International Organization of MS Nurses

Treatment of MS: Choices and Challenges

Supported by Novartis Pharmaceuticals Corporation

MS Disease Management

- Treat relapses
- Reduce relapses and prevent and/or slow progression
- Assess and manage symptoms
- Improve the quality of life of all those affected by MS

CHALLENGE OF MS RELAPSES AND RELAPSE MANAGEMENT

Definition of MS Relapse

- Episode of focal neurological disturbance lasting more than 24 hours continuously, without an alternate explanation or infection, and with a preceding period of clinical stability lasting at least 30 days

National MS Society; Ontaneda D, Rae-Grant A. *Ann Indian Acad Neurol*. 2009;12:264-272.

Hallmarks of MS Relapses

- Onset of neurological symptoms that evolve over days to weeks
- Plateaus within 1 to 2 weeks
- Recovery within 4 to 12 weeks
  - Depends on severity
  - Some symptoms persist and become permanent, equaling disability
- Relapse rates have been declining over past decade, presumably due to efficacy of DMTs

DMTs=disease modifying therapies.

National MS Society; Stoppe M et al. *BMC Neurology.* 2017;17:151;
Lublin FD et al. *Neurology.* 2003;61:1528-1532;
Kalincik T. *Neuroepidemiology.* 2015;44:199-214.

Common Signs of MS Relapses

- Spinal Cord/Transverse Myelitis
  - Sensory or motor changes
  - Band-like abdominal or chest sensation (MS Hug)
  - Bowel and bladder dysfunction common
- Optic Neuritis
  - Typically unilateral, painful vision loss
  - Retrobulbar (no retinal exudates or disc swelling)
- Lesions in Brainstem and Cerebrum
  - Ocular motor syndrome (eg, intranuclear ophthalmoplegia [INO])
  - Double vision
  - Trigeminal neuralgia
  - Vertigo or balance issues
  - Swallowing difficulty
  - Facial weakness or sensations
  - Poor balance and coordination

McGinley MP et al. *JAMA.* 2021;325:765-779; Frohman et al. *Neurotherapeutics*. 2007;4:618-626.

Pseudo-Relapses

- Transient worsening or return of neurological symptoms due to environmental, systemic, or other influences; NOT a new area of CNS inflammation:
  - Increased core or environmental temperature
  - Physical exertion
  - Fatigue
  - Infection or illness
  - Stress/anxiety
  - Medications/alcohol use
  - Menstrual cycle
  - Surgical or medical procedure (colonoscopy)

CNS=central nervous system.

Mills EA et al. *Front Neurol.* 2017;8:116;
O'Connor P. *Multiple Sclerosis: The Facts You Need to Know*. 4th ed. 2009. Canadian Medical Association.

Management of Relapses

- First: Determine if acute relapse, pseudo-relapse, or disease progression
  - Onset/evolution of symptoms
  - Rule out contributing factors
- Severity of relapse
  - Impact on function/role
  - Patient's perception
  - Continued worsening
- Determine if treatment of relapse is required

Treatment Options

- Corticosteroids*
  - High-dose steroid options
    - IV methylprednisolone (MP): 500 mg–1 g for 3–5 days
    - Oral MP: 500 mg–1 g for 3–5 days
    - Oral prednisone 1250 mg daily 3–5 days
    - ACTH 80–120 units SC for 5 days–3 weeks
  - Oral steroid taper
    - No documented difference in neurologic outcome
    - Practitioner or patient preference
- Plasmapheresis
  - May be used for severe relapses that don't respond to steroids

**No evidence that steroid treatment changes long-term outcome of the disease*

IV=intravenous; SC=subcutaneous.

Lattanzi S et al. *J Neurol.* 2017;264:1697-1704; Sears ES et al. *Arch Neurol.*1978;35:426-434; Berkovich R. *Neurotherapeutics.* 2013;10:97-105.

Corticosteroids: Adverse Effects

- Hyperglycemia, hypokalemia, sodium and fluid retention
- Hypertension
- GI intolerance, dyspepsia, increased appetite
- Leukocytosis, thrombocytopenia
- Psychiatric manifestations, insomnia
- Cataracts, glaucoma, retinal necrosis
- Bone demineralization
- Skin: acne, impaired wound healing, hypersensitivity reactions
- Avascular necrosis of large joints
- Drug interactions: oral contraceptives, estrogen, anticonvulsants

GI=gastrointestinal.

National MS Society, 2008; Lattanzi S et al. *J Neurol.* 2017;264:1697-1704.

Non-Pharmacologic Relapse Management

- Rehabilitation
  - Severity and duration of relapse and recovery
  - Need for multidisciplinary team
    - Physical therapy - mobility and safety
    - Occupational therapy - equipment/aids, fatigue management
    - Speech therapy - swallowing, cognition
    - Social work - Coping with stress, resources, finances
  - Hospital vs community services
- Community-based resources
  - Home support
  - Equipment sources

National MS Society; Amatya B et al. *Cochrane Database Syst Rev.* 2019;1:CD012732.

DISEASE MODIFYING THERAPIES

Disease Modifying Therapies Aim to…

- Alter the natural course of the disease with goal of:

  No Evidence of Disease Activity (NEDA)

- Reduce frequency and severity of relapses
- Suppress magnetic resonance imaging (MRI) lesion activity and reduce new T2 lesions
- Delay disability progression as measured by Expanded Disability Status Scale (EDSS) and/or MS Functional Composite (MSFC)

Rae-Grant A et al. *Multiple Sclerosis and Related Disorders: Clinical Guide to Diagnosis, Medical Management, and Rehabilitation.* 2nd ed. 2018; MS Coalition, 2019; Rae-Grant A et al. American Academy of Neurology Practice Guideline: Disease modifying therapies for adults with multiple sclerosis, 2018.

NEDA-4 Levels

NEDA 1: No MRI lesion changes

NEDA 2: No relapses

NEDA 3: No confirmed progression of disability

NEDA 4: Annual brain volume loss <0.4%

NEDA=no evidence of disease activity.

Kappos L et al. Abstract 116. Presented at: The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress; October 7-10, 2015; Barcelona.

Escalation Versus Induction Therapy Approach

- **Escalation:** Start patients with moderately effective DMT that has less risk of incurring PML and other serious side effects
  - Switch to higher-efficacy DMT as needed if there is clinical and/or radiologic evidence of active disease
- **Induction:** Start patients on higher-efficacy therapies early in disease course
  - Emerging data show this approach can have long-term benefits over escalation approach
  - European study comparing an older high-efficacy infusible drug, newer high-efficacy infusible medication, and high-efficacy oral drug showed all three slowed disease progression better compared with older injectable DMTs and with low-to-moderately effective oral therapy
- Two ongoing trials are comparing these two approaches

PML=progressive multifocal leukoencephalopathy.

Simpson A et al. *Curr Treat Options Neurol.* 2021;23:19; Spelman T et al. *JAMA Eurol.* 2021;78:1197-1204.

General Immunotherapeutic Mechanisms of MS Therapies

- Immunomodulation/alteration of cell function
  - Beta interferons (SC or IM)
  - Dimethyl fumarate (oral)
  - Diroximel fumarate (oral)
  - Glatiramer acetate (SC)
  - Monomethyl fumarate (oral)
- Cell depletion (B-cell targeted therapies)
  - Alemtuzumab (IV)
  - Cladribine (oral)
  - Ocrelizumab (IV)
  - Ofatumumab (SC)
  - Ublituximab (IV)
- Cell trafficking
  - Fingolimod (oral)
  - Natalizumab (IV)
  - Ozanimod (oral)
  - Ponesimod (oral)
  - Siponimod (oral)
- Cell replication/proliferation
  - Mitoxantrone (IV)
  - Teriflunomide (oral)

IM=intramuscular; IV=intravenous; SC=subcutaneous.
Slide courtesy of Marie Namey.

Trading Efficacy for Safety

- Serious safety concerns
  - Immune surveillance
  - Infections (PML, etc)
  - Malignancies
  - Long-lasting and irreversible effects
  - Autoimmunity
  - Teratogenicity
  - Rare but serious infusion reactions
  - The unknown
- Manageable safety concerns
  - Bradycardia
  - Blood pressure elevations
  - Reactive airway disease
  - Liver function abnormalities
  - Flushing
  - GI discomfort
  - Arthralgias
  - Back/limb pain

MS Coalition 2019 DMT Treatment Recommendations

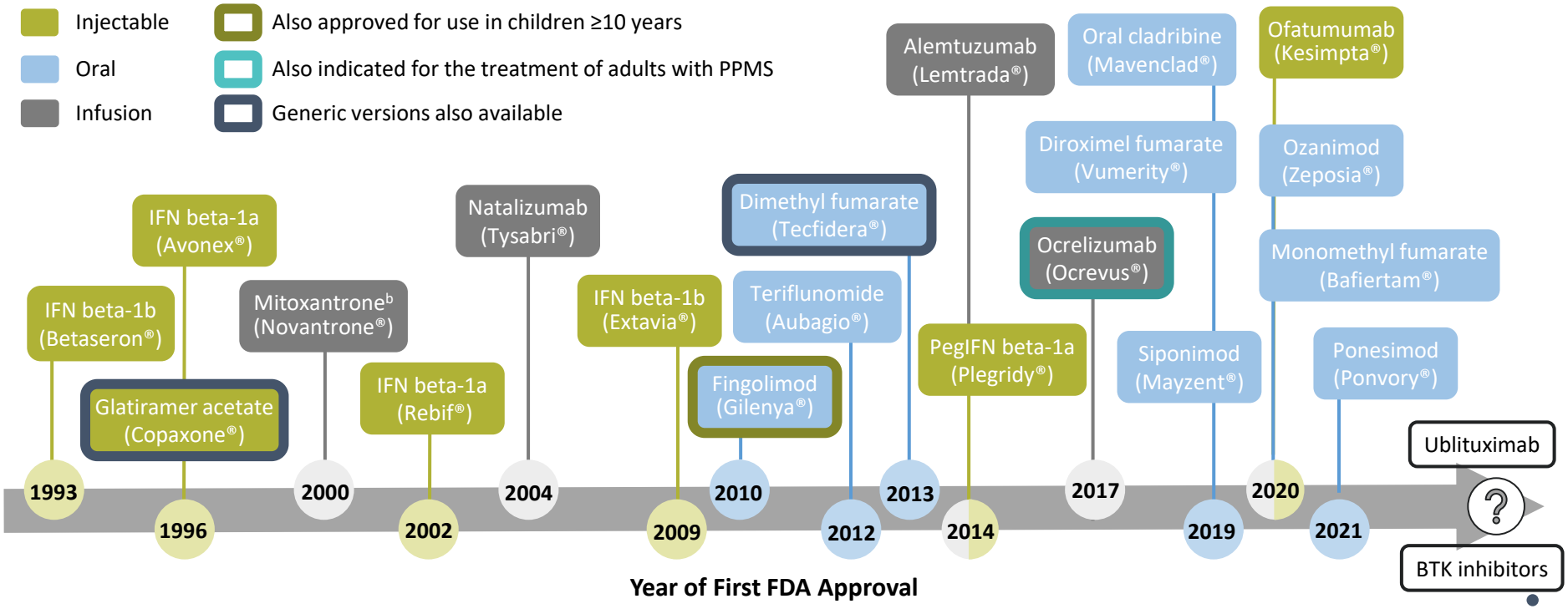
- Initiation of therapy with immunomodulator advised as soon as possible following diagnosis of CDMS and considered for those with CIS
- High-efficacy medication such as alemtuzumab, cladribine, fingolimod*, natalizumab, or ocrelizumab recommended for patients with very active MS
- Should also be considered for patients with breakthrough activity while on another DMT
- Continue treatment unless suboptimal response, intolerable side effects, poor adherence, availability of more-appropriate treatment option, benefits no longer outweigh risks
- Switches permitted for medically approved reasons
- Providers and patients should engage in shared decision-making to choose DMT

*Fingolimod was the only sphingosine 1 phosphate (S1P) receptor modulator available at the time these recommendations were made, but all S1Ps may be considered high-efficacy medications. Changes in practice since 2019 favoring an induction approach may influence treatment choices.

CDMS=clinically definite multiple sclerosis; CIS=clinically isolated syndrome.
MS Coalition, 2019.

MS Disease Modifying Therapy: *A Crowded Landscape*

All approved therapies are indicated for the treatment of adults with relapsing forms of MS[a]



[a]Including relapsing-remitting MS (RRMS) and active secondary-progressive MS (SPMS) for alemtuzumab and oral cladribine; SPMS, progressive relapsing, or worsening RRMS for mitoxantrone; clinically isolated syndrome (CIS), RRMS, and active SPMS for all other therapies. [b]Mitoxantrone is rarely used in North America due to safety concerns.

BTK=Bruton's tyrosine kinase; IFN=interferon; PPMS=primary progressive MS.

FDA, 2021. https://www.accessdata.fda.gov/scripts/cder/daf/.

FDA-Approved Disease Modifying Therapies

DMT	Maintenance Dose	Indications
High-dose IFNβ-1a	22 mcg or 44 mcg SC TIW	Relapsing forms, active SPMS
Low-dose IFNβ-1a	30 mcg IM weekly	Relapsing forms, active SPMS
High-dose IFNβ-1b	250 mcg SC QOD	Relapsing forms, active SPMS
Peginterferon β-1a	125 mcg SC Q 2–4 weeks	Relapsing forms, active SPMS
Glatiramer acetate	20 mg QD SC or 40 mg TIW	Relapsing forms, active SPMS
Ofatumumab	20 mg/0.4 SC monthly	Relapsing forms, active SPMS
Natalizumab	IV 300 mg Q4W	Relapsing forms, active SPMS
Alemtuzumab	IV 12 mg consecutive 5 days 1st yr; 3 days 2nd year	Relapsing forms, active SPMS
Ocrelizumab	IV 600 mg Q 24 weeks	Relapsing forms, active SPMS, PPMS
Ublituximab	IV 450 mg Q 24 weeks	Relapsing forms, active SPMS
Mitoxantrone	12 mg/m^2 IV protocol; max lifetime dose of 140 mg/m^2	Worsening RRMS, SPMS

FDA=Food and Drug Administration; PPMS=primary progressive MS; SPMS=secondary progressive MS.
Note: Some therapies require titration to achieve maintenance doses.

FDA-Approved Disease Modifying Therapies

DMT	Maintenance Dose	Indications
Fingolimod	0.5 mg PO QD	Relapsing forms, active SPMS
Ozanimod	0.92 mg PO QD	Relapsing forms, active SPMS
Ponesimod	20 mg PO QD	Relapsing forms, active SPMS
Siponimod	Titrate to 1 mg or 2 mg PO QD (starting tab 0.25)	Relapsing forms, active SPMS
Teriflunomide	7 mg or 14 mg PO QD	Relapsing forms, active SPMS
Dimethyl fumarate	240 mg PO BID	Relapsing forms, active SPMS
Diroximel fumarate	462 mg PO BID	Relapsing forms, active SPMS
Monomethyl fumarate	190 mg PO BID	Relapsing forms, active SPMS
Cladribine	1.75 mg/kg BW per year 1 and 2 PO	Relapsing forms, active SPMS

FDA=Food and Drug Administration; PPMS=primary progressive MS; SPMS=secondary progressive MS.
Note: Some therapies require titration to achieve maintenance doses.

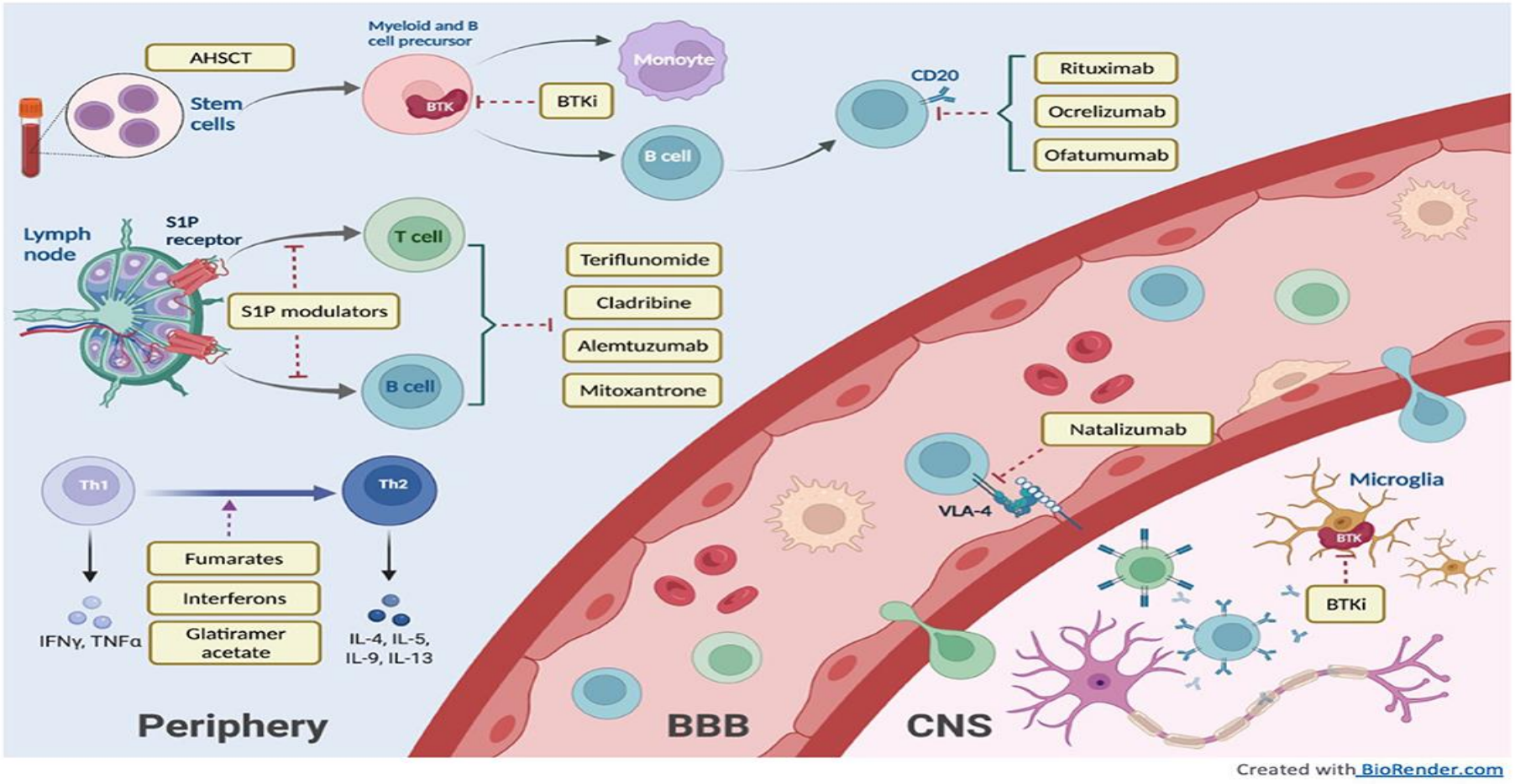
Approved DMT Mechanisms of Action

MS Therapy	Route	Mechanism/Site of Action
Interferon-β	Injectable	Cytokine; downregulates antigen presentation, blocks T cell migration, induces IL10
Glatiramer acetate	Injectable	Binds to myelin-specific autoantibodies
Dimethyl fumarate	Oral	Activates nuclear factor-like 2 pathway, protects against neuronal/astrocyte cell injury, loss
Teriflunomide	Oral	Inhibits pyrimidine synthesis, prevents proliferation of activated T and B cells
Fingolimod	Oral	Sphingosine-1 phosphate receptor modulators; inhibit lymphocyte egress from lymph nodes
Siponimod	Oral	
Ozanimod	Oral	
Ponesimod	Oral	
Alemtuzumab	IV	MAb targeting CD52 on lymphocytes and monocytes; changes adaptive immunity
Natalizumab	IV	MAb targeting α4β1 integrins; prevents leukocyte migration across blood-brain barrier
Ocrelizumab	IV	MAbs targeting CD20 on B cells; induce antibody-dependent and complement-mediated lysis of B cells
Ublituximab	IV	
Ofatumumab	Injectable	
Mitoxantrone	IV	Intercalates with DNA, breaks strands and inhibits DNA repair in T and B cells and macrophages
Cladribine	Oral	Disrupt cell metabolism, DNA synthesis and repair, mostly in lymphocytes

DMT=disease modifying therapy.

Alborghetti M et al. *Curr Neuropharmacol*. 2022;20:107-125;
Bierhansl L et al. *Nat Rev Drug Discov*. 2022;21:578-600;
Yang JH et al. *Front Neurol*. 2022;13:824926;
Pardo G, Jones DE. *J Neurol*. 2017;264:2351-2374.

DMT Mechanisms of Action



Alborghetti M et al. *Curr Neuropharmacol*. 2022;20:107-125;
Bierhansl L et al. *Nat Rev Drug Discov*. 2022;21:578-600.
Figure reprinted under Creative Commons-BY license from Yang JH et al. *Front Neurol*. 2022;13:824926.

IMMUNOMODULATING DISEASE MODIFYING THERAPIES

Beta Interferons

Indications: Relapsing MS, active SPMS

Dosage:

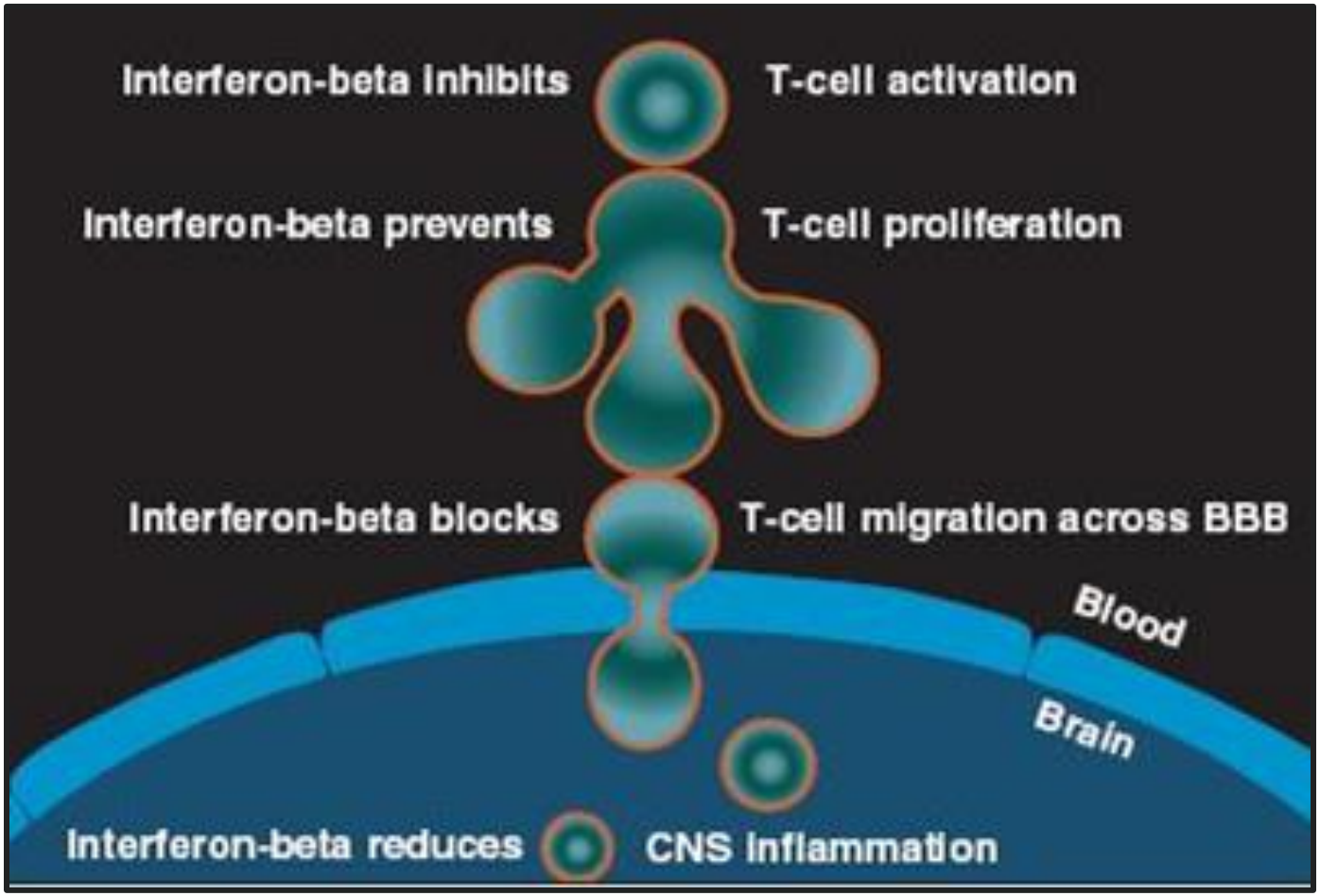
- Beta interferon 1-b (Betaseron®, Extavia®)
- Beta interferon 1-a IM, beta interferon 1-a SC (Avonex®, Plegridy®, Rebif®)

Adverse Effects:

- Flu-like symptoms – Can be managed with dose escalation, evening dosing, hydration, NSAIDs
- Elevated liver enzymes
- Injection-site reactions

NSAIDs=nonsteroidal anti-inflammatory drugs.

Beta Interferons Mechanism of Action



Glatiramer Acetate

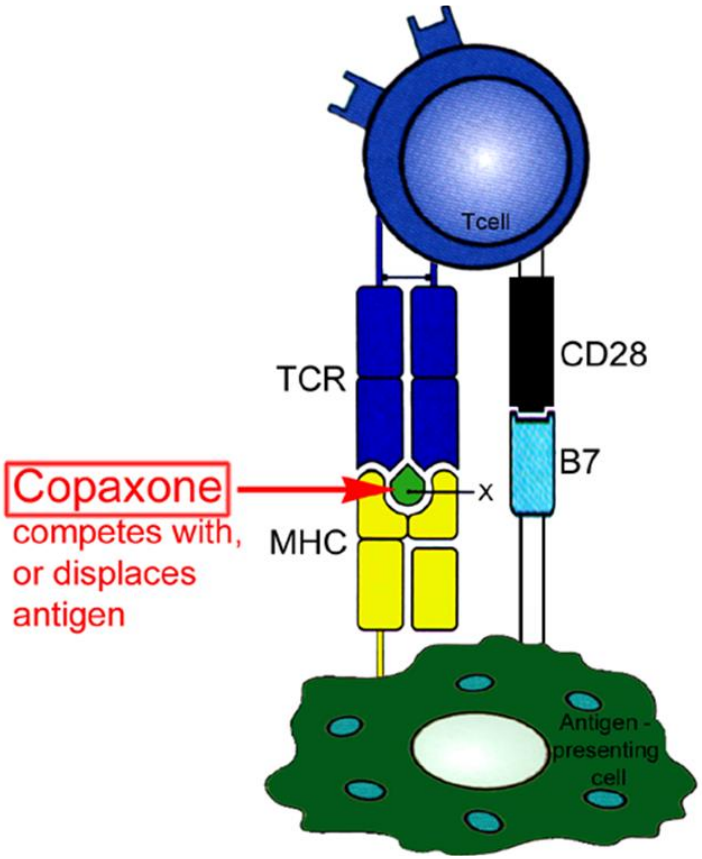
- Indications: Relapsing MS, active SPMS
- Dosage:
  - 20 mg/mL subcutaneous injection daily (Copaxone®, Glatec™, and Glatopa®)
  - 40 mg/mL subcutaneous injection 3x/week (Copaxone®, generic)

Adverse effects:

- Injection-site reactions
  - Localized erythema and/or hives
  - Lipoatrophy
- Post-injection reaction
  - Occurs immediately after injection and consists of facial flushing, chest tightness, palpitations, anxiety, and shortness of breath
  - Unrelated to serious sequelae
  - No long-term toxicity and not an allergic reaction

Teva Neuroscience, Inc., 2022; Sandoz, 2022; Mylan Pharmaceuticals, Inc., 2022.

Glatiramer Acetate (GA) Mechanism of Action

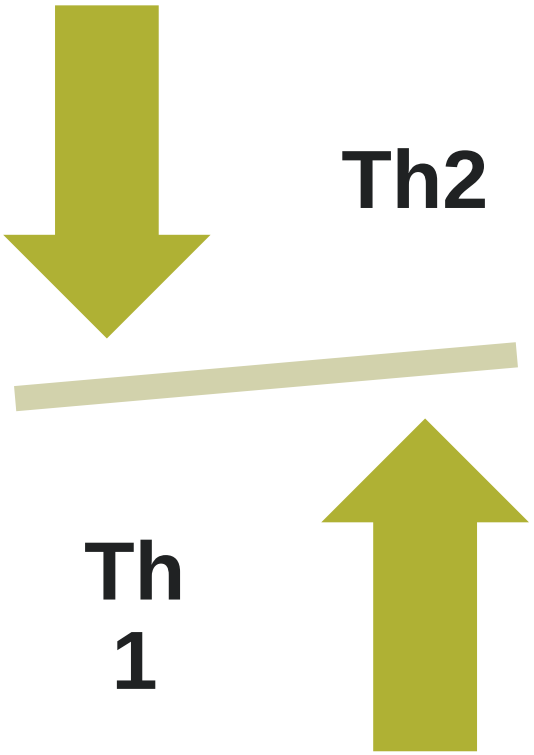


- **Action of GA in periphery:**
  - GA causes activation of beneficial suppressor cells (Th2 immune cells)
- **Action of GA in CNS:**
  - GA-reactive Th2 cells enter CNS
  - These T cells stimulated to multiply
  - Release anti-inflammatory cytokines
  - Decrease inflammation
  - Promote neuroprotection

Dimethyl Fumarate

Tecfidera®

- Fumarate
  - Breaks down to monomethyl fumarate
- Indications: Relapsing MS, active SPMS
- MOA: Anti-inflammatory oral agent
  - Decreases IL4, IL2, TNFα
  - Immunomodulator
    - Induces Th1 → Th2 shift
    - Apoptosis of active lymphocytes
    - Down-regulation of adhesion molecules
  - Nrf pathway – antioxidant effect



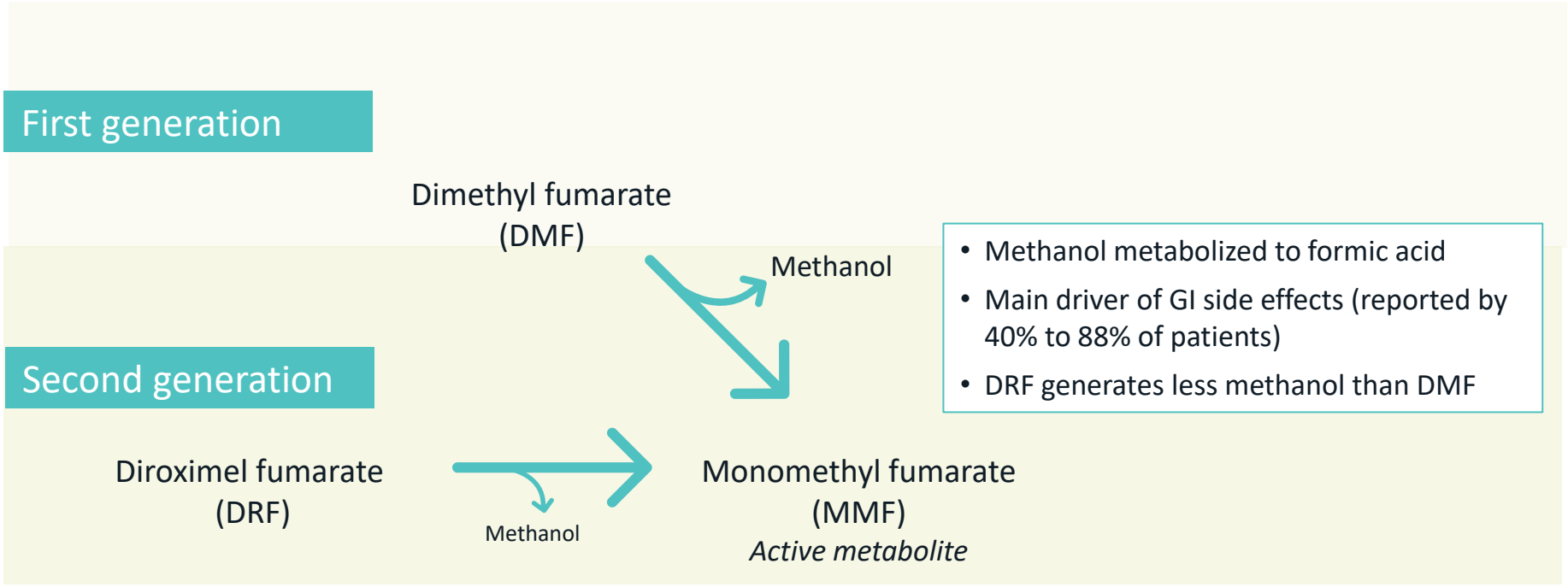
MOA=mechanism of action.
Tecfidera® (dimethyl fumarate) PI. Biogen, 2022;
Kappos L et al. *Lancet*. 2008;372:1463-1472.

Dimethyl Fumarate: Adverse Effects

- Dosage:
  - Starting: 120 mg BID PO for 7 days
  - Maintenance after 7 days: 240 mg BID PO
- Adverse events:
  - PML has been reported, but rarely
- Other side effects:
  - Generalized flushing (improves after first month)
  - GI: nausea, gas, diarrhea
  - Headache
  - Decrease in lymphocyte count

Tecfidera® (dimethyl fumarate) PI. Biogen, 2022.

Next Generation of Fumarates for MS



- Methanol metabolized to formic acid
- Main driver of GI side effects (reported by 40% to 88% of patients)
- DRF generates less methanol than DMF

- Efficacy data and FDA approvals for DRF and MMF are based on bioequivalence with DMF

Berger AA et al. *Neurol Int.* 2021;13:207-223;
Findling O, Sellner J. *Drug Discov Today.* 2021;26:416-428;
Jonasson E, Sejbaek T. *Neurodegener Dis Manag.* 2020;10:267-276;
Palte MJ et al. *Adv Ther.* 2019;36:3154-3165.

Diroximel Fumarate

Vumerity®

- Indications: Relapsing MS, active SPMS
- Dosage:
  - Starting dose 231 mg BID PO for 7 days
  - Maintenance dosage after 7 days: 462 mg (administered as two 231-mg capsules) BID PO
- Mechanism of Action:
  - Breaks down to active metabolite monomethyl fumarate (MMF,), which has been shown to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans

Vumerity® (diroximel fumarate) PI. Biogen, 2022.

Diroximel Fumarate: Adverse Effects

Common side effects:

- Flushing
- Redness, itching, rash
- Nausea, vomiting, diarrhea, stomach pain, or indigestion

Serious adverse effects:

- Allergic reaction
- PML
- Herpes zoster infections (shingles) and other serious infections
- Lymphopenia
- Liver injury

Vumerity® (diroximel fumarate) PI. Biogen, 2022.

Monomethyl Fumarate

Bafiertam®

- Not a prodrug like other two fumarates, meaning it provides active metabolite monomethyl fumarate directly without requiring gastrointestinal metabolic conversion
- Dosage:
  - Starting: 95 mg PO BID for 7 days
  - Maintenance: 190 mg PO BID after day 7

Common side effects:

- Flushing, abdominal pain, diarrhea, nausea
- Elevations in hepatic transaminases, eosinophilia adverse reactions

Serious adverse effects:

- Allergic reaction
- PML
- Herpes zoster infections (shingles) and other serious infections
- Lymphopenia
- Liver injury

Bafiertam® (monomethyl fumarate) PI. Banner Life Sciences, 2022.

CELL-TRAFFICKING DISEASE MODIFYING THERAPIES

Sphingosine 1-Phosphate Receptor (S1PR) Modulators for MS

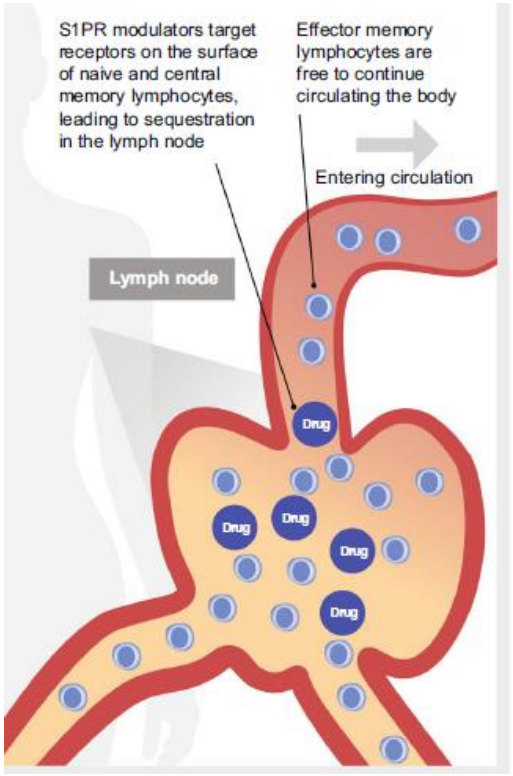
- Fingolimod (Gilenya®)
  - Reversible modulator of four S1PR subtypes
- Second-generation agents are
  - Narrower modulation of S1PR subtypes

S1PR Subtype Affinity

	S1PR1	S1PR2	S1PR3	S1PR4	S1PR5
Fingolimod	+	−	+	+	+
Siponimod	+	−	−	−	+
Ozanimod	+	−	−	−	+
Ponesimod	+	−	−	−	−

McGinley MP, Cohen JA. *Lancet*. 2021;398:1184-1194; Roy R et al. *CNS Drugs*. 2021;35:385-402.

Proposed Mechanisms of Action of S1PR Modulators in MS



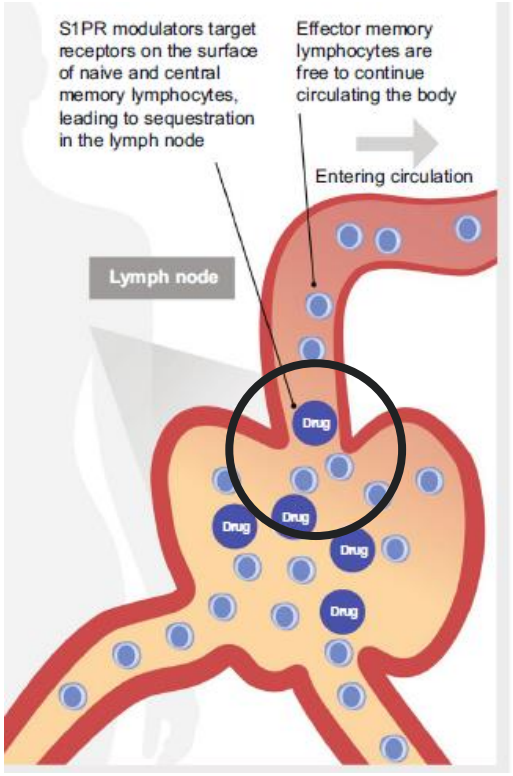
Therapeutic effects in MS

- Mainly attributed to inhibition of immune cell trafficking
  - Binding S1PR1 on a subset of lymphocytes
    - Removal of receptor from lymphocyte surface
    - Lymphocytes cannot follow S1P gradient to egress from lymph node
- Possible direct CNS effects

CNS=central nervous system.

McGinley MP, Cohen JA. *Lancet*. 2021;398:1184-1194; Roy R et al. *CNS Drugs*. 2021;35:385-402.

Proposed Mechanisms of Action of S1PR Modulators in MS (Cont.)



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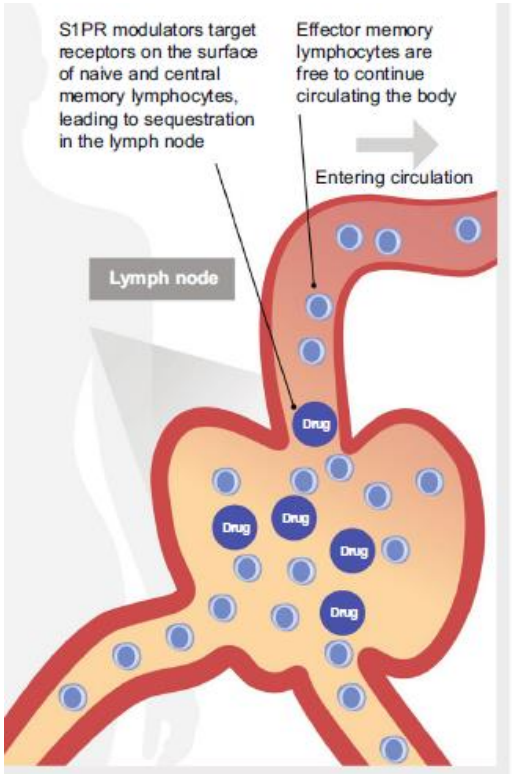

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Fingolimod

Gilenya®

- Sphingosine 1-phosphate receptor (S1PR) modulator
- Indications: Relapsing forms, active SPMS
- Dosage: 0.5 mg PO QD
  - First dose monitoring recommended for at least 6 hours
- MOA:
  - FTY720 binds to S1P receptor modulator receptors on lymphocytes
    - Circulating lymphocytes sequestered in lymph nodes
    - Thought to reduce the infiltration of reactive effector T cells and macrophages into the CNS
- Neurodegeneration/neuroprotection
  - Modulation of S1P receptors located within CNS may lead to neuroprotective effects

Gilenya® (fingolimod) PI. Novartis, 2019.

Fingolimod: Adverse Effects

- First dose bradycardia
- Macular edema
- Hypertension
- Pulmonary dysfunction (dyspnea)
- Skin cancers
- Hepatic enzyme elevations
- Cryptococcal Infections
- PML (<20 cases reported)

Gilenya® (fingolimod) PI. Novartis, 2019.

Ozanimod

Zeposia®

- Sphingosine 1-phosphate receptor (S1PR) modulator
- Indications: relapsing forms of MS, including CIS, RRMS, active SPMS
- Dosage: 0.92 mg PO QD
- Vaccination: avoid use of live attenuated vaccines during and for up to 3 months after treatment with Zeposia
- Side effects:
  - Upper respiratory infection
  - Hepatic transaminase elevation
  - Orthostatic hypotension
  - Urinary tract infection
  - Back pain
  - Hypertension

Zeposia® (ozanimod) PI. Celgene, 2022.

Ponesimod

Ponvory®

- Sphingosine 1-phosphate receptor (S1PR) modulator
- Indications: relapsing forms of MS, including CIS, RRMS, active SPMS
- Dosage:
  - Titration is required for initiation
  - Recommended maintenance dosage: 20 mg PO QD
  - First-dose monitoring is recommended for certain patients
- Vaccination: avoid use of live attenuated vaccines during and for up to 2 weeks after treatment
- Side effects:
  - Upper respiratory tract infections
  - Hepatic transaminase elevations
  - Hypertension
  - Bradyarrhythmia and atrioventricular conduction delays
  - Cutaneous malignancies
  - Fetal risk
  - Macular edema

Ponvory® (ponesimod) PI. Janssen Pharmaceuticals, 2021.

Siponimod

Mayzent®

- Sphingosine 1-phosphate receptor (S1PR) modulator
- Indications: relapsing forms of MS, including CIS, RRMS, active SPMS
- Dosage:
  - Titration is required for initiation
  - Recommended maintenance dosage: 2 mg PO QD
  - First-dose monitoring is recommended for certain patients
- Vaccination: avoid use of live attenuated vaccines during and for up to 4 weeks after treatment
- Side effects:
  - Headache
  - Hypertension
  - Hepatic transaminase elevations
  - Infections
  - Macular edema
  - Bradyarrhythmia and atrioventricular conduction delays
  - Respiratory effects
  - Liver injury
  - Cutaneous malignancies
  - Fetal risk

Mayzent® (siponimod) PI. Novartis Pharmaceuticals Corporation, 2022.

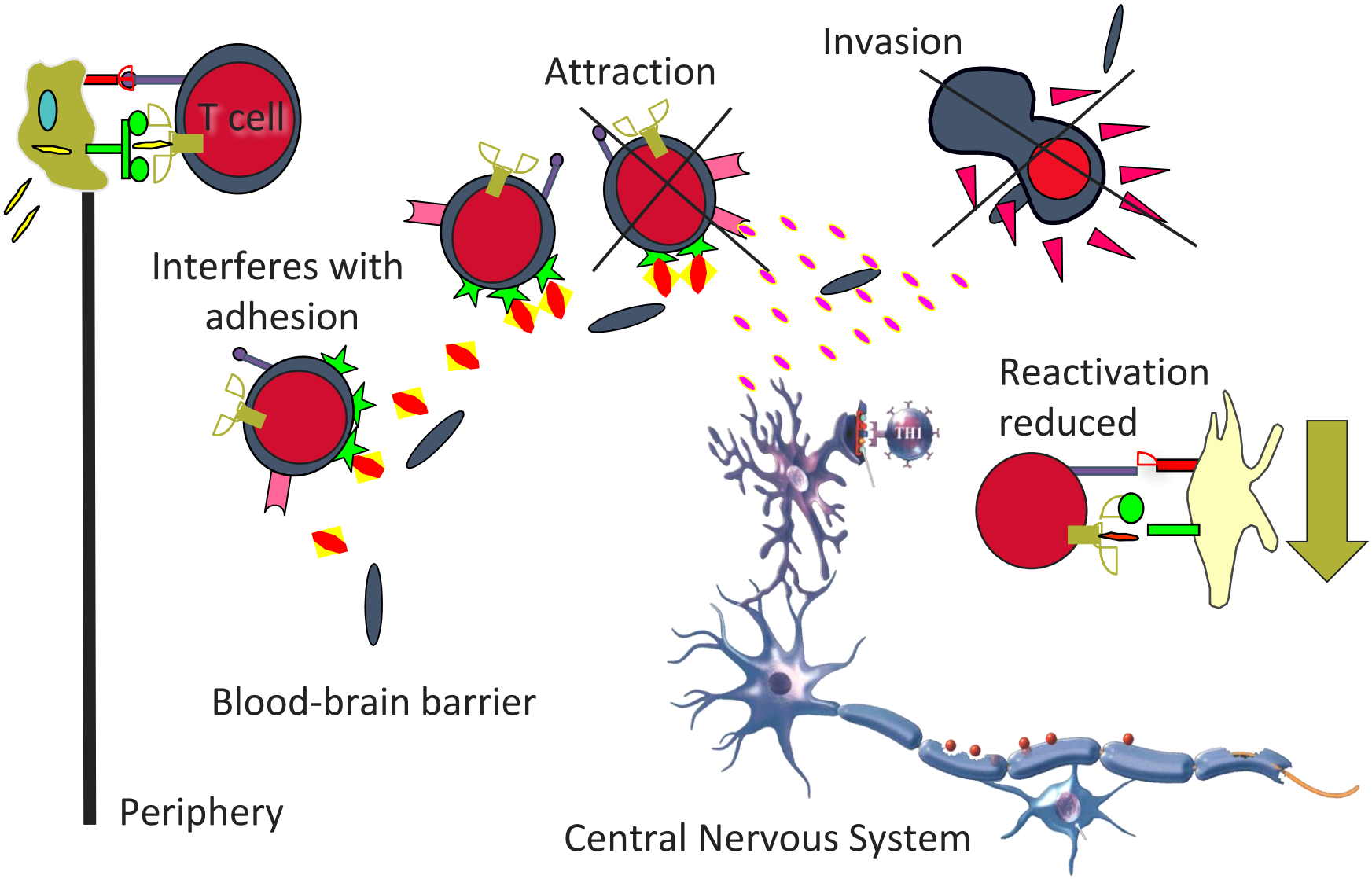
Natalizumab

Tysabri®

- Indications: relapsing MS, active SPMS
- Dosage: 300 mg Q4W IV
- MOA: monoclonal antibody directed against α 4-integrin (adhesion molecule expressed by LKCs)
  - Blocks T-cell migration into the CNS
  - May block T-cell activation in the CNS
- Reduction of gadolinium-enhancing lesions and T2 lesions
- Only available through TOUCH REMS Program

REMS=risk evaluation and mitigation strategy.
Tysabri® (natalizumab) PI. Biogen Inc., 2021.

Natalizumab Mechanism of Action



Natalizumab: Adverse Effects

- **Hypersensitivity reactions:** urticaria +/– systemic signs and symptoms, edema/swelling; rashes; difficulty breathing; angioedema; cardiac symptoms
- **Infusion reactions:** headache, nausea, diaphoresis, dizziness, fatigue, rigors
- **Hepatotoxicity:** elevated liver function tests
- **PML, most serious risk and consideration:**
  - Risk=0.01% for JCV– patients and ≤0.7% for JCV+ patients out to 8 years
  - Personality or behavioral changes, changes in thinking, seizure, disturbance in vision, hemiparesis

JCV=John Cunningham virus.

Tysabri® (natalizumab) PI. Biogen Inc., 2021.

CELL DEPLETING (B-CELL TARGETED) DISEASE MODIFYING THERAPIES

Therapeutic Monoclonal Antibodies

Mouse mAb	Chimeric mAb	Humanized mAb	Human mAb
			
-momab	-ximab	-zumab	-mumab
Not evaluated in MS	Rituximab (used off label in MS)	Alemtuzumab Natalizumab Ocrelizumab	Ofatumumab

Decreasing frequency of infusion reactions

Blue: protein sequences of murine origin; green: protein sequences of human origin.
Brück W et al. *JAMA Neurol*. 2013;70:1315-1324.

Alemtuzumab

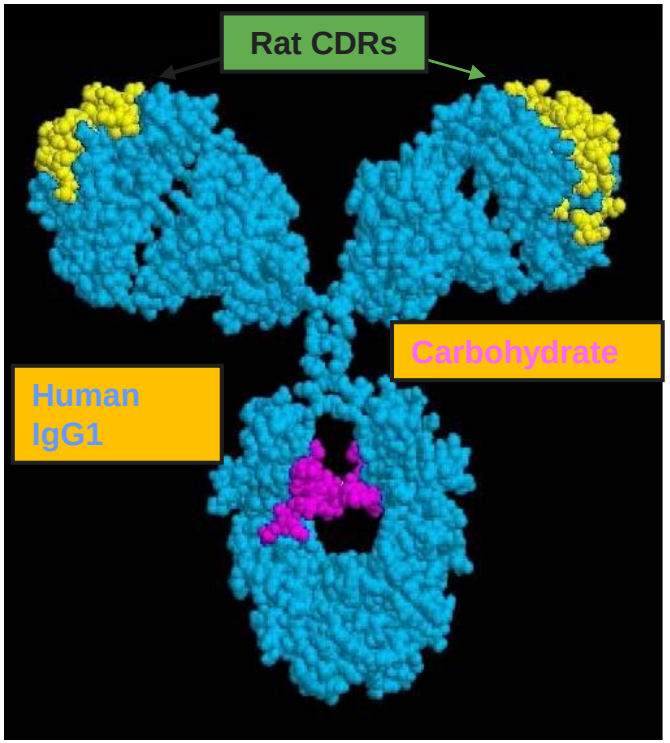
Lemtrada®

- Only available under the LEMTRADA REMS program
- Indications: Relapsing MS, active SPMS
- Generally reserved for patients who have had inadequate response to ≥2 other DMTs due to potential for severe and even life-threatening adverse events
- Dosage:
  - Year One: 12 mg/day IV on 5 consecutive days
  - Year Two: 12 mg/day on 3 consecutive days
  - 50% of patients do not need further treatment at 6 years

Lemtrada® (alemtuzumab) PI. Genzyme Corporation, 2022.

Alemtuzumab Mechanism of Action

- **Humanized monoclonal antibody directed at CD52** (an antigen found on T lymphocytes, B lymphocytes and monocytes)
- Cytolytic effect - reduces circulating:
  - T-cells
  - B-cells
  - Natural killer cells



Muraro P et al. *Neurotherapeutics.* 2007;4:676-692; Coles A et al. *J Neurol.* 2006;253:98-108.

Alemtuzumab: Adverse Effects

- Autoimmune disease
  - ITP (2%), Good Pasture's (0.3%), thyroid disease (36%)
- Stroke and cervicocephalic arterial dissection
- Immunosuppression
  - Risk of infection
  - Potential of malignancy
- Infusion reactions (3% have serious reactions)
- Common Side Effects
  - Rash, headache, pyrexia, nasopharyngitis, nausea, UTI, fatigue, insomnia, URI, herpes viral infection, urticarial, pruritus, thyroid disorders, fungal infection, arthralgia, pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, vomiting

ITP=immune thrombocytopenia.

Lemtrada® (alemtuzumab) PI. Genzyme Corporation, 2022.

Ocrelizumab

Ocrevus®

- Humanized antibody to CD20
- MOA: Binds to CD20 found on surface of B cells causing cell lysis, leading to dose-dependent depletion of B cells
- Indications: Only DMT approved for relapsing forms of MS, active SPMS, and PPMS
- Dosage:
  - Starting: 300 mg IV, followed 2 weeks later by a second 300-mg IV infusion
  - Maintenance: 600 mg IV Q24 weeks

Ocrevus® (ocrelizumab) PI. Genentech, Inc., 2021.

Ocrelizumab: Safety, Tolerability, and AEs

- Infusion reactions, but responsive to pre-dose steroids, antihistamines, and slowing infusion if needed
- Upper respiratory tract infections, skin infections, and lower respiratory tract infections were common adverse reactions in both RMS and PPMS patients
- Delay administration in patients with an active infection until the infection is resolved
- Vaccination with live attenuated or live vaccines is not recommended during treatment and after discontinuation, until B cell repletion
- Malignancies: An increased risk of malignancy, including breast cancer, may exist with ocrelizumab

AEs=adverse effects.

Ocrevus® (ocrelizumab) PI. Genentech, Inc., 2021.

Ofatumumab

Kesimpta®

- Indications: relapsing MS, active SPMS
- Dosage:
  - 20 mg SC at weeks 0, 1, 2
  - 20 mg SC monthly starting at week 4
- Adverse effects:
  - Upper respiratory tract infections
  - Injection-site reactions (systemic and local)
  - Headache
  - Urinary tract infection
  - Back pain
  - Decreased immunoglobulin in blood

Kesimpta® (ofatumumab) PI. Novartis, 2020.

Ofatumumab Mechanism of Action

- Selectively binds to sites on both small and large extracellular loops of CD20
- Makes CD20+ B cells vulnerable to immediate and delayed B-cell lysis by mechanisms such as complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity
- Delivered subcutaneously, appears to promote preferential depletion of B cells in lymph notes
- May spare B cells in spleen that help maintain immune function

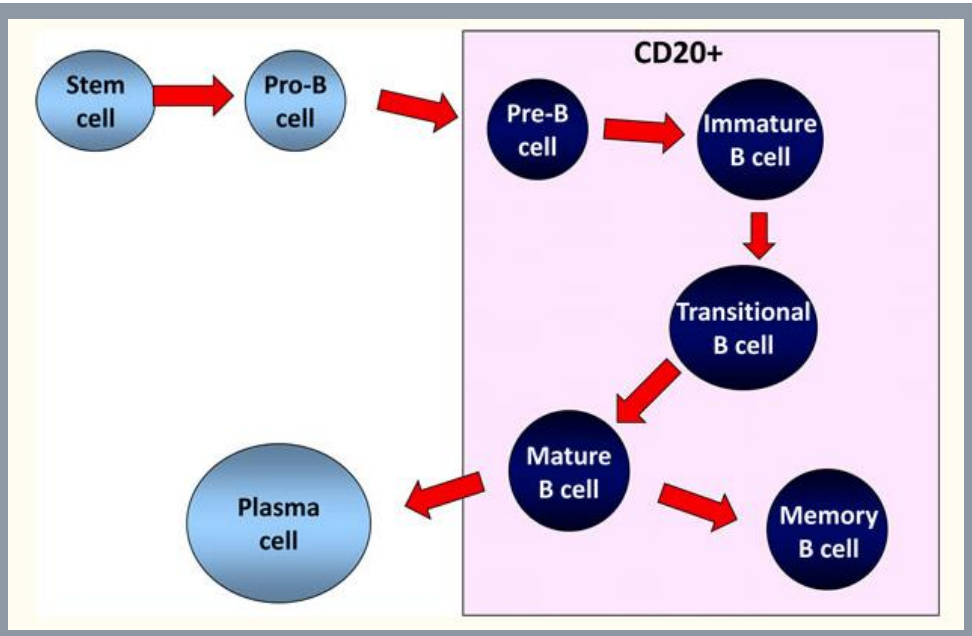
Kesimpta® (ofatumumab) PI. Novartis, 2020.

Ofatumumab

- Infections and vaccines
  - Delay administration if patient has active infection
  - Administer any needed live or live-attenuated vaccines at least 4 weeks prior to initiation and any inactivated vaccines at least 2 weeks prior
  - Immunization with live or live-attenuated vaccines not recommended during treatment and after discontinuation until B cell repletion
- Increased risk for new and reactivated infections due to immunosuppression
- Fetal risk

Kesimpta® (ofatumumab) PI. Novartis, 2020.

Ocrelizumab, Ofatumumab, and Ublituximab Target CD20 Surface Antigen on Pre-B and Mature B Lymphocytes



- Ocrelizumab's epitope binding overlaps with rituximab's; ofatumumab binds two novel epitopes

Figure reproduced from Leandro MJ. *Arthritis Res Ther.* 2013;15 Suppl 1:S3 under Creative Commons License (CC BY 2.0); Florou D et al. *Brain Sci*. 2020;10:758; Briumvi PI. TG Therapeutics, Inc. 2022.

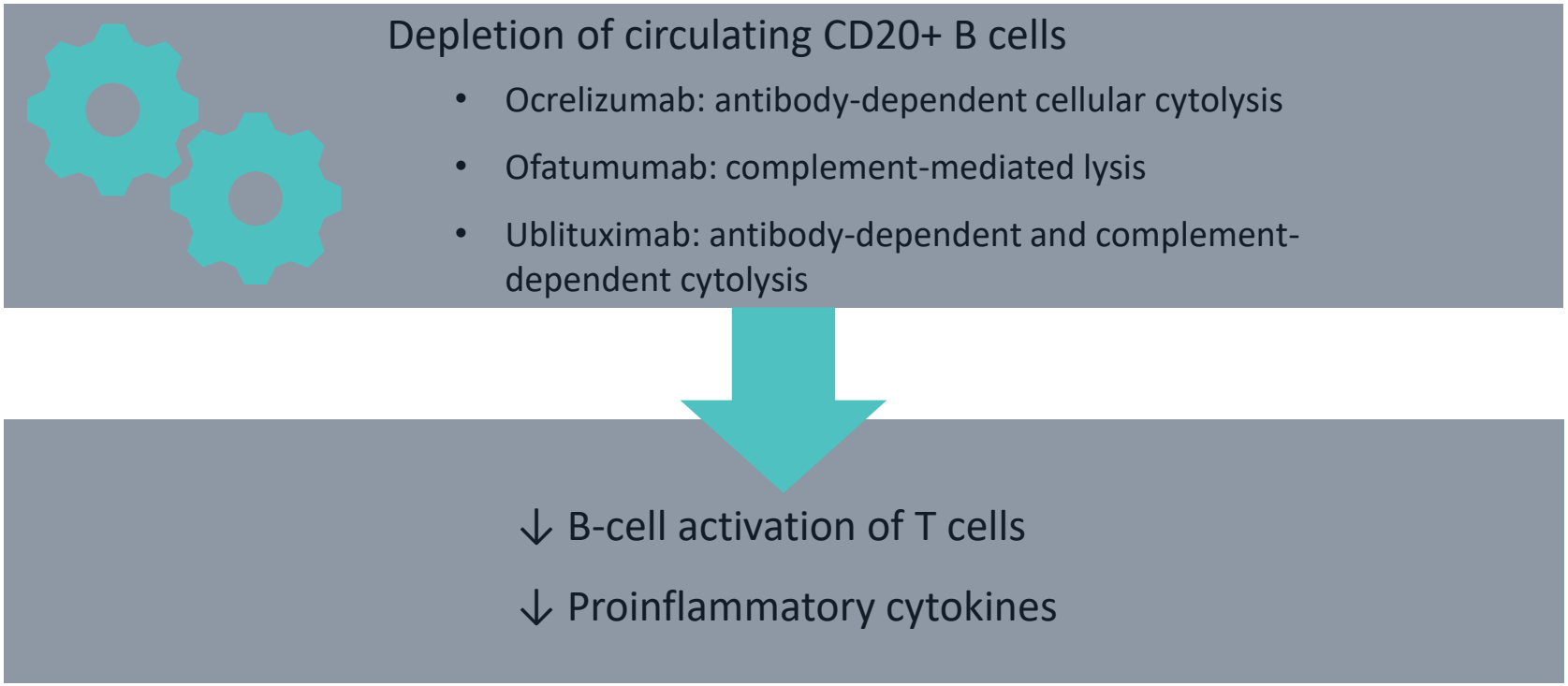
Ublituximab

Briumvi®

- Newest DMT to be approved by the FDA (December 2022)
- Indications: relapsing MS, active SPMS
- Dosage:
  - 150 mg IV to start
  - 450 mg IV 2 weeks after first dose
  - 450 mg IV Q 24 weeks after first dose
- Adverse effects:
  - Infusion reactions
  - Upper and lower respiratory tract infections
  - Herpes virus-associated infections
  - Pain in extremity
  - Insomnia
  - Fatigue

Briumvi® (ublituximab) PI. TG Therapeutics, Inc. 2022.

Ocrelizumab, Ofatumumab, and Ublituximab: Proposed Mechanism of Action



Mulero P et al. *Ther Adv Neurol Disord.* 2018;11:1756286418773025;
Memon AB et al. *PLoS One*. 2018;13:e0190425;
Florou D et al. *Brain Sci*. 2020;10:758.
Briumvi PI. TG Therapeutics, Inc. 2022.

Cladribine

- Mavenclad®
- Indications: relapsing MS (but not CIS) and active SPMS
- Dosage: administered as 2 treatment courses over 2 years
  - Cumulative dose of 3.5/kg, given as 1.75/kg per year
- Treatment course:
  - 4–5 consecutive days of dosing in first week and then another 4–5 consecutive days of dosing 1 month later
- MOA: selectively targets and accumulates in certain types of white blood cells (T and B lymphocytes) by interfering with target cell's ability to process DNA

Mavenclad®(cladribine) PI. EMD Serono, 2019.

Oral Cladribine: A Formulation For MS

- Synthetic purine nucleoside analog
  - Interferes with DNA synthesis
  - Depletes resting and proliferating lymphocytes

Originally developed for hematological malignancies → Early studies in MS IV administration promising → Oral formulation approved for MS with a short-course, limited-cycle dosing schedule

Oral cladribine (Mavenclad®) indication, per US FDA labeling

- Relapsing forms of MS, including RRMS and active SPMS, in adults
- Because of its safety profile, use of oral cladribine is generally recommended for patients with inadequate response or intolerance to an alternate drug indicated for the treatment of MS
- Not recommended for use in patients with CIS because of its safety profile

CIS=clinically isolated syndrome.

Giovannoni G. *Neurotherapeutics.* 2017;14:874-887; Rammohan K et al. *Drugs*. 2020;80:1901-1928; Mavenclad (cladribine) PI. EMD Serono, Inc, 2019.

Proposed Mechanisms of Action of Cladribine in MS

- Activated upon intracellular phosphorylation
- Active metabolite accumulates within cells, disrupting DNA synthesis, causing death in rapidly reproducing cells
- Preferentially affects lymphocytes (ie, adaptive immune system)
  - B cells depleted to a greater extent than T cells, although with faster recovery
  - Innate immune cells (eg, NK cells and monocytes) depleted to a lesser extent
- May have other immune effects independent of cell depletion

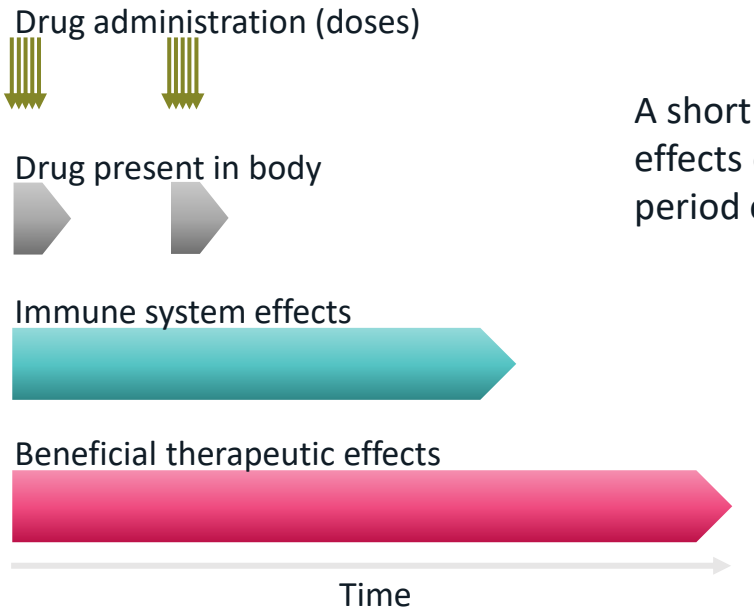
Clinical effects are thought to be mediated, at least in part, by the transient reduction of selective lymphocyte subtypes, followed by a recovery period during which cell subtype ratios are altered, resulting in a reduction in autoreactive lymphocytes

NK=natural killer.

Giovannoni G. *Neurotherapeutics.* 2017;14:874-887;
Jacobs BM et al. *J Neurol Neurosurg Psychiatry.* 2018;89:1266-1271;
Rammohan K et al. *Drugs.* 2020;80:1901-1928.

Oral Cladribine as Pulsed Immune Reconstitution Therapy (IRT)

General Principles of IRT



A short course of treatment produces effects on disease activity that outlast period of immune suppression

Sorensen PS, Sellebjerg F. *Ther Adv Neurol Disord.* 2019;12:1756286419836913;
AlJumah M et al. *Neurol Ther.* 2020;9:11-23.

Cladribine: Adverse Effects

- Common side effects
  - Upper respiratory infection, headache, lymphopenia (infections), nausea
- More serious adverse effects
  - Tuberculosis
  - Herpes viral infection
  - Potential increase in cancers
  - Hematologic toxicity
  - Liver injury
  - Risk of teratogenicity

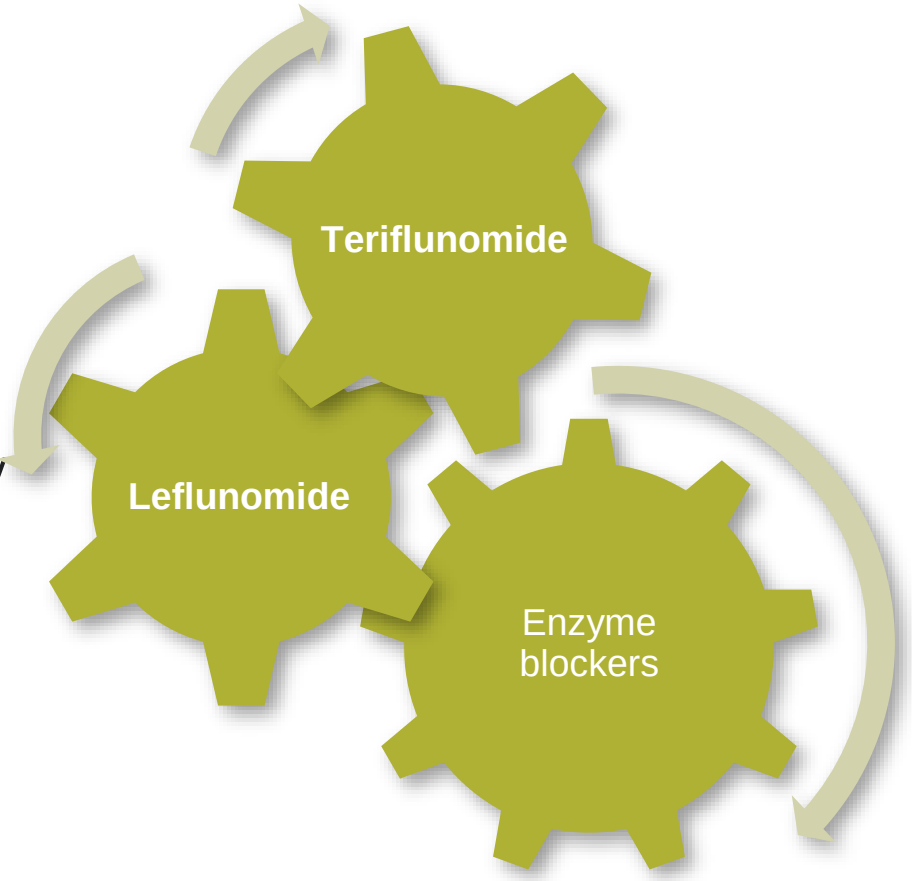
Mavenclad®(cladribine) PI. EMD Serono, 2019.

CELL REPLICATION/PROLIFERATION DISEASE MODIFYING THERAPIES

Teriflunomide

Aubagio®

- Immunosuppressive enzyme blocker
- Indications: relapsing MS, active SPMS
- Dosage: 7 or 14 mg PO QD
- MOA: Inhibitor of dihydro-orotate dehydrogenase, enzyme necessary to pyrimidine synthesis and essential in production of DNA and RNA
  - Inhibits rapidly dividing cells, such as T and B cells
- Parent compound leflunomide (Arava®) used in treatment of rheumatoid arthritis



Aubagio® (teriflunomide) PI. Genzyme, 2021.

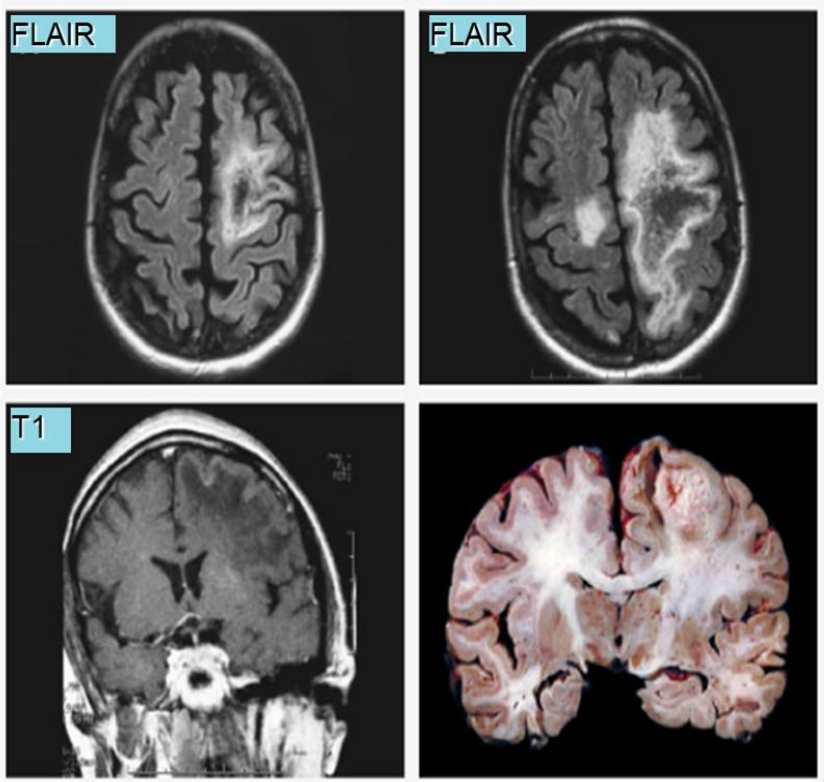
Teriflunomide: Adverse Effects

- Elevated liver enzymes/risk of liver dysfunction
  - Monthly LFTs for at least 6 months
- Teratogenic for men and women
  - Pregnancy category: X
- Hair thinning (13% reported in trial)
- Lymphopenia-rare
- Slow excretion, not dialyzable
  - 8–24 months after discontinuation for plasma levels to be undetectable
  - Accelerated elimination is available
    - Cholestyramine 4–8 gm, po q 8 hours x 11 days
    - Activated charcoal 50 gm po q 12 hours x 11 days
- Other side effects
  - GI side effects (nausea, diarrhea)
  - Headache

Aubagio® (teriflunomide) PI. Genzyme, 2021.

IMPORTANT CONSIDERATIONS

Major Side Effect of Certain DMTs: PML



- Rare, progressive viral brain disease
- Mostly affects immuno-compromised patients (HIV, transplant, hematologic malignancy)
- Caused by JC virus
- Linked to use of certain DMTs
- Clinical suspicion: gradual onset of personality changes, aphasia, visual field loss, neglect
- Spinal tap: analysis of CSF for JC virus
- MRI: characteristic findings distinguish from MS
- No known cure

CSF=cerebrospinal fluid.

Sriwastava S et al. *J Neuroimmunol.* 2021;360:577721.

Immunizations and DMTs

- Currently no consensus on guidelines, but like other conditions where treatment can cause persistent immunosuppression, consideration should be given to the following immunization recommendations:
  - Obtain varicella zoster virus (VZV) serology
    - Vaccine recommended if VZV negative
  - Screen for tuberculosis with Mantoux skin testing or quantiferon gold serum test
  - Consider immunizations as recommended by CDC, AAN, and NMSS

AAN=American Academy of Neurology; CDC=Centers for Disease Control and Prevention; NMSS=National MS Society.

Vaccines for People with MS

The following vaccines are considered safe and effective to recommend
Chickenpox (varicella)
COVID-19
Flu (inactivated formulations only)
Human papillomavirus
Hepatitis B
Measles-Mumps-Rubella (MMR)*
Pneumonia
Polio
Shingles
Smallpox/Monkeypox
Tetanus
Tuberculosis (Bacillus Calmette-Guerin)

*Should not be given to people on immunosuppressants.

American Academy of Neurology. Practice Guideline Update Summary: Vaccine-preventable Infections and Immunization in Multiple Sclerosis. 2019; Centers for Disease Control and Prevention. Adult Immunization Schedule by Vaccine and Age Group. 2022; Mailand MT, Frederiksen JL. *J Neurol.* 2017;264:1035-1050; National MS Society. Vaccinations.

FDA Recommendations for Use of DMTs in Pregnancy and Breastfeeding

	Pregnancy and Breastfeeding
Interferon-β	• No clear relationship between use and major congenital malformations • Animal data: may cause fetal harm
Glatiramer acetate	• Human data: not sufficient to support conclusions about drug-associated risk for major birth defects and miscarriage
Monoclonal antibodies	• Animal data: may cause fetal harm
Fumarates	• Animal data: may cause fetal harm • Fumarates appear to be safe to use while breastfeeding
S1PR modulators	• Animal data: may cause fetal harm • Females of reproductive potential should use effective birth control during treatment and after stopping treatment (from 1 week to 2 months for different S1PR modulators)
Pyrimidine synthesis inhibitors	• Contraindicated for use in pregnant women and in females of reproductive potential who are not using effective contraception because of the potential for fetal harm
Purine antimetabolite	• Contraindicated for use in pregnant women and in women and men of reproductive potential who are not using effective contraception because of the risk of fetal harm • It is unknown if it passes into breast milk. Do not breastfeed on the days, during treatment, and for 10 days after the last dose

GA=glatiramer acetate; S1PR=sphingosine-1-phosphate receptor.

https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-The-MS-Disease-Modifying-Medications.pdf; Drugs.com, Dimethyl fumarate while breastfeeding, 2022.

Incorporating Patient Preferences: Family Planning and Supportive Healthy Choices

Initial counseling on family planning[1]

- Therapeutic choice at diagnosis should consider desire for family in the future, whenever possible[1,2]
- MS is not directly transmitted to offspring: child of 1 parent with MS has 2% risk of MS
- Delay of 1 year to assess evolution of MS and response to therapy
  - Stable disease is best for beginning pregnancy
  - 3-month washout period before pregnancy recommended for all DMTs except GA[3]
- Counseling includes both parents and discusses responsibilities in light of MS activity and severity

Supportive healthy choices[1]

- Correct vitamin D deficiency with supplementation (1000–2000 IU/day)
  - Maternal levels <12.0 ng/mL during pregnancy increased offspring's risk of MS by 200%
- Ensure sufficient folate or include folic acid supplementation (0.4–1 g daily)
- Cessation of smoking
- Adequate sleep (7–9 hours)
- Physical activity (exercise)[3]

1. Amato MP et al. *Neurol Sci*. 2017;38:1849-1858;
2. Pozzilli C et al. *Neurol Neuroimmunol Neuroinflamm*. 2015;2:e120;
3. McGinley MP et al. *JAMA*. 2021;325:765-779.

Treatment Decisions for Individual MS Patients

Combine assessment of disease activity, risk for aggressive MS, and patient preferences[1]

Considerations for escalation approach

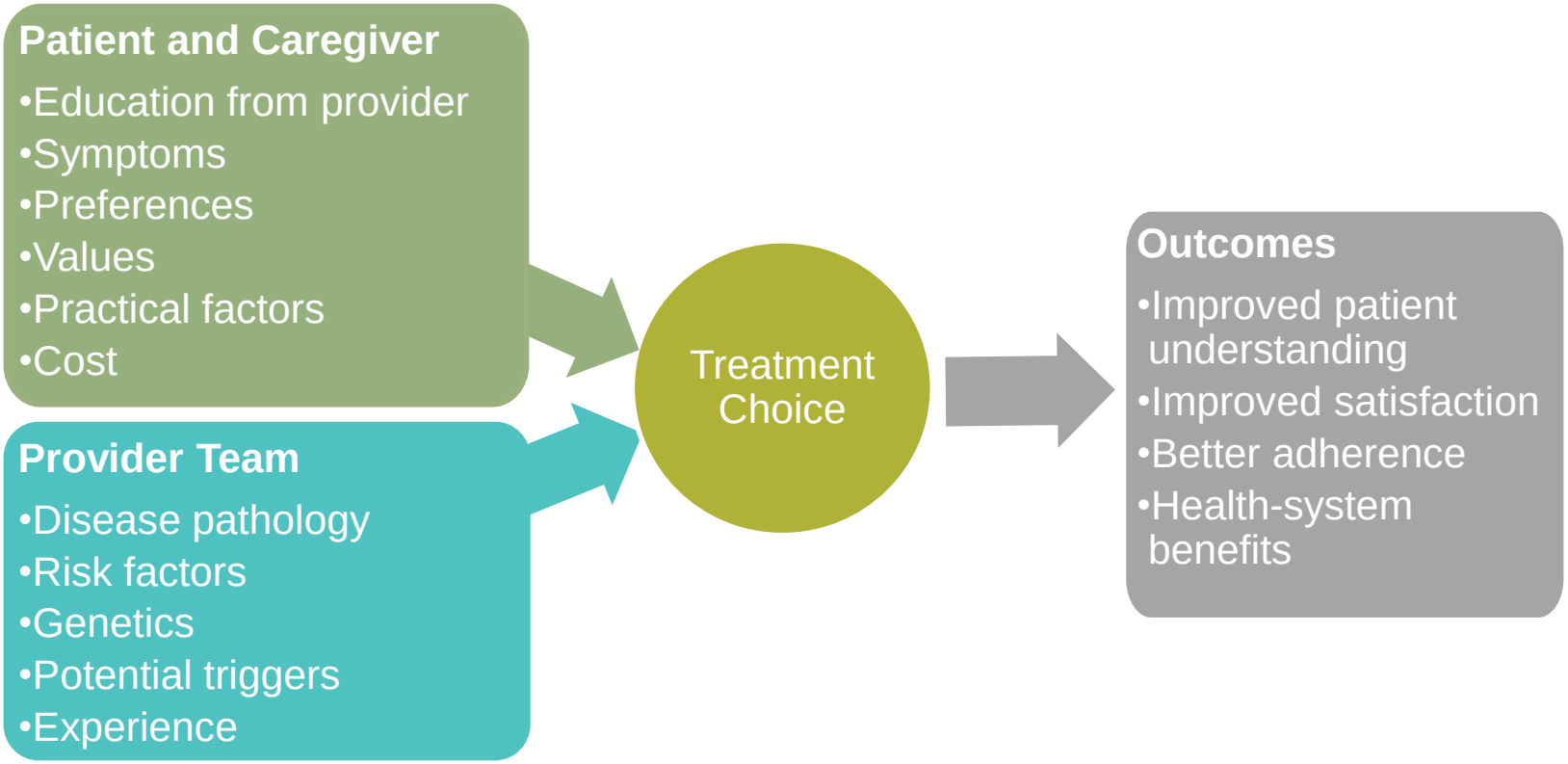
- Lower risk for aggressive MS[1]
  - <9 brain lesions, no spinal cord lesions, good cognitive function and mobility, monofocal presentation
- Interested in planning for family[2]
- Infection risk in home and/or work environments
- Patient's willingness to incorporate supportive healthy choices
- Patient lower risk tolerance for adverse events

Considerations for initial more potent therapy

- Several risk factors for aggressive MS[3]
  - Spinal cord lesions, multifocal presentation, frequent relapses, incomplete recovery, reduced cognition, hospitalization, reduced mobility
- Low infection risk in home and work environments
- Patient's desire for more potent therapy and tolerance of risks

1. Moisset X et al. *Eur J Neurol*. 2021;28:2026-2036;
2. Amato MP et al. *Neurol Sci*. 2017;38:1849-1858;
3. Bowen JD. *Continuum (Minneap Minn).* 2019;25:689-714.

Shared Decision-making



"The more patients are involved in shared decision-making, the more likely they will be adherent to the therapy and lifestyle recommendations we might be making for them."[1]

1. Ross AP. *Pract Neurol*. April 2017;
2. Day GS, et al. *Neurol Clin Pract*. 2018;8:179-185.

Discussing DMT with Patients/Caregivers

- Patients' goals often differ from clinicians'[1]
  - Feeling better, keeping their jobs, and caring for their families
- Provide realistic and accurate information
- Discuss new/emerging therapies as appropriate
- Avoid rushing into DMT immediately after diagnosis; give patient time to clearly decide
- Explore reasons for nonadherence
- Patients may need more in-depth discussion at DMT switch[2]

1. Ross AP. *Pract Neurol*. April 2017;
2. Manzano A, et al. *Mult Scler Relat Disord*. 2020;46:102507.

Nursing Implications

- Acute and long-term management of relapses and the disease itself requires nursing knowledge and vigilance
- We have entered a new era of complex choices that challenges the professional community with the need to keep current and constantly updated
- Patient and family education is essential to understanding and follow-through needed for all treatment options

Conclusion

- Focus of MS disease management is to reduce relapses, address symptoms, slow progression, and improve patient's quality of life
- Treatment of relapses is individualized
- Goals of disease modifying therapy are to:
  - Reduce frequency and severity of relapses
  - Suppress lesion activity
  - Delay disease progression