THE 12TH ANNUAL LINDA MORGANTE

Multiple Sclerosis Nurse Leadership Program

2021

TREATMENT OVERVIEW DISEASE-MODIFYING THERAPIES & RELAPSE MANAGEMENT

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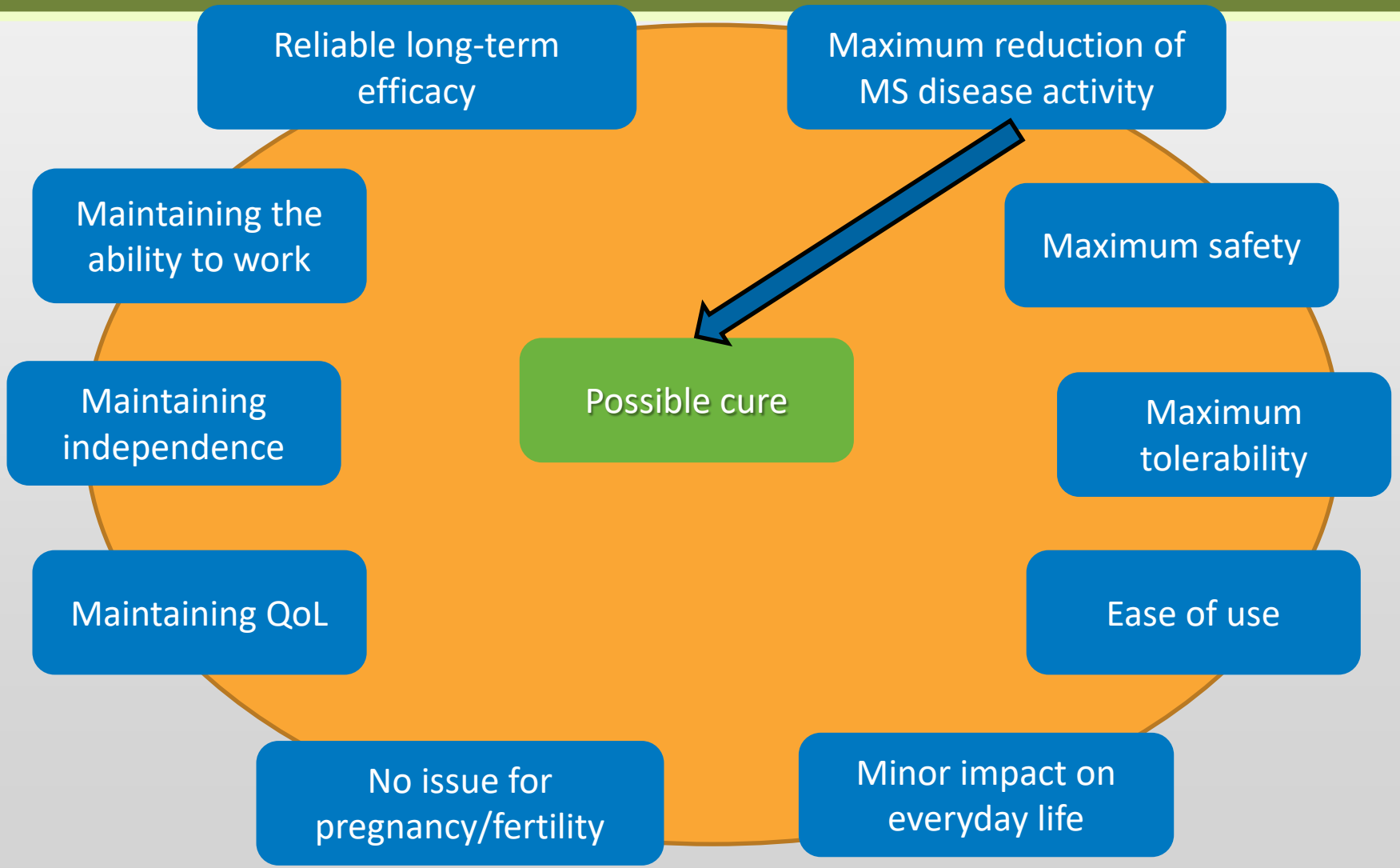
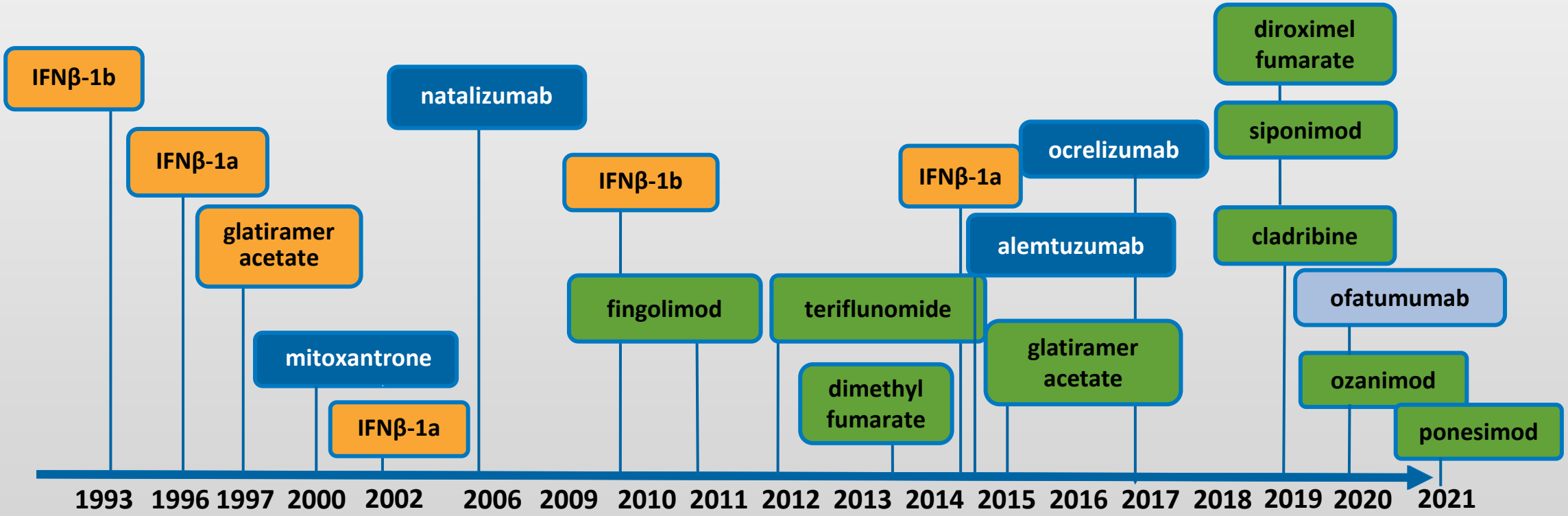
Ideal MS Therapy



https://www.aan.com/Guidelines/home/GuidelineDetail/898. Accessed May 12, 2021.

MS = multiple sclerosis; QoL = quality of life

FDA-Approved MS Therapies – 2021



https://www.nationalmssociety.org/Treating-MS/Medications. Accessed May 12, 2021.

MS 2021

Current DMT Landscape

- >20 distinct MS DMTs (includes generics)
- 10 different MoAs
- All approved for relapsing forms of MS
  - 1 approved for PPMS
- Timely initiation is emphasized
- Set expectations with patients
- 3 administration categories
  - Injectable (IM, SQ)
  - Oral
  - Infusion

Goals of Treatment

- Modify or reduce relapses and delay disability progression
- Decrease new MRI activity
- Facilitate acceptable QoL

Bross M et al. *Int J Mol Sci*. 2020;21(12):4312.

MoA = mechanism of action; MRI = magnetic resonance imaging; PPMS = primary progressive MS

General Immunotherapeutic Mechanisms of MS Therapies

- Immunomodulation/alteration of cell function
  - Interferon ß (SQ/IM)
  - Glatiramer acetate (SQ)
  - Dimethyl fumarate (oral)
  - Monomethyl fumarate (oral)
  - Diroximel fumarate (oral)
  - Teriflunomide (oral)
- Immunosuppressive
  - Mitoxantrone (IV)
- Cell trafficking/migration
  - Natalizumab (IV)
  - Fingolimod (oral)
  - Ozanimod (oral)
  - Siponimod (oral)
  - Ponesimod (oral)
- Cell depletion
  - Alemtuzumab (IV)
  - Cladribine (oral)
  - Ocrelizumab (IV)
  - Ofatumumab (SQ)

Bruck W et al. *JAMA Neurol.* 2013,70(10):1315-24. Freedman MS et al. *Can J Neurol Sci*. 2020;47(4):437-55.

DMT Armamentarium: 2 Perspectives

- MS practitioners should consider the entire armamentarium of DMTs and consider all DMT choices for all patients

OR

- MS practitioners should move towards precision medicine, personalizing DMTs to target the individual's disease characteristics

https://www.aan.com/Guidelines/home/ByTopic?topicId=18. Accessed May 18, 2021.

Consider Entire DMT Armamentarium

- Factors to consider when selecting DMT: Lifestyle, availability of care partner, acceptability of injection, availability of infusion services, mental health concerns, future plans regarding pregnancy, comorbidities
- DMT considerations: Medication efficacy, safety factors, MoAs, adverse effects, schedule of treatment, ease and route of administration, previous use of DMTs
- Severity of disease: More aggressive treatment may not be appropriate in patients with multiple risk factors
- Cost considerations, as many 2nd- and 3rd-line medications may not be covered until 1st-line treatment is tried
- Insurance considerations: Insurance companies want to know that patients are receiving benefit for costly medications

https://www.aan.com/Guidelines/home/ByTopic?topicId=18. Accessed May 18, 2021.

Consider Precision Medicine When Managing Patients With MS

- Look at biomarkers to focus on disease characteristic for optimum treatment of patients with MS
- Spinal fluid biomarkers may help predict future disease progression or more objective measures, such as cerebrospinal fluid [CSF] markers → next wave of precision medicine
- Certain DMTs may be given only to patients shown via biomarkers to respond to that particular immunomodulatory approach
- It may become important to “estimate disease severity and activity before the initiation of treatment”
- Precision medicine is being studied as part of a clinical trial at NIH, "Targeting Residual Activity by Precision, Biomarker-Guided Combination Therapies of Multiple Sclerosis (TRAP-MS)"

Bielekova B. Chief of the Neuroimmunological Disease Section at the National Institutes of Health (NIH) presentation. Americas Committee for Research and Treatment in Multiple Sclerosis (ACTRIMS) Forum. February 28, 2020.

Escalation vs Induction

- Escalation therapy
  - Escalation paradigm may minimize medication risks and long-term disability in MS
  - Treatment side effects should be proportional to disease state
  - 1st-line therapy continues for at least 6 months to assess treatment response; if patient experiences relapse or breakthrough disease activity, consider another treatment option (if patient has been adherent to treatment)
  - Increased risk of infections target immunocompromised people; can sometimes have fatal consequences
- Induction therapy
  - Consider high-efficacy agents as initial therapy for an informed patient who has high level of disease activity
  - Start with a highly effective agent, considering efficacy over safety
  - Initiate treatment of aggressive immunosuppressant drugs to retard or prevent progression
  - Consider course of B-cell depleting therapy to start induction paradigm

https://www.aan.com/Guidelines/home/ByTopic?topicId=18. Accessed May 18, 2021.

Trading Efficacy for Safety

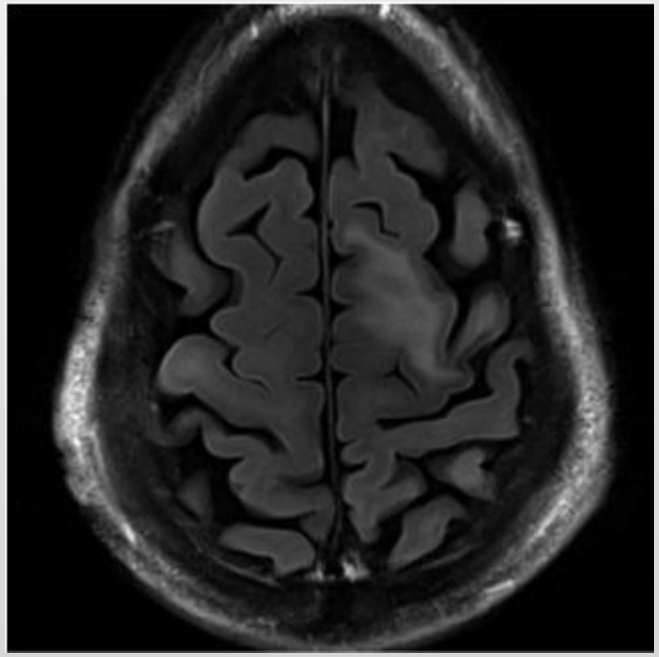
- Manageable safety concerns
  - Liver function abnormalities
  - Bradycardia
  - Reactive airway disease
  - Pro inflammatory
  - Blood pressure elevations
  - GI disturbance
  - Hair thinning
  - Infusion reactions
- Serious safety concerns
  - Immune surveillance
  - Infections
  - Malignancies
  - Long lasting and irreversible effects
  - Autoimmunity
  - Teratogenicity
  - PML
  - The unknown

Zadeh AR et al. *Int J Physiol Pathophysiol Pharmacol.* 2019;11(4):105-14.

GI = gastrointestinal;
PML = progressive multifocal leukoencephalopathy

Progressive Multifocal Leukoencephalopathy (PML)

- Risk factors
  - Previous immunosuppression, exposure to natalizumab >2 years, JC virus positivity
- Clinical symptoms
  - Motor function abnormalities, hemiparesis, ataxia
  - Cognitive impairment, behavioral changes, language disorders, visual problems
  - Headache, sensory loss, seizures
- Radiological
  - T2 FLAIR multifocal lesions, coalescence of new lesions
  - Involves subcortical and juxtacortical white matter
  - T1 hypointense
  - Mass effect absent
  - Enhancement present in ~9% patients



Chalkey JJ et al. *Curr Neurol Neurosci Rep*. 2013;13(12):408. https://my.clevelandclinic.org/departments/neurological/depts/multiple-sclerosis/ms-approaches/pml-diagnosis-management. Accessed May 20, 2021.

IMMUNOMODULATION/ALTERATION OF CELL FUNCTION

Interferons/Glatiramer acetate

Fumarates

Teriflunomide

Immunomodulation/Alteration of Cell Function

- Interferons
  - MoA: Promotes shift from Th1-Th2, inhibits antigen presentation, enhances apoptosis of autoreactive T cells
  - Side effects: Flu-like symptoms, injection-site reactions, increased LFTs, decreased WBCs
  - Dosing: IM or SQ injection
- Glatiramer acetate (GA)
  - MoA: Promotes differentiation to Th2 and T reg cells leading to bystander suppression in CNS, deletion of myelin reactive T cells
  - Side effects: Injection-site reactions, postinjection reaction, lipoatrophy
  - Dosing: Daily or 3x/wk SQ injection

Graber JJ et al. *Clin Neurol Neurosurg*. 2010;12(7):583-91.

CNS = central nervous system; LFT = liver function test; WBC = white blood cell

Interferons and GA

- Approved for relapsing MS (RMS), active secondary progressive MS (SPMS), and clinically isolated syndrome (CIS)
- Slowly shrinking market
- Advantages
  - Long-term safety and efficacy data
  - No surprises, well known side-effect profile/tolerability
  - Low risk
- Disadvantages
  - Inconvenience of injectables
  - Lower efficacy
  - Concern re: adherence
  - Flu-like side effects with interferons
  - Possible immediate postinjection reaction with GA
  - Lipoatrophy with GA

Marrie RA et al. *Nat Clin Pract Neurol*. 2006;2:34-44. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020622s102lbl.pdf. Accessed May 18, 2021.

Fumarates (Dimethyl fumarate, Monomethyl fumarate, Diroximel fumarate)

- MoA: Esterase conversion to monomethyl fumarate (MMF); exact MoA not clear, MMF activates Nrf2 pathway, Nrf2 pathway involved in cellular response to oxidative stress, anti-inflammatory, cytoprotective, immunomodulating properties
- Side effects
  - Flushing (~40%)
  - GI (abdominal pain, diarrhea, nausea, vomiting)
  - Pruritis
  - Lymphopenia
  - LFT elevation
  - PML (10 cases/>500,000 patients, all over age 50 years, with chronic persistent lymphopenia)
- Dosing: Dose titration
  - Temporary dose reductions/extend titration period if necessary
- Elimination: Terminal half-life of fumarates approximately 1 hour; accumulation of MMF does not occur with multiple doses

Gold R et al. *N Engl J Med.* 2012;367(12):1098-107.

Teriflunomide

- MoA: Noncompetitive/selective/reversible inhibitor of dihydroorotate dehydrogenase (DHODH)
  - DHODH enzyme necessary for proliferating T/B cells; other cells untouched
  - Active metabolite of leflunomide
- Side effects
  - Hepatic metabolism → hepatotoxicity
  - Teratogenicity
  - Hair thinning
  - Paresthesia
  - Clear contraindications for teriflunomide include pregnancy, significant liver dysfunction, and concomitant use of leflunomide
- Dosing: 7 or 14 mg/d
- Elimination: Effect of drug may stay in the blood for 8 months to 2 years
  - 11-day accelerated elimination procedure with cholestyramine, oral activated charcoal powder

O'Connor P et al. *N Engl J Med*. 2011;365(14):1293-303.

CELL TRAFFICKING

Natalizumab

S1P Receptor Modulators

Natalizumab

- MoA: Selective mAb directed at $\alpha 4\beta$-1 integrin, blocks attachment of activated lymphocytes to VCAM-1 on endothelial cells and subsequent migration into CNS
- Immune selective blockade
- TOUCH REMS program
- Adverse events
  - Headache, fatigue, UTI, URI, gastroenteritis, joint pain, diarrhea
  - Infections, hepatotoxicity, thrombocytopenia
  - PML
- Dosing: 300 mg administered q28d via infusion
  - Elimination: Pharmacokinetic studies showed that natalizumab can be effectively removed from the blood compartment using plasmapheresis
  - Mean half-life 11 days

Miller DH et al. *N Engl J Med*. 2003;348(1):15-23.

mAb = monoclonal antibody; REMS = Risk Evaluation and Mitigation Strategies; URI = upper respiratory tract infection; UTI = urinary tract infection

Sphingosine-1-Phosphate (S1P) Receptor Modulators

- MoA
  - Immune selective blockade
  - Binds with high affinity to S1P receptors
  - Blocks lymphocytes to egress from lymph nodes, therefore reducing number of lymphocytes in peripheral blood
  - Precise mechanism by which SP1 receptor modulators exert therapeutic effects in MS is unknown but may involve reduction of lymphocyte migration into CNS
- Adverse effects
  - Bradycardia and atrioventricular (AV) conduction delays
  - Risk of infections
  - Herpes viral infections
  - Cryptococcal infections
  - Respiratory effects
  - Liver Injury
  - Macular edema
  - Posterior reversible encephalopathy (PRES)
  - Immune system effects after stopping
  - Potential risk of rebound

Chaudhry B et al. *Neurotherapeutics.* 2017;14(4):859-73.

S1P Agents

Fingolimod: Receptor targets 1, 3-5

- 2 studies
  - Fingolimod vs placebo
  - Fingolimod vs IFNß-1a IM weekly
- Requires 6-hour 1st-dose observation (FDO)
- Dosing: Adults 0.5 mg/d
- Approved for pediatric patients >10 years: 0.25 mg
- Washout: Pharmacologic effect can last up to 2 months after stopping medication

Siponimod: Receptor targets 1,5

- Largest controlled clinical study of SPMS patients
- Dose requires brief upward titration to mitigate decreased heart rate associated with initial dosing. Titration and maintenance dose regimens are determined by CYP2C9 genotype
- Dosing: Initiate with 5-day titration, then 1 or 2 mg on Day 6 and maintenance
- Washout 7 days

Cohen JA et al. *N Engl J Med.* 2010;362(5):402-15. Kappos L et al. *Lancet.* 2018;391(10127):1263-73.

Selective S1P Agents

Ozanimod: Receptor targets 1,5

- Compared to IFNß-1a IM in studies
- 0.92-mg dose
  - 7-day starter pack to slowly increase dose over 1st week
- No requirement for genotyping before initiation; no required FDO
- Elimination approximately 11 days

Ponesimod: Receptor targets 1

- Most recently approved S1P modulator (March 2021)
- Ponesimod proved superior to teriflunomide for improving annualized relapse rate, fatigue, MRI activity, brain volume loss, and disease activity status in patients with RMS
- 20-mg dose
  - 14-day starter pack
- No FDO requirement
- Elimination 1 week

Cohen JA et al. *Lancet Neurol*. 2019;18(11):1021-33.
Kappos L et al. *JAMA Neurology.* Published online March 29, 2021.

FDO = first-dose observation

IMMUNOSUPPRESSIVE AGENTS

Mitoxantrone

Mitoxantrone

- MoA: Disrupts DNA synthesis and repair; inhibits B-cell, T-cell, and macrophage proliferation; impairs antigen presentation as well as secretion of interferon γ, TNF, and IL-2
- Indicated for worsening RRMS, PRMS, SPMS
- Adverse events: Temporary blue discoloration of sclera and urine, nausea, alopecia, menstrual disorders including amenorrhea and infertility, infections (URI, UTI, stomatitis), and cardiac toxicity (arrhythmia, abnormal EKG, CHF)
- Dosing: 12 mg/m^2 every 3 months
- **Warnings:** Severe tissue damage if extravasation from IV site, cardiotoxicity, acute myelogenous leukemia, myelosuppression

CHF = congestive heart failure; IL = interleukin; PRMS = progressive relapsing MS; RRMS = relapsing-remitting MS; TNF tumor necrosis factor

https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019297s030s031lbl.pdf. Accessed May 18, 2021.

CELL-DEPLETION THERAPIES

Cladribine

Alemtuzumab

Ocrelizumab

Ofatumumab

Cladribine

- MoA: Not fully elucidated but thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes. Causes a dose-dependent reduction in lymphocyte counts followed by recovery
  - Prolonged effect on T cells, transient effect on B cells
- Approved for RRMS and active SPMS **not** clinically isolated syndrome (CIS)
  - Recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate drug indicated for treatment of MS
- Adverse reactions (>20% compared to placebo)
  - URI, headache, lymphopenia, hematologic toxicity, liver Injury, tuberculosis, complications with blood transfusions
- **Warnings:** Malignancies and risk of teratogenicity
  - Long-term monitoring for malignancies
- Dosing: Short course of oral treatment
  - 3.5 mg per kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg/y, each consisting of 2 treatment weeks
  - Median time to recovery from lymphocyte counts <500 cells/microliter to at least 800 cells/microliter was approximately 28 weeks

Grieb P et al. *Lancet.* 1994;344(8921):538.

Alemtuzumab

- MoA: Directed against CD52 antigen found on T and B lymphocytes and monocytes (induction strategy)
- FDA-mandated REMS program, IV infusion
- Adverse events
  - Infusion reactions (cytokine release syndrome, premedicate (IVMP, acetaminophen, diphenhydramine)
  - Antibody-mediated autoimmunity (thyroid disease 34% of patients), immune thrombocytopenia , glomerular nephropathies, miscellaneous autoimmune conditions
  - Infection due to prolonged CD4 +T-cell depletion (herpes virus, human papilloma virus [HPV], tuberculosis, fungal infections, Listeria meningitis)
  - Malignancy (thyroid cancer, melanoma, lymphoproliferative disorders)
  - Pneumonitis
- Dosing: 12 mg IV daily on 5 consecutive days at Month 0 then 3 consecutive days at Month 12
- After IV administration, elimination half-life of alemtuzumab is approximately 2 weeks
- Requires monthly lab draws x 5 years → risk of loss for follow-up

Coles AJ et al. *Lancet.* 2012;380(9856):1829-39. Coles AJ et al. *J Neurol.* 2006;253(1):98-108.

IVMP = intravenous methylprednisolone

Ocrelizumab

- MoA: Anti-CD20 B cell mAb, humanized immunoglobulin (Ig)G1
- Approved for RMS and PPMS
- No REMS program
- Side effects: Infusion reactions, infections
- Less common adverse events
  - Hepatitis B reactivation, decreased IgG/IgM, malignancies
- Contraindications
  - Hepatitis B infection
- Dosing: 600 mg administered IV q6mo
  - (1st dose given 2 weeks apart)
- Premedications: IVMP, acetaminophen, diphenhydramine
- Elimination: Terminal elimination half-life 26 days

Kappos L et al. *Lancet.* 2011;378(9805):1779-87.

Ofatumumab

- MoA: Anti-CD20 mAb
- Compared to teriflunomide in study
- Common side effects
  - Injection-related reactions, low immunoglobulins, URI, headache
- Serious adverse events
  - Infections, reactivation of hepatitis B, decreased immunoglobulins
  - Contraindications: active hepatitis B virus infection
- Dosing: Administered via SQ injection
  - 20 mg SQ at Weeks 0, 1, 2, 4, then monthly
  - Stored in refrigerator
- Half-life: Approximately 14 days (range: 2-61 days)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125326s060lbl.pdf. Accessed May 18, 2021.

Agents in Late-Stage Development for MS

- Weak uncompetitive antagonist of NMDA
  - Amantadine
- Selective GABA type B receptor agonist
  - Arbaclofen
- Cannabis extract
  - Nabiximols (for MS spasticity)
- CD20-directed mAb
  - Ublituximab
- BTK inhibitors
  - Evobrutinib
  - Fenebrutinib
  - Masitinib
  - Tolebrutinib

ClinicalTrials.gov. Accessed May 14, 2021.

BTK = Bruton's tyrosine kinase; GABA = gamma aminobutyric acid; NMDA = N-methyl-D-aspartate

Patient and Family Education/Learning Needs

- Promote active participation in care
- Ability to make informed choices
- Ability to engage in self care with confidence and competence
- Assess ability to learn
- Level of education
- Cognition
- Readiness to learn
- Cultural literacy/cultural health beliefs
- Healthcare literacy
- Role of family/family support
- Coping mechanisms

https://practicalneurology.com/articles/2017-apr/shared-decision-making-in-multiple-sclerosis-management. Accessed May 18, 2021.

Key Factors for Patient Education

- Lifestyle, availability of care partner, acceptability of route of administration (injection), availability of infusion services, mental health concerns, future plans regarding pregnancy, comorbidities
- DMT considerations: Medication efficacy, safety factors, MoAs, adverse effects, schedule of treatment, ease and route of administration, previous use of DMTs
- Severity of disease; more aggressive treatment may not be appropriate in patients with multiple risk factors
- Cost considerations: Many 2nd- and 3rd-line medications may not be covered until 1st-line treatment is tried
- Insurance considerations: Insurance companies want to know patients are receiving benefit for costly medications

https://practicalneurology.com/articles/2017-apr/shared-decision-making-in-multiple-sclerosis-management. Accessed May 18, 2021.

MS RELAPSE

MS Relapse

- Episode of focal neurological disturbance lasting more that 24 hours without alternate explanation and with preceding period of clinical stability lasting at least 30 days
- Onset of neurological symptoms that evolve over days or weeks
- Plateaus within 1-2 weeks
- Recovery time varies
- Depends on severity of relapse
- Some symptoms become permanent
- Relapse rate and degree of recovery after relapses predict long-term disability
- Relapse is usually not a medical emergency

Goodin DS et al. *Mult Scler Relat Disord*. 2016;6:10-20.

Management of Relapse

- Assess if acute relapse, pseudo-relapse, or disease progression
- Treatment options
  - Corticosteroids
  - IVMP 1-2 g/d for 3-5 days
  - High-dose oral MP 500mg-1g for 3-5 days
  - Oral prednisone 1250 mg/d for 3-5 days
  - Oral dexamethasone 96-160 mg PO for 3-5 days
- Repository corticotropin injection 40-80 U IM or SQ once daily for 2-3 weeks
- Plasmapheresis (used as 2nd-line therapy after systemic corticosteroids)
- Assess for adherence to treatment
- Consider escalating DMT treatment

Ontaneda D et al. *Ann Indian Acad Neurol*. 2009;12(4):264-72. Weiner H et al. *Neurology.* 1989;39(9):1143-9.

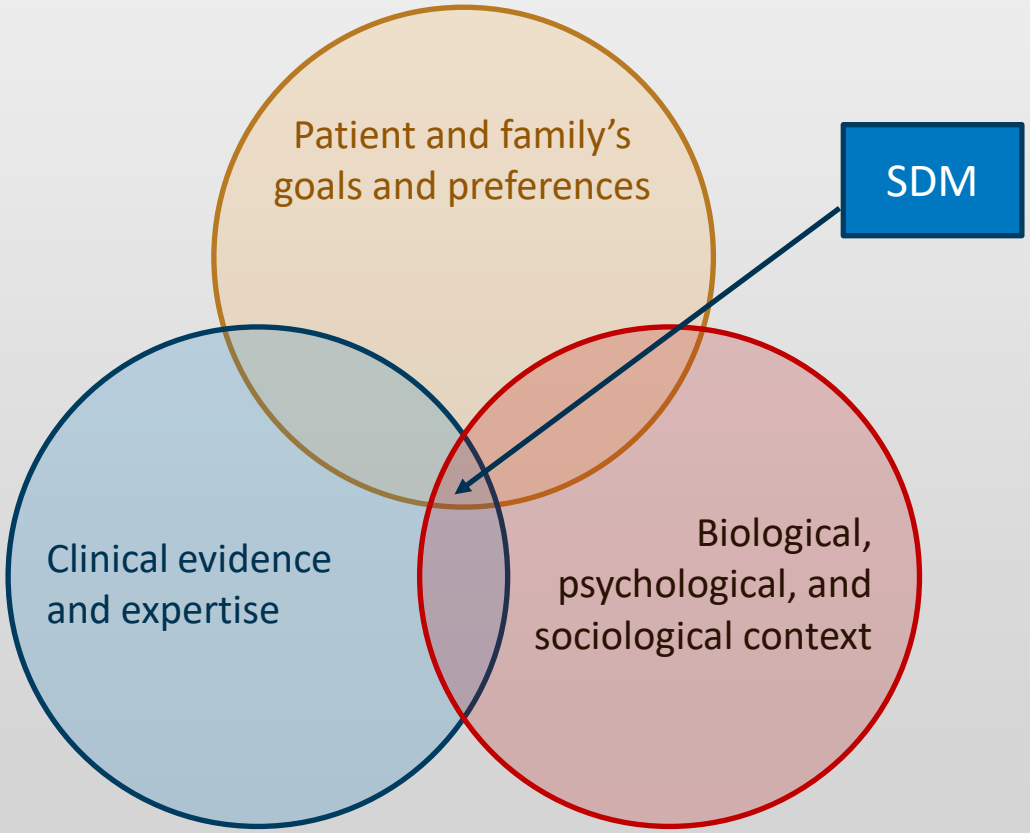
Management of Relapse: Nonpharmacologic

- Maximize recovery
- Refer to rehabilitation therapy
  - Physical therapy
  - Occupational therapy
  - Speech therapy
- Refer to psychology or social work

https://emedicine.medscape.com/article/1146199-treatment#showall. Accessed May 18, 2021.

Shared Decision-Making

Decision-making process



https://www.cincinnatichildrens.org/

- Patient-centered care
- Collaborative relationship between clinicians and patients
- Incorporates patient preferences and values
- Patient education
- 2-way communication
- Positive impact on patient adherence

https://practicalneurology.com/articles/2017-apr/shared-decision-making-in-multiple-sclerosis-management. Accessed May 18, 2021.

Summary

- MS treatment landscape is increasingly complex and crowded
- We have entered a new era of complex choices that challenges the professional community with the need to keep current and constantly updated
- Abundance of choice for RRMS
- Acute and long-term management of relapses, and the disease itself, require nursing knowledge, vigilance, and patient and family education
- Multiple considerations
  - Risk factors for disease course and progression
  - Sequencing of DMTs
  - Patient factors
  - Shared decision-making
- PML is rare, but can be associated with significant disability

THANK YOU!

THE 12TH ANNUAL LINDA MORGANTE MS Nurse Leadership Program