Recent Advances in the Treatment & Management of Multiple Sclerosis

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Disclosures

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Recent Advances in the Treatment and Management of MS

- Background
- Recent advances
- Future advances
- Summary and new initiatives

Background

- Disease features
- Consensus statements
- Current treatment approach
- Current therapies
**MS**

- Major acquired CNS disease of young adults (short of trauma)
- At least 400,000 diagnosed in United States, over 2.3 million worldwide
  - increasing among women
- Characteristic features
  - young age of onset (90% from ages 15 to 50; <1% under age 10, or over age 60)
  - female predominance (approaching 3:1)
  - Caucasian (>90%)
  - variable course (no two patients are alike)

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**MS Phenotypes**

- Clinically isolated syndrome (CIS) recognized as MS phenotype
  - first attack/relapse, classified as low/high risk for MS based on brain MRI
- Relapsing MS
  - 85% to 90% of MS at onset
**MS Phenotypes**

- **Primary progressive MS**
  - 10% to 15%; slow worsening (typically in gait) from onset; equal gender onset, decade later age of onset; may have superimposed relapses

- **Secondary progressive MS**
  - initial relapsing patient who transitions to slow worsening disease

**MS Mortality**

- Life expectancy ↓ 7 to 14 years
- >2.5 fold ↑ mortality risk
- Death can reflect secondary MS issues (>50%), suicide, or MS relapse (medulla)
- MS (vs. matched controls) show higher ICU admission rates
- Lifespan improved from a generation ago

**MS Morbidity**

- Clinically apparent untreated MS results in disability (motor, cognitive, vocational)
- This is typically in the setting of progressive MS
- All progressive MS patients become disabled
- Natural history of MS is to start out as relapsing, then transition to progressive subtype
- MS symptoms provide additional morbidity factors, with negative impact on ADL, QOL

**Treatment Principles: 2014 MS Coalition Consensus Paper**

- Initiate DMT
  - as soon as possible following relapsing MS diagnosis
  - for CIS and MRI c/w MS, with other possible causes excluded
  - for SPMS with relapses or inflammatory MRI changes
- Factors affecting DMT choice are complex; most appropriately analyzed/addressed collaboratively by individual and treating clinician
There should be full access to range of treatment options

Treatment access should not be limited by relapse frequency, disability level, personal characteristics (age, gender, ethnicity)

Lack of relapses on DMT is not justification to d/c

DMT should not be stopped while payor coverage is being evaluated

DMT is indefinite, unless

- suboptimal treatment response (determined by patient and treating clinician)
- intolerable side effects
- inadequate adherence to DMT regimen
- more appropriate DMT available

Moving between DMTs should occur only for medically appropriate reasons
When evidence of breakthrough clinical/MRI activity suggests suboptimal response

- consider switch to different MOA DMT

Rationale for having multiple DMT options

- different MOAs to allow suboptimal response switch
- potential DMT contraindications
- variable risk tolerance
- adherence/QOL issues (route of delivery, side effects)
- individual differences in tolerability/adherence issues

Increasingly accepted to treat early, high risk CIS and all relapsing forms of MS

- rapid institution of therapy

Monitoring/surveillance brain MRIs typically done annually, at least for first years of therapy

Unacceptable clinical/MRI activity results in switch to different MOA DMT

- the first 6-24 months are particularly crucial to judge poor responder

Expectation is that patients should be well controlled

- minimal relapses, disability, new MRI lesions

Active measures to assure adherence/compliance
**Current MS DMTs**

Approved for relapsing forms of MS

First line parenterals
- SC IFNβ-1b 250 mcg every other day (Betaseron; Extavia)
- SC IFNβ-1a 44, 22 mcg 3x weekly (Rebif)
- IM IFNβ-1a 30 mcg weekly (Avonex)
- SC peg IFNβ-1a 125 mcg every 14 days (Plegridy)
- SC glatiramer acetate 40 mg 3x weekly, or 20 mg daily (Copaxone)

Second line parenterals
- IV natalizumab 300 mg monthly (Tysabri)
- IV mitoxantrone 12 mg/m² every 3 months, to lifetime max 140 mg/m² (Novantrone)

First line orals
- fingolimod 0.5 mg (Gilenya)
- teriflunomide 7, 14 mg (Aubagio)
- dimethyl fumarate 240 mg twice a day (Tecfidera)
**First Line Oral Agents**

**Fingolimod**
- 0.5 mg PO daily (0.25-mg dose is being tested)
- Sphingosine 1-phosphate receptor modulator (binds to receptors 1, 3, 4, 5)
- Phosphorylated product blocks ability of naïve and central memory T cells to exit lymph nodes; CCR7-effector memory T cells are not affected
- Also enters CNS to potentially have direct effects


**First Line Oral Agents (cont’d)**

**Teriflunomide**
- 14 mg PO daily (7 mg also available)
- Dihydroorotate dehydrogenase inhibitor (de novo pyrimidine synthesis)
- Cytostatic for rapidly dividing B cells and T cells (salvage pyrimidine pathway unaffected)
- Active ingredient of leflunomide (treatment for RA and psoriatic arthritis)

First Line Oral Agents (cont’d)

Dimethyl Fumarate

- 240 mg PO twice daily
- Fumaric acid (citric acid energy cycle) ester
- Affects Nrf2 oxidative stress, direct effects on lymphocytes and dendritic cells
- 1 of 2 key components of psoriasis product in Germany

Pros

- Oral convenience
- Very good efficacy
- Well tolerated (for the most part)

Cons

- Limited experience
- No long-term safety or efficacy data
- Each oral agent has its own unique adverse events and tolerability issues


Natalizumab

- Excellent efficacy
- Assured adherence/compliance
- Well tolerated
- Has been used first line
- Only issue is progressive multifocal leukoencephalopathy (PML)

PML Risk Stratification Factors

- Accurate counseling on PML risk is critical
- This provides the context for treatment initiation and continuation decisions
- Factors involve
  - JC virus antibody titer and index
  - duration of natalizumab therapy
  - prior immunosuppression therapy
**PML Risk Stratification Factors**

- Possible factors
  - low L-selectin expression on CD4+ Tcells
  - intrathecal JC virus antibody production
  - absent CSF IgM oligoclonal bands
  - low body mass

**MS Unmet Needs**

- No cure
- No effective therapies for neurodegeneration or CNS repair
- Variable individual therapeutic response
- MS heterogeneity with multiple damage mechanisms
- Need for safe, effective and convenient therapies with good compliance
Recent Advances

- UK MS risk sharing data
- Double dose glatiramer acetate
- Pegylated interferon beta
- Generics issue
- Wellness emphasis

UK MS Risk Sharing Scheme*

- Six year study involved over 5,000 MS patients treated with IFNβ or GA
  - largest observational study to date
- Compared to British Columbia natural history database
- DMT use determined to be cost effective in preventing EDSS disability
- Ongoing assessment continues (planned for 10 years)

*ECTRIMS-ACTRIMS 2014:LB1.2
GA

- GA 20 mg SC daily
- GA 40 mg SC 3x weekly
- Generics
  - Pros include long term safety and efficacy data; patients may do very well; no laboratory testing; best pregnancy rating
  - Cons include needle injections

The GALA Trial

- Phase 3 trial of 40 mg glatiramer acetate SC 3x weekly (N=943) vs. placebo (N=61)
  - ARR 0.33 vs. 0.51 at 1 year, ↓ 34%; (P<0.0001)
  - Cumulative contrast brain lesions ↓ 44.8%; new/enlarging T2 lesions ↓ 34.7%
  - Now approved for relapsing MS

Pegylated IFNβ-1a

Pegylation provides longer half-life, exposure

ADVANCE trial (N=1516)
- 125 µg pegylated IFNβ-1a SC every 2 or 4 weeks vs. placebo
- relapse, disability at 1 year
- placebo re-randomized after 1 year for safety, efficacy at 2 years

ARR (Year 1)
- 0.256 (↓ 36%), 0.288 (↓ 28%) vs. 0.397
- risk reduction in 12-week confirmed EDSS 38%


Pegylated IFNβ-1a

T2 lesions
- 3.6 (↓ 67%), 7.9 (↓ 28%) vs. 10.9

Contrast lesions at 48 weeks
- 0.2 (↓ 86%), 0.9 (↓ 36%) vs. 1.4

Two year data
- better results with immediate vs. delayed therapy (ARR, confirmed disability, MRI, NEDA: 36.7% vs. 15.8%)

ECTRIMS-ACTRIMS 2014
Generics

- Raises issues of what is acceptable for the approval of biosimilar products, generic nonbiologic complex drugs
- Generic IFNβs available in other countries
  - NA 100 (IFNβ-1b) being evaluated
- Several generic glatiramer acetates
  - second-generation peptide copolymer (PI 2301, plovamer acetate) in trial


Generic GAs

- GTR (GATE study) from Synthon
  - randomized study, 20 mg showed equivalence
- Probioglat (in Mexico) from Probiomed
- Momenta/Sandoz/Novartis generic
  - 20 mg and 40 mg
- Natco pharma generic (partnered with Mylan)
  - 20 mg and 40 mg
Brain is shrinking 0.1-0.3% per year
  - this is accelerated in MS
Hypertension, diabetes, smoking, obesity all increase brain shrinkage
There is loss of neural circuits, and brain plasticity
Exercise can improve brain function
  - aerobic exercise and strength training
  - over 30 minutes per session

Optimum body weight, no smoking, moderate alcohol
Good sleep hygiene
Healthy diet (no vitamin issues), limited salt
Regular exercise several times a week (aerobic and muscle strengthening)
**Wellness/Health Maintenance/Vascular Risk Factor Program**

- Take care of blood pressure, glucose issues (hemoglobin A1c), lipids
- Dental health
- Regular mental exercise, socialization

**Memory Retraining in MS***

- Pilot study evaluated 10 session memory training over 5 weeks in MS (N=86) vs. placebo treatment
- The memory training cohort showed improved memory and learning
  - functional MRI showed increased patterns of cerebral activation
- Memory improvement and increased cerebral activation was maintained over 6 months

*Brain Imaging Behav 2014;June 14*
Future Advances

- Alemtuzumab
- Daclizumab
- Anti-CD20s
- Progressive MS/repair strategies

Alemtuzumab

- Humanized IgG1-kappa anti-CD52 monoclonal antibody
- Cytolytic antibody depletes T cells (CD4 more than CD8), and to a lesser extent B cells; NK cells; monocytes and dendritic cells
- Initially approved for B cell-CLL
- Treatment cycle involves 5 days of 12 mg/day IV during year 1; 3 days of 12 mg/day IV during year 2 (given with IV methylprednisolone)

**Alemtuzumab**

- This is induction strategy (effects last ≥5 years)
- Risk mitigation program involves mandatory monitoring for several years
  - thyroid dysfunction (17%-33%)
  - ITP (1%-3%)
  - kidney (<1%)
- Debate regarding use in treatment naïve
- Therapy will apply to small minority of patients
- Over seven year follow up, 48% required additional treatment cycles*

*JNNP 2014;May 21

**Alemtuzumab Two Year Phase III Trials**

- ARR 0.18, 0.26
- Confirmed disability 8%, 13%
- Less MRI disease
- Compared to SC IFNβ-1a 3x weekly
Alemtuzumab

Recent FDA Review

- In Dec 2013, FDA declined approval, citing:
  - the need for adequate and well-controlled studies
  - safety concerns
- Genzyme has resubmitted application for FDA approval


Daclizumab

- Humanized anti-CD25 monoclonal antibody
- Targets activated T cells and B cells
- Expands CD56 bright NK cells (may predict treatment response)
- Originally approved for renal transplant
- Given IV or SC (high yield product, HYP)

Daclizumab

Three year phase 3 trial (DECIDE) N=1,841

- 45% ↓ in ARR vs. IM IFNβ-1a, 0.216 vs. 0.393 (P<0.0001)
- 54% ↓ in new/enlarging T2 lesions (P<0.0001)
- 16% ↓ in disability (ns)

Concerns about cutaneous reactions, liver toxicity

DECIDE = Efficacy and Safety of Daclizumab High Yield Process versus Interferon β 1a in Patients with Relapsing-remitting Multiple Sclerosis.

Anti-B Cell Strategies

- Anti-CD20 monoclonal antibodies
  - rituximab (chimeric)
  - ocrelizumab (humanized)
  - ofatumumab (human)

Ocrelizumab

- Humanized anti-CD20 IgG
- Binds to different overlapping epitope (vs rituximab)
- Enhanced ADCC, reduced CDC

ADCC = antibody-dependent cell-mediated cytotoxicity; CDC = complement-dependent cytotoxicity.

Ocrelizumab Phase 2 Study: Gd-Enhancing T1 Lesions

Lesions on MRI by Week (ITT)

↓ 89%–96%, P < 0.0001 for both ocrelizumab doses vs placebo

Gd = gadolinium; IFN = interferon; ITT = intention-to-treat.
IFNβ-1a arm was open-label; all efficacy comparisons were exploratory.
**Ocrelizumab Phase 3 Trials**

**OPERA I, II**
- phase 3 trials in RRMS (N=800 each)
- ocrelizumab 2 × 300 mg IV over 2 weeks, then 600 mg every 24 weeks vs IFNβ-1a 44 µg SC
- primary outcome: ARR at 96 weeks; time to confirmed disability progression (24 weeks)

ARR = annualized relapse rate; IFN = interferon; RRMS = relapsing-remitting multiple sclerosis.

Montalban X, et al. 63rd AAN Annual Meeting; Honolulu, HI; April 9-16, 2011.
ClinicalTrials.gov

**ORATORIO**
- phase 3 in PPMS (N=360)
- ocrelizumab, 2 infusions of 300 mg per cycle vs placebo
- age 18–50 years, EDSS 3–6.5, abnormal CSF
  - EDSS ≤5, disease duration <10 years
  - EDSS >5, disease duration <15 years

CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; PPMS = primary-progressive multiple sclerosis.
Montalban X, et al. 63rd AAN Annual Meeting; Honolulu, HI; April 9-16, 2011.
ClinicalTrials.gov
**Ofatumumab**

- Human IgG1-kappa
- Approved for refractory CLL
- Binds to novel membrane-proximal CD20 epitope
  - dissociation rate slower than rituximab
- Increased CDC

CDC = complement-dependent cytotoxicity; CLL = chronic lymphocytic leukemia; Ig = immunoglobulin.


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**Phase 2 Ofatumumab Study**

- Randomized, double-blind, placebo-controlled 24-week study (N=38)
  - patients received 2 ofatumumab infusions 2 weeks apart (100 mg, 300 mg, 700 mg, placebo)
  - patients received alternate therapy at 24 weeks
- New brain MRI lesions (T2, T1, contrast) suppressed >99% by all doses at 24 weeks
  - monthly MRIs; measured weeks 8–24
- Safe and well tolerated

Phase 2 Ofatumumab Study (cont’d)

- Relapsing MS patients (N=232) treated for 24 weeks
- SC 3 mg, 30 mg, 60 mg every 12 weeks; 60 mg every 4 weeks; or placebo
- Contrast lesions ↓ 65% weeks 0–12, ↓ ≥90% weeks 4–12 in all ofatumumab arms
- No unexpected safety issues

Anti-CD20 Monoclonal Antibodies

Pros
- Selective biologic
- Efficacy
- Potential for progressive MS
- Infrequent delivery

Cons
- Long-term adverse events for MS unknown
- Novel anti-CD20 monoclonal antibodies offer unknowns
**Progressive MS**

- Reflects neurodegeneration
- Clinical expression is age-related
- Specific injury mechanisms suggested
- No proven DMT yet

**CNS Repair Strategies**

- None yet established
- Strategies include remyelinating antibodies, stem cells, agents which protect axons/neurons/mitochondria, reduced microglia activation
Other Agents

MIS416
- microparticle adjuvant contains TLR-9 and NOD-2 ligands
- given IV; activates innate immune cells
- being studied in progressive MS

Mesenchymal stem cells
- given IV
- being studied in relapsing and progressive MS

Other Agents

Tcelna
- given SC; phase II SPMS
- personalized vaccine (Tcells reactive to MBP, MOG, PLP)

rHlgM22
- remyelinating monoclonal IgM (phase I trial)
Other Agents

Ant-LINGO1

- Remyelinating antibody, promotes oligo differentiation
- Phase II RENEW trial: acute optic neuritis trial; 100 mg/kg, Q4w x 6; assessing VEPs, OCT, visual function
- Phase II SYNERGY trial: relapsing and SPMS on IM IFNβ-1a; placebo; 3, 10, 30, 100 mg/kg Q4w x 18; assessing EDSS, 25 FTW, PASAT

Implications for New MS Drug Development

- Crowded market, for both orals and injectable DMTs
- Financial/cost focus will be increasingly emphasized
- Emphasis will now be on what is novel
  - Neuroprotection/progressive therapy
  - Improved efficacy/safety for monotherapy and combination therapies
Oral DMTs will increasingly be used in treatment naïve

IFNβ/GA use will decrease
  one IFNβ likely to become dominant

Anti-CD20 will replace natalizumab, and will be used first line in high disease activity/poor prognosis patients
  will be viewed as optimal switch agent

Concerted push for progressive MS therapies, and CNS repair strategies

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Multiple MS DMTs
They have focused on relapsing MS
Early therapy, close follow up, appears optimal
There is need for biomarkers to select and validate DMT choice, and therapies for progressive MS/CNS repair
Issues such as induction, combinations, and costs will need to be dealt with