Multiple Sclerosis

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conflicts of interest

- Research Support: Biogen Idec, Novartis, Mallinkrodt, Genzyme, Sanofi-Aventis, Teva, Opexa, Roche
- Advisory Boards: Biogen Idec, Genzyme, Novartis,
- Speaking Honoraria: Biogen Idec, Novartis, Genzyme, Acorda
Multiple Sclerosis

- Multiple sclerosis is an auto-immune, inflammatory, degenerative disease of the CNS.
- Left untreated, MS results in progressively worsening disability, with 85% of such patients becoming permanently and severely disabled within 30 years of onset.
The Course of MS
Historical Progression of Untreated MS

Frequency of Conversion from RRMS to Progressive MS

Weinshenker BG, et al
Multiple Sclerosis
Epidemiology

- MS is most common cause of severe disability in young and middle aged adults in North America.
- Has 2.6-2.9 fold increase in age-adjusted mortality compared to the general population under age 65.
Multiple Sclerosis Epidemiology

- There are between 400,000 and 500,000 cases of MS in North America.
- The further from the equator a person lives, the greater the risk of having MS.
- MS is common in the Pacific NW, with an estimated 8,000 cases in Oregon, or greater than 2:1000 vs 1.3-1.4:1000 nationwide.
Multiple Sclerosis
Epidemiology

- There is considerable evidence linking low Vitamin D levels, particularly early in life, and perhaps in utero, to the risk developing MS.

  a. Frequent monitoring and maintaining serum vitamin D, 25-OH levels at high physiological range is becoming a mainstay of MS management.
Multiple Sclerosis
Epidemiology

Although MS is found in all racial groups, the disease risk is highest in individuals of European, and lowest in those of African and East Asian heritage.

To date, over 100 different single nucleotide polymorphisms that confer genetic risk for MS have been identified, and almost all are immune reg. genes
Multiple Sclerosis

- Multiple Sclerosis prevalence is much higher in females, and is continuing to rise with the current F/M ratio of 3-4:1
- The risk of MS, which is approx 1/700 in North America, is 10 times higher in first-order relatives of MS patients, 1/20 in a dizygotic and 1/3 in a monozygotic twin
Multiple Sclerosis Pathogenesis

- It is believed that the disease has an exogenous “trigger”, possibly viral.
- There have been many candidate infectious agents in the past, but currently EB virus is the leading candidate.
- Exogenous toxins have also been implicated as possible candidate.
Multiple Sclerosis Pathogenesis

- Auto-reactive B-cell and T-cell lymphocytes appear to be the primary disease mediators.

- Although abnormal antibodies are produced in the CNS, oligoclonal globulins, there is no direct evidence that they are pathogenic in MS, but instead may be anti-viral globulins.
Inflammatory MS Lesion

Inflammatory Trafficking into the CNS in Multiple Sclerosis

1. Immune cells pass through blood-brain barrier
2. Immune cells may re-activate and produce cytokines
3. Immune cells stimulate autoimmune attack against myelin
Gd-Enhanced T1-Weighted Scans

- T1-weighted scans with Gd contrast
- Show areas of BBB disruption, the MS-initiating event
- Indicative of acute inflammatory activity within CNS

Miller et al., 1999.
Axonal Demyelination in MS Lesions

Trapp et al. 1998.
Axonal Changes in MS Lesions

Trapp et al. 1998
Although typically thought of as primarily a demyelinating white matter disease, cortical and deep gray matter atrophy also occur and are strongly correlated with disability progression.
Clinical Course of Multiple Sclerosis

- Relapsing-remitting
- Secondary progressive
- Primary progressive
- Progressive relapsing
Multiple Sclerosis Diagnosis

- Diagnosis of Relapsing form of MS
  1. One or more episodes of acute or subacute CNS impairment of brain, optic nerve or spinal cord localization
  2. MRI findings typical of MS and/or
  3. CSF oligoclonal bands or increased CSF IgG
The diagnosis of progressive MS requires:
1. progressive worsening of neurological impairment without acute attacks and,
2. MRI findings and/or CSF findings consistent with the diagnosis
3. If there is a prior history of relapses, it is secondary progressive and if no prior relapses, it is primary progressive MS
Multiple Sclerosis
Symptoms

1. Visual loss, especially monocular
   Diplopia
   Vertigo
2. Weakness, especially monoparesis or paraparesis, and hemiparesis
3. Gait impairment
4. Ataxia
Multiple Sclerosis Symptoms

5. Sensory symptoms, particularly numbness, tingling, burning or electricity-like pain, especially but not limited to the lower extremities, one upper extremity, or the face

6. Trigeminal neuralgia

7. Neurogenic bladder impairment
Multiple Sclerosis
Symptoms

8. Fatigue, can be incapacitating and found in up to 90% of MS patients

9. Depression, in 42% of patients in the Pacific NW MS Registry

10. Cognitive impairment affecting short term memory, concentration, multitasking, speed of thinking and word/name recall.
Multiple Sclerosis Differential

- ADEM/Transverse Myelitis
- Neuromyelitis Optica
- Lupus
- Sarcoidosis
- CNS vasculitis
- HIV
- Neoplasia, especially CNS lymphoma
- Syphilis
Multiple Sclerosis

Until 1995, there were no medications of proven benefit, approved for use in patients with MS. There are now 11 FDA-approved disease modifying therapies of proven benefit for relapsing forms of MS. In addition, high dose corticosteroids and ACTH are approved for acute relapse treatment only.
Multiple Sclerosis
When to start treatment?

- As soon as the diagnosis of relapsing MS is made.
- The sooner therapy is initiated:
  a. the better the long term outcome in preventing future relapses, and disability
  b. possibly forestalling onset of progressive form of the disease

Rio et al, 2006; Rudick et al, 2009; Scalfari et al, 2010; Jacobs et al, 2000;
Multiple Sclerosis
Disease Modifying Therapies

- Interferon beta:
  1. reduces production of pro-inflammatory cytokines such as gamma interferon, interleukin 2 and tumor necrosis factor-α
  2. inhibits immune cell migration into target organ
  3. promotes anti-inflammatory T-cell (Th 2) lymphocyte production
Multiple Sclerosis
Interferon beta

1. Interferon beta-1a
   - 30 mcg IM weekly
   - 44 mcg subQ TIW

2. Pegylated IFN b-1a
   - 125 mcg subQ q14 days

3. Interferon beta-1b
   - 250 mcg subQ TIW

IFNBMSSG, 1995; Rudick et al, 1997; PRISMS 1998; Johnson et al, 1998;
Multiple Sclerosis
Interferon Beta Risks

- Flu-like symptoms - treat with NSAIDs and hydration
- Cutaneous reactions to subQ preparations
- Respiratory & urinary tract infections
- Increased depression and suicidality
- Hepatic failure
- Pregnancy Category C
Multiple Sclerosis
Glatiramer Acetate

- Causes shift away from pro-inflammatory (Th 1) to anti-inflammatory (Th 2) T-cell lymphocyte phenotype
  1. 20 mg subQ daily or
  2. 40 mg subQ TIW

Risks: Cutaneous injection site reactions
Pregnancy category A
Multiple Sclerosis

Beta-interferons and glatiramer

1. all reduce relapse rate
2. all reduce disease activity on MRI
3. IFN-beta 1a significantly reduces risk of sustained disability progression (over 2 years observation in placebo-controlled trials)
Multiple Sclerosis
Oral agents

- Fingolimod
- Dimethyl fumarate
- Teriflunomide

Each reduces relapse risk, MRI disease progression and sustained disability progression (over 2 year duration of controlled trials).
Multiple Sclerosis
Fingolimod

1. 0.5 mg PO daily
2. Putative mechanism of action is to prevent release of reactive central memory T- and B-cell lymphocytes from peripheral lymphoid organs
3. Superior to interferon beta in head-to-head trial in reducing relapses and MRI changes

Multiple Sclerosis
Fingolimod

- Risks: Cardiac conduction impairment and sudden death, hypertension, bronchoconstriction, macular edema and increased risk of herpetiform infections, severe lymphopenia, and one ALL and one PML case
- Contraindicated in patients with heart block, use of anti-arrhythmics, coronary artery disease, reactive airway disease, hx of uveitis
Multiple Sclerosis
Fingolimod

Relative contraindication for diabetics or concurrent use of SSRIs and neuroleptics.

All patients must have ECG immediately before and 6 hours after first dose, with hourly BP and pulse for the first 6 hours, with follow up 24 hour in-hospital telemetry if heart rate dose not begin to increase by 6 hours after the first dose.

Pregnancy Category C
Multiple Sclerosis
Dimethyl Fumarate

240 mg PO BID.

Putative mechanism of action is the up-regulation of anti-oxidants, and reduction of oxidative stress

Risks/side effects:
a. sustained lymphopenia

Multiple Sclerosis
Dimethyl Fumarate

Risks/side effects:
b. One case of progressive multifocal leukoencephalopathy (PML)
c. cutaneous flushing, itching, burning (40%)
d. nausea, abdominal pain, diarrhea (40%)

Pregnancy Category C
Multiple Sclerosis
Teriflunomide

- 7 or 14 mg a day, but 14 mg dose more effective.
- Putative mechanism of action is reduced de novo mitochondrial pyrimidine synthesis, leading to reduced number, maturation and function in auto-reactive lymphocytes

Multiple Sclerosis
Teriflunomide

- Risks/side effects

Pregnancy Category X with documented high spontaneous abortion rate. Also passed on in semen of male users.

Has very long half-life of elimination and may be found in blood up to 2 years after last dose. If being DC’d, should be actively removed with 10-12 day course of cholestyramine or activated charcoal.
Multiple Sclerosis
Teriflunomide

Risks/side effects
Hair thinning
Sustained lymphopenia
Hepatic enzyme elevation
Nausea, abdominal pain, diarrhea
Cutaneous reactions or rash
Multiple Sclerosis
Natalizumab

300 mg IV every 4 weeks

A humanized monoclonal antibody directed against the alpha-4 subunit of the docking molecule used by lymphocytes and monocytes to adhere to the endothelial wall of venules in the CNS and colon.

Its putative mechanism is blocking the ingress of immune cells into the CNS.
Multiple Sclerosis
Natalizumab

Reduces risk of recurrent relapses, disease activity on MRI, and increased sustained disability progression

It is regarded by many as the most efficacious medication for the treatment of relapsing MS, but no Class 1 evidence, or head-to-head trials to prove this.
Multiple Sclerosis
Natalizumab

Risks/Side Effects:
Infusion reactions, including severe allergic reactions (<1% of patients, and usually by the second or third infusion)
Hepatic enzyme elevation, and rarely, hepatic failure
Herpetiform infections, including meningitis and encephalitis
Multiple Sclerosis
Natalizumab

Progressive Multifocal Leukoencephalopathy

There have been over 400 cases of PML diagnosed in MS patients using natalizumab, with a 20% mortality.

There are 3 recognized risk factors in these patients: a. duration of natalizumab use
b. evidence of JC virus exposure
c. past use of immunosuppressants
Multiple Sclerosis
Natalizumab

JCV exposure is detected by positive anti-JCV ab titer (The test has a 3% false negative rate). Recheck every 6 months.

For a JCV+ patient on natalizumab for 2 years the PML risk is 3.2/1000 and 7/1000 after 4 years.

For a JCV+ patient with past history of immunosuppressant use, risk is >12/1000 at 2 years.
Multiple Sclerosis
Alemtizumab

- Monoclonal anti-CD52 antibody, 12 mg/d, given 5 consecutive days to initiate therapy and again for 3 days at initiation of year 2.
- Rapidly destroys T-Cell, B-Cell lymphocytes with lesser reduction of monocytes
- Was superior to interferon B-1a in head to head trials:
Multiple Sclerosis
Alemtizumab

♦ a. Relapse risk decreased
♦ b. Reduced MRI enhancing, new /enlarging T2 lesions and reduced brain atrophy.
♦ c. Reduced disability progression only when compared to patients who had failed other therapies but not in previously treatment-naïve patients
Multiple Sclerosis
Alemtuzumab

- Nadir in T & B cells by 1 month.
- Recovery to normal B-cell level - 6 months
- Recovery to normal T-cell level - 12 months
Risks and Adverse Events

Infusion reactions in > 90% of patients and serious infusion reactions in 2.7%

a. All patients receive pre-infusion anti-histamines and antipyretics and IV solumedrol 1000mg for at least first 3 days prior to alemtuzumab infusion
Risks and Adverse Events

- Autoimmune thyroid disorders - 36%
- Idiopathic thrombocytopenia - 2%
- Anti-glomerular BM disease - 0.3%
- Serious infections including fatal - 2.7%
- Fungal infections - 12%
Multiple Sclerosis
Alemtuzumab

- Prophylaxis
- PCP, herpes infection
- Pretreatment Screening for Hep B and C
- Human Papilloma virus, TB, HIV
Safety Monitoring

a. Monthly CBC, Creatinine and UA
b. TSH every 3 months

Monitoring should continue for 48 months after last dose.

c. Pregnancy – in rodents crosses placenta and increased fetal loss. In maternal milk
Multiple Sclerosis Progressive Disease

- There are no approved agents for treating progressive forms of MS, other than mitoxantrone, which is of marginal benefit, has high risk profile for congestive heart failure and Acute Myelogenous Leukemia.
Multiple Sclerosis Symptom Management

It is not sufficient to treat with disease modifying therapies, since the long term symptom impact of MS may be the major measure of therapeudic success.

1. Depression - Suicidal risk
2. Fatigue
3. Spasticity
4. Weakness
Multiple Sclerosis
Symptom Management

5. Fall Risk
6. Pain and paresthesias
7. Bladder/Bowel impairment
   urinary tract infections
8. Sleep Disturbances
9. Obesity and cardiovascular co-morbidity