**Patient Case: Emily**

Emily is a 32 yo WF presenting with headaches, right leg numbness, urinary incontinence, “pins and needles” in her right arm and fingertips, and feeling uncoordinated to where she looses her balance often. Three years ago soon after a minor motor vehicle accident where she was uninjured, she later reported pain and vision loss in her right eye. This was resolved after a course of corticosteroids.

She was sent for an MRI, and positive findings for T2 hyperintense lesions were noted using FLAIR image and gadolium enhancement. She also had a spinal tap which had increased lymphocytes and was positive for oligoclonal bands. According to the International McDonald Criteria, Emily's findings are suggestive of multiple sclerosis.

**PMH:**
- Asthma x 27 years
- OCD & MDD x 5 years
- Miscarriage x 8 months ago

**Current meds:**
- Albuterol Inh 2 puffs Q6H prn SOB
- Advair 250/50mcg 1 inhalation twice a day
- Luvox 150mg po BID

Case Question 1: Which of the following likely a symptom of multiple sclerosis in Emily?

**SELECT ALL THAT APPLY:**
- Incontinence
- Numbness
- “Pins and needles”
- Loss of balance
- Vision loss
- Fatigue
- Depression

Case Question 2: Four weeks after Emily's acute MS attack, she decides to start interferonβ- 1a therapy. Which of the following is **TRUE** regarding β-interferon therapy?

A. It decreases disease activity and reduces the annualized relapse rate by an average of 33%.
B. Studies have found that early initiation of treatment with β-interferons reduces the progression of disability
C. Combining glatiramer acetate and interferon β-1a will not provide additional benefits
D. All of the above are TRUE

Case Question 3: One year after starting Avonex®, Emily comes in reporting numbness that started in her feet and having an unsteady gait. She states to “almost never” miss her weekly dose of medication and is afraid this is another attack.

Which of the following should you consider in treating Emily?

**SELECT ALL THAT APPLY:**
- Noncompliance is an important factor that can cause breakthrough of disease symptoms.
- Since she is on an IMβ-interferon therapy, her risk of developing NABs is lower than SCβ-interferon therapy and doesn’t require testing.
- Changing therapy from injection to infusion therapy is a good option at this time.
- Switching her to fingolimod would be appropriate.
Case Question 4: Emily would like to change to an oral DMT. Which of the following would be the best choice?

A. Dimethyl fumarate (Tecfidera®)
B. Fingolimod (Gilenya®)
C. Natalizumab (Tysabri®)
D. Teriflunomide (Aubagio®)

**Evaluation Questions:**

1. Which of the following is/are **TRUE**?
   - A. Symptoms usually present between 20 to 40 years old.
   - B. More men than women are affected by MS.
   - C. Worldwide, the disease prevalence is evenly distributed and does not vary by geographic location.
   - D. Roughly 50% of patients with MS have a disease course that is benign, with minimal to no physical disability and almost complete remission between attacks.
   - E. All of the above are statements are TRUE

2. Which of the following is **TRUE** regarding pregnancy with teriflunomide?
   - A. Throughout the pregnancy, administer folic acid to the patient
   - B. Upon detection of pregnancy, cholestyramine should be administered to increase elimination
   - C. Teriflunomide should be discontinued two months before conception
   - D. Before pregnancy, cholestyramine should be administered to increase elimination

3. Which of the following medications requires the patient to be observed for 6 hours after the first dose to monitor for bradycardia?
   - A. teriflunomide
   - B. natalizumab
   - C. mitoxantrone
   - D. fingolimod
   - E. dimethyl fumarate

4. According to DMT combination studies, which of the following medication combinations should be recommended?
   - A. Interferon b-1b SQ and glatiramer acetate
   - B. Interferon b -1b SQ and natalizumab
   - C. Interferon b -1a IM and fingolimod
   - D. Interferon b -1a IM and dimethyl fumarate
   - E. None of the above
Multiple Sclerosis: The Role of New Oral Therapies

Devon A. Sherwood, PharmD, BCPP
dsherwood@une.edu
LEARNING OBJECTIVES:

* Describe the pathophysiology and complications of multiple sclerosis (MS).
* Discuss drug profiles for relapsing-remitting MS treatments and identify when to utilize the newer oral disease modification therapies (DMT).
* Evaluate the advantages and disadvantages of injectable versus oral DMT’s available.
Definition of Multiple Sclerosis (MS)

“A potentially debilitating disease which the body's immune system eats away at the protective sheath that covers the nerves. This interferes with the communication between the brain and the rest of your body. Ultimately, results in deterioration of the nerves themselves, a process that's not reversible.”

Mayo Foundation for Medical Education and Research. 2015.
Etiology

- Damage to myelin sheath surrounding nerve cells

- Nerve damage is caused by inflammation which occurs when the body's own immune cells attack the nervous system.

- Triggers of the inflammation are unknown, but theories are virus, genetic defect or combination
Epidemiology of MS

* Average person in the United States = 1/750 (0.1%) chance of developing MS.
* First-degree relative = 2.5-5%
  * Risk being potentially higher in families that have several family members with the disease.
* Identical twin = 25%
* Female:Male = 3:1
* Median age = 29 years old
  * ~ 70% of patients manifest symptoms between ages 21 and 40
  * Most commonly diagnosed between 20 – 40yo
  * Rare prior to 10 or after 60 yo, though patients 3-67 yo have been diagnosed.

Epidemiology of MS

Very specific geographic distribution of this disease:
- Significantly higher incidence in Scandinavia, northern United States, Canada, Australia and New Zealand.
- Data from migration studies shows if exposed to a higher risk environment during adolescence (before 15 years of age), the migrant assumes the higher risk of the environment.

Second most common disease in young adults
- $$$ chronic disease
  - Total annual costs per affected individual exceeding $50,000 (2007)

National MS Society, 2015 ®
Prognosis

* Variable outcomes = difficult to predict
  * Though chronic and incurable, life expectancy can be normal or almost normal.
  * Most patients continue to walk and function at work with minimal disability for 20 or more years.

* Most patients return to normal or near-normal function between attacks. Slowly, there is greater loss of function with less improvement between attacks.
  * In roughly 10% to 15% of patients with MS, the disease course is benign

* Those with a support system are often able to remain in their home.
Prognosis

* Best outlook:
  * Females
  * Young (less than 30 yo) when the disease started
  * People with infrequent attacks
  * People with a relapsing-remitting pattern
  * People who have limited disease on imaging studies

* Disability and discomfort depends on:
  * How often attacks occur
  * How severe they are
  * The part of the central nervous system that is affected by each attack
Diagnosis of MS

* Mimics many other nervous system disorders.
* Suspect MS if there are decreases in the function of two different parts of the central nervous system (ie. abnormal reflexes) at two different times.
* Clinically Isolated Syndrome (CIS) = One (1) attack, where 90% of patients eventually develop clinically definite MS
* Relapsing-remitting (RRMS) vs. Primary-progressive (PPMS)
  * 85% patients have RRMS
  * 15% have “benign” MS
  * 60-70% convert to secondary progressive (SPMS) in 1 – 3 decades post RRMS diagnosis
  * RRMS patients have a history of at least two attacks, separated by a period of reduced or no symptoms.
## 2010 McDonald criteria

### Clinical presentation

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Additional data needed for MS diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 attacks with either: Objective clinical evidence* of ≥2 lesions</td>
<td>None</td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack†</td>
<td></td>
</tr>
<tr>
<td>≥2 attacks with objective clinical evidence of 1 lesion</td>
<td>Documentation of DIS by either:</td>
</tr>
<tr>
<td></td>
<td>• MRI</td>
</tr>
<tr>
<td></td>
<td>• Awaiting a further clinical attack implicating a different CNS site</td>
</tr>
<tr>
<td>1 attack with objective clinical evidence of ≥2 lesions</td>
<td>Documentation of DIT by either:</td>
</tr>
<tr>
<td></td>
<td>• MRI</td>
</tr>
<tr>
<td></td>
<td>• Awaiting a further clinical attack</td>
</tr>
<tr>
<td>1 attack with objective clinical evidence of 1 lesion (CIS)</td>
<td>Documentation of both DIS and DIT by either:</td>
</tr>
<tr>
<td></td>
<td>• MRI</td>
</tr>
<tr>
<td></td>
<td>• Awaiting a further clinical attack</td>
</tr>
</tbody>
</table>

*May include findings on neurological examination, visual evoked response in patients reporting prior visual disturbance, or MRI consistent with demyelination in the implicated area of the CNS.

†Can include historical events with symptoms and evolution characteristics of a prior inflammatory demyelinating event.
Figure 1  The left panel shows a FLAIR image with several typical T2 lesions (scars). The right panel shows the same level of the brain with a T1 weighted image after Gadolinium enhancement. The arrow demonstrates which one of the lesions was active at the time of the MRI.
<table>
<thead>
<tr>
<th>Density</th>
<th>T₂</th>
<th>FLAIR</th>
<th>Segmented</th>
<th>T₁ Gadolinium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td><img src="image1" alt="Initial Density" /> <img src="image2" alt="Initial T₂" /> <img src="image3" alt="Initial FLAIR" /> <img src="image4" alt="Initial Segmented" /> <img src="image5" alt="Initial T₁ Gadolinium" /></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 Month</td>
<td><img src="image6" alt="1 Month Density" /> <img src="image7" alt="1 Month T₂" /> <img src="image8" alt="1 Month FLAIR" /> <img src="image9" alt="1 Month Segmented" /> <img src="image10" alt="1 Moon T₁ Gadolinium" /></td>
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<td></td>
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<td>4 Months</td>
<td><img src="image11" alt="4 Months Density" /> <img src="image12" alt="4 Months T₂" /> <img src="image13" alt="4 Months FLAIR" /> <img src="image14" alt="4 Months Segmented" /> <img src="image15" alt="4 Months T₁ Gadolinium" /></td>
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<tr>
<td>7 Months</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Brain and Nerve Symptoms

- Abnormal nerve sensation and reflexes in one area or spread over many parts of the body
- Numbness, tingling, crawling, pain, burning in arms/legs
- Decreased ability to move part of the body
- Dizziness and balance problems
- Hearing loss
- Fatigue
- Other loss of nervous system functions
Brain & Nerve Symptoms

* Psychiatric Symptoms
  * Cognitive impairment (decline)
    * Decreased attention span, poor judgment, memory loss
    * Difficult reasoning and solving problems
  * Depression or feelings of sadness

* Sexual symptoms:
  * Erectile dysfunction
  * Problems with vaginal lubrication

* Speech and swallowing symptoms:
  * Slurred or difficult-to-understand speech
  * Trouble chewing and swallowing
Muscular Symptoms

- Loss of balance
- Muscle spasms (may be painful, and includes facial pain)
- Problems with coordination and making small movements
- Problems moving arms or legs and walking
- Tremor and/or weakness in one or more arms or legs
- Later in disease paralysis, osteoporosis, skin ulcerations, decrease in self care abilities
Bowel and bladder symptoms:

- Constipation and stool leakage
- Difficulty beginning to urinate
- Frequent need to urinate
- Strong urge to urinate
- Urine leakage (incontinence)
  - Subsequent complications with UTI’s and need for indwelling catheter.
Vision Problems

- Vision loss (usually affects one eye at a time)
- Diplopia
- Eye discomfort

Eye exam may show:
- Abnormal pupil responses
- Changes in the visual fields or eye movements
- Decreased visual acuity
- Problems with the inside parts of the eye
- Uncontrollable rapid eye movements (triggered when the eye moves)
Typical progression of MS
Treatment delays can result in irreversible neurologic deficits!!!

- Steroids should be used to decrease the severity of attacks (reduce inflammation) and reduce recovery time.
  - Recommended if functionally impaired
  - Methylprednisolone 500-1000mg IV/day x 3-7 days (up to 10 days)

- Plasma exchange QOD x 7 treatments
  - Used in patients who fail to improve on steroid therapy
  - 40% response noted in this population
Pharmacotherapy – Symptomatic Treatment

* Medicines to reduce muscle spasms:
  * Lioresal (Baclofen),
  * Tizanidine (Zanaflex)
  * Benzodiazepines (not ideal therapy)

* Medications for neurogenic bladder and/or reducing urinary problems (cholinergic medications)

* Antidepressants for mood or behavior symptoms
Disease Modifying Therapy (DMT) - Goals

* Control symptoms and slow progression to maintain quality of life
  * Decreased formation of new brain lesions
    * Occurrence of on-treatment active lesions (gadolinium enhanced)
    * Prevent an increase in MRI T1 black holes (axonal loss)
  * Cerebral atrophy
* Relapse reduction
  * Comparison of pretreatment and on-treatment relapses
* Expanded Disability Status Scale (EDSS)
  * 0 (normal) – 10 (death from MS)

Early and Aggressive DMT

- Reduce inflammation
- Reduce relapse rates
- Prolong remission
- Limit the onset of new or enlarging T2 gadolinium-enhancing lesions
- Postpone the development of long term disability
- Slow the accumulation of cognitive dysfunction

Most DMT’s indicated for RRMS, not PPMS
First-line Therapy of Relapsing MS

- RRMS, SPMS, PRMS, and CIS = interferons-β-1a and β-1b, and glatiramer acetate
- 1st & 2nd line for relapsing forms of MS (not CIS) = fingolimod
- Relapse rates are decreased an average of 30%, improve measures of new MS activity on MRI, and delay accumulation of disability with first line therapy.
- Disease activity often continues for 1-3 months after therapy initiation.
- No agent has shown efficacy for PPMS.
β-interferons

- Antiproliferative and antiviral
- Downregulate costimulatory molecules, and antagonize pro-inflammatory cytokines.
- May also affect matrix metalloproteinases and adhesion molecules, thereby reducing the permeability of the blood-brain barrier and limiting trafficking of T lymphocytes into the CNS.
- In patients with CIS, effectively delay time to first relapse and prolong the time to conversion to MS, reducing disease activity on MRI and annualized relapse rates by 33%.

Interferon Therapy

* **Avonex / Rebif** (interferon beta-1a)
  * Administration: Injection therapy
    * Avonex® 30 mcg **IM once weekly**
    * Rebif® initial, 4.4 or 8.8 mcg **SubQ 3/wk** for wk 1 & 2; titrate to 11 or 22 mcg **SubQ 3/wk** for wk 3 & 4, then 22 or 44 mcg **SubQ 3/wk**

* **Betaseron/Extavia** (interferon beta-1b)
  * Administration: Injection therapy
    * 250mcg **SubQ every other day**

www.nationalmssociety.org, Micromedex 2015.
Copaxone (glatiramer acetate)

- Benefit-risk analysis:
  - Higher relapse-free rates with glatiramer acetate compared with placebo and similar rates as β-interferons in patients with RRMS.
  - Clinical progression was reduced by 33% vs placebo and 18% vs β-interferons.

- Using glatiramer acetate in combination with interferon β-1a has not been found to provide additional benefit to using either alone.

- Administration: Injection therapy
  - 20 mg SubQ once daily

Novantrone (mitoxantrone)

Indication: Treatment of rapidly worsening RRMS and for progressive-relapsing or secondary-progressive forms of MS

Administration: Infusion therapy

- Once every 3 months or four times a year.
- Maximum dose 8-12 doses

Common side effects: Nausea, hair thinning, decreased white blood cell count

Serious side effects: cardiotoxicity, hepatotoxicity, AML

www.nationalmssociety.org, Micromedex 2015.
Natalizumab (Tysabri®)

- Class: Selective adhesion molecule inhibitor
- Indication:
  - When other meds have not worked or were intolerable
- MOA: Prevents cells of the active immune system from reaching the brain
  - Decrease the number of attacks
  - Slow the progression of disability
  - Decreases number and volume of active brain lesions (damaged brain areas).

www.nationalmssociety.org, Micromedex 2015.
Natalizumab (Tysabri®)

- **Administration: Infusion therapy**
  - 300 mg IV infused over approximately 1 hr, given at 4-week (28-day) intervals

- **Serious side effects:**
  - Progressive multifocal leukoencephalopathy (PML), hepatotoxicity, anaphylaxis, depression

- **Common side effects:**
  - Rash, nausea, arthralgia, headache, UTI, respiratory infection, fatigue
Concerns over Neutralizing Antibodies (NABs) – Biological Markers

* Patients with a decline in clinical status while receiving β interferons or natalizumab should be tested for NABs
  * Loss of biologic activity and efficacy
  * Contributes to treatment failure

* β-interferon therapies:
  * Several reports show that NABs to β-interferon are most common with SC β-interferon and are least common with IM β-interferon.
  * NABs that are persistently present in high titers to β-interferon blunt clinical effectiveness and block the biological response to injections.
  * Patients who test positive for NAB

* Natalizumab:
  * Persistent presence of antibodies to natalizumab occurs in about 6% of treated patients and blocks clinical effectiveness.
Oral DMT’s –
The New Therapies in our Toolbox
Fingolimod (Gilenya®)

* New class:
  * Sphingosine 1-phosphate receptor modulator
  * Binds to all S1PR except S1PR2

* MOA: Retains naïve T and central memory T cells (lymphocytes) in lymph nodes, thereby preventing those cells from crossing the BBB into the CNS.
  * Increases # of progenitor and mature oligodendrocytes and protects them from cell death
  * Increases BDNF
  * Preventing the entry of these cells into the CNS reduces inflammatory damage to nerve cells.

www.nationalmssociety.org, Micromedex 2015.
Treatment with fingolimod

Autoreactive lymphocytes remain in the lymph nodes away from the CNS

Blood

S1P gradient

Efferent lymph

Lymphoid organ

Fingolimod
Downmodulates S1P1
Lymphocytes are unable to egress

Lymphocyte

Source: Expert Rev Neurother © 2011 Expert Reviews Ltd
## Fingolimod - Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Annualized Relapse Rate</th>
<th>Relapse-free New or Enlarged MRI Lesions (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fingolimod 0.5mg vs.:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo, 2 year-study</td>
<td>1033</td>
<td>F = 0.18/y</td>
<td>F = 70.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = 0.40/y</td>
<td>P = 45.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F = 2.5</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>P = 9.8</td>
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<tr>
<td>Interferon β−1a IM Qweek, 1-year study</td>
<td>1153</td>
<td>F = 0.16/y</td>
<td>F = 82.6%</td>
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<tr>
<td></td>
<td></td>
<td>I = 0.33/y</td>
<td>I = 69.3</td>
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<td></td>
<td>F = 1.7</td>
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<td></td>
<td></td>
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<td>I = 2.6</td>
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<tr>
<td>FREEDOMS II: Placebo, 2-year study</td>
<td>1083</td>
<td>F = 0.21/y</td>
<td>F = 71.5%</td>
</tr>
<tr>
<td></td>
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<td>P = 0.40/y</td>
<td>P = 52.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F = 2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 8.9</td>
</tr>
</tbody>
</table>

Fingolimod PK

- Administration:
  - 0.5mg orally *once daily*
- $T_{\text{max}} = 12-16$ hours
- Time to $C^{\text{ss}} = 1-2$ months
- Metabolism = CYP 4F2 (major), 2D6, 2E1, 3A4, 4F12 (minor)
- $T^{\frac{1}{2}} = 6-9$ days
  - Some activity up to 2 months
Fingolimod - Pharmacodynamics

- 73% reduction in lymphocytes within hours
  - Normalizes 6 weeks after discontinuation
- Bradycardia
  - Observe for 6hrs after 1st dose (max decrease at 6 hours of a mean 8bpm)
- First and second degreee AV block
- Pulmonary effects
  - FEV1 decreases 3.1%
Fingolimod

✶ Common side effects:
   ✶ Diarrhea, increased LFT’s, backache, headache, increased risk of infection

✶ Serious side effects:
   ✶ Atrioventricular block, bradyarrhythmia, lymphocytopenia, macular retinal edema (0.4%, 20% in patients with prior uveitis), fatal herpetic infection
Fingolimod – Monitoring

* Baseline:
* Heart rate x 6 hours
* Test for varicella zoster virus in patients without vaccine or history
* Ophthalmologic evaluation at baseline and repeat 3-4 months
* Pregnancy test
* LFT’s
* CBC
* ECG within 6 months
Fingolimod – Place in Therapy

- Monotherapy medication: Avoid in patients with immunosuppressive therapy
  - 30 days after corticosteroid treatment
  - 2-3 months after natalizumab
  - 6 months after mitoxantrone or azathioprine

- Caution in patients taking antiarrhythmics, β-blockers, calcium channel blockers.

- Caution in patients with compromised pulmonary function
Teriflunomide (Aubagio®)

* Decreases flare-ups
* Active metabolite of leflunomide

* MOA: Inhibits dihydro-orotate dehydrogenase (which inhibits T and B-lymphocytes), which is a mitochondrial enzyme involved in de-novo pyrimidine synthesis
* Likely involves reduction in activated lymphocytes in CNS

* Administration
* 7 – 14mg orally once daily
Overactive T- and B-cells multiply and then travel through the blood vessels into the CNS where they attack the nerves.

AUBAGIO appears to reduce the number of overactive T- and B-cells available to attack the nerves.

https://www.aubagio.com/teriflunomide
## Teriflunomide - Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>n =</th>
<th>Annualized Relapse Rate</th>
<th>Relapse Free Change in MRI lesion volume from baseline (relative reduction vs. placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMSO: Teriflunomide 7mg, 14mg, or placebo; 108-week study</td>
<td>1086</td>
<td>T7 = 37% T14 = 37% P = 54%</td>
<td>T7 = 53.7% T14 = 56.5% P = 45.6% T7 = 39.4% (7mg) T14 = 67.4 (14mg)</td>
</tr>
<tr>
<td>TOWER: Teriflunomide 7mg, 14mg, or placebo; 48-week study</td>
<td>1169</td>
<td>T7 = 39% T14 = 32% P = 50%</td>
<td>T7 = 71.9% T14 = 76.3% P = 60.6% N/A</td>
</tr>
<tr>
<td>TENERE: Teriflunomide 7mg, 14mg, or IFN-β-1a SQ; 48-week study</td>
<td>324</td>
<td>T7 = 41% T14 = 26% (ns) I = 22%</td>
<td>Measured time to treatment failures; no difference observed N/A</td>
</tr>
</tbody>
</table>

O’Connor P, et al. NEJM 2011; 365: 1293-1303
Teriflunomide

* Contraindicated in severe hepatic impairment and pregnancy (Category X)
  * Give with oral contraceptive in women of childbearing age
  * Do not use in men trying to conceive

* PK:
  * Over 99% protein bound – Watch DDI’ s!
  * $T^{1/2} = 18-19$ days, but drug can remain in system up to 2 years

* Accelerated elimination
  * Cholestyramine 8mg po q8h x 11 days
  * Activated charcoal 50g po q12h x11days
Teriflunomide – Adverse Effects

- Common: Alopecia, diarrhea, nausea, increased liver enzymes, headache, paresthesia
- Serious: neutropenia, peripheral neuropathy, renal failure, liver failure, SJS
- Black box warning for pregnancy and hepatotoxicity
Teriflunomide - Monitoring

* Baseline
  * Pregnancy test
  * CBC/diff within 6 months before treatment
  * AST, ALT, bilirubin within 6 months before treatment
  * Blood pressure

* Monitoring
  * ALT (SGPT) at least monthly for first 6 months of therapy
  * blood pressure periodically
Dimethyl Fumarate (Tecfidera®)

- Newest FDA approved MS medication
- MOA: Methyl ester of fumaric acid that elicits immunomodulatory effects
  - Macrophages in CNS likely by effect on adhesion molecules
- May reduce oxidative stress by activating Nrf2 to minimize progressive damage.
- Administration
  - 240mg orally **twice daily**
  - *Take with food to minimize flushing/GI sx*
Patient Case: Emily

Emily asks you about a “newer DMT therapy that has less side effects and is taken by mouth”. She hands you a paper with “Tecfidera” written on it, but states she’s concerned it could interact with her other medications. What is the metabolism of dimethyl fumarate that would address some of Emily’s concern?

- a. Krebs cycle
- b. UGT 1A4
- c. CYP 4F2
- d. CYP 3A4
- e. CYP 1A2
# Dimethyl Fumarate Efficacy

<table>
<thead>
<tr>
<th>Study</th>
<th>n =</th>
<th>Annualized Relapse Rate</th>
<th>Number of gadolinium enhanced lesions at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFINE: Dimethyl Fumarate vs: DM 240mg BID, DM 240mg TID, placebo; 2 years</td>
<td>1237</td>
<td>0.19 (BID) 0.17 (TID) 0.36 (placebo)</td>
<td>0.1 (BID) 0.5 (TID) 1.8 (placebo)</td>
</tr>
<tr>
<td>CONFIRM: Dimethyl Fumarate vs: DM 240mg BID, DM 240mg TID, glatiramer acetate, placebo; 2 years</td>
<td>1430</td>
<td>0.22 (BID) 0.20 (TID) 0.29 (glatiramer) 0.40 (placebo)</td>
<td>0.5 (BID) 0.4 (TID) 0.7 (glatiramer) 2.0 (placebo)</td>
</tr>
</tbody>
</table>

Dimethyl Fumarate - PK

- Rapidly metabolized by presystemic hydrolysis from estermerases in GI tract, blood and tissues & converted to monomethyl fumarate (active metabolite)
- Metabolized by the Krebs Cycle into water and CO$_2$
- Eliminated by respiration
Dimethyl Fumarate – Adverse Effects

* Common:
  * Flushing (40%) – may be accompanied with itching
  * Slow titration; administer aspirin/antihistamines, food
  * GI (up to 25%): Abdominal pain, diarrhea, nausea, vomiting
    * Slow titration; administer with food

* Serious:
  * Lymphocytopenia (2-6%)
Role of Oral DMT’s

* Fingolimod:
  * Moderate efficacy
  * CV contraindications, lab & ophthalmologic monitoring

* Teriflunomide
  * Similar efficacy to injectable drugs
  * Pregnancy category X, potential hepatotoxicity, long T½

* Dimethyl fumarate
  * Moderate efficacy
  * Self-limited flushing, GI symptoms and side effects
## Comparison of FDA Approved Agents

<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>Dose</th>
<th>Route of Administration</th>
<th>AWP/Year, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl fumarate, delayed release</td>
<td>240 mg twice daily</td>
<td>Oral</td>
<td>64 800</td>
</tr>
<tr>
<td>(Tecfidera)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingolimod (Gilenyia)</td>
<td>0.5 mg once daily</td>
<td>Oral</td>
<td>72 507</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>20 mg once daily</td>
<td>Subcutaneous</td>
<td>66 305</td>
</tr>
<tr>
<td>Interferon-β-1a (Avonex)</td>
<td>30 µg once weekly</td>
<td>Intramuscular</td>
<td>56 362</td>
</tr>
<tr>
<td>Interferon-β-1a (Rebif)</td>
<td>22 µg or 44 µg 3 times/week</td>
<td>Subcutaneous</td>
<td>56 583 (22 µg)</td>
</tr>
<tr>
<td>Interferon-β-1b (Betaseron; Extavia)</td>
<td>0.25 mg every other day</td>
<td>Subcutaneous</td>
<td>38 251</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>12 mg/m² every 3 months</td>
<td>Intravenous</td>
<td>656 (based on BSA 1.8 m²)</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>300 mg every 4 weeks</td>
<td>Intravenous</td>
<td>58 097</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio)</td>
<td>7 mg or 14 mg once daily</td>
<td>Oral</td>
<td>54 148</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethyl fumarate, delayed release (Tecfidera)</td>
<td>30% decrease in lymphocytes during therapy; flushing common</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>Requires extensive monitoring including varicella zoster immunity evaluation, FEV₁, pulse, blood pressure, ophthalmology examination, dermatologic examination, CBC count, ALT, and AST</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>First-line therapy; skin reactions common</td>
</tr>
<tr>
<td>Interferon-β-1a (Avonex)</td>
<td>First-line therapy; flu-like symptoms common</td>
</tr>
<tr>
<td>Interferon-β-1a (Rebif)</td>
<td>First-line therapy; skin reactions and flu-like symptoms common</td>
</tr>
<tr>
<td>Interferon-β-1b (Betaseron; Extavia)</td>
<td>First-line therapy; skin reactions and flu-like symptoms common</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>Reserve for patients with rapidly advancing disease or who have failed other therapies</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>Requires registration of patient, pharmacy, and prescriber before use because of concerns of progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio)</td>
<td>Hepatotoxicity and teratogenicity risk</td>
</tr>
</tbody>
</table>
DMT’s may be used as sequential monotherapies or as part of escalation or induction and maintenance strategies.

Other maintenance medications indicated to slow MS progression without FDA approval used when appropriate:

- Alemtuzumab (Campath®), Methotrexate, azathioprine (Imuran®), cladribine (Leustin®), intravenous immunoglobulin (IVIG) and cyclophosphamide (Cytoxan®) may be used if approved DMT’s drugs are not working well.
Sequential monotherapy is generally the current approach

- Partially supported by available controlled trials
- Will vary by patient presentation/disease activity, tolerability, adherence, safety issues.
- Oral therapies vs. injectable for RRMS
- For treatment escalation, sparse high-quality evidence exists to support clinical decision making of next agent

Evidence-based recommendations suggest:

- First line therapies:
  - Glatiramer acetate, interferons
- More aggressive or long-standing disease:
  - Natalizumab, fingolimod
- Reserve for rapidly advancing disease:
  - Mitoxantrone

<table>
<thead>
<tr>
<th>Current DMT</th>
<th>Next DMT</th>
<th>Efficacy escalation</th>
<th>Different MOA</th>
<th>Other factors</th>
<th>Evidence for efficacy from controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM interferon beta-1a</td>
<td>GA</td>
<td>Yes</td>
<td>Yes</td>
<td>NAbs</td>
<td>CombiRx\textsuperscript{126}</td>
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<tr>
<td>SC interferon beta-1a</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NAbs</td>
<td>EVIDENCE\textsuperscript{35}</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Yes</td>
<td>Yes</td>
<td>Possibly</td>
<td>NAbs</td>
<td>TRANSFORMS\textsuperscript{73}</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NAbs</td>
<td>None</td>
</tr>
<tr>
<td>DMF/BG-12 Natalizumab Alemtuzumab</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NAbs</td>
<td>None</td>
</tr>
<tr>
<td>SC interferon beta-1a</td>
<td>Alemotuzumab</td>
<td>Yes</td>
<td>Yes</td>
<td>NAbs</td>
<td>CARE-MS I\textsuperscript{96}</td>
</tr>
<tr>
<td>SC interferon beta (any)</td>
<td>Other DMT (non-interferon beta)</td>
<td>Yes</td>
<td>Yes</td>
<td>NAbs</td>
<td>CARE-MS II\textsuperscript{97}</td>
</tr>
<tr>
<td>GA</td>
<td>Interferon beta</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>DMF/BG-12</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>CONFIRM\textsuperscript{90}</td>
</tr>
<tr>
<td>Other DMT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>Natalizumab</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Teriflunomide DMF/BG-12</td>
<td>Other DMT</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Other DMT</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Other DMT</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
</tr>
</tbody>
</table>

\textsuperscript{a}CARE-MS = Comparison of Alemtuzumab and Rebif Efficacy for Multiple Sclerosis; CONFIRM = Comparator and an Oral Fumarate in Relapsing Remitting Multiple Sclerosis; DMF = dimethyl fumarate; DMT = disease-modifying therapy; EVIDENCE = Evidence of Interferon Dose-response: European North American Comparative Efficacy; IM = intramuscular; GA = glatiramer acetate; MOA = mechanism of action; NAab = neutralizing antibody; PML = progressive multifocal leukoencephalopathy; SC = subcutaneous; TRANSFORMS = Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing Remitting Multiple Sclerosis.

\textsuperscript{b}Rationale for efficacy escalation is based on the magnitude of DMT effect on relapses in placebo-controlled trials, recognizing that caution is required when comparing between trials. Efficacy evidence indicates whether and which head-to-head studies found superior efficacy of 1 DMT vs another, though not necessarily in the context of treatment failure.
Early and aggressive immunotherapy

- More aggressive therapy might provoke a long-term immunological “reset” (parallels approaches used in cancer)
- Once in sustained remission, patients can transition to “safer” immunomodulatory therapies
- More evidence needed for full insight whether this strategy should be utilized

Uncontrolled studies found benefits using mitoxantrone followed by GA or IFN-β for aggressive RRMS

- Alemtuzumab trials
  - Mixed for disability measures

Efficacy Comparator Trials

* Few randomized comparator trials
* Outcome measures are complicated and difficult to compare across studies due to variation in definition, patient characteristics, study design, and methods of analysis
* Patient severity changes over time (ARR fallen dramatically over last decade; decreased \( \sim 0.36 \))
  * Earlier trials may have enrolled more severe patients
  * Patients may be removed from the trial if relapse occurred
  * More rigid definitions of relapse

## Comparator Studies To Date

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriflunomide</td>
<td>IFN-β-1a SQ</td>
<td>No difference</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>Glatiramer acetate</td>
<td>DF improved ARR, MRI</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>IFN-β-1a IM</td>
<td>F improved ARR, MRI</td>
</tr>
<tr>
<td>Glatiramer acetate (2 trials)</td>
<td>IFN-β-1b</td>
<td>No difference both trials</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>IFN-β-1a SQ</td>
<td>No difference</td>
</tr>
<tr>
<td>IFN-β-1a SQ</td>
<td>IFN-β-1a IM</td>
<td>SQ improved relapses, MRI</td>
</tr>
<tr>
<td>IFN-β-1b SQ</td>
<td>IFN-β-1a IM</td>
<td>SQ improved relapses, MRI</td>
</tr>
</tbody>
</table>

Fox RJ, et al. NEJM 2012; 367: 1087-97  
## Combination Studies

- **Problems with immunosuppression**
- **Efficacy is questionable**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon</td>
<td>Glatiramer acetate</td>
<td>No difference</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>IFN-β (all)</td>
<td>Improvement in 7mg combo arm, but not in 14mg combo arm for ARR and MRI vs IFN-β alone</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>IFN-β-1a IM</td>
<td>Improvement in ARR and MRI vs INF alone</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Glatiramer acetate</td>
<td>Improvement in MRI vs GA alone</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>IFN-β-1a IM</td>
<td>No difference</td>
</tr>
</tbody>
</table>

Freedman MS, et al. Neurol 2012; 78: 1877-85
Summary

- Several treatment advances and treatment options have been developed over the past 20 years
  - Biomarkers & pharmacogenomics likely in future treatment

- DMT’s provide both acute and chronic MS treatment, but many unmet needs remain.

- New oral DMT therapies provide more options for patients.

Questions

http://www.une.edu/pharmacy/oce/events

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