Best practices for using MS disease modifying therapies

CMSC Annual Meeting 2015

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Objectives

- Use best practices to select initial and subsequent disease modifying therapies for MS
- Apply an individualized approach to clinical decision making
- Understand the economic issues impacting MS management and therapeutic decisions

Current Treatments for MS (10 with 7 MOA's)

Drug	MOA
❖Interferon Beta (IM or SQ) ▪ 4 products: two IFN-beta-1a, two IFN-beta-1b)	Decreased inflammation and T-cell trafficking BBB
❖Glatiramer acetate (daily SQ), now 40mg TIW)	Molecular mimicry; bystander suppression
❖Natalizumab (iv q month)	Inhibits integrins; reduced T-cell infiltration
❖Fingolimod (oral qd)	Traps autoreactive T-cells in lymph nodes
❖Teriflunomide (oral qd)	Interferes with T-cell proliferation
❖Dimethyl-fumarate (oral bid)	Nrf2 activation cytoprotective
❖Alemtuzumab (iv once per year)	CD52, eliminates B and T-cells from circulation
❖On horizon	
▪ Daclizumab (SQ q month)	Inhibits IL-2 induced proliferation of T-cells
▪ Ocrelizumab (iv 2 times per year)	CD20, eliminates B-cells from circulation
▪ Laquinimod (oral)	Anti-inflammatory pathways; neuroprotective

Where Are the Gaps in Consensus Treatment Algorithms?

- ❖The treatment of multiple sclerosis has become complex as a result of success in clinical research and drug development
- ❖There is no single consensus approach to prescribing disease modifying drugs; there is no cookbook
- ❖The drugs for MS are exceedingly expensive and engender high intensity, rapid response marketing campaigns from pharmaceutical industry
- ❖Data needed for true evidence-based best practices is lacking and existing drugs cannot be targeted to the patients most likely to benefit
- ❖Absent consensus guidelines, payers feel the need and assume the right to define prescribing patterns

Mixed

Signals

Motivations for developing a best practices guideline

- Physicians, nurses, and other professionals who treat MS need decision making tools, vetted by experts, to help them determine appropriate DMT selections for relapsing remitting MS (RRMS) and clinically isolated syndrome (CIS).
- Practitioners who treat MS would benefit from a clear consensus about **when to switch therapies**, how to approach **aggressive presentations of MS**, how to **balance safety and efficacy** in MS therapies, and how to take the **patient's and payer's perspectives** into account.
- Among the hallmarks of MS are its heterogeneous presentation and lack of predictable patterns of progression. These characteristics are not unique to MS, but are common to many chronic diseases for which detailed, dynamic guideline statements exist
- 15 distinguished MS experts met in Dallas, TX, in May 2013.
  - Physicians, nurse specialists, managed care professionals
  - Published "best practices" guidelines in IJMSC in October 2014

Expert Participants

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Complicating factor of cost in MS DMT use

- The top 3 most expensive diagnoses for health care payers:

1.	Cancer	~14.5 million survivors in 2014
2.	Multiple sclerosis	~400,000 with diagnosis in US
3.	Rheumatoid arthritis	

- How did this come to be?
  - MS pharmacotherapy consumes **$1 of every $40** pharmacy benefit dollars
  - Total medication expenditures increased 13.6% each year between 2010 and 2013, driven primarily by drug price increases

Standard treatment outcomes in MS

- Reduce relapses; extend time between relapses
- Reduce severity of relapses
- Prevent or extend time to disability milestones as measured by the Expanded Disability Status Scale (EDSS) and other disability measures
- Prevent or extend time to onset of secondary progressive
- Prevent or reduce the number and size of new and enhancing lesions on MRI
- Limit overall MRI lesion burden in the central nervous system (CNS)

Newer treatment outcomes in MS

- Reduce measures of axonal damage, CNS atrophy, and evidence of microscopic disease via conventional MRI and advanced imaging modalities
- Modify biomarkers associated with inflammatory disease activity and neurodegeneration in MS
- Extend time during which there is no evidence of disease activity (NEDA). NEDA is a new concept for outcome deriving from success in number and efficacy of therapies

Narrowing the choice of DMT's in MS

- Is there a reasonable expectation that this drug will be effective for this individual?
- Does this person meet the contingencies for safe use of the drug? Are there any comorbid conditions that may rule out this agent or influence the risk of future adverse events?
- What are the patient's thoughts, concerns, and preferences about the drug: overall safety, administration method, monitoring requirements?
- Is the patient able to adhere to correct administration methods and monitoring requirements for the agent selected? What forms of support can be provided?
- Is the cost of this drug covered by the patient's health plan in the sequence being considered? If not, could a viable appeal be made to the plan for coverage of the drug?

Safety

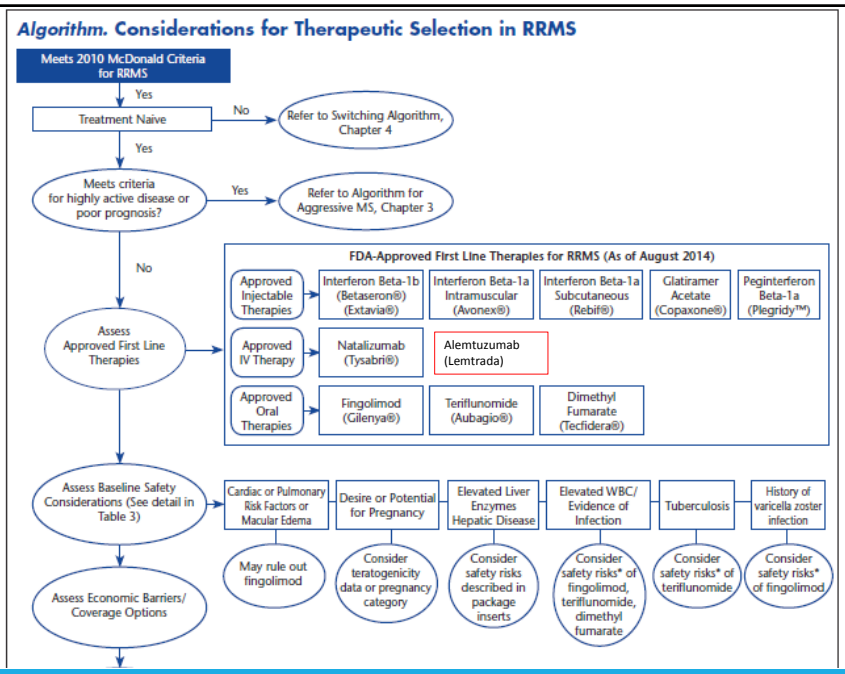
- Short and long term safety are critical factors in the selection of DMTs for MS
- The injectable therapies for MS (interferon beta-1a, interferon beta-1b, and glatiramer acetate) have established long term safety profiles over more than 20 years of continuous use
- Oral immunomodulatory agents and monoclonal antibodies for MS are welcome additions to the selection of DMTs. The long term safety profiles of these drugs in MS have yet to be elucidated.
- Safety concerns associated with some therapies and added requirements for safety monitoring may increase the complexity of a therapeutic selection.

Tolerability and Adherence

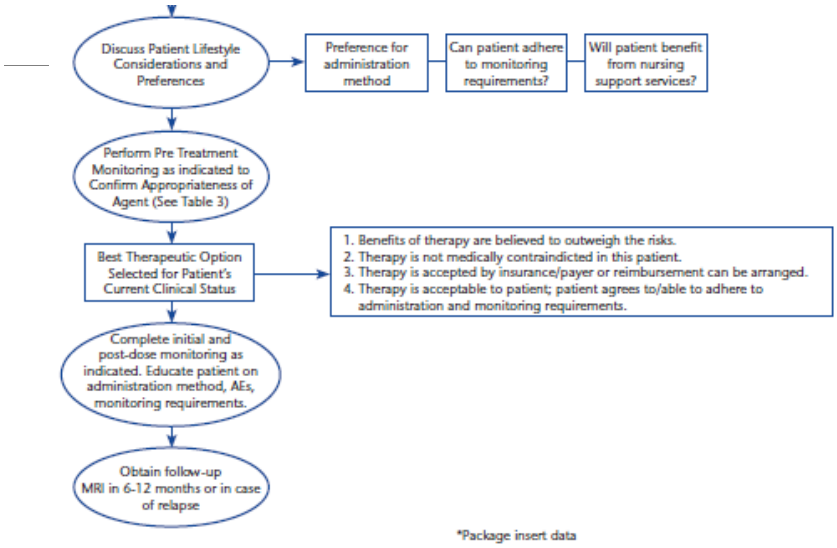
- In MS, tolerability may affect the patient's willingness to
  - Self-administer an injectable therapy
  - Maintain continuous use of an injectable drug
  - Tolerate systemic effects of an oral or parenteral therapy, or a combination of these factors.
- Tolerability and convenience should not be the only considerations in selection of a therapy, but they should be included in the decision making process for initial therapy and determinations for switching therapies

Cost and Reimbursement Issues

- The high costs of managing MS are receiving scrutiny from managed care organizations (MCOs) and other payers
- It is hard to put a price on benefits of treatment such as years of productive life gained by delaying disability. Cost benefit ratios are difficult to calculate.
- In 2012 annual treatment costs exceeded $56,000 per year for the highest priced agents
- Payers often limit the DMTs they make available to their insured members as first line agents, and this frequently influences the selection of therapy



RRMS guideline (continued)



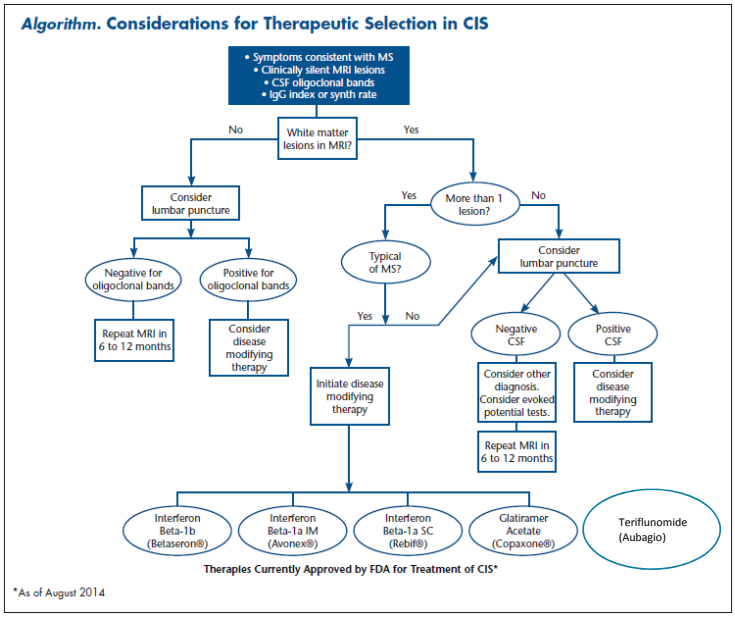
*Package insert data

Treatment guidelines for the Clinically Isolated Syndrome (CIS)

- CIS describes a condition that appears to be an early clinical manifestation or neurologic event suggestive of multiple sclerosis (MS), but does not satisfy the full diagnostic criteria for MS
- Abnormal magnetic resonance imaging (MRI) results are not always initially present in CIS, but frequently there are 1 or more lesions on T2 or FLAIR MRI consistent with CNS demyelination. One to two or more lesions predicts second relapse in 10-15 years.
- An estimated 30% of untreated patients with CIS will have a second neurologic event within 12 months.
- Most presentations of CIS are considered to be the **earliest manifestation of MS**, especially in the presence 1 or more MRI lesions consistent with MS

Double-Blind, Placebo Controlled Trials in CIS

Drug	Trial Name (N) Trial Duration	Conversion to MS		P Value/ Odds ratio	Days to Conversion	
		Drug	Placebo		Drug	Placebo
Interferon beta-1b (Betaseron)[16]	BENEFIT (487) 2 years	28%	45%	P<0.0001 OR = 0.50	(n/a)	(n/a)
Interferon beta-1a IM (Avonex)[17]	CHAMPS (383) 3 years	35%	50%	P=0.02 OR = 0.56	(n/a)	(n/a)
Interferon beta-1a SC (Rebif) low-dose (22 mcg)[18]	ETOMS (309) 2 years	34%	45%	P=0.09 OR = 0.61	569	252
Interferon beta-1a SC (Rebif) 3x/wk (44 mcg)[20]	REFLEX (515) 2 years	20.6%	37.5%	P=0.0004		
Glatiramer acetate (Copaxone)[19]	PreCISe (481) 3 years	25%	43%	P<0.0001 OR = 0.55	772	336
Teriflunomide (Aubagio) (unapproved)[24]	TOPIC (618) 2 years	43% reduced risk of MS vs placebo (14 mg) 37% reduced risk (7 mg)		P=0.0087 P=0.271		
Cladribine (unapproved)[25]	ORACLE MS (903) 96 weeks	Hazard ratio 0.38 (5.25 mg) Hazard ratio 0.33 (3.5 mg)		P<0.0001 P<0.001		



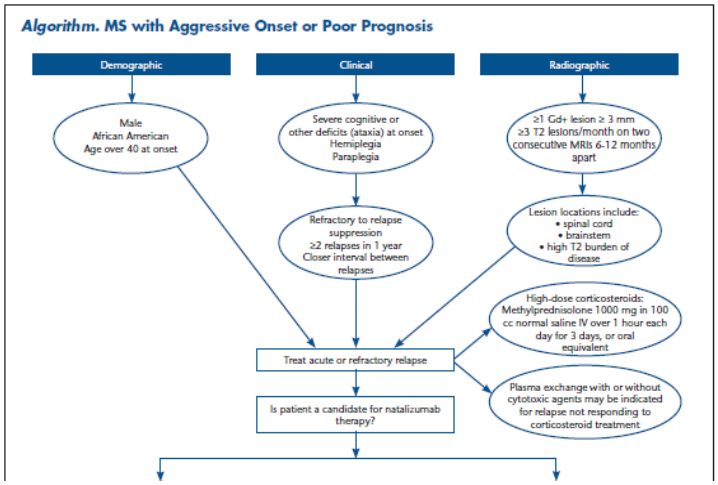
Approaches to patients with aggressive MS

- Multiple sclerosis (MS) that has an unusually severe onset or rapidly progressing course has been described by a variety of terms: Aggressive MS; Marburg variant MS; Malignant MS
- Early identification of patients with the potential for a more aggressive disease course will allow early consideration of different therapeutic strategies
- Signs of aggressive MS
  - onset with significantly disabling symptoms, often related to spinal cord disease
  - onset refractory to relapse suppression, with poor recovery from relapses
  - significant recurrent or breakthrough disease over a short period of time
  - significant MRI findings (enhancing, tumefactive lesions and/or overall lesion burden)
  - MS that progresses quickly to disability
- This presentation represents between 4% and 15% of patients with RRMS.

Indicators Suggestive of Aggressive Course or Poor Prognosis in MS

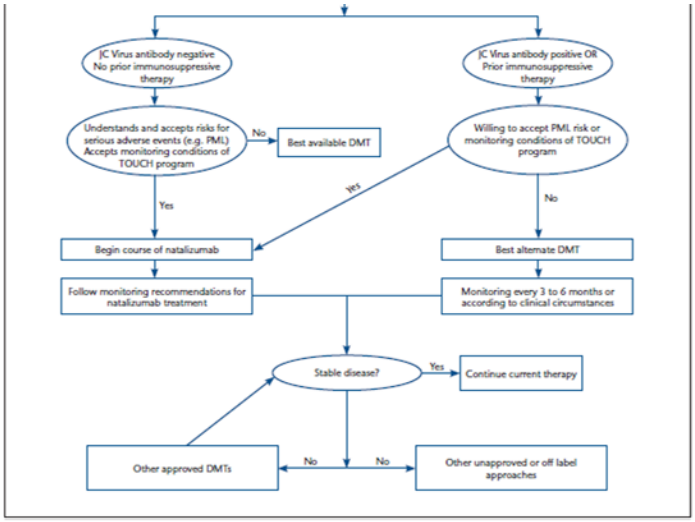
- age at onset ≥ 40
- male gender
- African American
- motor, sphincter, cerebellar symptoms
- MRI lesions in brainstem or spinal cord at onset
- Spinal cord or cerebellar symptoms
- ≥ 2 attacks in first 2 years of onset
- incomplete recovery from relapse

MS with Aggressive Onset or Poor Prognosis



MS with Aggressive Onset or Poor Prognosis (continued)

- **Alternatives including off label**
  - **Alemtuzumab**
  - **Natallzumab**
  - **Orelizumab (Rituximab)**
  - **Stem cell theraples**



Alternative treatments in aggressive MS

- Cytotoxic agents such as mitoxantrone and cyclophosphamide are sometimes utilized in aggressive RRMS.
  - cardiotoxicity, treatment-related leukemia, and severe infections
- Plasma exchange (also called plasmapheresis) can be utilized as an adjunctive treatment for exacerbations in relapsing forms of MS and is sometimes used to treat fulminant demyelinating disease that fails to respond to high-dose corticosteroid
- Academy of Neurology issued an evidence based guideline update on plasmapheresis in MS
  - In relapsing forms of MS, plasma exchange may be effective as a secondary therapy for exacerbations not responding to treatment with corticosteroids.
- Stem Cell therapies

Reasons to Switch Disease Modifying Therapies

Efficacy
- No response or suboptimal therapeutic response
- Initial response followed by breakthrough disease
- Neutralizing antibodies leading to suboptimal response

Safety
- Significant adverse events such as liver toxicity or decreased blood counts
- Comorbid condition or new safety consideration (e.g., pregnancy, development of renal disease)
- Change in patient's risk profile for adverse events (e.g., JC virus antibody conversion)
- Development of tolerability problems over time (e.g., skin damage)

Patient-related Reasons
- Difficulties with adherence to therapy
- Desire to try different administration method
- Perceived lack of efficacy of current therapy

Prescriber- or Payer-related Reasons
- Patient has new prescriber who switches therapy
- Changes in practice of existing prescriber
- Change in payer or payer formulary choices forces switch due to lack of coverage

Goals of MS Therapy and Indicators of Suboptimal Response

Therapeutic Goals and Indicators of Poor Response to Treatment

- Ongoing or increased relapse rate while on therapy
- Incomplete recovery from relapses
- Slow or unrelenting worsening on neurologic exam
  - Sustained, objective worsening on EDSS, 25-foot walk test
  - Cognitive testing, especially those affecting ADLs, employment, or quality of life.
- Active or new lesions on MRI (T2, T1, enhancing), and other indicators of neurologic damage (nonconventional measures to detect microscopic injury such as atrophy)
  - ≥ 2 gadolinium enhancing lesions in the first year of treatment
  - 2 or 3 new T2 lesions in the first year of treatment (on scans ≥3 months apart

Switching DMT in RRMS

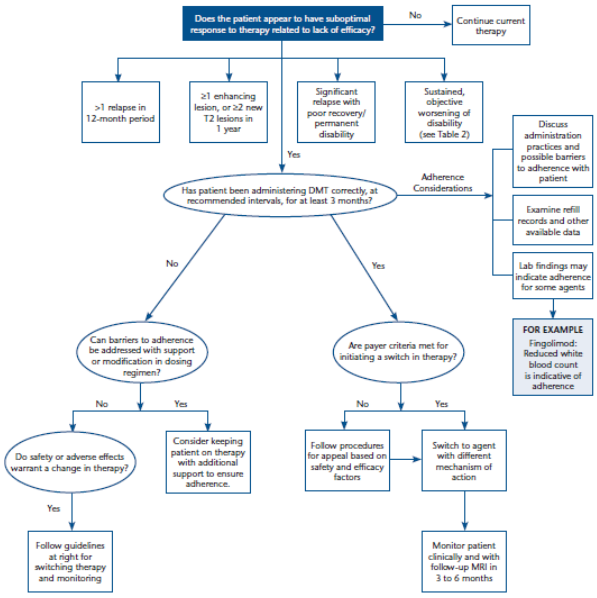
Criteria for switching:

- Relapses while on treatment
- 1 significant relapse and poor recovery with permanent disability
- MRI activity characterized by:
  - ≥1 enhancing lesions, or
  - ≥ 2 or more new T2 lesions in 1 year
  - MRI activity on consecutive MRIs done at intervals ranging from 3 to 12 months

Options for switching to another agent include:

- Switch to another agent from a different class if disease severity appears mild
- Increase the dose or dosing frequency of the initial agent, if the drug is tolerated and a higher dose option is available
- Switch to a second line agent if disease characteristics meet criteria for aggressive MS or if patient has tried 2 or more first line agents.

Switching Disease Modifying Therapies Due to Lack of Efficacy



Patient and Payer Perspectives in Therapeutic Selection for Multiple Sclerosis

- MS pharmacotherapy consumes $1 of every $40 pharmacy benefit dollars
- Total medication expenditures increased 13.6% each year between 2010 and 2013, driven primarily by drug price increases
- From 2006 to 2013:
  - Copaxone $15,100/y to $55,250/y
  - Tysabri $23,200/y to $51,900/y
  - Gilenya $59,600/y = $165 per capsule per day

Annual CPI	2.5%	4.1%	0.1%	2.7%	1.5%	3.0%	1.7%	1.5%
Year	2006	2007	2008	2009	2010	2011	2012	2013

Current Cost Containment Strategies of Payers

- Offering more limited drug choices on MS formularies
- Creating tier systems to incentivize patients/prescribers to select the lowest priced agents on the formulary
- Negotiating arrangements with manufacturers to freeze prices or provide discounts in exchange for a priority position in the formulary
- Requiring prior authorization for initiating or switching therapy
- Requiring patients to "fail" preferred therapies before reimbursing for non-preferred therapies
- Increasing patient cost sharing

Discontinuation of therapy

- 17–41% patients ultimately discontinue therapy, most in first 2 years
- 30–50% discontinue therapy due to lack of efficacy
- 22–70% due to adverse effects
- 75% switch to another DMT 1 time
- 11% switch 2 times
- 14% switch 3 or more times

Common Barriers to Adherence in MS

- Unrealistic expectations about the impact of therapy on MS
- Lack of belief in the benefits of therapy
- Fear of or intolerance to injection (with injectable agents)
- Adverse effects/tolerability problems
- Complacency, “treatment fatigue”
- Cognitive decline or declining motor skills
- Change in family or financial circumstances

Common reasons for patients to request a switch in therapy

- Want to try another dosage form (injection fatigue, injection-site reactions)
- Feel that therapy is not working for them
- Nonadherence (may not be reported or obvious)
- Side effects or tolerability issues
- Concerns about risks of therapy (e.g., PML serious AEs)
- Pregnancy, planning a pregnancy
- Cost/reimbursement of therapy

Switching considerations for healthcare professionals

- How long has patient been on the current agent?
- How well has this agent controlled disease?
- Are there safety or tolerability issues that may guide selection of a new therapy?
- How often is it safe to change therapies?
- Will the patient really have better adherence with the new therapy?
- What monitoring is involved?
- Age/gender/race
- Comorbid conditions
- Will the insurance cover a different agent?

Recommendations and needs for future

- As a "call to action" for groups of payers and providers, we need added rigor and a more consistent approach to the management of MS, including:
- Better tools and markers for selecting the right drug for each patient
- Shared decision making tools for payers and healthcare providers
- Clinical decision support
- Patient assessment tools
- Guidance on sequencing drugs to minimize complications

Thank you!

Questions??