed 1.10.2022.

43

Monoclonal Antibodies

- Key features
  - High efficacy DMTs
  - Immunosuppressives
  - Some carry higher risks
- Natalizumab (binding)
- Alemtuzumab (cytolytic)
- Anti-CD 20s (cytolytic)
  - Ocrelizumab
  - Ofatumumab

44

Natalizumab

- Humanized anti-α4 integrin (adhesion molecule) monoclonal
- 300 mg IV every 4 weeks
  - Extended dosing every 6 to 8 weeks
- Prescreening
  - CBC+diff, hepatic panel, JC virus Ab/index (then every 3 months), VZV IgG
- Safety
  - Black box for PML; TOUCH program
  - PML risk depends on JC virus AB/index, Rx duration, prior immunosuppression; risk 1:10,000 in Ab-
  - Herpes infections
  - Hepatotoxicity, low platelets
  - Risk for rebound: washes out by 3 months
  - Antidrug antibodies (6%)

Khoy K, et al. *Front Immunol*. 2020;11:549842. Natalizumab (Tysabri®) PI 2021 (https://www.tysabri.com/content/dam/commercial/tysabri/pat/en_us/pdf/tysabri_prescribing_information.pdf). Accessed 1.10.2022.

45

Alemtuzumab

- Humanized anti-CD52 monoclonal
- Lyses T and B cells, monocytes, eosinophils
  - B cells and monocytes return by 6 months; T cells take up to a few years
- Recommended as a third line choice; mandatory REMS program
- Induction strategy
  - 12 mg IV daily x 5 days in Year 1, daily x 3 days in Year 2
  - About 33% may go 12 years without retreatment
- Prescreening
  - Skin exam, then annually
  - Review vaccines
  - VZV IgG, TB, HIV, hepatitis B/C, CBC+diff, hepatic panel
  - Infusion premedication, herpes prophylaxis
  - Minimize listeria exposures
- Safety
  - Black box for secondary autoimmune disease requires monthly blood/urine x 4 years
  - Additional black box warning on infusion reactions (must premedicate), serious strokes within 3 days, ↑ risk for malignancies

Kasarello K, et al. *Immunotargets Ther*. 2021;10:237-246. Alemtuzumab (Lemtrada®) PI 2022 (https://products.sanofi.us/lemtrada/lemtrada.pdf). Accessed 1.10.2022.

46

Anti-CD20s

Anti-CD 20	Type	CD 20 Epitope	MS Approval	Dosing	Immune Impact
Rituximab (+ Biosimilar)	Chimeric (25-30% mouse Ig)	Distinct (large extracellular loop)	Off-label	1,000mg IV Q6 mos	ADCC/CDC
Ocrelizumab	Humanized (5-10% mouse Ig)	Rituximab overlap (but not identical)	Relapsing forms of MS; PPMS	600mg IV Q6 mos	ADCC
Ofatumumab	Human (0% mouse Ig)	2 distinct sites (large, small extracellular loops)	Relapsing forms of MS	20mg SC Q4 wks	CDC
Ublituximab	Glycoengineered chimeric	Distinct	In front of FDA (relapsing forms)	450mg IV Q6 mos	ADCC

Rituximab and ublituximab are not FDA-approved for MS.

Kang C, Blair HA. *Drugs*. 2022 (doi:10.1007/s40265-021-01650-7). Margoni M, et al. *J Neurol*. 2021;1-19.

47

Anti-CD20s

- Pros
  - High efficacy
  - Convenience (infusion 2 times a year or home injection)
  - Relatively safe (rare: neutropenia, inflammatory bowel disease)
  - First line or switch option
- Prescreening
  - CBC+diff, hepatic panel, hepatitis B and C, TB, VZV-IgG, quantitative immunoglobulins, vaccine status (especially live)
- Safety
  - Infusion reactions (IV)
  - Immunosuppression/prolonged effect (N=2 PML cases)
  - Hypogammaglobulinemia, ↑ infection risk
  - ↑ COVID-19 vulnerability, severity
  - Negative impact on vaccine (especially COVID-19) humoral response
  - Hepatitis B reactivation

Ocrelizumab (Ocrevus®) PI 2020 (https://www.gene.com/download/pdf/ocrevus_prescribing.pdf). Accessed 1.10.2022. Ofatumumab (Kesimpta®) PI 2020 (https://www.novartis.us/sites/www.novartis.us/files/kesimpta.pdf). Accessed 1.10.2022.

48

AAN Treatment Guidelines

- Dedicated DMT visit
- Recommend DMT for CIS high risk; relapsing forms of MS with recent activity; PPMS likely to benefit
  - High efficacy DMTs for highly active MS
- Endorse shared decision-making/ongoing communications/realistic expectations
- Emphasis on adherence, barriers
- Monitor for clinical, MRI activity; laboratory abnormalities
- ≥ 1 relapse, ↑ disability, and/or ≥2 new lesions over 1 year should trigger switch discussion
- Assess vaccine status prior to starting ISIM therapy

ISIM = immunosuppressive/immunomodulatory therapy.

Rae-Grant A, et al. *Neurology*. 2018;90:777-788. Farez MF, et al. *Neurology*. 2019;93:584-594.

49

Emerging Agents

- Additional anti-CD20s
  - Ublituximab
- Oral Bruton's tyrosine kinase (BTK) inhibitors
- Oral tyrosine kinase inhibitor (masitinib)
- Oral ibudilast
- Oral alpha lipoic acid
- Anti-Epstein Barr virus (EBV) agents
- Autologous hematopoietic stem cell transplant

50

Anti-CD20 Monoclonal Antibodies

- Ublituximab (chimeric IgG1): IV
  - Third generation glycoengineered monoclonal antibodies (mAbs); novel chimeric; ↑ affinity for FcγR IIIa receptor
  - Unique CD20 epitope
  - Enhanced ADCC
  - 450 mg IV every 6 months; 1-hour infusion (150 mg – 450 mg load over 15 days)
  - Also impacts cells with lower CD20 expression

Not FDA-approved for MS.

Rommer PS, et al. *Clin Exp Immunol*. 2014;175:373-384.

51

Ultimate I, II: Ublituximab

- Identical 96-week phase III trials; N=545 ULTIMATE I (N=271 ublituximab, N=274 teriflunomide) and N=544 ULTIMATE II (N=272 ublituximab, N=272 teriflunomide)
- Annualized relapse rate (ARR) 0.076 vs 0.188 (↓ 60%, *P*< .0001) and 0.091 vs 0.178 (↓ 49%, *P*= .0022)
- Contrast lesions decreased 0.016 vs 0.491 (↓ 97%, *P*< .0001) and 0.009 vs 0.250 (↓ 96%, *P*< .0001)
- New/enlarging T2 lesions decreased 0.213 vs 2.789 (92% ↓, *P*< .0001) and 0.282 vs 2.831 (90% ↓, *P*< .0001)
- 12-week confirmed disability progression (CDP) 5.2% vs 5.9% and 24-week CDP 3.3% vs 4.8% (not significant [NS])

Not FDA-approved for MS.

Steinman L. 2021 American Academy of Neurology (AAN) annual meeting; Poster 9056.

52

Ultimate I, II: Ublituximab

- 12-week confirmed disability improvement (CDI) 12% vs 6% (*P*= .0003), 24-week CDI 9.6% vs 5.1% (*P*= .0026)
- No evidence of disease activity (NEDA) (Week 24-96) 44.6% vs 15% (*P*< .0001) and 43% vs 11.4% (*P*< .0001)
- Most common adverse events (AEs) were infusion related reactions (IRRs) (47.7%), headache (30.3%), and nasopharyngitis (17.8%)
- Conclusion: Ublituximab showed better relapse, MRI suppression, CDI (pooled), and NEDA

Not FDA-approved for MS.

Steinman L. 2021 AAN annual meeting; P15.074.

53

BTK Inhibitors

- Oral agents; BTK is member of Tec family of cytoplasmic tyrosine kinases
- Targets B cell, Mϕ, microglial signaling (B cells and innate immunity myeloid cells): prevents their activation
- BTK inhibitors variability
  - May or may not be CNS penetrant
  - Reversible (noncovalent) vs irreversible (covalent) binding to cysteine 481
  - Highly selective (minimal off-target effects) or not

Not FDA-approved for MS.

Montalban X, et al. *N Eng J Med*. 2019;380(25):2406-2417. Sun, JS, et al. *Leukemia*. 2019;33:2105-2110.

54

BTK Inhibitors

- 4 BTK inhibitors in MS trials
  - Evobrutinib: Evolution RMS1, 2 phase 3 relapsing MS trials vs teriflunomide; phase 2 trial noted 75 mg daily ↓ contrast lesions
  - Fenebrutinib (highly selective, reversible noncovalent): FENhance 1,2 phase 3 relapsing MS trials vs teriflunomide, FENtrepid PPMS vs ocrelizumab
  - Tolebrutinib (SAR442168): GEMINI 1, 2 phase 3 relapsing MS trials vs teriflunomide; PERSEUS PPMS vs placebo, HERCULES nonrelapsing SPMS vs placebo; phase 2B trial noted highest dose (60 mg) ↓ contrast lesions
  - Orelabrutinib: In phase 2 relapsing MS trial (NCT04711148), N=160; core 24 weeks vs placebo; OLE low, medium, high dose
- BIIB091 in phase 1 healthy controls (non-CNS penetrating)

Not FDA-approved for MS.

Montalban X, et al. *N Eng J Med*. 2019;380(25):2406-2417. Neys SFH, et al. *Front Cell Dev Biol.* 2021;9:668131.

55

Evobrutinib in Relapsing MS

CNS penetrant irreversible oral BTK inhibitor

- Double-blind, randomized, phase 2 trial; placebo-controlled phase: 24 weeks, blinded extension phase: 24 weeks
- Subjects: Relapsing MS
  - 87% RRMS, 13% active SPMS; 69% women; all White
- 5 arms: Placebo, evobrutinib × 3 doses, open-label DMF (52-54 subjects/arm)
- Primary outcome: Total # of Gd+ lesions on MRI at Weeks 12, 16, 20, and 24
- Results: Total number of Gd+ lesions, measured at Weeks 12 to 24, was significantly lower among patients in the evobrutinib 75 mg once-daily group than placebo group
- Safety: Elevated liver enzymes (LFTs); nasopharyngitis

Not FDA-approved for MS.

Montalban X, et al. *N Engl J Med.* 2019;380(25):2406-2417.

56

Tolebrutinib in Relapsing MS

- CNS penetrant, irreversible oral BTK inhibitor
  - No lymphopenia
- Phase 2B study (N=130 relapsing MS; 2 SPMS)
- 16-week study (12 weeks on drug)
  - Group 1 (N=64) randomized to 5, 15, 30, 60 mg, then placebo x 4 weeks
  - Group 2 (N=66) randomized to placebo x 4 weeks, then 1 of 4 BTK doses
  - N=129 (99%) completed treatment; N=126 in final analysis
- 85% relative risk reduction in new contrast lesions after 12 weeks (1^o outcome) for 60 mg dose (*P*= .03; exponential model)
  - Mean 1.03 vs 1.39, 0.77, 0.76, 0.13
  - 89% relative risk reduction in new/enlarging T2 lesions after 12 weeks (2^o outcome) for 60 mg dose (*P*< .0001; linear model)
- Well tolerated (headache 3%-13%; upper respiratory tract infection [URTI] 3%-6%; nasopharyngitis 3%-9%)

Not FDA-approved for MS.

Reich DS, et al. *Lancet Neurol*. 2021;20:729-738. Multiple Sclerosis Treatment. Neurology Live. 2020;3(3):June 30.

57

Masitinib

- Oral selective tyrosine kinase inhibitor; CNS penetrant
- Acts on innate immune cells (mast cells, microglia, Mϕ)
- Phase 3 trial was prospective, randomized (2:1), double-blind, placebo-controlled, 96 weeks
  - Entered progressive (PP, nonactive SP) MS; N=656
  - 2 parallel groups: 4.5 mg/kg/day, and escalated to 6 mg/kg/day, vs 2 placebos
- 4.5 mg/kg/day (N=200) vs placebo (N=101) showed less change in EDSS (0.001 vs 0.098, *P*= .0256)
  - Benefits for both PPMS and nonactive (relapse free) SPMS; ↑ time to EDSS 7
- No benefit for 6 mg/kg/day (N=203) vs placebo (N=107)
- Clinical trials were on hold in June 2021 for cardiac ischemia concerns; hold released in November 2021
- Phase 3 trial in progressive (PP, nonactive SP) MS planned; N=800

Not FDA-approved for MS.

AB Science Press Release. Feb 20, 2022. Available at: https://www.ab-science.com/news-and-media/press-releases/.

58

Ibudilast (MN-166)

- Oral small molecule phosphodiesterase-4 and PDE-10 inhibitor; Mφ-MIF inhibitor, toll like receptor 4 inhibitor
  - ↓ proinflammatory cytokines, ↑ neurotrophic factors, attenuates activated glia
- Approved in Japan/Korea for poststroke dizziness, asthma
- Phase 2B SPRINT trial entered N=255 patients with progressive (N=134 PP, N=121 SP) MS randomized to up to 50 mg twice daily (N=129) vs placebo (N=126) for 96 weeks
  - Could be on IFNβ, GA
- Whole brain atrophy ↓ 48% reduction vs placebo (-0.0010 vs -0.0019 annually, *P*= .04)
  - Measured by BPF
  - Cortical atrophy ↓ 80% (*P*= .004)
- Significant impact on MTI but not DTI
- Well tolerated (GI, headache, depression)

Not FDA-approved for MS.

Fox RJ, et al. *N Eng J Med*. 2018;379:846-855.

59

Ibudilast (MN-166)

- Post hoc analysis indicates PPMS (*P*= .005) drove atrophy effect vs SPMS (*P*= .97)
  - Faster atrophy in PPMS (*P*= .016)
- Additional MRI endpoints at 96 weeks: GM atrophy ↓ 35% (*P*= .038), new/enlarging T2 lesions in 37.2% ibudilast vs 29% controls (*P*= .82); new T1 33.3% vs 23.5% (*P*= .11); SIENA brain volume loss ↓ 20% (*P*= .08)
- OCT not significant for most outcomes (↓ macular volume change, *P*= .044) but trended favorably

Not FDA-approved for MS.

Fox RJ, et al. *N Eng J Med*. 2018;379:846-855. Bermel RA, et al. *Mult Scler*. 2021;27(9):1384-1390. Naismith RT, et al. *Neurology*. 2021;96(4):e491-e500.

60

Lipoic Acid in MS

- Lipoic acid is an inexpensive oral antioxidant
  - Lipoic acid/dihydrolipoic acid redox couple a key cofactor for mitochondrial pyruvate dehydrogenase
- Preliminary studies indicated oral doses well tolerated and reach therapeutic levels
- 96-week double-blind, randomized trial in SPMS
  - 1200 mg by mouth vs placebo
  - Primary outcome brain volume loss

Not FDA-approved for MS.

Spain RI, et al. *Neurol Neuroimmunol Neuroinflamm*. 2017;4:e374.

61

Lipoic Acid in MS

- N=54 randomized
  - N=51 (27 lipoic acid, 24 placebo) took at least 1 dose
  - Average age 58.5 years, 61% female, median EDSS 6
  - ↓ annualized brain atrophy
    - -0.21 vs -0.65, 68% reduction (*P*= .002)
  - Trend for improved walking speed
  - AEs similar (↑ GI upset, ↓ falls with lipoic acid)
- New trial recruiting N=118 PP/SP MS from 7 sites; 1º outcome T25 FW; brain volume change, number of falls, 2-minute timed walk; estimated completion August 31, 2023

Not FDA-approved for MS.

Spain RI, et al. *Neurol Neuroimmunol Neuroinflamm*. 2017;4:e374.

62

EBV-Targeted Therapies

- EBV strongest infection risk factor for MS (100% AB+ in adult-onset MS; mono ↑ MS risk 2 to 10 times (HLA-DR15+)
  - 32-fold ↑ risk for MS
- Adoptive cytotoxic CD8+ T cells (autologous, allogeneic)
  - NCT02912897: Autologous T cells for CIS
  - NCT032838261: ATA188 allogeneic for progressive MS (EMBOLD phase 1/2)
- Prophylactic and therapeutic vaccines

Not FDA-approved for MS.

Cui X, Snapper CM. *Front Immunol*. 2021;12:734471. Bjornevik et al. *Science*. 2022;375:296.

63

Autologous Hematopoietic Stem Cell Therapy (AHSCT)

- Goal of AHSCT is to reprogram-reboot immune system
- Not for progressive MS; works better in younger, shorter disease duration, less severe MS (still ambulatory)
- Initial ↑ brain atrophy
- Hard to separate immune suppression vs stem cell effects
- NEDA rates of 78% to 83% (2 years), 60% to 68% (5 years)

Not FDA-approved for MS.

Lee H, et al. *Mult Scler.* 2017;23:420-431. Muraro PA, et al. *JAMA Neurol*. 2017;74(4):459-469. Burman J, et al. *Bone Marrow Transplant*. 2017;52:1133-1137. Bakhuraysah MM, et al. *Stem Cell Res Ther*. 2016;7:12.

64

BEAT-MS Study

- Best available therapy vs autologous hematopoietic stem cell transplant for MS
  - Cladribine, natalizumab, alemtuzumab, anti-CD20s
  - Cyclophosphamide mobilization, BEAM/antithymocyte globulin conditioning
- 6-year study being conducted by Autoimmune Tolerance Network
  - N=156; 1:1 randomization
  - Estimated completion October 2029
  - EDSS 2 to 5.5
  - ≥2 treatment failures in prior 36 months (at least 1 relapse)
- 1° outcome relapse free survival up to 36 months (until relapse/death)

Not FDA-approved for MS.

ClinicalTrials.gov. NCT04047628 (https://clinicaltrials.gov/ct2/show/NCT04047628).

65

CNS Repair Strategies

- May involve remyelination, axon sprouting, blocking inhibitory factors; treating gliosis, moderating microglia/astrocytes; replacing cells (oligos, neurons)
- No successful CNS repair strategy established
- Recent failures
  - Opicinimab (anti-lingo-1) monoclonal antibody
  - High grade, high dose biotin
  - Elezanumab (anti-repulsive guidance molecule A) monoclonal antibody
- Ongoing studies
  - Oral clemastine
  - Gold nanoparticles
  - Mesenchymal stem cells/exosomes

Not FDA-approved for MS.

Villoslada P, Steinman L. *Expert Opin Investig Drugs*. 2020;29(5):443-459.

66

Part III: A Holistic, Personalized Approach to MS

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67

Personalized Approach

- Consider the totality of the patient
  - Their perspectives, opinions, reports
- Use shared decision-making, with clear communication and partnership
- Choose the best DMT with the individual
- Optimize adherence/compliance
- The long term is as important as the short term
- Focus on measures to enhance CNS reserve
  - To promote better CNS aging
  - Optimize lifestyle choices, wellness program
  - Recognize/manage comorbidities
- Evaluate and optimize management of symptoms

68

Case: Laura

Laura is a 32-year-old female just diagnosed as relapsing MS after an attack of optic neuritis. Brain MRI shows 3 lesions (periventricular and juxtacortical, 4-5 mm). Spinal cord is clear. CSF shows + oligoclonal bands. The patient is complaining of fatigue, poor appetite, and poor sleep. She is a newlywed (married 1 year ago). When asked what an MS relapse is, she did not know.

What are issues for Laura's personalized care?

-Comorbid depression raising concerns about adherence, MS severity

-Knowledge about MS

-Pregnancy concerns

69

Initiating DMT: Real-World Considerations

- Disease factors
  - MS severity and prognosis (clinical, demographic, MRI, laboratory factors)
  - Disease duration
  - Disease phenotype
- Access factors
  - Formulary restrictions
  - Out-of-pocket costs
- Drug factors
  - Efficacy
  - Safety
  - Risk/benefit
  - Monitoring requirements
  - Route of administration
- Patient factors
  - Age
  - Pregnancy concerns
  - Comorbidities
  - Impairment impacting monitoring or adherence
  - Ethnicity
  - Risk tolerance

EDSS = Expanded Disability Status Scale.

Kalincik T, et al. *Brain.* 2017;140:2426-2443. Wingerchuk DM, Weinshenker BG. *BMJ.* 2016;354:i3518. Rush CA, et al. *Nat Rev Neurol* .2015;11:379-389.

70

Improving Engagement in Patient Care

Elicit individual risk/benefit preferences

- Relative values of preventing future disability vs fear of side effects
- Present data in understandable terms
- Recognize potential for conflicting information from alternate sources
- Patient tolerance for risk may be greater than that of their physician(s)
- Establish a nonjudgmental trusting relationship, even if the patient's treatment decision may conflict with your recommendation

Strategies to optimize DMT adherence

- Educate patients
  - Disease course
  - Treatment rationale and accurate expectations
  - Potential adverse effects and management
- Empathic attention
  - Adjustment to coping with a chronic disease
  - Recognizing treatment impacts on lifestyle
  - Anticipate doubts when breakthrough occurs or when long-term stability leads to questions regarding need for DMT
  - Reinforce treatment adherence and evidence of benefit

Wilson L, et al. *J Neurol Sci.* 2014;344:80-87. Clanet MC, et al. *Mult Scler.* 2014;20:1306-1311. Giovannoni G, Rhoades RW. *Curr Opin Neurol.* 2012;25(suppl):S20-S27. Johnson FR, et al. *J Neurol.* 2009;256:554-562. Cohen BA. *Int J MS Care.* 2006;8(suppl 1):32-37.

71

DMT Adherence Factors

- MS has reported rates of adherence from 41% to 88%
- Shared decision-making will enhance adherence
- Factors influencing adherence include
  - Age (younger less adherent)
  - Sex (females less adherent)
  - Type of DMT (injectables less adherent)
  - Depression (5 times less adherent)

Higuera L, et al. *J Manag Care Spec Pharm*. 2016;22:1394-1401. Rabadi MH, et al. *J Central Nervous Sys Dis*. 2021;13:1-10. Washington F, et al. *J Neurol*. 2021 (doi: 10.1007/s00415-021-10850-w).

72

Barriers, Gaps, Unmet Needs

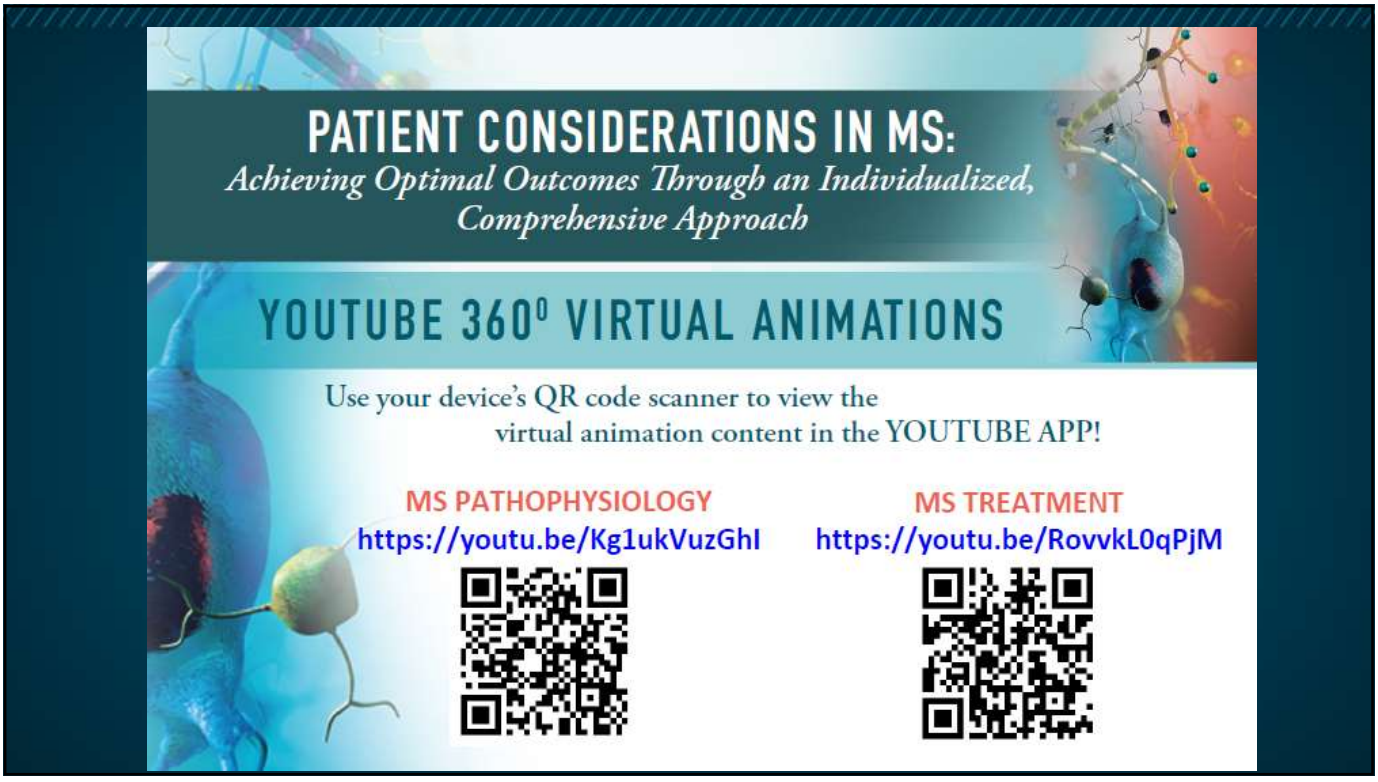
- Early diagnosis and optimized initial management
- Better tracking of disease activity, performance, symptoms
  - Biomarker development
  - Monitoring outside the office
- Better progressive MS identification and treatment
- Improved measures to track and treat cognitive aspects

73

Thank You!

Questions & Answers

77



78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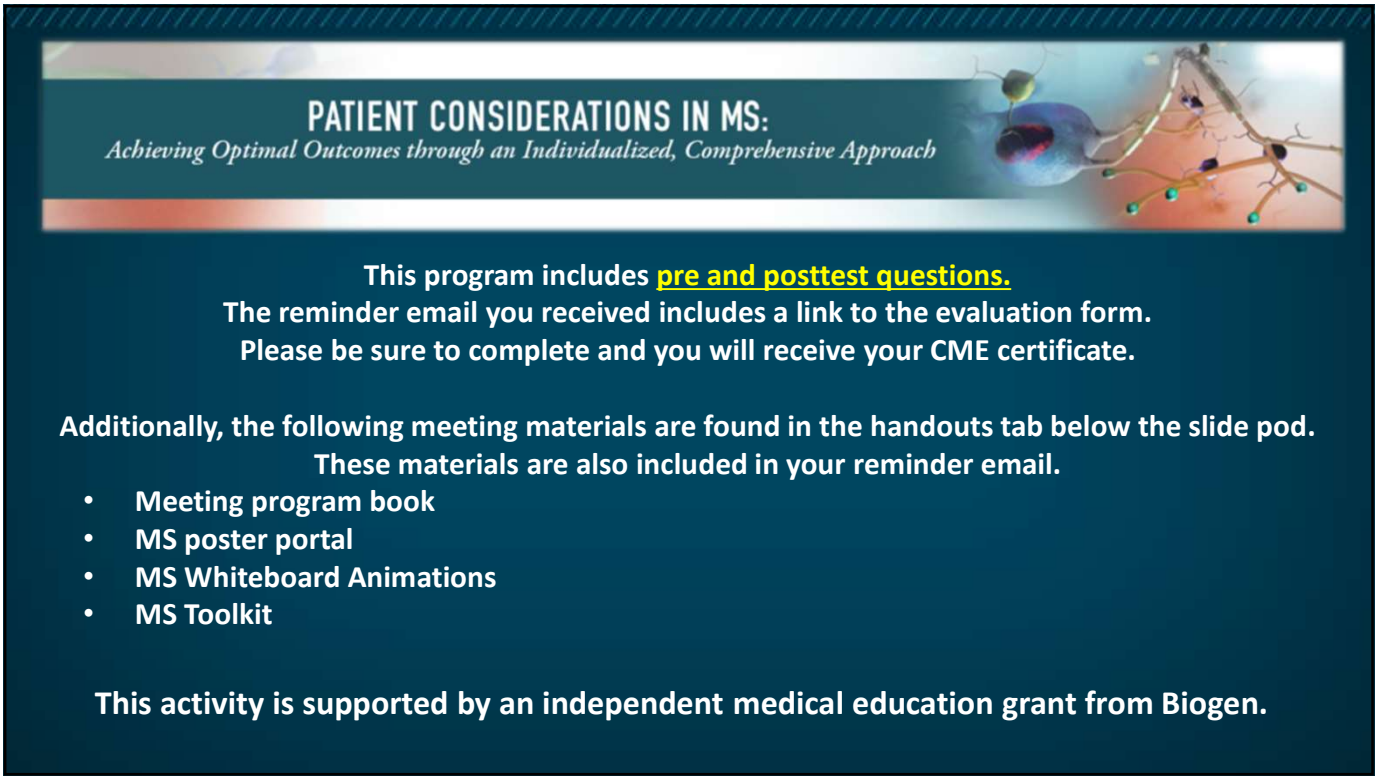
79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80