Disease Management:

Acute Relapses & Disease-Modifying Therapies

IOMSN

International Organization of Multiple Sclerosis Nurses

Goals of Disease Management

- Reduce relapses and slow progression
- Treat serious relapses
- Manage symptoms
- Improve quality of life

Relapses and Relapse Management

Definition of MS Relapse

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

Ontaneda, Rae-Grant. *Ann Indian Acad Neurol*. 2009;12(4):264

MS Relapses

- **Onset of neurological symptoms that evolve over days to weeks**
- **Plateaus within 1 to 2 weeks**
- **Recovery 4 to 12 weeks**
  - Depends on severity
  - Some symptoms persist and become permanent

Wingerchuk, D. CMSC 2007; Presentation: Impact of Acute Attacks

Common Symptoms of MS Relapses

- **Spinal cord/Myelitis 50%**
  - Partial sensory or motor (sensory more common)
  - Band like abdominal or chest sensation
  - Bowel and bladder dysfunction common
- **Optic Neuritis 25%**
  - Typically unilateral, painful
  - Retrobulbar (no retinal exudates or disc swelling)
- **Brainstem 15%**
  - Ocular motor syndrome
    - Intranuclear ophthalmoplegia (INO)
  - Trigeminal neuralgia

O'Riordan et al. *J Neurol Neurosurg Psychiatry.* 1998; Frohman et al. *Neurotherapeutics*. 2007.

Pseudo-Relapses

- **Transient worsening or return of neurological symptoms that can be attributable to environmental, systemic or other influences:**
  - Increased core or environmental temperature
  - Physical exertion
  - Fatigue
  - Systemic illness
  - Stress/anxiety
  - Medications/alcohol use
  - Menstrual cycle

O'Connor P. Multiple Sclerosis: The Facts You Need to Know. 4th edition (2009). Canadian Medical Association.

Management of Relapses

- **First: Determine if acute relapse, pseudo-relapse or disease progression**
  - Onset/evolution of symptoms
  - Contributing factors ruled out
- **Severity of relapse**
  - Impact on function/role
  - Continued worsening
- **Determine if treatment of relapse is required**

Corticosteroid Treatment

- **Treatment options ***
  - High dose
    - IV Methylprednisolone (MP): 1g/day for 3-5 days
    - Oral MP: 500mg-1g for 3-5 days
    - Oral Prednisone 1250mg daily or q2d 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

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

Beck et al. *NEJM.* 1992; Beck et al. *NEJM*.1993; Beck. *Arch Ophthalmol*. 1995; O'Connor. Multiple Sclerosis: The Facts You Need to Know. 4th edition (2009). Canadian Medical Association.

Adverse Effects of Corticosteroids

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

Metz et al. *Neurology.* 1999; Sellebjerg and the EFNS guidelines. *Eur J Neurol.* 2005; Leary et al. *Postgrad J Med.* 2005.

Non-Pharmacologic Relapse Management

- **Rehabilitation**
  - Severity and duration of relapse
  - 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

Craig et al. *J Neurol Neurosurg Psychiatry.* 2003;74:1225

Disease Modifying Treatments

Disease Modification

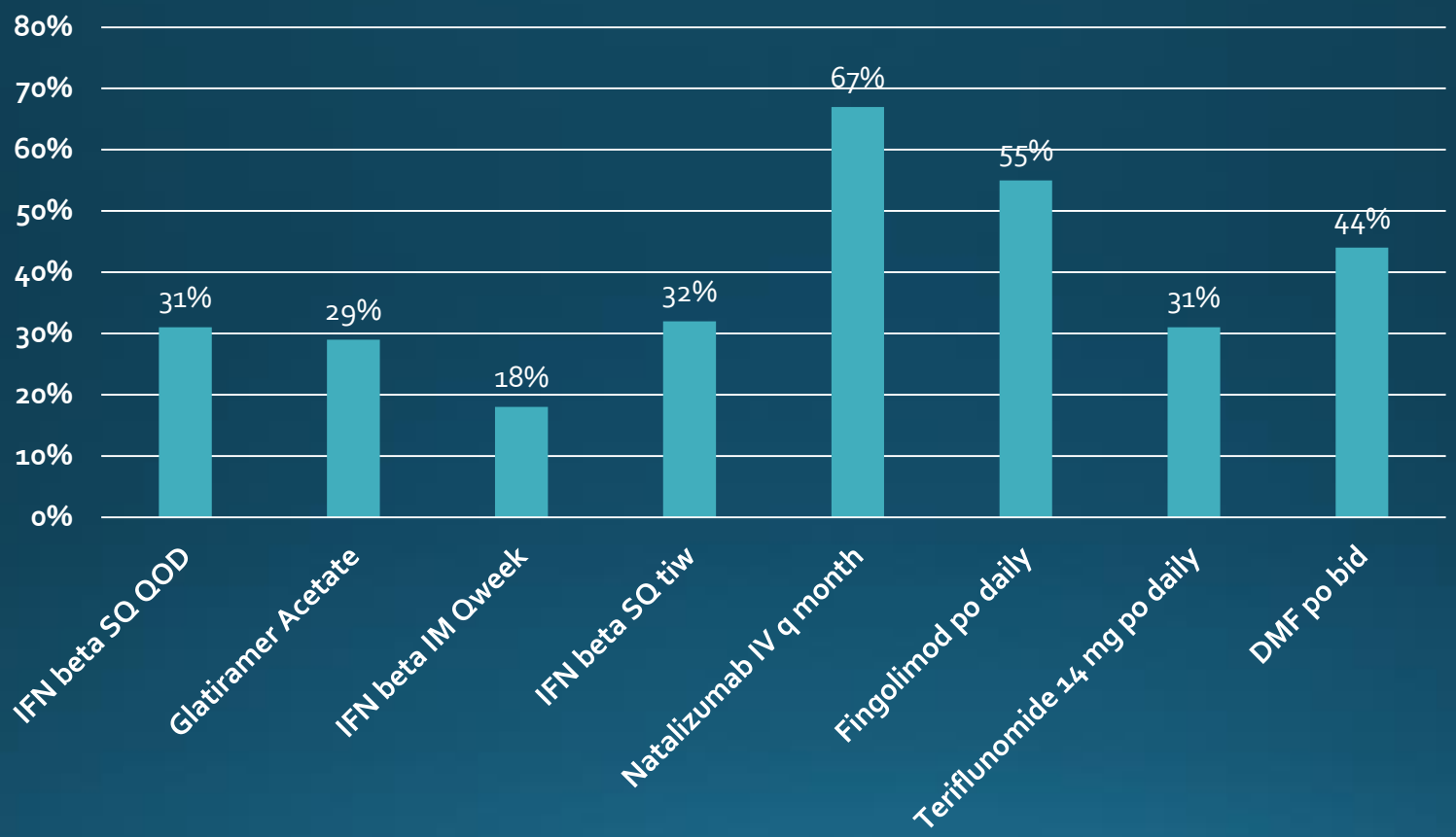
- Aim to alter the natural course of the disease
- Reduce frequency and severity of relapses
- Suppress magnetic resonance imaging (MRI) lesion activity and reduce new T2 lesions
- May delay disease progression

Noseworthy JH et al. *N Engl J Med*. 2000;343:938-952.

Current FDA - Approved MS DMTs

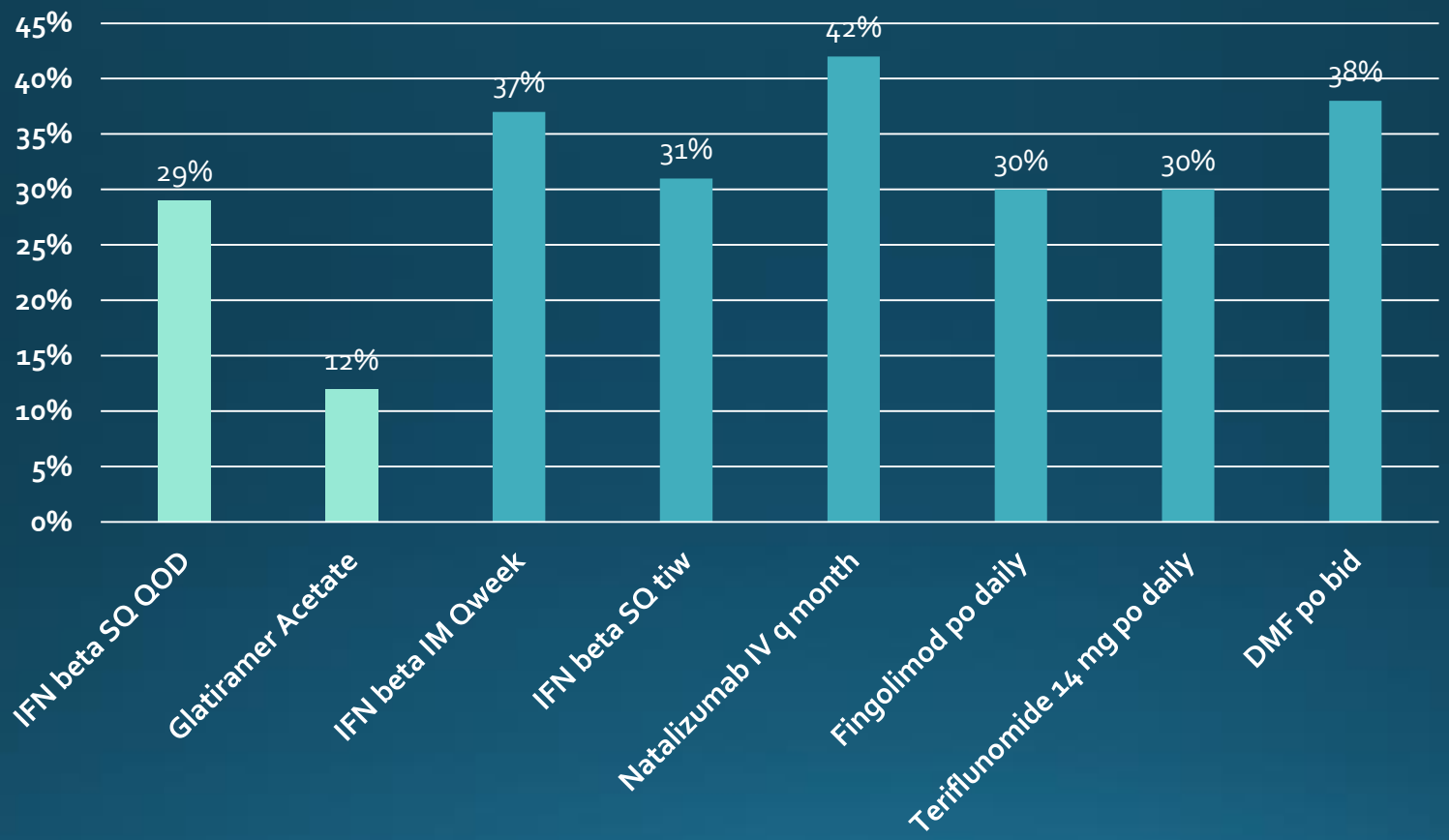
Year	Agent	Route
1993	Interferon beta-1b	SC QOD
1996	Interferon beta-1a	IM QW
1996	Glatiramer Acetate	SC QD
2000	Mitoxantrone	IV Q 3 Mo
2002	Interferon beta-1a	SC tiw
2004	Natalizumab	IV Q Mo
2010	Fingolimod	PO QD
2012	Teriflunomide	PO QD
2013	Dimethyl Fumarate	PO BID
2014	Glatiramer Acetate	SC 3-times-weekly

Non-comparative Relapse Rates



The IFNB MS Study Group. *Neurology*. 1995; 45:1277-85; Johnson KP et al. *Multiple Sclerosis.* 2000; 6:255-66; Jacobs LD et al. *Ann Neurol*. 1996; 39:285-94; *Lancet*. 1998;352:1498-1504; Polman CH et al. *NEJM.* 2006; 354:899-910; Kappos L et al. *NEJM.* 2010:362:387-401; O'Connor et al. *NEJM.* 2011;365: 1293-1303; Fox et al. *NEJM*. (2012) 367, 1087-1097.

Non-comparative Reduction in Sustained Disability



The IFNB MS Study Group. *Neurology*. 1995; 45:1277-85; Johnson KP et al. *Multiple Sclerosis*. 2000; 6:255-66; Jacobs LD et al. *Ann Neurol*. 1996; 39:285-94; *Lancet*. 1998;352:1498-1504; Polman CH et al. *NEJM*. 2006; 354:899-910; Kappos L et al. *NEJM*. 2010:362:387-401; O'Connor et al. *NEJM*. 2011;365: 1293-1303; Fox et al. *NEJM.* (2012) 367, 1087-1097.

Disease Modifying Agents

IFN β-1b	IFN β-1a	Glatiramer Acetate
▪ Flu-like symptoms		▪ Injection site reactions
▪ Injection site reactions		▪ Post-injection reaction†
▪ Headaches		▪ Vasodilation
▪ Allergic reactions		▪ Pregnancy category B
▪ Depression		
▪ ↑ Liver enzymes		
▪ ↓ WBC		
▪ Thyroid function		
▪ Neutralizing antibodies		
▪ Mild anemia		
▪ Pregnancy category C		

† Includes chest pain, anxiety, palpitations, shortness of breath, and flushing; WBC: white blood cell count

Avonex® (IFN beta-1a) [PI]. Cambridge, MA: Biogen Idec Inc; 1996-2012; Betaseron® (IFN beta-1b) [PI]. Bayer HealthCare Pharmaceuticals, Inc.; 2014; Copaxone® (glatiramer acetate) [PI]. Teva Neuroscience, 2014; Extavia® (IFN beta-1b) [PI]. Novartis Pharmaceuticals, 2012; Rebif® (IFN beta-1a) [PI]. EMD Serono, Pfizer, 2013; Hilas et al. *Open Neurol J*. 2010;4:15-24.

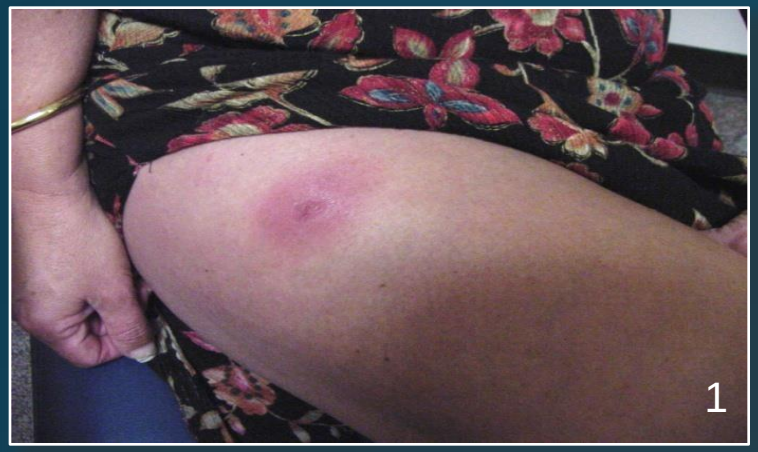
Adverse Effects Beta Interferons

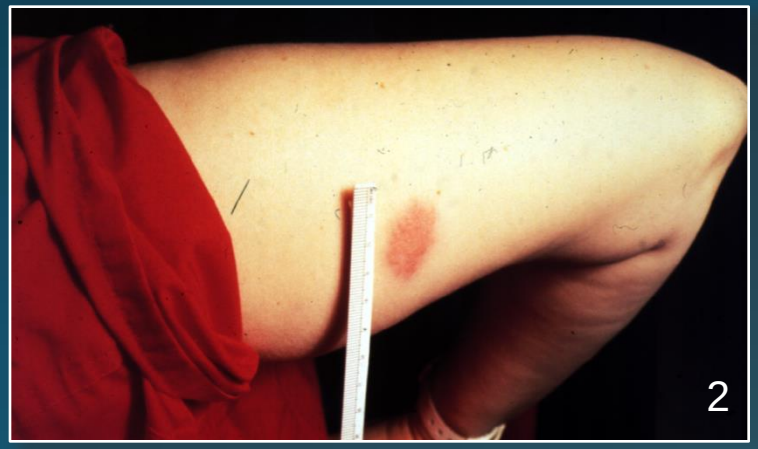
Flu-like Symptoms

- **Evening dose**
- **Dose escalation**
- **Premedication**
  - Acetaminophen and/or NSAIDs
    - Can repeat every 4 hours
    - Steroids
- **Combination of premedication and dose escalation[1]**

1. Rice GP, Ebers GC, Lublin FD, Knobler RL. *Neurology.* 1999; Jun 10;52(9):1893-5.

Injection Site Reactions
Beta Interferon





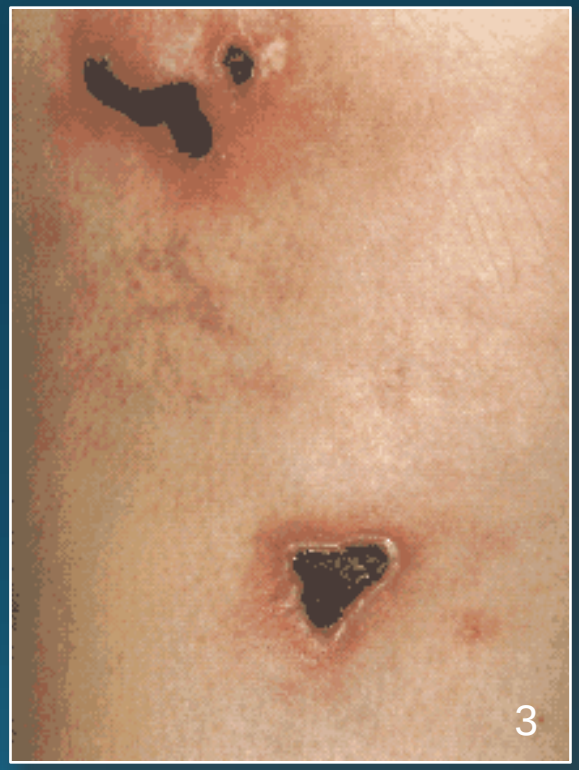


Photo 1 courtesy of Colleen Harris.
Photos 2 & 3 from Sheremata et al. *NEJM*. 1995;332:1584.

Glatiramer Acetate 40 mg

- **3-times-a-week injectable therapy for relapsing forms of MS**
- **Low frequency (GALA study)* of administration study showed that 40 mg of glatiramer acetate given 3 times weekly was as effective as 20 mg given daily**
  - Reduction of annualized relapse rate
  - Reduction of new/enlarging T2 lesions and gadolinium-enhancing T1 lesions
- **No new adverse effects identified in GALA but less injections = less skin insult**

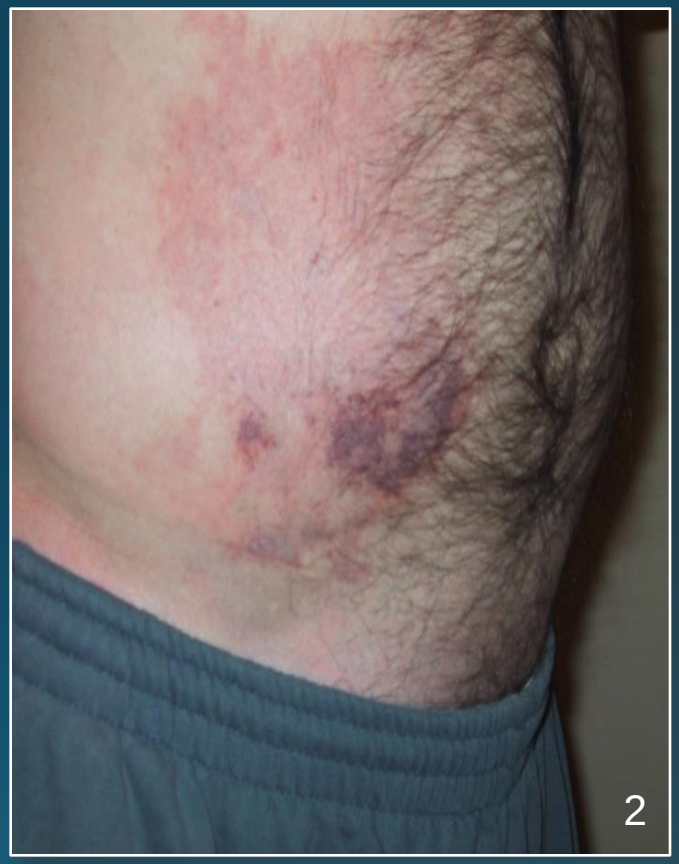
* Khan O, Rieckmann P, Boyko A, GALA Study Group et al. *Ann Neurol*. 2013;73(6):705-713.

Adverse Effects Glatiramer Acetate

- **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

Copaxone® (glatiramer acetate) [PI]. Teva Neuroscience, 2014.

GA Injection Site Reactions



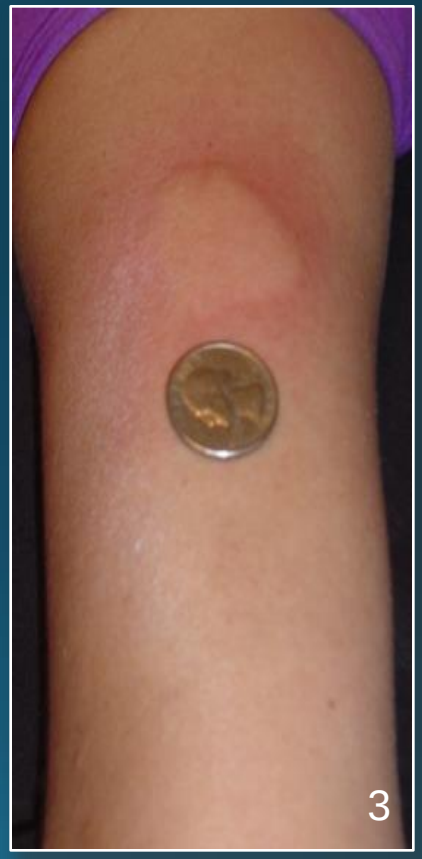


Photo 1 from Mancardi et al. *J Neurol.* 2000.
Photo 2 courtesy of Kathy Costello.
Photo 3 courtesy of Colleen Harris.

Natalizumab

- 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 annualized relapse rate
- Reduction of sustained progression
- Reduction of gadolinium-enhancing lesions and T2 lesions
- Pregnancy category: C

Tysabri® (natalizumab) [PI]. Biogen Idec, 2013.

Natalizumab Adverse Events

- **Hypersensitivity reactions:** Urticaria +/- systemic signs and symptoms, edema/swelling; rashes; difficulty breathing; angioedema; cardiac symptoms
- **Infusion reactions:** Headache, nausea, sweats, dizziness, fatigue, rigors
- **Hepatotoxicity:** Elevated liver function tests (LFTs)
- **PML:** Personality or behavioral changes, changes in thinking, seizure, disturbance in vision, hemiparesis

Tysabri® (natalizumab) [PI]. Biogen Idec, 2013.
Hilas O et al. *Open Neurol J.* 2010;4:15-24.

Progressive Multifocal Leukoencephalopathy (PML)

- Rare, progressive, demyelinating disease of CNS
- Caused by JC virus (polyomavirus)
- Can be fatal, higher incidence in anti JCV virus positive individuals
- Reactivates in settings of profound immunosuppression
- Primarily affects immunocompromised (HIV, transplant, hematologic malignancy)

Tysabri® (natalizumab) [PI]. Biogen Idec, 2013.

Immunosuppressive Agents

- **Rationale for use: Suppression of the activity of white blood cells that induce MS attack on the CNS**
- **FDA approved**
  - Mitoxantrone -12mg/m2 q 3 months for 24 months (lifetime dose of 140mg/m2)
- **Off Label**
  - Cyclophosphamide - dose adjusted to number of white blood cells (800mg/m^2) IV (monthly pulses)
  - Azathioprine - PO 150mg QD
  - Mycophenolate Mofitil - PO 2 grams QD
  - Methotrexate - PO 7.5mg weekly
- **Benefits: May reduce relapse rate and slow progression of the disease**

Novantrone® (mitoxantrone) [PI]. EMD Serono, 2010; Awad, Stuve. *Ther Adv Neurol Disord.* 2009;2(6):50-61; Casetta et al. *Cochrane Database Syst Rev*. 2007; Oct 17;(4):CD003982. Frohman et al, *Clin Neuropharmacol*. 2004; Mar-Apr;27(2):80-83; Gray et al. *Cochrane Database Syst Rev*. 2004;(2):CD003208.

Mitoxantrone Adverse Effects

- Decrease in exacerbations, disability progression, and MRI activity in aggressive MS
- Cardiotoxicity limits lifetime dosing
- Other risks: infections, sterility, secondary leukemia
- Side effects: nausea, vomiting, alopecia
- Pregnancy category D

Novantrone® (mitoxantrone) [PI]. EMD Serono, 2010.

Fingolimod: Mechanism of Action

- **Fingolimod is a novel, orally active, synthetic molecule**
- **FTY-720P binds to S1P1, S1P3, S1P4, S1P5 receptors**
  - Induces internalization of the receptor on thymocytes and lymphocytes preventing their egress from lymph nodes and other lymphoid tissue
  - Naïve and central memory T cells are sequestered in LNs but not peripheral effector memory T cells
  - Only affects lymphocytes, not monocytes, granulocytes, eosinophils, and macrophages

Brinkmann et al. *Am J Transplant.* 2004; 4:1019; Kappos et al. *NEJM*. 2010;362:387-401.
Cohen et al. *NEJM*. 2010;362:402-415; Hilas O et al. *Open Neurol J.* 2010;4:15-24.
Groves A et al. *J Neurol Sci.* 2013;328(1-2):9-18.
Fingolimod. NMSS website. http://www.nationalmssociety.org/Treating-MS/Medications/Gilenya.
GILENYA™ (fingolimod) [PI]. Novartis Pharmaceuticals Corporation; 2012.

Fingolimod: Pre-treatment Surveillance

- Recent (within 6 mos) CBC, LFT's
- EKG within 6 months of treatment initiation
- Baseline ophthalmologic exam
- Obtain varicella zoster virus (VZV) serology. Recommend vaccine if VZV negative. If vaccine given, wait one month before initiating treatment
- Anyone with an active infection should not start treatment until infection is resolved
- Medication not advisable for people with a history of heart attack, stroke, cardiac irregularities, those taking cardiac medications

Fingolimod. NMSS website. http://www.nationalmssociety.org/Treating-MS/Medications/Gilenya.
GILENYA™ (fingolimod) [PI]. Novartis Pharmaceuticals Corporation; 2012.

Adverse Effects of Fingolimod

- First dose bradycardia
- Macular edema
- Hypertension
- Pulmonary dysfunction (dyspnea)
- Skin cancers
- Hepatic enzyme elevations

Fingolimod. NMSS website. http://www.nationalmssociety.org/Treating-MS/Medications/Gilenya.
GILENYA™ (fingolimod) [PI]. Novartis Pharmaceuticals Corporation; 2012.
Hilas O et al. *Open Neurol J.* 2010;4:15-24.

Fingolimod: Special Considerations

First dose Observation:

- Measure baseline pulse and blood pressure
- Observe ALL patients for 6 HOURS
- EKG pre and post
- If symptomatic, monitor until symptoms resolve

While on therapy:

- Report any symptoms of infection
- Avoid live attenuated vaccines such as:
  - Flu mist
  - VZV
- Perform ophthalmological exam 3-4 months after starting fingolimod
- Pregnancy category: C

Fingolimod. NMSS website. http://www.nationalmssociety.org/Treating-MS/Medications/Gilenya.
GILENYA™ (fingolimod) [PI]. Novartis Pharmaceuticals Corporation; 2012.

Teriflunomide Mechanism of Action

- Active metabolite of leflunomide, FDA-approved for rheumatoid arthritis
- An oral immunomodulator with anti-inflammatory activity
- Inhibits pyrimidine synthesis by binding to the enzyme dihydro-orotate dehydrogenase (DHO-DH)
- DHO-DH is the 4th enzyme and rate-limiting step in the de novo synthesis pathway of pyrimidines (crucial for replicating DNA and RNA)
- It inhibits rapidly dividing cell populations and is non-specific to T cells

Rammohan, Shoemaker. *J Neurol.* 2010 74:S47-S53; O'Connor et al. *NEJM.* 2011;365: 1293-1303; Gold, Wolinsky. *Acta Neurol Scand*. 2011;124(2):75-84; Brück et al. *JAMA Neurol*. 2013 Oct;70(10):1315-24
AUBAGIO® (teriflunomide) [PI]. Genzyme Corporation; 2012.
Aubagio. NMSS website. http://www.nationalmssociety.org/Treating-MS/Medications/Aubagio.

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**
- **Lymphopenia**
- **Slow excretion, not dialyzable**
  - 8-24 months after discontinuation for plasma levels to be undetectable
  - Accelerated elimination is available
    - Cholestyramine 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)
  - Hypertension
  - Polyneuropathy

AUBAGIO® (teriflunomide) [PI]. Genzyme Corporation; 2012.
Aubagio. NMSS website. http://www.nationalmssociety.org/Treating-MS/Medications/Aubagio.

Dimethyl Fumarate: Mechanism of Action

- **Oral dimethyl fumarate (DMF) activates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway**
  - Defends against oxidative stress-induced neuronal death
  - Protects the blood brain barrier
  - Supports maintenance of myelin integrity in the CNS

- **Experimental evidence suggests that DMF may provide anti-inflammatory and cytoprotective effects in the treatment of MS**
  - Induces anti-inflammatory Th2 cytokines
  - Shown to increase IL-10 and decrease TNF-α and IL-6
  - Induces apoptosis in activated T cells
  - Induces expression of phase 2 detoxification enzymes in astroglial and microglial cells
  - Reduces the expression of adhesion molecules

Gold R, et al. *Mult Scler* 2011;17 (Suppl 10):S34 (abstract 95); Selmaj K, et al. *Mult Scler* 2011;17 (Suppl 10):S451 (abstract P994). Arnold D et al. *Mult Scler* 2011;17 (Suppl 10):S369; Fox et al. *NEJM.* (2012) 367, 1087-1097; Gold et al. *NEJM.* 2012;367:1098-1107; Lee DH et al. *Int J Mol Sci*. 2012;13(9):11783-11803.

Dimethyl Fumarate

- **Adverse events:**
  - Unclear if a signal for risk of PML based on previous adverse events with psoriasis patients on fumarate
- **Other side effects:**
  - Generalized flushing
  - GI: nausea, gas, diarrhea
  - Headache
  - Decrease in lymphocyte count
- **Pregnancy category: C**

TECFIDERA™ (dimethyl fumarate) [PI]. Biogen Idec Inc.; 2013.
Tecfidera. NMSS website. http://www.nationalmssociety.org/Treating-MS/Medications/Tecfidera%e2%84%a2.
Hilas O et al. *Open Neurol J.* 2010;4:15-24.

Conclusion

- Focus of disease management is to reduce relapses, manage symptoms, slow progression of disease and improve the patient's quality of life
- Depending upon severity of relapse, treatment may be required
- Goal of disease-modifying therapy is to reduce frequency and severity of relapses, suppress lesion activity and delay disease progression

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 the understanding and follow-through needed for all treatment options.

Question-and-Answer Session

Thank you for your participation!

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- For additional IOMSN educational opportunities and future webinars programs, please visit IOMSN at: www.IOMSN.org
- We look forward to seeing you for our next CNE webinars:
  - Alternative Therapies and Wellness on June 16th
  - Symptomatic Management of MS: Visible Symptoms on Sept. 22nd