Multiple Sclerosis

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Epidemiology of MS

- Most common cause of nontraumatic neurologic disability in young adults
- Higher prevalence in women (3.2:1 F:M)


Populations Affected

- 1 in 800 North Americans and Europeans are affected
- 300,000-500,000 affected in US
- 2+ million worldwide
- Uncommon among North and South American First Nationals, Chinese, Japanese, African blacks, Samis, Turkmen, Uzbeks, Kazakhs, Kyrgyz, native Siberians, and New Zealand Maori
- Mortality rate of 1.44/100,000


Treatment of MS

- 13 approved disease modifying therapies (DMTs)
- 20+ symptom management therapies

Objectives

- Discuss MS Disease Modifying Therapies (DMTs) and symptom management therapies that your patients might be taking
- Increase awareness of the benefits of these treatments, versus the possible adverse reactions and the required monitoring associated with such treatments
- FDA approved
- Future DMTs

Itinerary

- Symptom management
- DMTs
Owe My Soul to the Company Store

- No financial associations

11:35

Symptoms Therapy

- Spasticity
- Pain
- Fatigue
- Heat intolerance
- Depression
- Cognition

Spasticity

- Baclofen (Lioresal®) oral (10-80mg/d) intrathecal
  - Drowsiness, N/V, nausea, hypotonia
- Tizanidine (Zanaflex®) up to 32mg/d
  - Hypotension, somnolence, dizziness, vertigo, hypotonia

Spasticity

- Diazepam (Valium®)
  - 5-10mg qhs
- Dantrolene (Dantrium®)
  - Flushing, Drowsiness, N/V, Hepatitis: routine LFTs
- Gabapentin (Neurontin®)

Pain

- Occurs in 43-80% of MS patients
- Painful spasms
- Neuropathic pain: Dysesthesias or Alldynia;
  - Common qualities of neuropathic pain includes burning or coldness, "pins and needles" sensations, numbness and itching and episodic electric shocks

MS Pain Control

- Neuroleptics
  - gabapentin (Neurontin®) up to 3600mg/d
  - pregabalin (Lyrica®) 75-225mg BID
  - Drowsiness, dizziness, ataxia, edema, H/A, blurred vision, weight gain
- TCAs
  - Nortriptyline 25-150mg/d
  - Amitriptyline
  - Anticholinergic effects, sedation
- Opiates can be beneficial
Fatigue

- Fatigue is a major problem for most MS patients
- Most have good energy level in morning but by noon are intensely “fatigued” but rarely take naps.
- Most likely due to axonal loss

Depression is Common

- Significant depressive symptoms found in 42% of the subjects, and 29% of the subjects had moderate to severe depression
- Advanced multiple sclerosis patients much more likely to experience clinically significant depressive symptoms than subjects with minimal disease

Depression

- SSRIs preferred because of activating properties.
  - Citalopram
  - Clomipramine
  - Desvenlafaxine
  - Duloxetine
  - Escitalopram
  - Fluoxetine
  - Fluvoxamine
  - Nefazodone
  - Paroxetine
  - Sertraline
  - Venlafaxine

Cognition

- 30-70% of MS patients have cognitive deficits, which may present early even in the absence of physical disability
- About 10% have severe cognitive dysfunction
- Frequent complaints of poor memory
- Processing speed
- No therapy “F”

Fatigue Symptom Management

- Reduce fatigue-producing medications
- Evaluate for medical condition (OSA, depression, anemia)
- Energy conservation counseling
- Drugs:
  - Amantadine (100-200mg AM and Noon)
  - Modafinil (Provigil®, 100-200mg AM and Noon)
  - Left ventricular hypertrophy
  - Mitral valve prolapse
  - Armodafinil (Nuvigil®)
  - Ritalin®

Natural History of RR/SP-MS

- Measures of brain volume
- Relapses and impairment
- MRI burden of disease
- MRI activity


Sir Augustus Frederick d’Este

His symptoms began at age 28 (1822) with a sudden transient visual loss after the funeral of a friend. During the course of his disease he developed weakness of the legs, clumsiness of the hands, numbness, dizziness, bladder disturbances, and erectile dysfunction. By 1843 he was experiencing persistent symptoms including tremor and nocturnal spasms, and by age 50 was using a wheelchair.

Treatments for Sir Augustus Frederick d’Este

“bleded from the temple by leeches”
“Purges were administered; One Vomit”
“twice lost blood from the arm”
“A course of electricity”
“Tincture of Cantharidae”
Ingestion of strychnine, metallic salts, tonics, laxatives various powders and potions.

Acute Relapse Treatment

- High potency steroids are the treatment of choice to suppress acute MS relapses
- 1 gram of methylprednisolone IV qd for 3-5 days, may be followed by an oral prednisone taper:
  \[ \text{1mg/kg/day} \]
- Out patient IV therapy

Primary Progressive MS

- Primary Progressive MS: ~15% of MS cases
- Sx onset about 10 years later than RRMS (mean 39 yo) even though MRI lesions are present much earlier
- Progressive paraparesis is the most common presentation (most often of the legs)
- Irreversible disability
- The course of PPMS disability is similar to SPMS (50% of RRMS pts. are in SPMS by age 39)

Treatment of PPMS

- Current treatments are “anti-inflammatory”
- Reduced inflammatory signs in progressive MS
- Several trials designed specifically for PPMS
- No DMT has shown definite modification of the patients’ course of MS

“First-Line” DMTs

1993 - Interferon-β-1b (Betaseron®) [250 mcg, SQ qod]
1995 - Interferon-β-1a (Avonex®) [30 mcg/wk IM]
1996 - Glatiramer copolymer (Copaxone®) [20 mg SQ qd]
2000 - Mitoxantrone approved for SPMS
2002 - Interferon-β-1a (Rebif®) [44 mcg, SQ MWF]
**Mitoxantrone Risk management**

- Pregnancy: Category D

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk Factors</th>
<th>Risk Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac toxicity</td>
<td>Prior cardiovascular diseases, prior radiotherapy, total cumulative mitoxantrone dose</td>
<td>Echocardiography or multigated acquisition scan before each dose. Limit total cumulative dose to less than 120-140 mg/m².</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Unknown</td>
<td>Unknown, but may occur many years later</td>
</tr>
</tbody>
</table>

**Interferon Beta**

- The mechanism of effect(s) are not completely understood.
- Reduce annualised relapse rates by about 30%.
- Have beneficial effects on MRI measures of disease activity.
- Decrease sustained disability accumulation by 12–37% compared to placebo.
- Generally used as first-line drugs because of their benign adverse event profile.

**Interferon Beta Risk Management**

- Pregnancy: Category C

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<thead>
<tr>
<th>Complication</th>
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</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>History of cytopenia or bone marrow suppressant use</td>
<td>Baseline and periodic CBC.</td>
</tr>
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</table>

**Pegylated Interferon (Plegridy®)**

- Interferon beta-1a with attached polyethylene glycol group.
- 125 mcg SQ injection. Twice a month.
- Relapse rate and disability progression slightly better than plain INFB.
- Adverse reactions: same as INFB.
Glatiramir Acetate
Glutamic Acid-Lysine-Alanine-Tyrosine
- The mechanism of effect(s) are not completely understood
- Reduce annualised relapse rates by about 30%
- Have beneficial effects on MRI measures of disease activity,
- Decreased sustained disability accumulation by 12–37%
- Generally used as first-line drugs because of their benign adverse event profile

Generic Glatiramir
- Mylan Pharmaceuticals has released 20mg qd dosing with planned 40mg 3x/wk dosing
- Momenta Pharmaceuticals approved for Glatopa 20mg qd

Glatiramir Risk Management
- Pregnancy Category B

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk Factor</th>
<th>Risk Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic reaction</td>
<td>Previous sensitivity to glatiramer acetate</td>
<td>None needed as syndrome is self-limited</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td></td>
<td>Injection site rotation</td>
</tr>
</tbody>
</table>

Glatiramir Double Dose
- Usual dose has been 20mg 80 qd
- GALA Study: 40mg formulation 3x/week 1900 patients study against placebo
- FDA approved January 2014
- Total yearly dose 20mg qd: 7300mg
  40mg 3x/week: 6240mg

Natalizumab
- 11/2004 - Natalizumab (Tysabri®) FDA approved
- 2/2005 - Natalizumab withdrawn by manufacturer
- 7/2006 - Natalizumab limited approval (TOUCH program)

Natalizumab
Humanized monoclonal antibody that binds to the α4β1 integrin dimer cell-surface adhesion molecule on activated T-cells preventing attachment to endothelium and thus blocking passage through the blood–brain barrier.
**Natalizumab**

- 68% reduction in annualized relapse rates
- 92% reduction in mean GD+ MRI lesions
- Significant decrease in disability progression
- Evidence of axonal preservation
- Reduction in the percentage of patients with MS-related inpatient stays (7.6% versus 2.4%, P<0.001)

**Natalizumab Risk Management**

- Pregnancy: Category C

<table>
<thead>
<tr>
<th>Complication</th>
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<tbody>
<tr>
<td>Progressive multifocal leukoencephalopathy (PML)</td>
<td>JC virus antibody test results, previous treatment with natalizumab, previous anaphylaxis-like reactions</td>
<td>JC virus antibody test results, at least every 6 mo. Repeat MRI? Reconsideration of risk/benefit after seroconversion Prompt evaluation for PML if suspected, even if JC virus seronegative</td>
</tr>
</tbody>
</table>

**Estimated Risk of Natalizumab-Related Progressive Multifocal Leukoencephalopathy According to Currently Known Risk Factors**

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Negative</td>
<td></td>
<td>1/1000</td>
<td>1/1000</td>
<td>1/1000</td>
</tr>
<tr>
<td>Positive No</td>
<td></td>
<td>1/1000</td>
<td>3/1000</td>
<td>6/1000</td>
</tr>
<tr>
<td>Positive Yes</td>
<td></td>
<td>1/1000</td>
<td>12/1000</td>
<td>13/1000</td>
</tr>
</tbody>
</table>

**MRI in PML**
Most common presenting symptoms are cognitive, motor, language, visual impairment and seizures

Plasmapheresis has been shown to accelerate removal of natalizumab, accelerate desaturation of the targeted alpha-4 integrin receptor, and restore leukocyte transmigration in vivo

3 sessions of plasma exchange over 5-8 days.

PML - Plasmapheresis - IRIS

- Immune reconstitution inflammatory syndrome (IRIS) has been reported in the majority of TYSABRI-treated patients who developed PML. IRIS occurred after plasma exchange and may occur days to months after plasma exchange
- Massive inflammation
- IRIS can lead to severe clinical manifestations, including brain swelling and death
- Tx after IRIS develops: IV methylprednisolone and a minimum of 1 month of oral tapering of corticosteroid

Estimated Risk of Natalizumab-Related Progressive Multifocal Leukoencephalopathy According to Currently Known Risk Factors

PML incidence in Natilizumab patients is 3.96/1000 pts

Of those who developed PML:
77% patients survived but with varying levels of disability
23% of patients have died

New DMTs – The Orals

- Sep 22, 2010 - Fingolimod (Gilenya®)
- Sep 12, 2012 - Teriflunomide (Aubagio®)
- Mar 27, 2013 - Dimethyl Fumarate (Tecfidera®)

Dimethyl Fumarate (Tecfidera®)

- 165,000 MS pts world wide, about 1600 in Iowa
- Increased production of anti-inflammatory “TH2” cytokines IL-4 and IL-5 in stimulated T-cells
- First used in 1959 to treat psoriasis in Germany but is used in a different dosing pattern
- Also effective in treatment of a number of other skin disorders
**Dimethyl Fumarate**

- Starting dose: 120 mg twice a day, orally, for 7 days
- Maintenance dose after 7 days: 240 mg twice a day, orally
- DEFINE and CONFIRM trials
  - Reduced annualized relapse rate ~50% (P<0.001)
  - Reduced Gd enhancing lesions 80+% vs placebo (P<0.001)

**Risk Management**

<table>
<thead>
<tr>
<th>Complication</th>
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<th>Risk Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Unknown</td>
<td>Tx symptoms</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>Unknown</td>
<td>Pretreatment with NSAID</td>
</tr>
<tr>
<td>Lymphopenia, PML</td>
<td>Unknown</td>
<td>Err complete blood count (abs. lymphocyte count)</td>
</tr>
</tbody>
</table>

**Teriflunomide**

- Active metabolite of anti-rheumatic drug leflunomide
- Affects pyrimidine synthesis and thus inhibits rapidly dividing cells, e.g. activated T cells

**Adverse Reactions**

- Leucopenia
- Alopecia
- Hyperkalemia
- Serious skin problems
- Breathing problems (new or worsening)
- High blood pressure

**Risk Management**

<table>
<thead>
<tr>
<th>Complication</th>
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<th>Risk Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver toxicity</td>
<td>History of liver disease, concomitant hepatotoxic medications</td>
<td>Baseline and monthly LFTs during first 6 mo. of treatment</td>
</tr>
</tbody>
</table>
Teriflunomide Risk Management

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk Factors</th>
<th>Risk Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactivation of tuberculosis</td>
<td>Latent tuberculosis</td>
<td>Baseline purified protein derivative or QuantiFERON test</td>
</tr>
</tbody>
</table>

- Pregnancy Category: X

Teriflunomide Clearance

- Very slow elimination unless:
- Cholestyramine 8 gm po q8 hours or 50 gm activated charcoal powder po BID for 11 days

Fingolimod

- Derived from myriocin, extracted from a traditional Tibetan-Chinese medicinal fungus Isaria sinclairii
- Sphingosine-1-Phosphate receptors agonist (S1P)
- Binds to 4 of 5 known S1P isoforms
- Blocks release of T-cells from lymph nodes
- May also modulate B-cell circulation
- Impairs CD8 T-cell function
- Direct effects on CNS glia

Fingolimod Dosage: 0.5 mg orally once daily.

- Reduced annualized relapse rate 55% (P=0.003)
- MRI lesions reduced 61% (P=0.006)
- Modest decrease in disability progression in patients treated for five years

Fingolimod Adverse Reactions

- Deaths: disseminated primary varicella zoster and herpes simplex encephalitis
- PML: 3 cases
- H/A: Influenza, diarrhea, back and extremity pain, posterior reversible encephalopathy syndrome
### Fingolimod Risk Management

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk Factors</th>
<th>Risk Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular edema</td>
<td>Diabetes, Hx of Uveitis</td>
<td>Fundus exam prior to treatment and 3-4 months after initiation of treatment</td>
</tr>
<tr>
<td>Liver Injury</td>
<td></td>
<td>LFTs and bilirubin prior to initiation and routinely</td>
</tr>
<tr>
<td>Bradyarrhythmias</td>
<td>History of cardiac disease or stroke</td>
<td>Cardiology consultation for those with cardiac risk factors or abnormal baseline EKG.</td>
</tr>
<tr>
<td></td>
<td>Current treatment with antiarrhythmic agents</td>
<td>Aliing baseline EKG. Prolonged cardiac monitoring for both those with baseline cardiac risk factors and those with events in first 6 hr.</td>
</tr>
</tbody>
</table>

### New DMTs – The Big Gun

- More Monoclonal antibody treatments

### Alemtuzumab (Lemtrada®)

- CamPath 1H: Humanized monoclonal antibody against the CD52 receptor present on at least 95 per cent of all human peripheral blood lymphocytes.
- Near complete depletion of targeted cells, probably forever
- Effectiveness is most likely due to change in the composition of lymphocyte population
  - In first 8 months post treatment, T-cell population consists predominantly of memory T cells of a regulatory phenotype and reduced cytokine expression
  - B lymphocytes are predominately naive, and there is a slow reconstitution of memory B lymphocytes

### Alemtuzumab vs Rebif

<table>
<thead>
<tr>
<th></th>
<th>Interferon beta-1a</th>
<th>Alemtuzumab pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from relapse</td>
<td>K-M estimate, no event (95% CI): 51.2%</td>
<td>77.6%</td>
</tr>
<tr>
<td>Freedom from CDA: K-M estimate no event (95% CI):</td>
<td>42.6%</td>
<td>71.8%</td>
</tr>
</tbody>
</table>

CDA: defined as no relapses and no sustained accumulation of disability.
All trials showed reduction in cerebral atrophy.

Alemtuzumab

- Initial treatment: Daily infusions x 5 days.
- One year later 3 daily infusions.
- There are no current recommendations for further treatments after second round of infusions.
- >90% have infusion reactions: nausea, hives, itching, difficulty sleeping, chills, flushing, fatigue, shortness of breath, congestion of the lungs, upset stomach, dizziness and more.

Alemtuzumab Risk Management

- Pregnancy Category C

<table>
<thead>
<tr>
<th>Complication</th>
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<th>Risk Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid dysfunction</td>
<td>Interleukin-21 levels</td>
<td>Monthly CBC, creatinine, U/A, TSH for 4 years after last dose.</td>
</tr>
<tr>
<td>Immune thrombocytopenic purpura</td>
<td>One Death</td>
<td></td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B-cell anti-CD20 antigens

- Rituxumab
- Ocrelizumab
- Ofatumumab

Ocrelizumab

- Immune-suppression by depleting mature B cells primarily through antibody-dependent cellular cytotoxicity
- Reduces presentation of autoantigens to T cells.
- When CD20 labeled B cells re-emerge, they are less pro-inflammatory than before depletion

Ocrelizumab

- Infusion once every 4 months
- In Phase II: relative reduction annualized relapse rate as much as 80%
- Phase III: one against INFB, results to be announced at ECTRIMS in Barcelona next month

Ocrelizumab

- Infusion-related events during first infusion: 35%
- Decreased to rates comparable to placebo with the second infusion
- Adverse events associated with ocrelizumab, including serious infections, "was similar to beta interferon"
Daclizumab (Zinbryta®)
- Approved 1997 for treatment of acute renal transplant rejection

Daclizumab for MS
- 150 mg SQ injections every 4 weeks
- Reduced relapse rate 50-64%
- Reduced new/newly-enlarging T2 lesions in highly active RRMS by 76%, p<0.0001
- SELECTION trial: disability progressed in 11% of patients in first year and 5% second year
- Phase III against INFβ (DECIDE trial ended 3/14)
- Phase III OBSERVE open label trial

Daclizumab Adverse events:
- Up to 20% patients reported skin reactions and alopecia, mostly mild to moderate but about 1% hypersensitivity reactions
- LFT ≥5x normal in 4% of daclizumab-treated patients. One death due to autoimmune hepatitis. In clinical trials onsite testing of LFT immediately prior to each dosing
- Increased URI and UTI. One death due to psoas abscess
- 7-9%, fever, fatigue, tremor, headache, arterial hypertension, dyspnoea, gastrointestinal side effects lymphadenopathy and oedema, breast nodules

Future
What will the providers of 2020 have to say about our “modern” treatments for our patients with Multiple Sclerosis?
**Baclofen (Lioresal®)**

- Adverse reactions: Drowsiness, h/a, nausea, hypotonia
- Monitoring: None

**Tizanidine (Zanaflex®)**

- Adverse reactions: Hypotension, somnolence, dizziness, xerostomia, hypotonia
- Monitoring: None

**Amantadine**

- Adverse reactions: Dreams, agitation, confusion, orthostatic hypotension, edema, xerostomia

**Modafinil (Provigil®)/Armodafinil (Nuvigil®)**

- Contraindications: Left ventricular hypertrophy. Mitral valve prolapse
- Monitoring: None

**Interferon-β-1b (Betaseron®)/Interferon-β-1a (Avonex®)/Interferon-β-1a (Rebif®)**

- Adverse reactions: Leukopenia, liver toxicity, Depression/Suicide risk
- Antidepressant medications, Psychology/psychiatry referral. Prompt discontinuation if severe depression develops
- Monitoring: Baseline and routine CBC, LFTs

**Natalizumab**

- Adverse reactions: PML: Changes in cognition, strength speech, visual impairment or Seizures
- Monitoring: JC virus titre 2-3x/yr.

**Dimethyl Fumarate (Ticfedera®)**

- Adverse reactions: Leukopenia, PML
- Monitoring: CBC every 6 months

**Teriflunomide (Aubagio®)**

- Adverse reactions: Leucopenia, alopecia, hyperkalemia, serious skin problems, breathing problems (new or worsening), High blood pressure, teratogenicity:
  - Very slow elimination unless: Cholestyramine 8 gm po q8 hours or 50 gm activated charcoal powder po BID for 11 days
- Monitoring: Baseline and monthly LFTs for first 6 months. Baseline PPD or QuantiFERON test, Baseline pregnancy test and reliable contraception.

**Fingolimod (Gilenya®)**

- Adverse reactions: H/As, Influenza, diarrhea, back and extremity pain posterior reversible encephalopathy syndrome, bradyarrhythmias: PML
- Monitoring: With initiation—ALL patients must have EKG, be observed for 6-hr. and EKG at end of observation.

**Alemtuzumab (Lemtrada®)**

- Adverse reactions: infusion reactions: nausea, hives, itching, difficulty sleeping, chills, flushing, fatigue, shortness of breath, congestion of the lungs, upset stomach, dizziness and pain. Thyroid dysfunction, Immune thrombocytopenic purpura, Goodpasture syndrome.
- Monitoring: Monthly CBC, creatinine, U/A, TSH for 4 years after last dose.

**Daclizumab (Zinbryta®)**

- Adverse reactions: skin reactions and alopecia, Liver toxicity, URI and UT, fever, fatigue, tremor, headache, arterial hypertension, dyspnoea, gastrointestinal side effects lymphadenopathy and oedema, breast nodules