MULTIPLE SCLEROSIS
Management and Therapy

115th Oklahoma Osteopathic Association Annual Convention
April 30th, 2015
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  - Migraine/headache
  - Neuroimmunology
  - Downtown & Edmond

Disclosures
- None
Objectives

- Define relapses in multiple sclerosis
- List treatment options for acute exacerbations
- List current FDA approved disease modifying therapies (DMTs)
- Identify and treat secondary symptoms associated with multiple sclerosis

Clinical Scenarios

- Acute Relapse, Exacerbation, Flare Up
  - Steroids
  - PLEX
- Disease Modifying Therapies (DMT’s)
  - Self-Injectables (3 options, 7 formulations)
  - Oral Meds (3 options)
  - Infusions (3 options)
- Symptomatic Management
  - Anything in ePocrates/Pharmacoepia

Relapse, Exacerbation, Flare Up

- New neurological symptom > 24 hrs
- Worsening neurological symptom > 24 hrs that had been stable for at least 30 days
- Paroxysms are brief but persist > 24 hrs
- No better explanation
- Relapses are associated with worsening disability and decreased quality of life
Pseudo-Relapse

- Uhthoff's Phenomenon: Worsening symptoms in the setting of heat exposure, overexertion, fever, infection
- Symptoms fluctuation (fatigue, pain, spasticity)

Treatment of Relapses

Classic Approach

- IV Steroids
  - Methylprednisolone
    - 1000 mg IV for 3 to 5 days
    - Speeds up recovery
    - Consider side effects
      - Insomnia, Psychosis
      - Hyperglycemia
      - GERD
      - Infection (primary or exacerbation)
      - Polyphagia

Modern Approach

- Oral Steroids (not for optic neuritis!!)
  - Methylprednisolone “Smoothie medrol”
    - 1000 mg powder in 25 cc of D5W
  - Dexamethasone (Decadron)
    - 140-200 mg PO daily x 3 days (max: 6 mg tablet)
    - 40-200 mg mixed in 25 cc of D5W (max: 1 mg/ml)
  - Prednisone
    - 500-1250 mg daily (max: 50 mg tablet)
  - ACTH (ACTHAR Gel)
    - 80-120 units daily IM/SQ for 1 week
Treatment of Relapses

Fulminant Course

- Intolerance to steroids or fulminant course
  - Plasmapheresis/Plasma Exchange (PLEX)
    - 5-7 cycles over 10-14 days

- Please note the following…
  - IVIg: highly controversial and no data supports use currently

Clinical Scenarios

- Acute Relapse, Exacerbation, Flare Up
  - Steroids
  - Plasmapheresis/Plasma exchange (PLEX)

Disease Modifying Therapies (DMT’s)

- Self-Injectables (3 options; 7 formulations)
- Oral Meds (3 options)
- Infusions (3 options)

Symptomatic Management

- Anything in ePocrates/Pharmacoepia

Disease Modifying Therapy

Primary Endpoints

- Decrease relapse rate
  - 1 relapse/2 yrs

- Slow progression of disability
  - As measured by EDSS
  - Multiple Sclerosis Functional Composite Score (MSFC)

- Stabilize the MRI
  - Reduce new T2 FLAIR lesions
  - Reduce Gd+ MRI activity
### Disease Modifying Therapy
### Therapeutic Options

#### Self-Injectables
- interferon beta 1a
  - Avonex, Rebif, Plegridy
- interferon beta 1b
  - Betaseron, Extavia
- glatiramer acetate
  - Copaxone (daily or 3/wk)

#### Oral Agents
- fingolimod (Gilenya)
- teriflunomide (Aubagio)
- dimethyl fumarate (Tecfidera)

#### Infusion Therapy
- natalizumab (Tysabri)
- alemtuzumab (Lemtrada)
- mitoxantrone (Novantrone)

### interferon beta (1a and 1b)
**Avonex, Rebif, Plegridy, Betaseron, Extavia**

- FDA approved 1993
- Modulates T-cell and B-cell function
- Reduces
  - Relapses = 30%
  - CIS → CDMS = 50%
- Dosing
  - SQ or IM
  - QOD, MWF, Weekly dosing, Biweekly dosing
  - Titrate up
- Side Effects
  - Flu-like symptoms
  - CBC (leukopenia)
  - LFT’s
  - TSH/Free T4
  - Worsening headaches
  - Worsening depression
  - Injection site necrosis
  - Neutralizing Antibodies

### glatiramer acetate
**Copaxone**

- FDA approved 1997
- Synthetic polypeptide mixture of glutamic acid, lysine, alanine and tyrosine
- Molecularly similar to myelin basic protein
- Reduces
  - Relapses = 30%
  - CIS → CDMS = 45%
- Dosing: daily or 3/wk
- Side Effects
  - Injection site
    - Redness, swelling, itching
    - Lipoatrophy
  - Post injection reactions
    - Chest/neck tightness
    - Tachycardia
    - Diaphoresis
    - Dyspnea
    - Anxiety
### Summary of Injectables

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dosing</th>
<th>Adverse Reactions</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF Beta 1a 40 mcg</td>
<td>IM</td>
<td>Weekly</td>
<td>Flu-like symptoms, Headaches, Depression, Injection site reactions, Injection site necrosis, Leukopenia, Neutropenia, Thrombocytopenia, Thyroid dysfunction, Hepatotoxicity, Seizures</td>
<td>CBC, LFTs, TSH</td>
</tr>
<tr>
<td>INF Beta 1a 22-44 mcg</td>
<td>SQ</td>
<td>Mon-WedFri</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pegIFN Beta 1a 125 mcg</td>
<td>SQ</td>
<td>Every 14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INF Beta 1b 250 mcg</td>
<td>SQ</td>
<td>Every other day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>glatiramer acetate 20 mg or 40 mg</td>
<td>SQ</td>
<td>Daily (20 mg), Mon-Wed-Fri (40 mg)</td>
<td>Lipatophy injection site reactions, Post-injection reactions</td>
<td>none</td>
</tr>
</tbody>
</table>

### fingolimod (Gilenya)
- FDA approved 2010
- Sphingosine-1-phosphate receptor modulator
- Peripheral T-cell sequestration
- Reduces
  - Relapses = 54%
  - EDSS = 30%
  - MRI = 74%, 82%
- Dose: 0.5 mg daily
- Side Effects
  - 1st dose bradycardia
  - AV Block
  - QTc prolongation
  - Torsades
  - Leukopenia
  - Hepatotoxic
  - VZV Immunity
  - Macular Edema
  - Pregnancy Class C (2 month washout)
  - P.M.L.

### teriflunomide (Aubagio)
- FDA approved 2012
- Depletes pyrimidine pool
- Reduces
  - Relapses = 31%
  - EDSS = 30%
  - MRI = 67%, 80%
- Dose: 7 or 14 mg daily
- Side Effects
  - Hair thinning
  - GI Upset
  - Hepatotoxic
  - Teratogenicity (M=F)
  - Washout needed
    - Cholestyramine
    - Activated charcoal
  - Persists for 2 years without washout
**dimethyl fumarate (Tecfidera)**
Also known as BG-12

- FDA approved 2013
- Nuclear factor-like 2 (Nrf2) pathway
- Reduces
  - Relapses = 53%
  - EDSS = 38%
  - MRI = 85%, 90%
- Dosing
  - Titrate up
  - 240 mg BID

- Side Effects
  - Cutaneous flushing
  - Nausea
  - Abdominal pain
  - Diarrhea
  - Leukopenia
  - Lymphopenia
  - P.M.L.

**Summary of Oral Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dosing</th>
<th>Adverse Reactions</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>fingolimod 0.5 mg</td>
<td>PO</td>
<td>Daily</td>
<td>Cardiac arrhythmias VZV encephalitis</td>
<td>Eye Exam</td>
</tr>
<tr>
<td>(Gilenya)</td>
<td></td>
<td></td>
<td>Macular edema Hepatotoxic Leukopenia</td>
<td>EKG CBC</td>
</tr>
<tr>
<td>terifluonmide 7 or 14</td>
<td>PO</td>
<td>Daily</td>
<td>GI Upset Hepatotoxic</td>
<td>LFT's JC Virus?</td>
</tr>
<tr>
<td>mg (Aubagio)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dimethyl fumarate 240</td>
<td>PO</td>
<td>BID</td>
<td>GI Upset Lymphopenia</td>
<td>CBC JC Virus?</td>
</tr>
<tr>
<td>mg (Tecfidera)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aka BG-12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**natalizumab (Tysabri)**

- FDA approved 2004, 2006
- Prevents CNS lymphocyte migration through the blood brain barrier
- Reduces
  - Relapses = 68%
  - EDSS = 42%
  - MRI = 83%, 92%
- Dose: 300 mg IV infusion q4 weeks x2 years
- TOUCH program

- Side Effects
  - Anxiety, fatigue, pharyngitis
  - Infusion reactions
  - Hypersensitivity reactions
  - Neutralizing Antibodies
  - P.M.L.
  - JC virus activation within the CNS
  - P.M.L. Risk
    - Serum JC Ab (+)
    - Previous immunosuppression
    - Duration of therapy
  - Maximum dose
    - 6 months – 2 years
    - Longer than 2 years??
### mitoxantrone (Novantrone)

- **FDA approved 2000 (SPMS, RRMS)**
- **T-cell killer**
- **Reduces**
  - Relapse: 67%
- **Dose:** 12 mg/m² IV infusions q3 months x2 years
- **Side Effects**
  - Max dose 140 mg/m²
  - Cardiotoxicity
    - Systolic dysfunction
    - CHF
    - Delayed
  - Leukemia

### alemtuzumab (Lemtrada)

- **FDA approved 2014**
- **Monoclonal antibody against CD52 T-cells**
- **Reduces**
  - Relapse = 54.9%
  - EDSS = 30%
- **Dose:** 12 mg IV daily for 5 days then annually for 3 days
- **Side Effects**
  - Autoimmune reactions
  - Pancytopenia
  - Opportunistic infections
    - Herpes prophylaxis
    - PCP prophylaxis
    - Thyroid dysfunction
    - Thyroid cancer
    - Renal problems
    - Lymphoma

### Summary of Infusions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dosing</th>
<th>Adverse Reactions</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>natalizumab 300 mg (Tysabri)</td>
<td>IV</td>
<td>Every 4 weeks</td>
<td>Anaphylactic reactions Opportunistic infections P.M.L.</td>
<td>JCV status LFT's</td>
</tr>
<tr>
<td>mitoxantrone 12 mg/m² (Novantrone)</td>
<td>IV</td>
<td>Every 3 months</td>
<td>Cardiotoxic (dose dependent) Leukemia</td>
<td>Echo's (for life) CBC</td>
</tr>
<tr>
<td>alemtuzumab 12 mg (Lemtrada)</td>
<td>IV</td>
<td>Annually</td>
<td>Autoimmune pancytopenia Glomerular basement membrane disease Glomerulonephritis Autoimmune thyroiditis Thyroid cancer Lymphoma Opportunistic infections</td>
<td>CBC TSH-Free T4 Renal Tests Urinalysis</td>
</tr>
</tbody>
</table>
Novel Drugs

- Laquinimod (FDA approval not being sought)
- Daclizumab (CD25)
  - SQ injection x1 monthly
  - DECIDE: phase 3 trial against avonex
- Ocrelizumab (CD20 B-cells; rituximab [89%])
  - IV infusion (f frequency)
  - ORATORIO, OPERA I & II

Example Comparison of DMT’s

<table>
<thead>
<tr>
<th>Study Agent</th>
<th>Natalizumab</th>
<th>Fingolimod</th>
<th>Teriflunomide</th>
<th>Laquinimod</th>
<th>BG-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse rate reduction</td>
<td>68%</td>
<td>54%</td>
<td>31%</td>
<td>27%</td>
<td>53%</td>
</tr>
<tr>
<td>Annualized relapse rate reduction</td>
<td>0.22</td>
<td>0.18</td>
<td>0.37</td>
<td>0.28</td>
<td>0.17</td>
</tr>
<tr>
<td>Absolute relapse rate reduction</td>
<td>0.50</td>
<td>0.22</td>
<td>0.17</td>
<td>0.05</td>
<td>0.19</td>
</tr>
<tr>
<td>Number needed to treat (2-year relapse)</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Relative reduction in new T2 and gadolinium-positive lesions at 12 months</td>
<td>92% in T2</td>
<td>82% in T2+</td>
<td>86% in T2+</td>
<td>76% in T2+</td>
<td>90% in T2+</td>
</tr>
<tr>
<td>Relative reduction in expanded disability status scale progression</td>
<td>42%</td>
<td>35%</td>
<td>36%</td>
<td>38%</td>
<td>38%</td>
</tr>
<tr>
<td>Absolute reduction in proportion progressing</td>
<td>0.120</td>
<td>0.064</td>
<td>0.071</td>
<td>0.036</td>
<td>0.110</td>
</tr>
<tr>
<td>Number needed to treat (2-year progression)</td>
<td>8</td>
<td>14</td>
<td>14</td>
<td>26</td>
<td>9</td>
</tr>
</tbody>
</table>

Clinical Scenarios

- Acute Relapse, Exacerbation, Flare Up
  - Steroids
  - Plasmapheresis/Plasma exchange (PLEX)
- Disease Modifying Therapies (DMT’s)
  - Self-Injectables (3 options; 7 formulations)
  - Oral Meds (3 options)
  - Infusions (3 options)
- Symptomatic Management
  - Anything in ePocrates/Pharmacoepia
Fatigue

- >90% of patients, disability
- Consider
  - Apnea, RLS, spasticity, pain, bladder issues
  - Endocrine, metabolic, anemia, nutritional
  - Temperature effects
- Management
  - Address secondary causes
  - Rehab and cooling
  - Pharmacologic interventions

Fatigue – Management

- Amantadine: 100 mg QD to TID
- Modafinil: 25-200 mg BID
- Methylphenidate: 5-20 mg QD
- Adderall: 5-40 mg QD
- Fluoxetine: 10-40 mg QD
- Bupropion: 100-450 mg QD
- 4-Aminopyridine (4-AP): 10 mg BID-TID
Weakness

- PT, OT, orthotics, mobility equipment
- Rehabilitation goals
  - Maintain functional independence
  - Minimize the impact of existing impairments
  - Restore function after a relapse
  - Adaptation to change

Walking Speed (and fatigue!)

- 4-aminopyridine, Dalfampridine (Ampyra)
  - Broad spectrum potassium channel blocker that enhances action potential conduction across demyelinated axons
  - 10 mg BID
  - Seizures, renal failure
- T25-FW at baseline and at 3 months

Ataxia

- Non-pharmacologic
  - Rehabilitation
- Pharmacologic
  - Clonazepam
  - Gabapentin
  - Primidone
  - Propranolol
- Surgical
  - DBS
Neuropathic Pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants: amitriptyline, desipramine, duloxetine</td>
<td>Pain</td>
<td>Generally paroxysmal and transient</td>
</tr>
<tr>
<td>Gabapentin: 300 mg to 4800 mg</td>
<td>Pregabalin: 75 mg to 600 mg</td>
<td>to help fatigue in some cases</td>
</tr>
<tr>
<td>Carbamazepine: 200 mg</td>
<td>Severe facial pain</td>
<td></td>
</tr>
<tr>
<td>4 times daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin: 300 mg to 4800 mg</td>
<td>Pregabalin: 75 to 600 mg</td>
<td></td>
</tr>
</tbody>
</table>

Spasticity

- Tight muscles, resistant to stretch
- Often associated with weakness, spasms
- Lower >> upper extremities and may manifest early as gait disturbance
- Increase energy expansion leading to fatigue
- May be perceived as pain!

Spasticity – Management

- Non-pharmacologic
  - Physical therapy: stretching, positioning, range of motion
  - Orthotics
- Pharmacologic
  - Individualized treatment
  - Start at bed time and increase slowly
  - Spasticity helps weight bearing
Spasticity – Management

- Baclofen: 10 mg -160 mg/day
- Tizanidine: 4 mg – 36 mg/day
- Diazepam: 2.5 mg – 40 mg/day
- Gabapentin: 100 mg – 4800 mg/day
- Dantrolene: 25 mg – 400 mg/day
- Other agents:
  - levetiracetam
  - onabotulinumtoxinA (BOTOX)

Spastic Bladder

- oxybutynin (Ditropan and Ditropan XL)
  - 5 mg BID-TID...max 30 mg/day
- tolterodine (Detrol and Detrol LA)
  - 1 mg BID...max 4 mg/day
- trospium (Sanctura and Sanctura XR)
  - 20 mg BID or 20 mg QHS (elderly)
- darifenacin (Eneblex)
  - 7.5 mg – 15 mg/day
- Solifenacin (Vesicare)
  - 5 mg – 10 mg/day

Nocturia

- Desmopresin
  - Analog of antidiuretic hormone
  - 0.2 - 0.6 mg po QHS
  - Restrict fluid intake >1h before administration until next morning
  - Hold treatment if acute illness
  - Frequent monitoring for hyponatremia
Other Symptoms Often Forgotten

- Depression
- Pseudobulbar affect
- Cognition
- Intimacy

Depression

Consider….
- Insomnia, anxiety, emotional liability
  - Paroxetine, trazodone, TCAs
- Panic attacks
  - Buspirone
- Lack of energy or concentration problems
  - Venlaxafine, buproprion
- Sexual dysfunction
  - Buproprion +/- SSRI

Pseudobulbar Affect

Nuedexta: dextromethorphan 20 mg/quinidine 10 mg
- Once a day for a week then bid
- EKG – QT prolongation risk
- S/E: thrombocytopenia, lupus-like syndrome, hepatitis, spasticity, peripheral edema
- C/I: MAO Inh, prolonged QT interval, heart failure, complete AV block
- Avoid if patient is taking SSRI or TCAs
Cognitive Impairment

- Impaired processing speed is one of the most common deficits
- Other: attention, executive functioning, reduced memory retrieval
- The ability to consolidate new memories usually remains intact
- Neuropsychological testing
- CBT, psychotherapy
- Pharmacologic interventions

Heat Sensitivity
Uhthoff’s Phenomenon

- Unmasking or worsening of neurological Symptoms
  - Heat, infection, prolonged exercise, perimenstrual period, psychological stress
- Cooling methods

A Word about Pregnancy

- Number of relapses usually decreased, especially during 3rd trimester
- Increase in attack rate post-partum
- Goal is not to use DMTs
- No difference in pregnancy outcomes
- DMTs
  - Category C drugs, except GA (category B)
  - Increase rate of spontaneous abortions
- Acute relapses: IV steroids or PLEX
Barriers to Better Outcomes in MS

- Disease Modifying Therapy
  - Poor adherence to therapy
  - Partial efficacy of available DMTs
  - Suboptimal prescribing of DMTs
- Diagnostic issues
  - Lack of a biological marker
  - Completing the puzzle
- Managing the individual patient
  - Heterogeneity of MS

Patient Assistance Programs

- National MS Society
  - http://www.nationalmssociety.org/
- Patient Access Network Foundation
  - http://www.panfoundation.org/
- Partnership for Prescription Assistance
  - https://www.pparx.org
- Needy Meds
  - http://www.needymeds.org/index.htm
- Local Pharmaceutical Representative!

Objectives

- Define relapses in multiple sclerosis
- List treatment options for acute exacerbations
- List current FDA approved disease modifying therapies
- Identify and treat secondary symptoms associated with multiple sclerosis