New Horizons in Multiple Sclerosis Management

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Disclosures

- Principal Investigator on numerous clinical trials for dementia; support from various pharmaceutical organizations including
  - Pfizer
  - Janssen
  - Elan
  - Forest
  - TEVA
  - Medivation

New Horizons in MS Management

- Mimics; Not all white matter lesions are MS
- Monophasic presentations
  - ADEM
  - Clinically Isolated Syndrome (CIS)
- RIS
- Treatment
  - DMT; importance of early intervention
  - Oral and other meds on the horizon
  - Symptomatic therapy
- Neuromyelitis Optica
- What’s all the fuss about CCSVI?

New Horizons in MS Management

- MS MIMICS; NOT ALL WHITE MATTER LESIONS ARE MS
  - Structural or compressive conditions
  - Vitamin B12 deficiency
  - CNS infection (e.g., Lyme, syphilis, HIV, HTLV-I)
  - CNS inflammatory condition (e.g., SLE, sarcoidosis, Sjögren’s syndrome)
  - Neuromyelitis optica (NMO)
  - CNS microvascular disease (e.g., hypertensive changes, vasculitis, CADASIL)
  - Genetic disorders (e.g., leukodystrophies, hereditary myelopathies, mitochondrial disease)

Not all White Matter Lesions are MS

- Mimes
- Not all white matter lesions are MS
- Not all demyelinating lesions are MS: monophasic presentations
  - ADEM
  - Clinically isolated syndrome (CIS)
    - Optic Neuritis
    - Transverse Myelitis
    - Single brainstem lesion

Clinical Diagnosis

- Mimics
- Not all white matter lesions are MS
- Not all demyelinating lesions are MS: monophasic presentations
  - ADEM
  - Clinically isolated syndrome (CIS)
**Acute Demyelinating Encephalomyelitis (ADEM)**

- Inflammatory/demyelinating CNS disorder
- Usually with a rapid onset; monophasic course
- Often occurs shortly after an immunization or infection; drug-induced; idiopathic
- Pathology: perivascular inflammation, demyelination

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**What is Acute Demyelinating Encephalomyelitis (ADEM)?**

- Site-restricted demyelinating event
  - Optic neuritis
  - Transverse myelitis
  - Isolated brainstem lesion

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**What is Clinically Isolated Syndrome (CIS)?**

- Site-restricted demyelinating event
  - Optic neuritis
  - Transverse myelitis
  - Isolated brainstem lesion

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**The MS Spectrum**

- CIS → No More Events
- RRMS (Relapsing-Remitting MS)
- PPMS (Primary-Progressive MS) → SPMS (Secondary-Progressive MS)

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**Should all CIS be treated?**

- In patients with CIS and lesions on MRI, the rate of conversion to MS is very high – 88% will have a new attack and 10% will have a new lesion on MRI (McDonald criteria MS) at 14 years of follow-up
- In patients with CIS and a normal MRI, roughly 40% will convert (17% will have a second attack and 23% will have new MRI lesions)
- In patients with CIS and +OCBs, 62% will convert to clinically definite MS at 6 years

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**The Evidence Favoring Early Treatment**

- CHAMPS: IFNβ-1a in CIS
- BENEFIT: IFNβ-1b in CIS
- PRECISE: glatiramer acetate in CIS
- ETOMS: IFNβ-1a in CIS
- In three trials, the rate of conversion to CDMS decreased by approximately 50%
- Treatment response is also better when therapy is started earlier in the disease course

- Jacobs 2000; Beck 2002; O’Connor 2003; Kappos 2006; Polman 2008; Comi 2001
RIS: The radiologically isolated syndrome
- Patients who, in the absence of symptoms, display lesions on MRI suggestive of MS
- Most have had MRIs for other reasons (eg, headache)
- Lesions may be typical periventricular lesions, but may also be atypical
- Recent evidence suggests that there is also a high rate of conversion to MS in those with typical MS-like lesions
- No clear evidence that all RIS patients should be treated

Siva 2009; Lebrun 2009; Okuda 2009

Tx Recommendations: Standard of Care
- Not the same worldwide
- Influenced by availability, enthusiasm for disease-modifying therapies (DMTs)
- Current gray areas
  - Progressive MS
  - Rapidly worsening MS
  - Suboptimal responders/treatment failures
- Consider immunomodulator therapy for:
  - Definite relapsing MS with active disease
  - First attack/high-risk MS (selected pts)

NMSS Disease Management Consensus
- Therapy is indefinite unless:
  - Clear lack of benefit
  - Intolerable side effects
  - Better therapy available
- Most concurrent medical problems do not contraindicate immunomodulator use
- No therapy approved for women who are pregnant, trying to become pregnant, nursing
- Immunosuppressant tx (mitoxantron) not used first-line
  - Reserved for worsening relapsing MS, SPMS

MS Disease Modifying Therapy (DMT)
- Current estimate: 62% of relapsing MS patients in the United States are on immunomodulator therapy (>200,000)

Standard of Care
- Unapproved treatment options may be used, especially in subtypes without accepted treatments, but not as first-line therapy
  - Pulse glucocorticoids
  - Immunosuppressives (azathioprine, cyclophosphamide, methotrexate, mycophenolate)
  - IVIg
  - Monoclonals
  - Combinations

Current Disease-Modifying Therapies
MS DMT: Immunomodulators

- Interferon (IFN β)
  - IFN β-1b
    - 250 μg (8 MIU) SC QOD (Betaseron®)
  - IFN β-1a
    - 30 μg IM weekly (Avonex®)
    - 44 μg SC 3 x weekly (Rebif®)
- Glatiramer acetate
  - 20 mg SC QD (Copaxone®)
- Natalizumab
  - 300 mg IV monthly (Tysabri®)

MS DMT: Immunosuppressants

- Mitoxantrone (Novantrone®)
  - 12 mg/m² IV Q3mo (to lifetime maximum of 140 mg/m²)

Fingolimod (Gilenya®)

- Sphingosine-1-phosphate receptor modulator
- Induces sequestration of lymphocytes in lymph nodes
- Prevents activated cells from migrating to target organs
- Lymphocytes remain functional and may still be activated as part of an immune response
- Fingolimod Phase II Study
  - N=281 RR or SP
  - 2 doses of Fingolimod vs placebo over 6 months; followed by open label extension
**MS DMTs**

- Successful phase III trials in relapsing MS
  - All agents
- Successful CIS phase III trials
  - SC IFN β-1b, IM IFN β-1a, SC IFN β-1a
  - GA
- Successful SPMS phase III trials
  - SC IFN β-1b (double-dose IM IFN β-1a trial, 1º outcome not accepted)
- Long-term data, although imperfect, suggests benefit for IFN βs and GA for at least 5–16 yrs

**MS DMTs: Agents have pros and cons**

- IFN b-1b: long track record, positive trials for multiple subtypes; neutralizing antibody (Nab) issue
- IM IFN b-1a: most convenient; low Nab rate; ?efficacy
- SC IFN b-1a: very positive relapsing trial; least frequent SC dosing; Nab issue
- GA: good side effect profile; no Nab issue; delayed onset; daily injection
- Natalizumab: very positive relapsing trial; use more restrictive (infusion centers, consent); PML issue
- Fingolimod: oral; very positive relapsing trial; very extensive risk mitigation procedures

**DMT Selection**

- Based on multiple factors
  - Drug factors
  - Disease factors
  - Patient factors
  - Personal experience
- Most important drug factor is efficacy
  - Safety
- DMTs validated in multiple phase III trials focused mainly on relapsing MS

- Efficacy measurements include both clinical and MRI assessments
  - Relapse suppression
  - Disability
  - MRI lesion activity
  - Brain atrophy
- The only valid way to compare efficacy is randomized, prospective, head-to-head trials

**DMT Selection**

- Completed head-to-head trials:
  - EVIDENCE (SC vs IM IFN β-1a)
  - INCOMIN (SC IFN β-1b vs IM IFN β-1a)
  - REGARD (SC IFN β-1a vs GA): OL
  - TRANSFORMS (Fingolimod vs IM IFN β-1a)

- These trials indicate high-dose/frequent- dose IFN β and Fingolimod are more effective than low-dose/weekly IFN β
- GA not inferior to IFN β
Treatment Summary

- Standard of care is to treat active relapsing forms of MS as soon as possible, consider selected CIS pts
- There are some data to offer alternative options for very aggressive MS, suboptimal responders
- Ongoing trials and studies needed to clarify
  - Optimal dosing
  - Head-to-head efficacy
  - Induction and combination strategies
  - New therapeutic approaches
- Better biomarkers needed to predict and evaluate disease activity and therapeutic response

Treatment of Relapses

- Treat those relapses that have a significant impact on function
- Steroids shorten the duration of the relapse and accelerate recovery
  - IV methylprednisolone 1000mg/day for 3-5 days
  - Oral steroid taper
- Plasmapheresis, IVIG
- Whether overall degree of recovery or long term course of MS is affected is unclear

Managing Symptoms

- Spasticity
- Fatigue
- Cognitive changes
- Depression
- Insomnia
- Pain
- Deconditioning

Fampridine-SR (dalfampridine): MoA


On the Horizon

- Other Monoclonal Antibodies
  - Daclizumab
  - Alemtuzumab
  - Rituximab
- Small Molecules
  - Teriflunomide
  - Laquinimod
  - Fumarate
- Cladribine

Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose-ranging study

Goodman et al, 2007
**Monoclonal Antibodies**
- Daclizumab
- Alemtuzumab
- Rituximab

**Daclizumab**
- Targets activated T cells (inhibits IL-2)
- Used to prevent rejection in kidney transplants
- CHOICE Trial (Phase 2, n = 230):
  - 2 mg/kg q 2 weeks, 1 mg/kg q 4 weeks, or placebo, added to ongoing interferon beta treatment
  - high dose group experienced 72% fewer new or enlarged Gd+ lesions compared to placebo (p=0.004) at 24 weeks
  - increased serious infections (4.6% vs 1.3%) and skin reactions in daclizumab groups
- Pivotal trial design currently being developed

**Alemtuzumab (Campath)**
- Approved for treatment of B-cell chronic lymphocytic leukemia; anti-CD52, depletion of CD4+ and CD8+ T cells
- CAMMS 223 Trial: Interim Efficacy Data
  - Phase 2, IFN-controlled, 3-year trial with two different doses (annual 5 day infusions) of alemtuzumab, n=334
  - 2-year results available for both high and low alemtuzumab doses vs Rebif Interferon β-2a SC
  - ≥75% reduction in risk for relapse (P<0.003*); ≥65% reduction in risk for progression of clinically significant disability (P<0.01*)

**Alemtuzumab: Safety Concerns**
- Grave’s & Hashimoto’s thyroiditis (20%)
- Immune-related thrombocytopenic purpura (3%)
  - 6 cases, 1 fatal
  - onset up to 16 months after last infusion
- Infusion reactions (neurologic worsening)
- Life long monitoring?
- Phase 2 trial completed
- Ongoing phase 3 trials include a robust monitoring program to manage the drug’s safety

**Small Molecules**
- Teriflunomide
- Laquinimod
- Fumarate
Teriflunomide
- Used in treatment of rheumatoid arthritis
- Inhibits pyrimidine synthesis and T-cell division
- Teriflunomide Phase II Study
  - 7 mg, 14 mg, placebo; n = 179
  - Cautionary note:
    - Teratogenic in animals

Fumarate (Fumaric acid esters)
- Derived from the plant *Fumaria officianalis*
- Used to treat skin disorders since the 17th century
- Fumaric acid esters used in severe psoriasis
- Inhibits T cell activity
- Fumarate Phase II Study
  - 3 doses of fumarate vs placebo, n=256
  - Only the highest dose (720 mg) showed any efficacy
    - 69% reduction (P<0.001) in mean number of new Gd+ lesions
  - Well-tolerated

The Importance of Early Diagnosis and Treatment
- Widespread axonal pathology, even early
- Subclinical MRI activity
- Transition from RRMS to SPMS over time

Neuromyelitis Optica
- Relapsing inflammatory CNS disorder that closely resembles MS
- Monophasic or recurrent attacks of opticomyelitis
- Myelitis is longitudinally extensive (≥3 segments)
- Limited cerebral and brainstem lesions
- CSF pleocytosis ≥50; only 10-30% have +OCBs
- NMO IgG, antibody to aquaporin-4
Treatment Options for NMO

- During an acute episode
  - IV methylprednisolone
  - Steroid refractory cases: consider plasma exchange, IV immunoglobulin
- Relapse Prevention: Key to Management
  - Immunosuppressants rather than interferon
    - Oral prednisone + azathioprine (or mycophenolate)
    - Rituximab: monoclonal antibodies
  - Treatment duration: 5 years longitudinally extensive myelitis; indefinite in established relapsing NMO

What’s all the fuss about CCSVI?

Chronic cerebrospinal venous insufficiency characterized by multiple stenoses of the principal pathways of extracranial venous drainage, including the internal jugular veins and azygous vein.

- insufficient venous drainage leads to disturbed microcirculation, extravasation of RBCs, iron deposition, autoimmune attack to myelin

Zamboni et al: Chronic cerebrospinal venous insufficiency in patients with MS. JNPP, 2009

- 65 pts with MS; 235 controls
- Ultrasound and venography
  - Azygous vein affected in 86%
  - Internal jugular veins affected in 91%
- PTA to open up veins (patients only)
  - RR patients improved at 18 months; 50% relapse free
  - Unblinded neurologist; no controls
  - Patients continued DMT from Gary Larson, The Far Side.

Multiple Sclerosis: Pathogenesis and mechanisms of therapy